Clinical Study Protocol

NCT Number: NCT04501614

Title: A Pivotal Phase 1/2, Single-Arm, Open-label Study to Evaluate the Safety and Efficacy of Ponatinib With Chemotherapy in Pediatric Patients With Philadelphia Chromosome-Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Who Have Relapsed or Are Resistant or Intolerant to a Prior Tyrosine Kinase Inhibitor-Containing Therapy, or Who Have the T315I Mutation

Study Number: Ponatinib-1501

Document Version and Date: Amendment 4.0, 02 November 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

A Pivotal Phase 1/2, Single-Arm, Open-label Study to Evaluate the Safety and Efficacy of Ponatinib With Chemotherapy in Pediatric Patients With Philadelphia Chromosome-Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Who Have Relapsed or Are Resistant or Intolerant to a Prior Tyrosine Kinase Inhibitor-Containing Therapy, or Who Have the T315I Mutation

Ponatinib With Chemotherapy in Pediatric Patients With Relapsed, Resistant, or Intolerant Ph+ ALL or Have the T315I Mutation

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

617-349-0200

Study Number: Ponatinib-1501

EudraCT Number: 2019-002549-39

Compound: Ponatinib

Date: 02 November 2023 **Amendment Number:** 4

Amendment History:

Date	Amendment Number	Amendment Type	Region
02 November 2023	Amendment 4	Substantial	Global
23 May 2023	Amendment 3	Substantial	Global
23 February 2021	Amendment 2	Substantial	Global
09 April 2020	Amendment 1	Substantial	Global
25 July 2019	Initial Protocol	Not applicable	Global

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 medical monitor and responsible medical officer are in the site operations manual.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

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 signatories, as applicable) can be found on the signature page.

Electronic signatures may be found on the last page of this document.

[redacted], MPH Date
Study Clinical Lead

[redacted], MD Date
Clinical Science
[redacted] –
Pediatric Development

[redacted], MD Date
[redacted]

[redacted], PharmD, PhD Date
Quantitative Clinical Pharmacology Lead
[redacted]

[redacted], PhD Date
[redacted] Study Statistician

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure, package inserts, 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 patients 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 serious adverse events 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)

1.3 Protocol Amendment 4 Summary of Changes

Protocol Amendment 4 Summary and Rationale:

This section describes the changes to the protocol incorporating Amendment 4. The primary reasons for this amendment are to incorporate Health Authority requests.

The protocol was updated to:

- Modify phase 1 cohort 2 to enroll a single cohort for determination of recommended phase 2 dose (RP2D) rather than 2 weight groups with separate evaluations.
- Modify the definition of related adverse events for dose-limiting toxicity (DLT) criteria to:
  - Clarify the definition of "related' causality assessment.
  - Modify the requirement for DLT criteria.
  - Modify the definition of "DLT-evaluable" patient.
- Modify dose modifications for ponatinib with the occurrence of lipase elevations and pancreatitis.
- Modify the criteria for beginning a consolidation block or optional continuation therapy.

In this amendment, minor grammatical, editorial, formatting (including bibliographic references format), and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only and may not be listed in the summary of changes below.

Protocol Amendment 4			
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 1.2 Approval	Updated the list of approvers.	Administrative change.
2.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 6.2 Number of Patients	Updated the number of patients in phase 1 portion of the study: "approximately 18 DLT-evaluable patients..." to "approximately 12 DLT-evaluable patients…").	Phase 1 enrollment will be reduced from a total of approximately 18 to approximately 12 patients, given the changes to cohort 2 to enroll approximately 6 instead of 12 patients.

Protocol Amendment 4			
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***
3.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 13.1.1 Analysis Sets	Updated the minimum percentage and number of days of ponatinib dosing required for a patient to be evaluable for DLTs: "for at least 50% of the reinduction block days (eg, 18 or more of the 35 days)" to "on at least 70% of the reinduction block days (eg, 25 or more of the 35 days)".	To modify based on Health Authority feedback on protocol amendment 3.
4.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design	Added that ponatinib doses for evaluation in phase 1 cohort 2 will target systemic exposures comparable to those achieved in adults receiving 15 mg QD.	To clarify.
5.	Section 2.0 STUDY SUMMARY (and Figure 2.a) Section 6.1 Overview of Study Design (and Figure 6.a)	Updated the number of patients in phase 1 cohort 2 (from 12 to 6-12 patients), added the minimum number of patients with a baseline body weight <30 kg, removed the 2 weight groups, and updated the minimum number of DLT-evaluable patients who must complete reinduction block and be without a DLT so that RP2D can be determined (6 instead of 5 patients in cohort 2). Added if 2 out of 6 patients experienced a DLT, the study will be paused to determine further tolerability of this combination.	To modify based on Health Authority feedback on protocol amendment 3 and to evaluate RP2D with a single cohort remaining consistent with the phase 1 rolling 6 design. A minimum number of patients <30 kg are to be enrolled in cohort 2 instead of requiring 2 separate weight groups.

Protocol Amendment 4			
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 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design	Added a sentence to clarify that patients enrolled into phase 1 cohort 2 will be assessed together for determination of DLTs and RP2D.	To clarify.
7.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design	Added how RP2D will be determined in cohort 2.	To clarify.
8.	Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures (Table 6.a)	Updated the definition of OS in phase 2 secondary endpoints: "from first dose of ponatinib until death due to any cause" to "from first dose of study drug until death due to any cause".	To correct, consistently with the definition of OS in Table 13.a.
9.	Section 8.1.1 Investigational Therapy: Ponatinib	Clarified information on ponatinib treatment in phase 1 cohort 2: "ponatinib treatment will be assigned according to the appropriate dose defined in Table 8.a" to "ponatinib treatment will be assigned at the starting dose (15 mg adult exposures) and dose reductions will be allowed according to the dose levels defined in Table 8.a".	To clarify.

Protocol Amendment 4			
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Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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10.	Section 8.2 Definitions of Dose-limiting Toxicities Section 10.1.2 Adverse Event Definition	Clarified the relatedness of events to be considered DLTs in phase 1: "events occurring during the first 35 days on treatment (reinduction) that are deemed by the investigator to be related to ponatinib therapy" to "events occurring during the first 35 days on treatment (reinduction block) that are assessed by the investigator as possibly, probably, or definitely related to ponatinib and must be reported as related". Modified the order of "possibly", "probably", and "definitely".	To modify based on Health Authority feedback on protocol amendment 3 and to clarify definition of related causality.
11.	Section 8.2 Definitions of Dose-limiting Toxicities	Clarified the relatedness of Grade ≥3 nonhematologic toxicity to be considered DLTs in phase 1: "attributable to ponatinib" to "possibly, probably, or definitely related o ponatinib".	To modify based on Health Authority feedback on protocol amendment 3 and to clarify that "related" includes any attribution whether possible, probable, or definite.
12.	Section 8.2 Definitions of Dose-limiting Toxicities	Updated the timeframe during which failure to recover peripheral ANC and platelet count is considered a DLT: "49 days" to "42 days".	To modify based on Health Authority feedback on protocol amendment 3.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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13.	Section 8.3 Criteria for Beginning a Consolidation Block or Optional Continuation Therapy Section 8.1.2 Study Treatment Regimen (Table 8.b, footnote f and Table 8.c, footnote a) Appendix A, Schedules of Events (Table 5, footnote i)	Added a reference (van Veen et al. 2010) to support the platelet count threshold required to start the consolidation block or optional continuation therapy.	To provide a literature reference for the 50,000 µL platelet count threshold as a safe baseline to start multiagent chemotherapy.
14.	Section 8.3 Criteria for Beginning a Consolidation Block or Optional Continuation Therapy Section 8.1.2 Study Treatment Regimen (Table 8.b, footnote f and Table 8.c, footnote a) Appendix A, Schedules of Events (Table 5, footnote i)	Modified criteria for beginning consolidation or optional continuation block with toxicity related to treatment from: "must have resolved to Grade ≤2, except for ALT <10 × ULN and direct bilirubin <2 × ULN, to the patient's baseline values, or to a level considered acceptable by the physician" to: "must have resolved to Grade 1 or baseline or to a level considered acceptable by the physician".	To modify based on Health Authority feedback on protocol amendment 3. Changes made to align with dose modification guidelines and the current USPI, and to clarify requirement for investigator determination of whether to hold or proceed with dosing.
15.	Section 8.3 Criteria for Beginning a Consolidation Block or Optional Continuation Therapy	Added the statement: "The physician may consult with the sponsor's medical monitor to determine levels that are acceptable based on the overall clinical status of the patient to continue therapy".	To clarify requirement for investigator determination of whether to hold or proceed with dosing.
16.	Section 8.4.1 Early Safety Stopping Rules	Added a sentence to clarify that any decision to restart enrollment after stopping for stopping rules must be approved by the applicable agencies.	To modify based on Health Authority feedback on protocol amendment 1.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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17.	Section 8.4.2.1 Nonhematologic Treatment-Related Toxicity: Ponatinib (Table 8.e)	Modified dose modification for ponatinib with the occurrence of pancreatitis and elevation of lipase.	To modify based on Health Authority feedback on protocol amendment 3 and to align with the current USPI.
18.	Section 8.4.2.1 Nonhematologic Treatment-Related Toxicity: Ponatinib (Table 8.e, footnote d)	Revised footnote d to remove "For Grade 2: LVEF <50%-40%, Grade 3: LVEF <39-20%, Grade 4: refractory CHF or LVEF <20%."	To correct an error as these gradings are not National Cancer Institute Common Terminology Criteria for Adverse Events gradings.
19.	Section 8.4.3 Chemotherapy Backbone	Added a sentence to identify the source of any reference safety information for expectedness of serious adverse reactions that may occur with the chemotherapy agents used in this trial.	To modify based on Health Authority feedback on protocol amendment 1.
20.	Section 8.4.4.4 Safety Monitoring for Cardiac Toxicity Section 9.3.13.3 Troponin and NT-proBNP Appendix A, Schedules of Events (Table 1, footnote i)	Added that cardiac troponin assessment can be performed with either troponin T or troponin I and that it should be ensured that the same type of testing is used throughout the study.	To provide additional guidance to sites.
21.	Section 9.3.13.1 Hematology and Chemistry Appendix A, Schedules of Events (Table 1, footnote z, and Table 2)	Clarified that hematology assessment is required while chemistry assessment is not required at Day 35 of the reinduction block and of the consolidation block.	To clarify because the required hematology assessment to evaluate the response was moved in protocol amendment 3 to the end of the reinduction block and of the consolidation block (ie, Day 35).
22.	Section 9.3.13.3 Troponin and NT-proBNP Appendix A, Schedules of Events (Table 1)	Clarified that that both troponin and NT-proBNP testing are required cardiac assessments.	To clarify and provide additional guidance to sites.

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Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
23.	Section 9.3.14.1 Evaluation of CR	Clarified the way CR status will be assessed: "CR status will be assessed by morphology, cytogenetics, and flow cytometry at a local laboratory" to "CR status will be confirmed by the investigator upon review of blasts in the BM morphology report from the local laboratory, extramedullary disease, neutrophil, and platelet recovery as well as blasts in peripheral blood, if applicable".	To clarify and provide additional guidance to sites.
24.	Section 9.3.14.1 Evaluation of CR	Clarified requirements if relapse from CR is confirmed: "results of the assessments used to confirm the relapse, including BM assessment, and their date must be provided in the electronic data capture (EDC); in addition, a peripheral blood sample must be collected for molecular mutation analysis" to "results of the assessments used to confirm the relapse, including peripheral blood, BM, CSF, or radiologic assessment, and their dates must be provided in the electronic data capture (EDC). If relapse from CR is confirmed, a peripheral blood sample must be collected for molecular mutation analysis".	To clarify and provide additional guidance to sites.

Protocol Amendment 4			
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***
25.	Section 9.3.15 Biomarkers and Pharmacokinetic Measurements	Added the statement: "MRD will be evaluated once CR assessment is performed and only for patients with CR status reported by the investigator by the end of the consolidation block".	To clarify the conditions of MRD evaluation.
26.	Section 9.3.15.1 Bone Marrow Samples for MRD Assessment	Clarified for which patients MRD will be evaluated: "MRD will be evaluated (only in patients with Ph+ ALL)" to "MRD will be evaluated (only in patients with Ph+ ALL and only those who achieve CR by end of consolidation as reported by the investigator)".	To clarify the conditions of MRD evaluation.
27.	Section 13.1.1 Analysis Sets	Updated the definition of response-evaluable population: "Patients who receive at least 1 dose of ponatinib…" to "Ph+ ALL patients at RP2D who receive at least 1 dose of ponatinib…".	To clarify.
28.	Appendix A, Schedules of Events (Table 2, footnote b)	Corrected that for patients in the Optional Continuation Regimen, follow-up visits after 2 years will occur annually for at least 3 years after EOT2 rather than after EOT1.	To correct that the follow-up begins after EOT2 and provide additional guidance to sites.

ALL: acute lymphoblastic leukemia; ALT: alanine aminotransferase; ANC: absolute neutrophil count; BM: bone marrow; CHF: congestive heart failure; CR: complete remission; CSF: cerebral spinal fluid; DLT: dose-limiting toxicities; EOT1: end of treatment 1; EOT2: end of treatment 2; LVEF: left ventricular ejection fraction; MRD: minimal residual disease; NT-proBNP: N-terminal pro brain natriuretic peptide; OS: overall survival; Ph+: Philadelphia chromosome–positive; QD: once daily; RP2D: recommended phase 2 dose; ULN: upper limit of normal; USPI: United States Prescribing Information.

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** Ponatinib
Title of Protocol: A Pivotal Phase 1/2, Single-Arm, Open-label Study to Evaluate the Safety and Efficacy of Ponatinib With Chemotherapy in Pediatric Patients With Philadelphia Chromosome-Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Who Have Relapsed or Are Resistant or Intolerant to a Prior Tyrosine Kinase Inhibitor-Containing Therapy, or Who Have the T315I Mutation	**EudraCT No.:** 2019-002549-39
Study Number: Ponatinib-1501	**Phase:** 1/2

Study Design:

This is a pivotal phase 1/2, single-arm, open-label, multicenter, study designed to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of ponatinib when administered in combination with multiagent chemotherapy in pediatric patients (aged ≥1 year to ≤21 years) with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), Ph+ mixed phenotype acute leukemia (MPAL), or Philadelphia chromosome–like (Ph-like) ALL with targetable kinase-activating lesions and either (i) or (ii) as follows: (i) **For non-US sites**: Patients who have relapsed or are resistant or intolerant to at least 1 prior therapy that contained a breakpoint cluster region (*BCR*)-Abelson (*ABL*) 1–targeted tyrosine kinase inhibitor (TKI), or **for US sites**: Patients who have relapsed or are resistant or intolerant to at least 1 prior therapy that contained a second-generation BCR-ABL1–targeted TKI; or (ii) have a BCR-ABL1 T315I mutation.

Patients will undergo screening assessments for up to 10 days to determine eligibility (Figure 2.a). In both phase 1 and phase 2, eligible patients will receive two 35-day blocks of therapy (reinduction block and consolidation block). Each block will include 29 days of study treatment consisting of daily ponatinib and a modified United Kingdom (UK) ALL R3 chemotherapy backbone regimen specified in Table 8.b and a rest period from chemotherapy for a minimum of 6 days consisting of daily ponatinib only. Disease assessment will occur at the end of each block. Patients will undergo an end of treatment (EOT) visit (EOT1) 25-30 days after the last dose of study treatment in the consolidation block, or earlier, if the patient is proceeding to alternate therapy or optional ponatinib continuation therapy (Appendix A, Table 1).

Patients completing the EOT1 visit can proceed to alternate therapies not containing ponatinib as off-protocol therapy. Alternatively, eligible patients may receive optional ponatinib continuation therapy (either ponatinib monotherapy or ponatinib in combination with maintenance-type chemotherapy regimen at the investigator's discretion and with sponsor agreement) after completing the 2 blocks of study treatment and the EOT1 visit. Patients who receive optional ponatinib continuation therapy will be followed per the schedule of events (SOE) and proceed to a second EOT visit (EOT2) 30 to 40 days after the last dose of ponatinib, or earlier, if the patient is proceeding to alternate therapy (Appendix A, Table 2). Patients who discontinue ponatinib early in the reinduction block or consolidation block will be discontinued from study treatment and proceed to the EOT1 visit. All patients will be followed for at least 3 years from EOT1, with primary analysis performed approximately 6 months after the last patient has been enrolled.

Phase 1 of the study (approximately 12 dose-limiting toxicities [DLT]-evaluable patients) is a PK/safety lead-in phase for dose confirmation to establish the recommended phase 2 dose (RP2D) of ponatinib administered either as the tablet formulation or the age-appropriate formulation (AAF: mini-tablet–containing capsules, ie minitab capsules) (Table 2.a) in combination with the chemotherapy backbone (Table 8.b).

The initial ponatinib doses evaluated in cohort 1 of the phase 1 portion of the study were selected to target systemic exposures comparable to those achieved in adults receiving 30 mg once daily (QD) based on the results of population PK modeling and simulation (see Section 4.2.4.1). The ponatinib doses evaluated in cohort 2 of the phase 1 portion of the study are expected to provide systemic exposures comparable to those achieved in adults receiving 15 mg QD based on the results of population PK modeling and simulation (see Section 4.2.4.2).

A staggered enrollment is being applied. Phase 1 cohort 1 was initiated with the tablet formulation in patients able to swallow solid oral dosage forms and weighing at least 30 kg (as the AAF was not available during that

enrollment period). As of protocol amendment 3, both the tablet formulation and AAF are available for use in phase 1.

The PK, safety, and tolerability data from phase 1 will inform selection of the recommended dose of ponatinib for confirmatory evaluation of safety and efficacy in the phase 2 portion of the study. A rolling 6 design will be followed for all phase 1 cohorts.

As of phase 1 cohort 2, patients will be reviewed on an ongoing basis to determine whether the patient meets the criteria to be DLT-evaluable. DLT-evaluable patients must have received ponatinib doses on at least 70% of the reinduction block days (eg, 25 or more of the 35 days) per protocol or experienced a confirmed DLT.

Ponatinib doses for evaluation in phase 1 cohort 2 will target exposures comparable to those achieved in adults receiving 15 mg QD based on the results of population PK modeling and simulation (see Section 4.2.4.3). For phase 1 cohort 2, approximately 6 DLT-evaluable patients with a body weight of at least 5 kg will be enrolled, with a minimum of 2 patients with a baseline body weight <30 kg. No more than 1 DLT-evaluable patient may be >16 years of age in cohort 2.

To determine the RP2D, a minimum of 6 DLT-evaluable patients in cohort 2 must complete the reinduction block. If 2 out of 6 patients experience a DLT, the study will be paused to determine further tolerability of this combination. All patients enrolled in cohort 2 under protocol amendment 3 and those enrolled under protocol amendment 4 will be assessed together in a single cohort for determination of DLTs and RP2D as defined in protocol amendment 4.

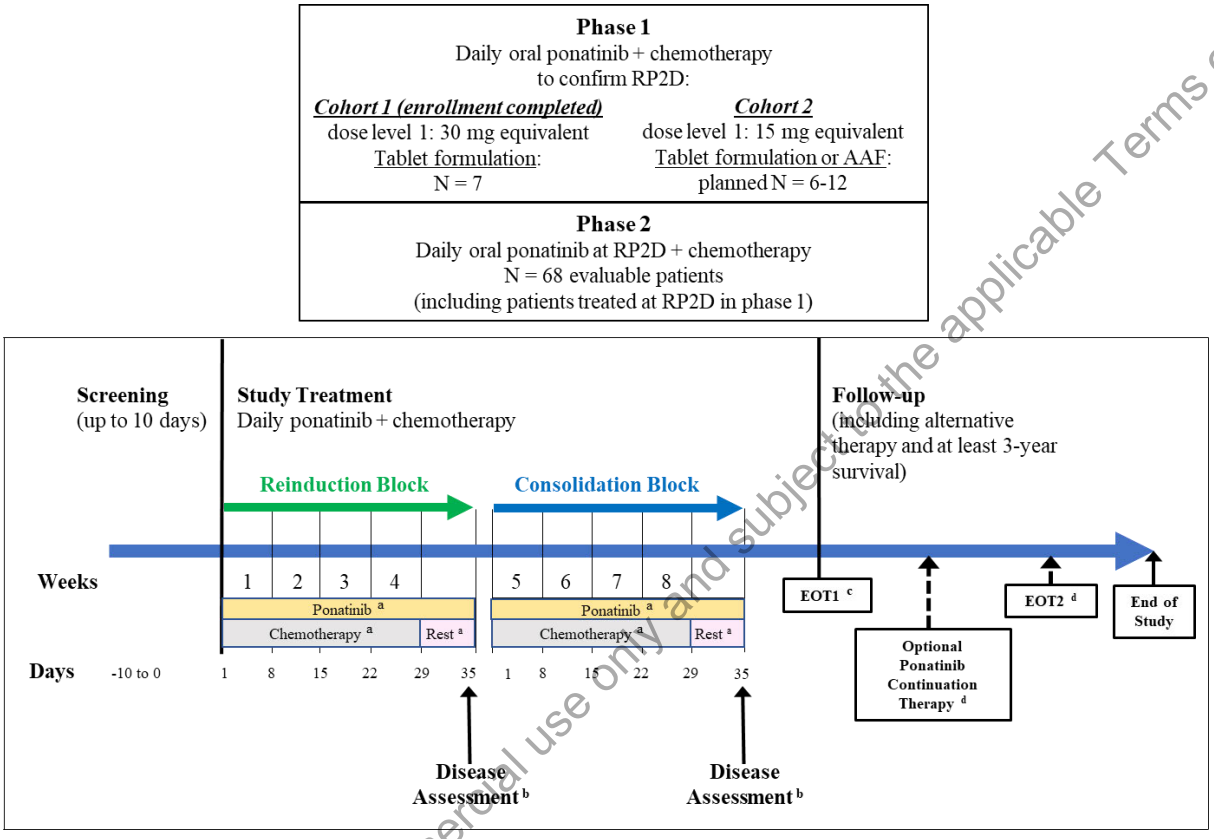
Upon review of patients in cohort 2, if dose level 1 is determined not to be tolerated or fails to achieve the desired target systemic exposures and RP2D is not confirmed with cohort 2, then no further cohorts are planned to be tested.

The RP2D of ponatinib will be determined after evaluating the available safety and PK data from the first 6 patients enrolled in phase 1 cohort 2. Up to an additional 6 patients may be enrolled to further characterize the safety, PK, and preliminary efficacy of the RP2D of ponatinib before the start of phase 2.

In phase 2, patients will receive daily ponatinib at the RP2D determined from the phase 1 portion of the study, in combination with the same chemotherapy backbone regimen (Table 8.b). Phase 2 will evaluate the efficacy and safety of ponatinib at the RP2D in combination with chemotherapy in the study population and include patients from phase 1 who completed the reinduction block at the RP2D in combination with chemotherapy.

Figure 2.a presents the design schema for the study.

Figure 2.a Study Design Schema



AAF: age-appropriate formulation; EOT1: end of treatment 1; EOT2: end of treatment 2; RP2D: recommended phase 2 dose.
"equivalent" refers to adult equivalent/target dose.

[a] Each block consists of 29 days of study treatment with ponatinib and chemotherapy followed by a chemotherapy rest period of a minimum of 6 days consisting of daily ponatinib only. Ponatinib should not be interrupted unless the patient has toxicity suspected to be related to ponatinib.
[b] Patients will undergo evaluation for disease status at the end of the reinduction block and the consolidation block. Patients tolerating treatment at the end of the reinduction block will proceed to the consolidation block regardless of their remission status.
[c] Patients will have their first EOT visit (EOT1) 25 to 30 days after last dose of ponatinib in the consolidation block, or earlier, if the patient is proceeding to alternate therapy or optional ponatinib continuation therapy.
[d] Patients who receive optional continuation therapy containing ponatinib will have an additional EOT visit (EOT2) 30 to 40 days after last dose of ponatinib, or earlier, if the patient is proceeding to alternate therapy. See Table 8.d for optional ponatinib continuation therapy regimen. Patients who are receiving clinical benefit from ponatinib treatment may continue therapy for a maximum of 12 months. If patients continue deriving clinical benefit after 12 months of optional continuation therapy, they may remain on ponatinib treatment if the investigator provides the evidence of clinical benefits and confirms with the sponsor.

Primary Objectives:

Phase 1 Primary Objective

- To determine the RP2D of ponatinib (tablet and AAF) in combination with chemotherapy.

Phase 2 Primary Objective

- To determine the efficacy of ponatinib in combination with chemotherapy as measured by the rate of CR at the end of the reinduction block.

Secondary Objectives (Including PK and Safety Objectives):

Phase 1 Secondary Objectives

- To define and describe the phase 1 efficacy of ponatinib (tablet and AAF) in combination with chemotherapy.

Phase 2 Secondary Objectives

- Ph+ ALL only: To describe the proportion of patients who achieved CR at the end of consolidation.
- Ph+ ALL only: To describe the proportion of patients with minimal residual disease (MRD) status <0.01% among those who achieved CR at the end of each treatment block.
- To determine the proportion of patients who relapsed or progressed.
- To determine event-free survival (EFS), progression-free survival (PFS), and overall survival (OS) at 6 months, 1 year, 18 months, 2 years, and 3 years.
- To determine duration of response (for CR).
- To determine the proportion of patients who underwent hematopoietic stem cell transplantation (HSCT) following study treatment.

Phase 1 PK Objective

- To characterize the PK of ponatinib in combination with chemotherapy.

Phase 2 PK Objective

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

Phase 1 and Phase 2 Safety Objective

- To describe the safety profile of ponatinib in combination with chemotherapy for each treatment block (ie, reinduction and consolidation).

Exploratory Objectives:

- To explore the risk of cardiotoxicity in patients with elevated cardiac troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP).
- Ph+ ALL: To characterize biomarkers of sensitivity and resistance to ponatinib-containing therapy, which may include molecular mutations (eg, *BCR-ABL1*, *IKZF1*, *CDKN2A/2B*) in samples both prior to and following ponatinib treatment.
- To assess the acceptability and palatability of the AAF of ponatinib using the palatability questionnaire (Appendix E).
- To determine OS for patients who receive HSCT and patients who do not receive HSCT.

Patient Population:

Patients (aged ≥1 year to ≤21 years and weighing at least 5 kg) with Ph+ ALL, Ph+ MPAL, or Ph-like ALL with targetable kinase-activating lesions must have bone marrow (BM) involvement and either (i) or (ii) as follows:

(i) **For non-US sites**: Patients who have relapsed or are resistant or intolerant to at least 1 prior therapy that contained a BCR-ABL1–targeted TKI; OR

For US sites: Patients who have relapsed or are resistant or intolerant to at least 1 prior therapy that contained a second-generation BCR-ABL1–targeted TKI; OR

(ii) Have a BCR-ABL1 T315I mutation. Referring institutions laboratory results will be accepted for enrollment; however, the mutation needs to be confirmed by the central laboratory. If the mutational status is not concordant, the patient will be withdrawn from the study and excluded from analyses.

Number of Patients:	**Number of Sites:**
Phase 1 of the study will enroll approximately 12 DLT-evaluable patients; phase 2 of the study will enroll approximately 68 patients, including DLT-evaluable patients enrolled to phase 1 who completed the reinduction block and dosed at the RP2D.	Approximately 74 study sites in approximately 17 countries.
Dose Level(s): In phase 1 cohort 1, only patients with a body weight of ≥30 kg and able to swallow solid oral dosage forms were enrolled because the AAF was not available. As of protocol amendment 3, patients weighing at least 5 kg or who are unable to swallow solid oral dosage forms are eligible for enrollment as the AAF is available. Ponatinib will be administered QD in combination with the chemotherapy backbone (Table 8.b). In phase 1 cohort 1, pediatric patients received fixed doses of ponatinib based on body weight ranges that were expected to achieve systemic exposures that approximately matched adult exposures at 30 mg QD based on simulations from an allometrically scaled adult population PK model. Patients who experienced treatment-emergent adverse events (TEAEs) that required dose reductions had their ponatinib dose reduced to dose level -1. For phase 1 cohort 2, patients will also receive fixed doses of ponatinib based on body weight ranges provided in Table 2.a that are expected to achieve systemic exposures that approximately match adult exposures after administration of 15 mg QD based on simulations from an allometrically scaled adult population PK model. Patients experiencing TEAEs will have their ponatinib doses reduced as per Table 2.a. The PK, safety, and tolerability of ponatinib at cohort 2 dose level 1 will be reviewed to inform selection of the RP2D. If the initially selected doses are not adequately tolerated or fail to achieve the target systemic exposures, then the study will close.	**Route of Administration:** Oral

Table 2.a Phase 1 Cohort 2 Ponatinib Doses

	Body Weight			
	≥45 kg	**30 kg to <45 kg**	**15 kg to <30 kg**	**5 kg to <15 kg**
Cohort 2 Dose Level 1	15 mg	10 mg	7.5 mg	5 mg
Cohort 2 Dose Level -1	10 mg	7.5 mg	5 mg	2.5 mg

In the phase 2 portion of the study, ponatinib will be administered QD in combination with the chemotherapy backbone at the RP2D determined after review of available data from the phase 1 portion of the study.

Duration of Treatment:

All patients enrolled will receive two 35-day blocks of study treatment (ponatinib in combination with chemotherapy).

At the discretion of the treating physician and with sponsor agreement, optional ponatinib continuation therapy may be used beyond the end of the consolidation block as monotherapy or in combination with maintenance-type chemotherapy until more definitive therapy is initiated.

Period of Evaluation:

At least 36 months

Main Criteria for Inclusion:

Phase 1 cohort 1 (enrollment and treatment completed) eligibility criteria at the time of enrollment for patients to be administered ponatinib as the tablet formulation:

- Patients must have a body weight ≥30 kg.
- Patients must be able to swallow solid oral dosage forms.

Phase 1 cohort 2 eligibility criteria at the time of enrollment:

- Patients must be aged ≥1 year and have a body weight of at least 5 kg.

Each patient must meet all the following inclusion criteria to be enrolled in the study for phase 1 and phase 2.

1. **Diagnosis:** Patients must have a diagnosis of Ph+ ALL, Ph+ MPAL, or Ph-like ALL with:
   - **a. Involvement of BM with ALL, including one of the following:**
     - i. **M2 BM (5%-24% lymphoblasts)**: by morphology with confirmatory testing consisting of at least one of the following: flow cytometry lymphoblasts ≥5%, or BCR-ABL1 fluorescence in situ hybridization, or $\geq 10^{-2}$ leukemic clone identified by immunoglobulin heavy chain–T-cell receptor polymerase chain reaction, OR
     - ii. **M3 BM (≥25% lymphoblasts)**: by morphology, OR
     - iii. **Patients with combined BM (as defined above) and extramedullary disease**.
   - **b. Evidence of Ph+ ALL, MPAL, or Ph-like ALL:**
     - i. Definite evidence of BCR-ABL1 fusion (Ph) for Ph+ ALL and MPAL, OR
     - ii. Definite evidence of Ph-like ALL with targetable kinase-activating lesions involving any of the following kinase genes: *ABL1*, *ABL2*, *CSF1R*, and *PDGFRB*.

       Ph-like ALL diagnosis requires the identification of specified targetable kinase-activating lesions preferably by RNA sequencing or by alternative accredited method used by the site. Referring institution's laboratory results will be accepted for diagnosis and study enrollment. No confirmation by a sponsor central laboratory is required.

c. Disease status:

i. **For non-US sites:** patients who have relapsed (post 0 or 1 HSCT) or are resistant or intolerant to at least 1 prior therapy that contained a BCR-ABL1–targeted TKI, OR
For US sites: patients who have relapsed (post 0 or 1 HSCT) or are resistant or intolerant to at least 1 prior therapy that contained a second-generation BCR-ABL1–targeted TKI (ie, dasatinib, nilotinib, and bosutinib); OR

ii. Have a BCR-ABL1 T315I mutation irrespective of relapse, resistance/intolerance, or transplant status and irrespective of any prior TKI use. Referring institution's laboratory results will be accepted for enrollment; however, the mutation needs to be confirmed by the central laboratory. If the mutational status is not concordant, the patient will be withdrawn from the study and excluded from analyses for RP2D and efficacy, but included for safety.

A patient will be defined as intolerant if they had a Grade ≥3 nonhematologic toxicity or a Grade 4 hematologic toxicity considered related to the last TKI and lasting for >2 weeks, and led to discontinuation of therapy.

2. **Age and weight:** Patients must be ≥1 and ≤21 years of age and weighing at least 5 kg at the time of enrollment.
3. **Performance Status:** Karnofsky performance status ≥50% for patients ≥16 years of age or Lansky Play Scale ≥50% for patients <16 years of age.

Prior Therapy

4. Patients must have recovered to less than Grade 2 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0, or to baseline, from any nonhematologic toxicities (except alopecia) due to previous therapy.
5. Patients must meet the following criteria related to prior therapies:

Cytoreduction with hydroxyurea: Hydroxyurea can be initiated and continued for up to 24 hours before the start of protocol therapy.

Patients who relapsed while receiving cytotoxic therapy: At least 14 days must have passed since the completion of the last dose of chemotherapy before the first dose of ponatinib can be given except for the following: intrathecal chemotherapy and/or maintenance therapy such as vincristine, mercaptopurine, methotrexate, or glucocorticoids. There is no waiting period for those relapsing on maintenance-like therapy.

HSCT: Patients who have experienced relapse after a HSCT are eligible, provided they have no evidence of acute or chronic graft-versus-host disease (GVHD), are not receiving GVHD prophylaxis or treatment, and are at least 90 days posttransplant at the time of enrollment.

Hematopoietic growth factors: Before the first dose of ponatinib, at least 7 days must have passed since completion of therapy with granulocyte colony-stimulating factor or other growth factors, and at least 14 days must have passed since completion of therapy with pegfilgrastim.

Biologics and targeted therapies: Before the first dose of ponatinib, at least 7 days must have passed since the last dose of a biologic agent. For agents that have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the sponsor's medical monitor/designee.

Monoclonal antibodies: After the last dose of monoclonal antibody, at least 3 half-lives of the administered antibody must have passed before the first dose of ponatinib.

Immunotherapy: Before the first dose of ponatinib, at least 30 days must have passed after the completion of any type of immunotherapy (eg, tumor vaccines, chimeric antigen receptor T-cell [CAR-T cell]).

Immunosuppressive therapy: Before the first dose of ponatinib, at least 14 days must have passed after the completion of immunosuppressive therapy (including regimens following stem cell transplant).

Radiotherapy: No washout period is necessary for radiation given to any extramedullary site other than central nervous system (CNS); ≥90 days must have passed if patient received prior total body irradiation or

craniospinal or cranial radiotherapy.

Anthracyclines: Patients must have had a lifetime exposure of <400 mg/m^2 of doxorubicin equivalents of anthracyclines.

Organ Function Requirements

6. Patients must have adequate renal and hepatic function as indicated by the following laboratory values:
   a) **Adequate renal function defined as**: Estimated glomerular filtration rate (eGFR) using the Schwartz formula, OR radioisotope glomerular filtration rate (GFR) ≥70 mL/min/1.73 m^2, OR a normal serum creatinine based on age and sex as in Table 2.b:

Table 2.b Maximum Serum Creatinine Value (mg/dL) by Age and Sex

Age (years)	Male	Female
1 to <2	0.6	0.6
2 to <6	0.8	0.8
6 to <10	1	1
10 to <13	1.2	1.2
13 to <16	1.5	1.4
≥16	1.7	1.4

The threshold creatinine values were derived from the Schwartz formula for estimating glomerular filtration rate (Schwartz and Gauthier 1985) using child length and stature data published by the Centers for Disease Control and Prevention.

Schwartz formula: eGFR (mL/min/1.73 m^2) = (k × L) / Pcr

k: proportional constant (see Table 2.c); L: height (cm); Pcr: plasma creatinine (mg/dL)

Table 2.c Mean Values of k by Age

Age Group	k (mean value)
Low birth weight infants ≤1 year	0.33
Full-term infants ≤1 year	0.45
Children >1-12 years	0.55
Females 13-21 years	0.55
Males 13-21 years	0.70

Source: (Schwartz et al. 1987)

   a) **Adequate liver function defined as**: Direct bilirubin ≤1.5 times the upper limit of normal (ULN) for age AND alanine aminotransferase ≤5 times the ULN for age.

7. No clinical, radiological or laboratory evidence of pancreatitis, including:
   a) Serum lipase must be <2 times the ULN, AND
   b) Serum amylase must be <2 times the ULN.

8. Adequate cardiac function defined as shortening fraction ≥27% by echocardiogram (ECHO) OR left ventricular ejection fraction of ≥50% by ECHO or multigated acquisition scan (MUGA).
9. Normal QT interval with Fridericia correction method (QTcF) on screening electrocardiogram (ECG), defined as QTcF of ≤450 ms.
10. Voluntary written informed consent and assent (as dictated by the institutional review board/independent ethics committee and required by applicable local regulations) 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 (if of the age of consent) or the patient's parent or legal guardian at any time without prejudice to future medical care.

Prevention of Pregnancy

11. Female patients who:
    a) Are surgically sterile, OR
    b) 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/assent through at least 6 months after end of therapy, OR
    c) 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.)
12. 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 at least 6 months after end of therapy, 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 for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Exclusion Criteria:

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. A history or current diagnosis of Burkitt leukemia/lymphoma or mature B-cell leukemia.
2. A history or current diagnosis of chronic myeloid leukemia.
3. Diagnosis of ALL, MPAL, or Ph-like ALL with targetable kinase-activating lesions after treatment with cytotoxic therapy for another cancer.
4. Diagnosis of another concurrent primary malignancy.
5. Clinically significant cardiovascular disease, including but not limited to:
    a) Any history of myocardial infarction or unstable angina.
    b) History of or presence of heart block, and/or clinically significant ventricular or atrial arrhythmias.
    c) Uncontrolled hypertension, defined as persistent elevation of systolic and/or diastolic blood pressures to ≥95th percentile based on age, sex, and height percentiles despite appropriate antihypertensive management.
6. Current systemic use of drug(s) that are known to have a risk of causing prolonged corrected QT interval or torsades de pointes unless drug(s) can be changed to acceptable alternatives (ie, an alternate class of agents that do not affect the cardiac conduction system) or the patient can safely discontinue the drug(s).
7. Uncontrolled hypertriglyceridemia (triglycerides ≥450 mg/dL).
8. Current systemic use of any medications or herbal supplements that are known to be strong inhibitors or strong inducers of cytochrome P450 3A (CYP3A) within 7 days before the first dose of study drug.
9. Previous treatment with ponatinib.
10. Planned non-protocol chemotherapy, radiation therapy, another investigational agent, or immunotherapy while patient is on study treatment.
11. Known allergy or contraindications to any of the drugs (active or excipient) used in the study.

12. Known gastrointestinal disease or gastrointestinal procedure that could interfere with the oral absorption of ponatinib.
13. Patients with DNA fragility syndromes, such as Fanconi anemia and Bloom syndrome.
14. Patients with Down syndrome.
15. Patients with uncontrolled systemic infection, known laboratory and/or clinical evidence of active infection with HIV, hepatitis B, or hepatitis C.
16. Patients with pre-existing significant CNS pathology, including history of severe brain injury, dementia, cerebellar disease, organic brain syndrome, psychosis, coordination /movement disorder, or autoimmune disease with CNS involvement are not eligible.
17. Patients with a history of cerebrovascular ischemia/hemorrhage with residual deficits are not eligible. (Patients with a history of cerebrovascular ischemia/hemorrhage remain eligible provided all neurologic deficits and causative factor(s) have resolved.)
18. Uncontrolled seizure disorder. (Patients with seizure disorders that do not require antiepileptic drugs, or are well controlled with stable doses of antiepileptic drugs are eligible.)
19. History of severe coagulopathy or cardiovascular or peripheral vascular events.
20. Any condition or illness that, in the opinion of the investigator or sponsor, would compromise patient safety or interfere with the evaluation of the safety or efficacy of ponatinib.
21. Admission or evidence of illicit use, drug abuse, or alcohol abuse.
22. Pregnancy and breastfeeding exclusions:
    a) Female patients who are pregnant are excluded since fetal toxicities and teratogenic effects have been noted for several of the study treatments. A pregnancy test is required for female patients of childbearing potential.
    b) Lactating women who plan to breastfeed their infants.
23. Treatment with live attenuated vaccinations within 30 days prior to initiation of study treatment regimen.

Endpoints and Assessments:

Primary Endpoints

Phase 1 Primary Endpoint

- RP2D of ponatinib (tablet and AAF) in combination with chemotherapy.

Phase 2 Primary Endpoint

- CR at the end of the reinduction block. CR is defined as <5% blasts in BM, normal maturation of all cellular components in the BM, no evidence of extramedullary disease, absolute neutrophil count (ANC) >1000/μL, and platelet count of >100,000/μL.

Secondary Endpoints (Including PK and Safety Endpoints)

Phase 1 Secondary Endpoints

- CR at the end of the reinduction block. CR is defined as <5% blasts in BM, normal maturation of all cellular components in the BM, no evidence of extramedullary disease, ANC >1000/μL, and platelet count of >100,000/μL.

Phase 2 Secondary Endpoints

- Ph+ ALL only: Proportion of patients who achieved CR at the end of consolidation.
- Ph+ ALL only: Proportion of patients with MRD-negative status (<0.01%) among those who achieved CR at the end of each treatment block.
- Proportion of patients who relapsed or progressed.
- EFS, PFS, and OS at 6 months, 1 year, 18 months, 2 years, and 3 years.
- Duration of response (for CR).
- Proportion of patients who underwent HSCT following study treatment.

Phase 1 PK Endpoint

- Summary statistics of ponatinib PK parameters including maximum observed plasma concentration (C_{max}), time of first occurrence of C_{max} (t_{max}), and area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).

Phase 1 and Phase 2 Safety Endpoint

- Adverse events (AEs), serious adverse events (SAEs), arterial occlusive events (AOEs), venous thrombotic/embolic events (VTEs), and any other AEs of special interest (AESIs).

Exploratory Endpoints

- Change from baseline in laboratory values and cardiovascular outcomes associated with elevated cardiac troponin and NT-proBNP.
- Ph+ ALL only: Biomarkers of potential sensitivity and resistance to ponatinib-containing therapy, which may include molecular mutations (eg, *BCR-ABL1*, *IKZF1*, *CDKN2A/2B*) in samples both prior and following ponatinib treatment.
- Acceptability and palatability of the AAF of ponatinib based on the palatability questionnaire administered during reinduction (Appendix E).
- OS for patients who receive HSCT and patients who do not receive HSCT.

Statistical Considerations:

Approximately 68 patients aged ≥1 to ≤21 years with Ph+ ALL with targetable kinase activating lesions (no minimum number) who either (i) (non-US sites) have relapsed or are resistant or intolerant to at least 1 prior therapy that contained a BCR-ABL1–targeted TKI or (US sites) have relapsed or are resistant or intolerant to at least 1 prior therapy that contained a second-generation BCR-ABL1–targeted TKI, or (ii) have the T315I mutation, will be enrolled in the study. Ph+ MPAL and Ph-like ALL are rare, and few patients with Ph+ MPAL or Ph-like ALL are expected to enroll in this study. Data from these patients will not be included in the response-evaluable population analysis and will be analyzed as a separate subset.

Patients with Ph-like ALL and Ph+ MPAL will not be included in efficacy analyses. These patients will be included in the safety and other descriptive analyses.

The phase 1 portion of the study will enroll approximately 12 DLT-evaluable patients, and a rolling 6 design will be followed to determine the RP2D. Once the pediatric RP2D has been confirmed, approximately 68 patients with Ph+ ALL will be enrolled in the phase 2 portion of the study (any patient dosed at the RP2D and completed the reinduction block during phase 1 will be counted towards the 68 evaluable patients for phase 2).

The primary data analysis will be conducted 6 months after the last patient is enrolled in the phase 2 portion of the study, where the major efficacy summary will focus on:

- CR at the end of reinduction block and duration of CR.
- Time-to-event analysis (EFS, PFS, and OS) at 6 months, 1 year, 18 months, 2 years, and 3 years.
- Proportion of patients who underwent HSCT.

In addition, the safety analysis will cover short-term AE, SAE, and AESI rates, and changes in laboratory values

from baseline.

Sample Size Determination:

The Wilson Score confidence interval (CI) approach will be used for the sample size determination. The Wilson Score interval is an improvement over the normal approximation interval in that the actual coverage probability is closer to the nominal value. Based on the Wilson Score CI approach and assuming N = 68 patients to reject the null hypothesis of a 67% CR rate (see Section 13.3 for justification of control rate assumption), a 2-sided type I error of 0.1, and that under the alternative hypothesis the ponatinib CR rate is 80% based on simulations with 1,000,000 iterations, the power of the trial equals 81.5%. This simulation also demonstrated that under the null hypothesis, the type I error is controlled at a nominal level of 0.1 (2-sided).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 Principal Investigator/Coordinating Investigator

The sponsor 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.

3.3 List of Abbreviations

AAF	age-appropriate formulation
ABL	Abelson
AE	adverse event
AESI	adverse events of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AOE	arterial occlusive event
AP	accelerated phase
AST	aspartate aminotransferase
AUC	area under the plasma concentration–time curve
AUC_{last}	area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration
BCR	breakpoint cluster region
BCR-ABL	breakpoint cluster region-Abelson
BID	twice daily
BM	bone marrow
BSA	body surface area
BP	blast phase
CAD	coronary artery disease
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum observed plasma concentration
CML	chronic myeloid leukemia
CMT	Charcot-Marie-Tooth disease
CNS	central nervous system
COG	Children's Oncology Group
COVID-19	coronavirus disease 2019
CP	chronic phase
CR	complete remission
CR2	second complete remission
CrCl	creatinine clearance
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computerized tomography
CYP3A	cytochrome P450 3A
DLT	dose-limiting toxicities
DTP	direct-to-patient
ECG	electrocardiogram

ECHO	echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
eGFR	estimated glomerular filtration rate
eIC	electronic informed consent
EMA	European Medicines Agency
EOT	end of treatment
EOT1	end of treatment 1
EOT2	end of treatment 2
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GVHD	graft-versus-host disease
HDPE	high-density polyethylene
HLT	High Level Term
HPMC	hydroxypropyl methylcellulose
HSCT	hematopoietic stem cell transplantation
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IM	intramuscularly
IRB	institutional review board
IT	intrathecal
IV	intravenous(ly)
LBBB	left bundle branch block
MACE	major adverse cardiac event
MaHR	major hematologic response
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MPAL	mixed phenotype acute leukemia
MR2	molecular response with 2-log reduction (BCR-ABL1/ABL1 ≤1%)
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMDA	*N*-methyl-d-aspartate
NOAEL	no observed-adverse effect level
NS	normal saline
NT-proBNP	N-terminal pro-brain natriuretic peptide
OS	overall survival
Pcr	plasma creatinine
PEG	polyethylene glycol
PFS	progression-free survival
Ph+	Philadelphia chromosome-positive
Ph-like	Philadelphia chromosome–like
PK	pharmacokinetic(s)
PO	by mouth (orally)
PP	predicative probability
PT	Preferred Term
QD	once daily
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction method
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SLT	Sponsor Liaison Team
SmPC	summary of product characteristics
SOC	System Organ Class
SOE	schedule of events
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
t_{max}	time of first occurrence of maximum observed plasma concentration
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

3.4 Corporate Identification

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	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION AND BACKGROUND

4.1 Background

4.1.1 Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in Pediatric Patients

Acute lymphoblastic leukemia (ALL) is the most common cancer in children, and is the most common form of childhood leukemia, representing 75% to 80% of leukemias among children (Brown et al. 2020). The age-adjusted incidence of ALL in the United States (US) is 1.38 per 100,000 individuals per year (Brown et al. 2020) with approximately 5930 new cases and 1500 deaths estimated in 2019 (Brown et al. 2020). The median age at diagnosis is 15 years with 55.4% of new diagnoses occurring in patients younger than 20 years of age (Brown et al. 2020). Philadelphia chromosome-positive (Ph+) ALL is a rare malignancy of the blood and bone marrow (BM), accounting for approximately 3% to 5% of pediatric ALL (Arico et al. 2010; Schlieben et al. 1996).

Ph+ ALL results from a translocation of chromosomes 9 and 22, referred to as the Philadelphia chromosome, and leading to the fusion of the breakpoint cluster region (*BCR*) coding sequence with the tyrosine kinase coding region of Abelson (*ABL*) 1. 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) (Deininger et al. 2000).

4.1.2 Ponatinib Design and Mechanism of Action

Ponatinib (Iclusig) is the product of a computational and structure-based approach to the design of a small-molecule tyrosine kinase inhibitor (TKI) (O'Hare et al. 2009). 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 other 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 (Zhou et al. 2011). This not only leads 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 Crk-like protein (pCRKL), thereby promoting apoptosis and cell death in BCR-ABL1–positive cells (O'Hare et al. 2009). Ponatinib has also been shown to potently inhibit the activity of other activated tyrosine kinases, including ABL2 (also known as ARG), CSF1R (also known as FMS), and PDGFRB (Gozgit et al. 2013).

4.1.3 Ponatinib Nonclinical Data

Nonclinical studies have demonstrated that ponatinib potently inhibits native BCR-ABL1, and all single-mutation variants, at clinically relevant concentrations (Gozgit et al. 2013; O'Hare et al. 2009). 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 (Bradeen et al. 2006), a concentration between 20 nM and 40 nM of ponatinib was found to suppress the emergence of any resistant BCR-ABL1 mutation (O'Hare et al. 2009).

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 (O'Hare et al. 2009; Zabriskie et al. 2014). 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 (Shah et al. 2007), whereby expansion of a leukemic progenitor cell that has a single resistance mutation provides a template on which a second mutation can develop.

Nonclinical safety assessment studies were performed on ponatinib, including 6-month oral toxicity studies in rats and cynomolgus monkeys. In a 6-month oral toxicity study, the no-observed-adverse-effect level (NOAEL) in the rat was 0.25 mg/kg/day. At 0.75 and 2.0 mg/kg/day, there was early mortality and moribundity, reduced body weight, and reduced food consumption with lymphoid depletion at 2.0 mg/kg/day. The early deaths occurred as early as Day 21, and cause of death or moribundity was generally not determined; however, moribundity was considered to be related to urinary tract or skin inflammation in 3 animals. Additionally, at 0.75 and 2.0 mg/kg/day there was a reduction in femoral physeal chondrocytes (sometimes with reduced trabecular bone); the physeal lesion was still present after a 2-month recovery period. Administration of ponatinib to cynomolgus monkeys for 6 months at oral dose levels of 0.25, 0.75, or 2 mg/kg/day was well tolerated, with no ponatinib-related microscopic findings being observed at any dose level. However, there were irreversible increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at all doses; therefore, the NOAEL was determined to be ≤0.25 mg/kg/day. Taken together, the rat and monkey toxicology studies indicate the following key target organs of ponatinib toxicity: gastrointestinal tract, skin, thyroid gland, kidney, bone, thymus, pancreas, liver, lung, testes, and ovaries.

A juvenile toxicity study was conducted in rats to assess relative sensitivity of immature versus mature animals to the effects of ponatinib, both before and after weaning, followed by a 4-week recovery period. Daily oral administration of ponatinib at 3 mg/kg/day to juvenile rats, beginning Day 15 postpartum, resulted in mortality related to inflammatory effects in several organs within 6 to 7 days of treatment initiation. Administration of 0.75 or 1.5 mg/kg/day ponatinib from

Days 15 to 35 postpartum caused adverse reductions in body weight gain during preweaning and early postweaning treatment phases. These reductions were recovered during posttreatment Days 35 to 63 postpartum. Importantly, despite clear evidence of overt toxicity and adverse effects on body weight gain in juvenile rats, no other adverse effects of ponatinib on juvenile rat developmental parameters (vaginal opening, preputial separation, or bone measurements) were observed, and there were no microscopic changes in bone. Based on the occurrence of adverse body weight changes at tolerated dose levels, the NOAEL of ponatinib in juvenile rats was not identified. However, the NOAEL for ponatinib on key developmental endpoints was 1.5 mg/kg/day. In conclusion, the toxicity profile in juvenile rats was comparable to that determined in general toxicity studies in adult rats.

The ages of animals at the beginning of the juvenile study (Day 15 postpartum) were considered equivalent to a human infant, and by the end of the study (Day 35 postpartum) were considered equivalent to a child; the ages of rats at the initiation of the 6-month study were 7 to 10 weeks postpartum and were equivalent to a human adolescent (Baldrick 2010). Thus, these nonclinical studies cover the pediatric population.

Additional details are provided in the investigator's brochure in the section describing nonclinical studies.

4.1.4 Clinical Studies

The phase 2 PACE study (Study AP24534-10-201) is the pivotal study upon which full marketing approval was granted by the US Food and Drug Administration (FDA) and the European Union (EU) European Medicines Agency (EMA). In the US, the indications described in the current Iclusig label are the following: (1) treatment of adult patients with chronic phase (CP), accelerated phase (AP), or blast phase (BP) CML or Ph+ ALL for whom no other TKI therapy is indicated and (2) treatment of adult patients with T315I-positive CML (CP, AP, or BP) or T315I-positive Ph+ ALL (Iclusig (ponatinib) Tablets for Oral Use 2022). In the EU, ponatinib is indicated in adults patients with (1) CP, AP, or BP-CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation or (2) Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation (Iclusig (ponatinib) 15 and 30 and 45 mg Film-Coated Tablets 2022).

The PACE study enrolled 449 CML (CP, AP, or BP) or Ph+ ALL patients resistant or intolerant to dasatinib or nilotinib, or with BCR-ABL1 T315I mutation (32 Ph+ ALL patients were included in this study) (Cortes et al. 2013). All patients had previously been treated with at least 1 approved BCR-ABL1 inhibitor, with the majority having been treated with 3 or more. A starting dose of ponatinib 45 mg was used, which was the recommended dose established in the phase 1 study (Study AP24534-07-101) (Cortes et al. 2012).

Patients were assigned to 1 of 6 cohorts in accordance with disease group, prior therapy, and presence of the T315I mutation. Ph+ ALL patients were combined with BP-CML patients (referred to as BP-CML/Ph+ ALL) and included in cohort E if they were resistant/intolerant or

cohort F if they had T315I mutation. Ninety-four patients were included in the BP-CML/Ph+ ALL group (48 in cohort E and 46 in cohort F). The primary response endpoints of the study were met, based on analysis of the primary endpoints of major cytogenetic response (MCyR) by 12 months (CP-CML patients) and major hematologic response (MaHR) by 6 months (AP-CML and BP-CML/Ph+ ALL patients) using 2-sided exact 95% confidence intervals (CIs) for MCyR and MaHR in the per protocol population in each cohort. For patients with BP-CML/Ph+ ALL, the prespecified variables for achieving the primary endpoint were met (95% CI, 10% to 30%). The overall MaHR rate by 6 months was 34.0% (treated population; 32/94 patients; 95% CI, 24.6% to 44.5%) and 35.6% (per protocol population; 32/90 patients; 95% CI, 25.7% to 46.3%). In cohort E (resistant/intolerant), the MaHR rates were 35.4% and 37.0% (treated and per protocol populations, respectively), with a 95% CI of 23.2% to 52.5% in the per protocol population. In cohort F (T315I), the MaHR rates were 32.6% and 34.1% (treated and per protocol populations, respectively), with a 95% CI of 20.5% to 49.9% in the per protocol population. Of note, the overall MaHR rate was also higher than the MaHR rate attained with the most recent dasatinib or nilotinib therapy (34.0% versus 24.2%); by cohort the rates were 35.4% vs 25.0% in cohort E (resistant/intolerant) and were 32.6% versus 23.3% in cohort F (T315I), indicating clinically meaningful responses in these patients with advanced disease.

The median progression-free survival (PFS) for the overall BP-CML/Ph+ ALL disease group (N = 94) was estimated as 91 days, with the probability of remaining progression-free at 26, 52, and 104 weeks estimated as 28.3%, 15.9%, and 7.9%, respectively. Median overall survival (OS) for the BP-CML/Ph+ ALL disease group was estimated as 209 days, and the probability of survival at 1, 2, and 3 years was estimated as 32.6%, 16.9%, and 9.7%, respectively.

Preliminary results of 2 ongoing investigator-initiated studies (ponatinib in combination with chemotherapy (Jabbour et al. 2015; Short et al. 2017) and ponatinib in combination with steroids (Martinelli et al. 2017)) have provided evidence of the benefit of ponatinib in the treatment of newly diagnosed patients with Ph+ ALL. In addition, an investigator-initiated phase 2 study in patients with chronic phase CML resistant or intolerant to 1 previous TKI showed that 4 out of 5 (80%) patients achieved a complete cytogenetic response, reinforcing the efficacy of ponatinib in patients failing a prior TKI (Sanford et al. 2015).

In summary, clinical data are consistent with the following: 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.

Details regarding the ponatinib clinical development program are provided in the investigator's brochure in the section describing clinical studies.

4.2 Rationale for the Proposed Study

4.2.1 Rationale for Relapsed Population (Ph+ ALL, Ph+ Mixed Phenotype Acute Leukemia, and Philadelphia Chromosome–like ALL)

Historically, Ph+ ALL was consistently associated with poor outcomes in children and adolescents, with a 5-year event-free survival (EFS) of 40%, despite intensive chemotherapy regimens and allogeneic hematopoietic stem cell transplantation (HSCT) (Arico et al. 2010; Cazzaniga et al. 2018; Schultz et al. 2009).

The introduction of treatment with imatinib, a first-generation TKI approved as front-line treatment for children with Ph+ ALL, dramatically improved the prognosis for these patients. Before the use of TKIs, only 45% of children with Ph+ ALL were alive 7 years after diagnosis (Arico et al. 2010). The combination of imatinib with standard chemotherapy led to an overall higher long-term disease-free survival in both adults and children (Leoni and Biondi 2015; Schultz et al. 2009; Schultz et al. 2014). However, the development of resistance to imatinib due to the presence or acquisition of mutations in the kinase domain is a common cause of disease recurrence (Leoni and Biondi 2015; Miller et al. 2014). In fact, some patients may harbor resistant mutations before TKI treatment (Pfeifer et al. 2012). Imatinib and the second-generation TKI dasatinib are the only BCR-ABL1 TKI treatments that are currently approved for use in pediatric patients with Ph+ ALL. The approach for the treatment of pediatric patients with suboptimal responses, resistance, or intolerance to imatinib and/or dasatinib is not well established.

Other second-generation TKIs approved for use in Ph+ CML (ie, nilotinib and bosutinib) have activity against many kinase domain mutations that are not inhibited by imatinib. However, none of these agents, including dasatinib, have shown the ability to inhibit the T315I mutation (Leoni and Biondi 2015; Miller et al. 2014; Tamai et al. 2018) and they are expected to have the same limitations of resistance to this and other BCR-ABL1 mutations in the proposed pediatric population as they do in adults. The incidence of resistant mutations in the pediatric population is unknown; however, ABL1-kinase domain mutations account for resistance in over 80% of cases of Ph+ ALL relapse in adults. Specifically, the T315I mutation is the most frequent mutation detectable in TKI-resistant adult patients (Foà et al. 2011; Soverini et al. 2014; Watanabe et al. 2012). In one study with dasatinib, the T315I mutation was observed in 75% of relapsed patients (Rousselot et al. 2016). Ponatinib may represent a major step in overcoming drug resistance for pediatric patients with relapsed or resistant Ph+ ALL (Leoni and Biondi 2015).

Mixed phenotype acute leukemia (MPAL) is a very rare type of acute leukemia with an approximate incidence of 1% to 2.5% of acute leukemias in the pediatric population (Weinberg and Arber 2010). Patients with Ph+ MPAL generally have inferior outcomes compared to patients with lineage-specific leukemias. However, patients who have Ph+ MPAL respond favorably to a TKI-containing regimen (Matutes et al. 2011; Shimizu et al. 2014).

Philadelphia chromosome–like (Ph-like) ALL has a similar gene expression profile to that of Ph+ ALL and is associated with a poor outcome. It has an incidence of 10% in children with standard-risk ALL, 21% in adolescents with ALL, and 27% among young adults with ALL

(Rheingold et al. 2017; Roberts et al. 2014; Roberts et al. 2012). Kinase activating mutations were found in 91% of patients with Ph-like ALL. Cell lines and human leukemic cells expressing ABL1, ABL1 CSF1R, and PDGFRB fusions were sensitive in vitro to dasatinib. The high frequency of kinase-activating lesions in patients with Ph-like ALL predicts that TKI therapy is likely to be effective in these patients.

Rationale therefore exists that there is an unmet medical need for a more potent TKI for the treatment of pediatric patients with Ph+ ALL, Ph+ MPAL, or Ph-like ALL with ABL1-class fusions who have relapsed or are resistant or intolerant to a prior TKI-containing therapy, or Ph+ ALL with T315I mutation. Compared with earlier generation TKIs, ponatinib is a more potent, pan-inhibitory TKI with the potential to be more effective than other TKIs. The increased potency of ponatinib, along with its activity toward the single mutations associated with resistance to earlier generation TKIs, supports the investigation of ponatinib in combination with chemotherapy in the treatment of pediatric patients with Ph+ ALL, Ph+ MPAL, or Ph-like ALL who have relapsed or are resistant or intolerant to a prior TKI-containing therapy, or with T315I mutation in this phase 1/2 study.

4.2.2 Rationale for Minimum Age of at Least 1 Year

ALL in infants (<1 year of age) is rare compared to the incidence of ALL in older children, and is biologically different from ALL in older children (Pieters et al. 2007). In addition to the vulnerability of infants to complications and toxicity of aggressive treatment regimens, there are several complex physiologic processes that undergo rapid changes during the first year of life such that infants have a distinct physiology that should be considered in designing chemotherapy treatment protocols (Brown 2013). Generally, specific protocols are used for ALL patients <1 year of age (Ibagy et al. 2013).

4.2.3 Rationale for Complete Remission as Primary Endpoint

The rationale for using complete remission (CR) as the primary endpoint for this study is based on findings that assessing for remission at the end of the induction phase of therapy, both in front-line and relapse salvage therapies, has long been common practice in pediatric ALL as this has been an important response milestone that predicts long-term outcome. Additionally, the degree of reduction of the leukemic clone during remission has independent prognostic value (Bruggemann et al. 2006; Dworzak et al. 2002; Panzer-Grumayer et al. 2000; Pui et al. 2001; Pui and Evans 2006; Zhou et al. 2007).

4.2.4 Rationale for the Doses of Ponatinib

Because relapsed Ph+ ALL is an aggressive disease, phase 1 of this study is a dose confirmation rather than a dose escalation phase.

4.2.4.1 Cohort 1 of the Phase 1 Portion of the Study

For phase 1 cohort 1, the ponatinib doses in combination with multiagent chemotherapy for the treatment of pediatric patients were selected to target exposures achieved in adults after

administration of 30 mg once daily (QD) doses. The selection of adult 30 mg exposures as the target for the pediatric population was based on benefit-risk considerations using the available adult clinical experience, and was additionally supported by a comparison of systemic exposures to in vitro estimates of pharmacologic potency for BCR-ABL1 inhibition.

The adult phase 1 Study AP24534-07-101 supported a 45 mg ponatinib dose as the recommended phase 2 dose (RP2D) in patients with resistant hematologic cancers, including CML and Ph+ ALL. Thus, the pivotal PACE study (Study AP24534-10-201), conducted in adult patients with refractory CML or Ph+ ALL, used a ponatinib dose of 45 mg. Continued follow-up in the PACE study demonstrated a high incidence of arterial occlusive events (AOEs) at the 45 mg dose. Two logistic regression analyses of dose intensity-adverse event (AE) relationships have been conducted on safety data collected in the ponatinib clinical development program. The first analysis was conducted using data from the PACE study, and a subsequent integrated analysis was conducted on data from across the phase 1 Study AP24534-07-101, the phase 2 PACE study, and the phase 3 Study AP24534-12-301 (EPIC, which was a study conducted in patients with newly diagnosed CP-CML). These analyses have consistently indicated a dose-dependent increase in AEs, and notably AOE rates, which are of specific importance for ponatinib. Dose intensity was a statistically significant predictor of AOE rates, and these analyses demonstrated that the 30 mg QD dose can be expected to have a superior safety profile compared with 45 mg QD. In addition, the 30 mg QD dose is anticipated to provide pharmacologically active exposures of ponatinib because the geometric mean steady-state average concentration was 36.5 ng/mL based on the adult population pharmacokinetics (PK) analysis, which exceeds the 21.3 ng/mL (40 nM) IC_{50} for all BCR-ABL1 mutations in a cell-based assay.

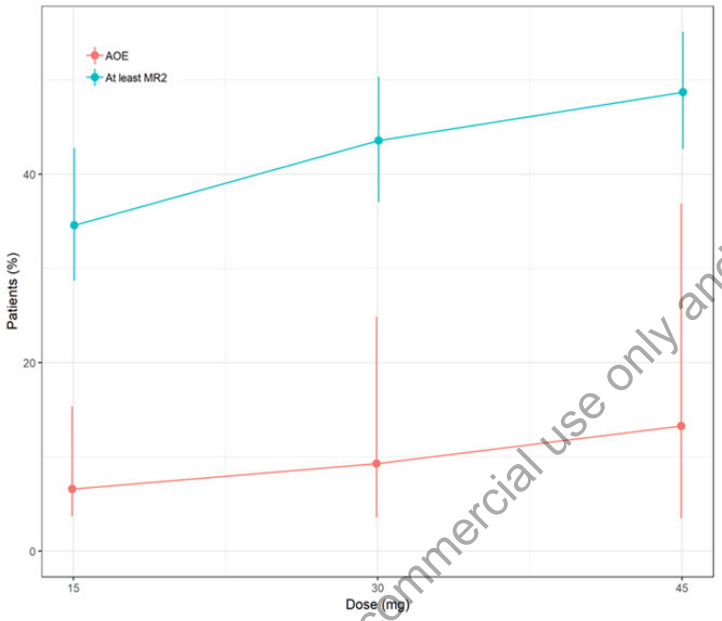
Preliminary exposure-response analyses have also been conducted using available preliminary data from the adult OPTIC study as of the 05 December 2018 data cutoff date. The OPTIC study is an ongoing, randomized, open-label, phase 2 study of ponatinib in patients with resistant CP-CML, in which eligible patients are randomized to receive QD administration of 1 of 3 starting doses of ponatinib: 45, 30, or 15 mg. Patients starting at 45 or 30 mg have their daily dose reduced to 15 mg upon achievement of a molecular response with 2-log reduction (ie, BCR-ABL1/ABL1 ≤1%) (MR2) or better.

For the preliminary exposure-efficacy analysis, the relationship between ponatinib exposure and molecular response states was described using a discrete-time, first-order, 4-state Markov model. The exposure-safety analysis described the relationship between ponatinib exposure and the risk of AOEs using a parametric time-to-event model. In these analyses, exposure-related increases were observed for both efficacy (MR2 or better response) and safety (AOEs). Simulations of dose-response using the developed exposure-response models were performed for the dosing regimens in the OPTIC study, and the results were overlaid (Figure 4.a).

In the model-based dose-response simulations, a starting dose of 30 mg was predicted to have an AOE rate of approximately 9% at 1 year, representing only a modest increase as compared to the 15 mg dose (approximately 7% AOE rate). In contrast, the starting dose of 45 mg was predicted to have an AOE rate of approximately 13%. The predicted dose-response relationship for

efficacy suggests a greater relative increase in the percentage of patients with MR2, or better response at 30 mg (44%) versus 15 mg (35%), as compared to 45 mg (49%) versus 30 mg (44%). Taken together, these preliminary analyses of the available OPTIC study data as of the 05 December 2018 data cutoff date indicate a potentially better benefit-risk profile for the 30 mg starting dose compared to the 15 or 45 mg starting doses.

Figure 4.a Dose-Response Relationships for Efficacy (MR2 or Better Response) and Safety (AOEs) at 1 Year for the Dosing Regimens in the Ongoing OPTIC Study Based on Simulations from the Preliminary Exposure-Response Models (Based on the Data Cutoff Date of 05 December 2018)



AOE: arterial occlusive event; MR2: molecular response with 2-log reduction.

Accordingly, pediatric doses in phase 1 cohort 1 targeted adult exposures achieved at the 30 mg dose as this dose provides pharmacologically relevant exposures in the efficacious range, while reducing the risk for treatment-related toxicities relative to the 45 mg dose. Furthermore, ponatinib is being administered in combination with multiagent chemotherapy, thereby favoring selection of a lower dose than the approved adult single-agent dose of 45 mg.

Because no pediatric clinical PK data are currently available for ponatinib, an allometric scaling approach was used to project the pediatric PK of ponatinib from the adult population PK model. The use of an allometric scaling approach is supported by knowledge of clearance mechanisms for ponatinib and their corresponding ontogeny. Ponatinib is metabolized predominantly by cytochrome P450 3A (CYP3A) with additional contributions by esterases and/or amidases. These clearance pathways are expected to be at adult levels by 1 year of age (CYP3A), or be at >60% of adult levels within the first year of life (esterases/amidases) (Boberg et al. 2017; Hines et al. 2016; Shi et al. 2011; Upreti and Wahlstrom 2016). Accordingly, simulations based

on the population PK model, developed using adult data, have been performed to guide dose selection for the phase 1 dose confirmation portion of the study.

The adult population PK model describes ponatinib PK in cancer patients as a 2-compartment model with linear clearance and absorption via 2 sequential transit compartments before entering the central compartment. Age and body weight on the central volume of distribution were the only significant covariates in the model (Hanley et al. 2022).

For the purpose of predicting pediatric doses that would match adult exposures at 30 mg QD, the model was adapted by removing the previously estimated adult covariate effects and including allometric scaling coefficients of 0.75 and 1 on clearance and volume parameters, respectively. The adapted model, through simulation, was used to predict the target exposure (area under the plasma concentration–time curve [AUC]) in adult patients and to simulate pediatric exposures after administration of fixed doses of ponatinib.

Ponatinib doses of 20 mg for pediatric patients weighing between 30 kg and 45 kg, and 30 mg for pediatric patients weighing ≥45 kg were predicted to result in systemic exposures that approximately match adult exposures following a 30 mg dose. Therefore, dose level 1 of phase 1 cohort 1 enrolled patients ≥30 kg who were able to swallow solid oral dosage forms (ie, tablets) as the age-appropriate formulation (AAF) was not available prior to protocol amendment 3. Patients weighing between 30 and 45 kg received 20 mg ponatinib, and patients weighing ≥45 kg received 30 mg ponatinib. Patients experiencing treatment-emergent adverse events (TEAEs) that required dose reductions had their ponatinib dose reduced to dose level -1.

Enrollment to cohort 1 of the phase 1 portion of the study is completed as of protocol amendment 3.

4.2.4.2 Safety Data from Cohort 1 of the Phase 1 Portion of the Study

Seven patients with Ph+ ALL, 3 male patients and 4 female patients, were enrolled and treated in cohort 1 of the phase 1 portion of the study. The median age at enrollment was 12.0 years (range, 9-17 years). Per protocol, up to 6 patients had to be concurrently enrolled into phase 1 cohort 1 to determine the RP2D; 1 patient aged >16 years and 6 patients aged ≤16 years were enrolled.

As of 21 October 2022, 4 patients were on study treatment and 3 patients were receiving ponatinib treatment, including 2 patients receiving continuation therapy.

As of 21 October 2022, all patients presented with TEAEs related to ponatinib and/or related to the backbone chemotherapy.

The most frequently reported TEAEs were anaemia (in 6 patients); ALT increased, AST increased, and hypoalbuminaemia (each in 5 patients); blood fibrinogen decreased, gamma-glutamyltransferase increased, lymphocyte count decreased, neutrophil count decreased, white blood cell count (WBC) decreased, headache, and constipation (each in 4 patients); and pyrexia, vomiting, lipase increased, platelet count decreased, and thrombocytopenia (each in 3 patients). The most frequently reported Grade ≥3 TEAEs were anaemia (in 5 patients); lymphocyte count decreased, neutrophil count decreased, and WBC decreased (each in

4 patients); and ALT increased, blood fibrinogen increased, platelet count decreased, and thrombocytopenia (each in 3 patients).

Four patients experienced 8 serious TEAEs: ALT increased (2 events), hepatotoxicity, hypertriglyceridaemia, and seizures in 1 patient; catheter site haemorrhage and dilatation ventricular in 1 patient; and pneumonia in 1 patient. No serious TEAEs related to ponatinib were reported.

Three patients experienced TEAEs leading to ponatinib dose reduction and 4 patients experienced TEAEs leading to ponatinib dose discontinuation.

Two patients experienced dose-limiting toxicities (DLTs) before completing the reinduction block and discontinued study treatment. Reported DLTs were Grade 3 skin rash; and Grade 3 liver toxicity (which included both Grade 3 ALT elevation and Grade 3 direct and total bilirubin elevation). Therefore, the available safety data indicate that ponatinib dose level 1 of phase 1 cohort 1 (ie, 30 mg QD adult exposures) was not adequately tolerated. Per Section 8.1.2 of protocol amendment 2, if 2 out of 6 patients experienced DLTs, the treatment regimen was to be considered not adequately tolerated and additional cohorts could be enrolled.

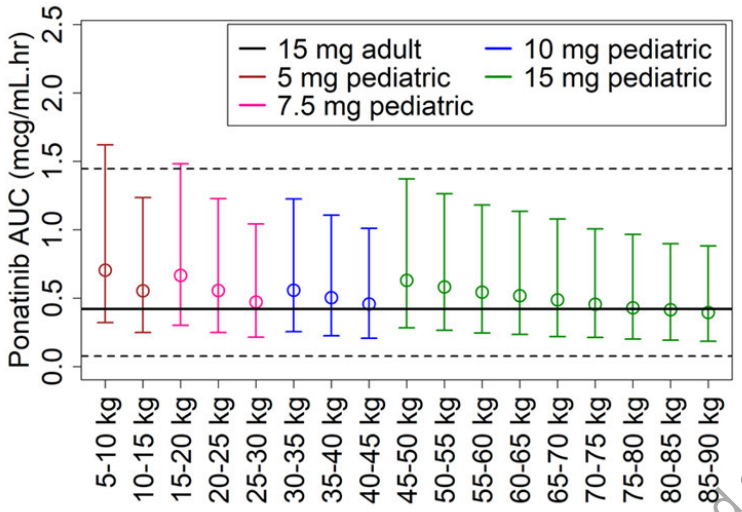
4.2.4.3 Cohort 2 of the Phase 1 Portion of the Study

Following review of safety data of phase 1 cohort 1, the dose of ponatinib will be reduced and the chemotherapy backbone will remain unchanged for patients enrolled starting phase 1 cohort 2 per protocol amendment 3 (see Section 4.2.5).

In adult patients, a ponatinib dose reduction to 15 mg QD is recommended for patients experiencing TEAEs at 30 mg QD (Iclusig (ponatinib) 15 and 30 and 45 mg Film-Coated Tablets 2022; Iclusig (ponatinib) Tablets for Oral Use 2022).

Thus, dose level 1 of phase 1 cohort 2 will target adult exposures achieved after administration of 15 mg QD. Simulations were performed using the allometrically scaled population PK model and indicated that ponatinib doses of 15 mg, 10 mg, 7.5 mg, and 5 mg for patients weighing ≥45 kg, 30 kg to <45 kg, 15 kg to <30 kg, and 5 kg to <15 kg, respectively, are predicted to result in systemic exposures that approximately match adult exposures following administration of 15 mg (Figure 4.b). Patients experiencing TEAEs that require a dose reduction will have their ponatinib dose reduced by 1 dose level (ie, cohort 2 dose level -1 in Table 8.a).

Figure 4.b Predicted Pediatric Exposures of Ponatinib in Pediatric Patients Compared With Adult Exposures at 15 mg



AUC: area under the plasma concentration-time curve; PK: pharmacokinetic(s).
Circles (error bars) denote the median (5th to 95th percentile) of AUC for pediatric patients in each 5 kg body weight bin. The solid (dashed) black line represents the median (range) of AUC for adult patients as estimated from the population PK analysis.

4.2.5 Rationale for Selection of Chemotherapy Backbone Regimen

A modified United Kingdom (UK) ALL R3 regimen has been selected as the chemotherapy backbone for this study. The UK ALL R3 regimen was used in a study for children with first relapse of ALL that compared idarubicin with mitoxantrone in reinduction (Parker et al. 2010). This trial reported the best survival results of any relapse regimen to date. However, when this reinduction regimen was used in combination with new agents (ie, temsirolimus, decitabine, and vorinostat) in recent Therapeutic Advances in Childhood Leukemia & Lymphoma consortium and Children's Oncology Group (COG) protocols, it resulted in severe toxicity, including life-threatening infections (Burke et al. 2016; Rheingold et al. 2017). Therefore, for this study, the R3 reinduction regimen has been modified by substituting the type of anthracycline while keeping the original schedule (Table 8.b). Also, the dexamethasone dose and schedule have been changed to a more conventional regimen. This reinduction regimen has been well tolerated when used in previous studies (Goulden et al. 2017; Larsen et al. 2016).

All 3 drugs, asparaginase, methotrexate, and ponatinib, could have contributed to the occurrence of liver toxicities observed in most patients in cohort 1, which required ponatinib dose reductions and interruptions. In addition, asparaginase has the potential for coagulopathy and pancreatitis as does ponatinib, particularly in combination with corticosteroid therapy.

4.3 Age-Appropriate Formulation for Ponatinib

As of protocol amendment 3, the AAF for ponatinib is available. The AAF is supplied as mini-tablet–containing capsules, ie minitab capsules, with dose strengths of 2.5 and 5 mg. A previous clinical study (Study INCB 84344-103) in healthy adult volunteers assessed the relative bioavailability of the AAF capsules administered intact, or the capsule contents sprinkled on yogurt or applesauce, versus the tablet formulation. The results of this relative bioavailability study indicated that the relative bioavailability (area under the plasma concentration-time curve from time 0 to infinity [AUC_∞] ratio) and 90% CIs for the AAF versus the tablet formulation comparisons were all within 80% to 125%. Therefore, ponatinib tablets, intact minitab capsules, and minitab capsules opened and sprinkled in yogurt or applesauce can be used interchangeably without dose adjustment.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

5.1.1.1 Phase 1 Primary Objective

- To determine the RP2D of ponatinib (tablet and age-appropriate formulation [AAF]) in combination with chemotherapy.

5.1.1.2 Phase 2 Primary Objective

- To determine the efficacy of ponatinib in combination with chemotherapy as measured by the rate of CR at the end of the reinduction block.

5.1.2 Secondary Objectives

5.1.2.1 Phase 1 Secondary Objectives

- To define and describe the phase 1 efficacy of ponatinib (tablet and AAF) in combination with chemotherapy.

5.1.2.2 Phase 2 Secondary Objectives

- Ph+ ALL only: To describe the proportion of patients who achieved CR at the end of consolidation.
- Ph+ ALL only: To describe the proportion of patients with minimal residual disease (MRD) status <0.01% among those who achieved CR at the end of each treatment block.
- To determine the proportion of patients who relapsed or progressed.
- To determine EFS, PFS, and OS at 6 months, 1 year, 18 months, 2 years, and 3 years.
- To determine duration of response (for CR).

- To determine the proportion of patients who underwent HSCT following study treatment.

5.1.2.3 Phase 1 PK Objective

- To characterize the PK of ponatinib in combination with chemotherapy.

5.1.2.4 Phase 2 PK Objective

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

5.1.2.5 Phase 1 and Phase 2 Safety Objective

- To describe the safety profile of ponatinib in combination with chemotherapy for each treatment block (ie, reinduction and consolidation).

5.1.3 Exploratory Objectives

- To explore the risk of cardiotoxicity in patients with elevated cardiac troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP).
- Ph+ ALL only: To characterize biomarkers of sensitivity and resistance to ponatinib-containing therapy, which may include molecular mutations (eg, *BCR-ABL1*, *IKZF1*, *CDKN2A/2B*) in samples both prior to and following ponatinib treatment.
- To assess the acceptability and palatability of the AAF of ponatinib using the palatability questionnaire (Appendix E).
- To determine OS for patients who receive HSCT and patients who do not receive HSCT.

5.2 Endpoints

5.2.1 Primary Endpoints

5.2.1.1 Phase 1 Primary Endpoint

The phase 1 primary endpoint is the following:

- RP2D of ponatinib (tablet and AAF) in combination with chemotherapy.

5.2.1.2 Phase 2 Primary Endpoint

The phase 2 primary endpoint is the following:

- CR at the end of the reinduction block. CR is defined as <5% blasts in BM, normal maturation of all cellular components in the BM, no evidence of extramedullary disease, absolute neutrophil count (ANC) >1000/µL, and platelet count of >100,000/µL.

5.2.2 Secondary Endpoints

5.2.2.1 Phase 1 Secondary Endpoints

The phase 1 secondary endpoints are the following:

- CR at the end of the reinduction block. CR is defined as <5% blasts in BM, normal maturation of all cellular components in the BM, no evidence of extramedullary disease, ANC >1000/μL, and platelet count of >100,000/μL.

5.2.2.2 Phase 2 Secondary Endpoints

The phase 2 secondary endpoints are the following:

- Ph+ ALL only: Proportion of patients who achieved CR at the end of consolidation.
- Ph+ ALL: Proportion of patients with MRD-negative status (≤0.01%) among those who achieved CR at the end of each treatment block.
- Proportion of patients who relapsed or progressed.
- EFS, PFS, and OS at 6 months, 1 year, 18 months, 2 years, and 3 years.
- Duration of response (for CR).
- Proportion of patients who underwent HSCT following study treatment.

5.2.2.3 Phase 1 PK Endpoint

The phase 1 PK endpoint is the following:

- Summary statistics of ponatinib PK parameters including maximum observed plasma concentration (C_{max}), time of first occurrence of C_{max} (t_{max}), and AUC from time 0 to the time of the last quantifiable concentration (AUC_{last}).

5.2.2.4 Phase 1 and Phase 2 Safety Endpoint

The phase 1 and phase 2 safety endpoint is the following:

- AEs, serious adverse events (SAEs), AOEs, venous thrombotic/embolic events (VTEs), and any other adverse events of special interest (AESIs).

5.2.3 Exploratory Endpoints

The exploratory endpoints are the following:

- Change from baseline in laboratory values and cardiovascular outcomes associated with elevated cardiac troponin and NT-proBNP.
- Ph+ ALL only: Biomarkers of potential sensitivity and resistance to ponatinib-containing therapy, which may include molecular mutations (eg, *BCR-ABL1*, *IKZF1*, *CDKN2A/2B*) in samples both prior and following ponatinib treatment.

- Acceptability and palatability of the AAF of ponatinib based on the palatability questionnaire administered during reinduction (Appendix E).
- OS for patients who receive HSCT and patients who do not receive HSCT.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a pivotal phase 1/2, single-arm, open-label, multicenter study designed to evaluate the safety, tolerability, PK, and efficacy of ponatinib when administered in combination with multiagent chemotherapy in pediatric patients (aged ≥1 year to ≤21 years) with Ph+ ALL, Ph+ MPAL, or Ph-like ALL with targetable kinase-activating lesions and either (i) or (ii) as follows:

(i) **For non-US sites**: Patients who have relapsed or are resistant or intolerant to at least 1 prior therapy that contained a BCR-ABL1–targeted TKI, OR

For US sites: Patients who have relapsed or are resistant or intolerant to at least 1 prior therapy that contained a second-generation BCR-ABL1–targeted TKI; OR

(ii) Have a BCR-ABL1 T315I mutation.

Patients will undergo screening assessments for up to 10 days to determine eligibility (Figure 6.a). In both phase 1 and phase 2, eligible patients will receive two 35-day blocks of therapy (reinduction block and consolidation block). Each block will include 29 days of study treatment consisting of daily ponatinib and a modified UK ALL R3 chemotherapy backbone regimen specified in Table 8.b and a rest period from chemotherapy for a minimum of 6 days consisting of daily ponatinib only. Disease assessment will occur at the end of each block. Patients will undergo an end of treatment (EOT) visit (EOT1) 25 to 30 days after the last dose of study treatment in the consolidation block, or earlier, if the patient is proceeding to alternate therapy or optional ponatinib continuation therapy (Appendix A, Table 1).

Patients completing protocol therapy and the EOT1 visit can proceed to alternate therapies not containing ponatinib as off-protocol therapy. Alternatively, eligible patients may receive optional ponatinib continuation therapy (either ponatinib monotherapy or combination therapy at the investigator's discretion and with sponsor agreement) after completing the 2 blocks of study treatment and the EOT1 visit. Patients who receive optional continuation therapy with ponatinib/ponatinib-containing therapy will be followed per the schedule of events (SOE) and proceed to a second EOT visit (EOT2) 30 to 40 days after the last dose of ponatinib, or earlier, if the patient discontinues ponatinib/ponatinib-containing therapy sooner than 30 days (Appendix A, Table 2). Patients who discontinue ponatinib before completing the consolidation block will be discontinued from study treatment and proceed to the EOT1 visit. All patients will be followed for at least 3 years from EOT1, with primary analysis performed approximately 6 months after the last patient has been enrolled.

Phase 1 of the study (approximately 12 DLT-evaluable patients) is a PK/safety lead-in phase for dose confirmation to establish the RP2D of ponatinib administered either as the tablet formulation or the AAF (Table 8.a) in combination with the chemotherapy backbone (Table 8.b).

The initial ponatinib doses evaluated in cohort 1 of the phase 1 portion of the study were selected to target systemic exposures comparable to those achieved in adults receiving 30 mg QD based on the results of population PK modeling and simulation (see Section 4.2.4.1).

A staggered enrollment is being applied. Phase 1 cohort 1 was initiated with the tablet formulation in patients able to swallow solid oral dosage forms and weighing at least 30 kg as the AAF was not available during that enrollment period. As of protocol amendment 3, both the tablet formulation and AAF are available for use in phase 1 (see Section 4.3). Additional details regarding administration of the AAF are provided in the study/pharmacy manual.

The PK, safety, and tolerability data from phase 1 will inform selection of the recommended dose of ponatinib for confirmatory evaluation of safety and efficacy in the phase 2 portion of the study. A rolling 6 design will be followed for all phase 1 cohorts.

As of cohort 2 of phase 1, patients will be reviewed on an ongoing basis to determine whether the patient meets the criteria to be DLT-evaluable. DLT-evaluable patients must have received ponatinib doses on at least 70% of the reinduction block days (eg, 25 or more of the 35 days) per protocol or experienced a confirmed DLT.

Ponatinib doses for evaluation in phase 1 cohort 2 will target systemic exposures comparable to those achieved in adults receiving 15 mg QD based on the results of population PK modeling and simulation (see Section 4.2.4.3). For phase 1 cohort 2, approximately 6 DLT-evaluable patients with a body weight of at least 5 kg will be enrolled, with a minimum of 2 patients with a baseline body weight <30 kg. No more than 1 DLT-evaluable patient may be >16 years of age in cohort 2.

To determine the RP2D, a minimum of 6 DLT-evaluable patients in cohort 2 must complete the reinduction block. If 2 out of 6 patients experience a DLT, the study will be paused to determine further tolerability of this combination. All patients enrolled in cohort 2 under protocol amendment 3 and those enrolled under protocol amendment 4 will be assessed together in a single cohort for determination of DLTs and RP2D as defined in protocol amendment 4.

Definitions of DLTs are provided in Section 8.2. The DLT observation period for each formulation will start on Day 1 and continue until the end of the reinduction block. If patients have residual hematologic toxicities at end of the reinduction block, they will be followed for up to an additional 7 days for DLT evaluation.

Cohort enrollment in a rolling 6 design is continuous and will proceed as follows:

- If ≤1 DLT for the first 3 to 5 patients, subsequent patients (the fourth, fifth, and/or sixth patient[s]) may be enrolled.
- If ≥2 DLTs occur in the first 3 to 5 patients, enrollment will be closed.

- If a patient becomes unevaluable for DLT assessment, an additional patient (ie, replacement) may be enrolled to ensure a minimum of 6 DLT-evaluable patients.

Upon review of patients treated in cohort 2, if dose level 1 is determined not to be tolerated or fails to achieve the desired target systemic exposures and RP2D is not confirmed with cohort 2, then no further cohorts are planned to be tested.

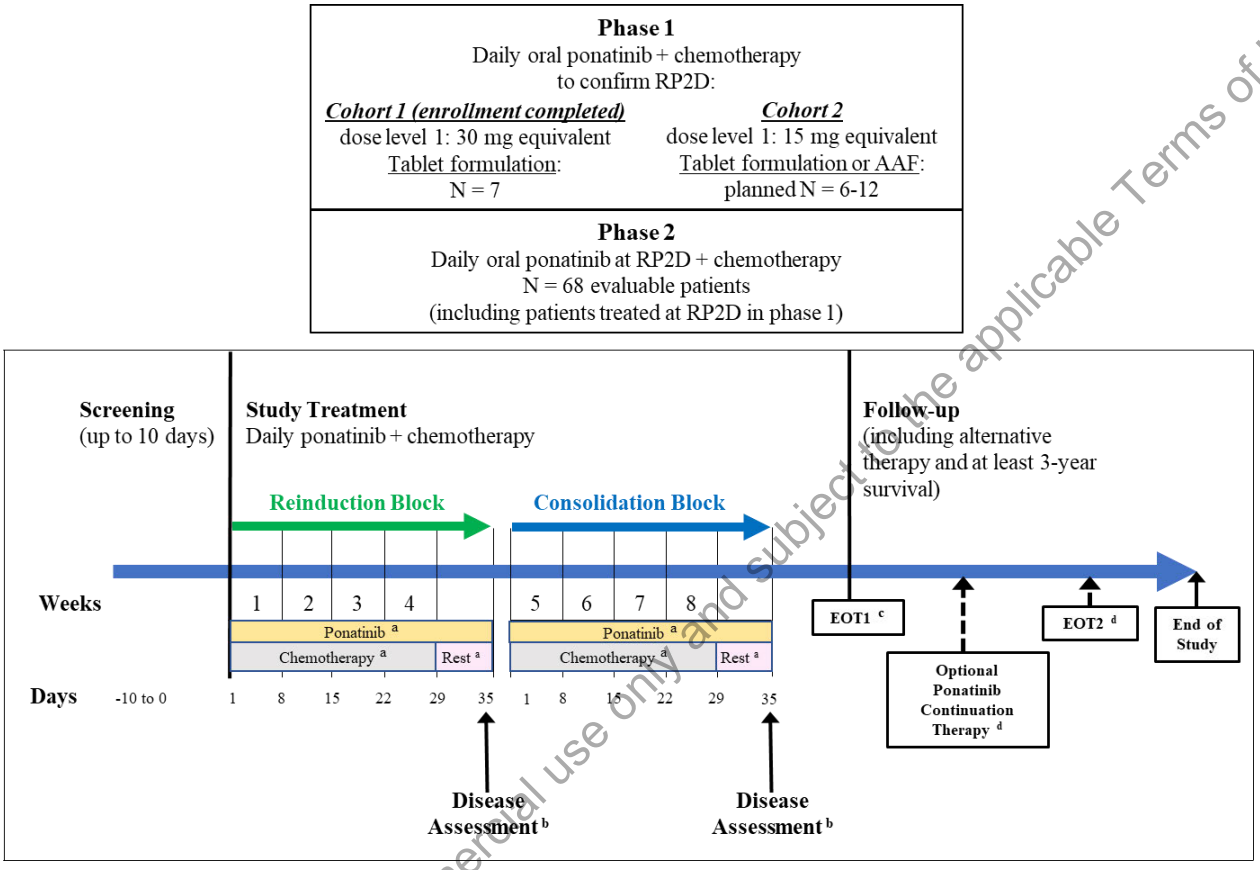
The RP2D of ponatinib will be determined after evaluating the available safety and PK data from the first 6 patients enrolled in phase 1 cohort 2. Up to an additional 6 patients may be enrolled to further characterize the safety, PK, and preliminary efficacy of the RP2D of ponatinib before the start of phase 2.

Phase 2 of the study will enroll approximately 68 patients, including DLT-evaluable patients enrolled to phase 1 who completed the reinduction block and dosed at the RP2D.

In phase 2, patients will receive daily ponatinib in combination with the chemotherapy backbone at the RP2D determined after review of available data from the phase 1 portion of the study (Table 8.b). Phase 2 will evaluate the efficacy and safety of ponatinib at the RP2D in combination with chemotherapy in the study population.

Figure 6.a presents the design schema for the study.

Figure 6.a Study Design Schema



AAF: age-appropriate formulation; EOT1: end of treatment 1; EOT2: end of treatment 2; RP2D: recommended phase 2 dose.

"equivalent" refers to adult equivalent/target dose.

[a] Each block consists of 29 days of study treatment with ponatinib and chemotherapy followed by a chemotherapy rest period of a minimum of 6 days consisting of daily ponatinib only. Ponatinib should not be interrupted unless the patient has toxicity suspected to be related to ponatinib.

[b] Patients will undergo evaluation for disease status at the end of the reinduction block and the consolidation block. Patients tolerating treatment at the end of the reinduction block will proceed to the consolidation block regardless of their remission status.

[c] Patients will have their first EOT visit (EOT1) 25 to 30 days after last dose of ponatinib in the consolidation block, or earlier, if the patient is proceeding to alternate therapy or optional ponatinib continuation therapy.

[d] Patients who receive optional continuation therapy containing ponatinib will have an additional EOT visit (EOT2) 30 to 40 days after last dose of ponatinib, or earlier, if the patient is proceeding to alternate therapy. See Table 8.d for optional ponatinib continuation therapy regimen. Patients who are receiving clinical benefit from ponatinib treatment may continue therapy for a maximum of 12 months. If patients continue deriving clinical benefit after 12 months of optional continuation therapy, they may remain on ponatinib treatment if the investigator provides the evidence of clinical benefits and confirms with the sponsor.

The ponatinib dose may be reduced or discontinued early if a patient experiences study treatment–related toxicities. Patients who must discontinue ponatinib due to toxicity before

completing the consolidation block will be discontinued from study treatment and proceed to the EOT1 visit. Patients may discontinue study treatment at any time. Patients who discontinue study treatment will proceed to the EOT1 visit 25 to 30 days after receiving their last dose of ponatinib (or earlier, if the patient is proceeding to alternate therapy or optional ponatinib continuation therapy) as specified in the SOE (Appendix A, Table 1). Patients who discontinue from optional ponatinib continuation therapy will proceed to the EOT2 visit (Appendix A, Table 2).

Patients will undergo assessments as described in the SOE (Appendix A, Table 1). Key assessments for efficacy include BM samples (aspirate and/or biopsy) for CR status and MRD, peripheral blood samples to assess hematological and molecular responses and for exploratory biomarker assessments. In addition, patients and/or their parents/legal guardians will be administered a questionnaire to assess the palatability of the ponatinib AAF (during the reinduction block only). Serial blood samples for the measurement of plasma concentrations of ponatinib will be obtained at prespecified time points as described in Appendix A, Table 3 and Table 4. These data will be used to characterize the PK of ponatinib.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0, effective 27 November 2017.

AEs will be assessed and may include results from laboratory tests, vital signs, and electrocardiograms (ECGs) to evaluate the safety and tolerability of ponatinib.

Development of mutations will be assessed both prior to ponatinib treatment and following study treatment.

6.2 Number of Patients

Phase 1 of the study will enroll approximately 12 DLT-evaluable patients; phase 2 of the study will enroll approximately 68 patients, including DLT-evaluable patients enrolled to phase 1 who completed the reinduction block and are dosed at the RP2D. Approximately 74 study sites in approximately 17 countries will enroll patients into the study.

A patient is considered to be enrolled in the study at the time of initiation of the first dose of study drug. Procedures for completion of the enrollment information are described in the site operations manual.

In phase 1, patients who are withdrawn from treatment during the reinduction block for reasons other than DLTs and become unevaluable for DLT assessment may be replaced.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

All patients enrolled will receive two 35-day blocks of therapy (ponatinib in combination with chemotherapy for 29 days followed by a rest period from chemotherapy for a minimum of 6 days consisting of daily ponatinib only). At the discretion of the treating physician and with sponsor agreement, a patient may continue in the optional ponatinib continuation therapy beyond the end of the consolidation block and receive ponatinib only or in combination with maintenance-type

chemotherapy until more definitive therapy is initiated. Patients who are receiving clinical benefit from ponatinib treatment may continue therapy for a maximum of 12 months. If patients continue deriving clinical benefit after 12 months of optional continuation therapy, they may remain on ponatinib treatment if the investigator provides the evidence of clinical benefits and confirms with the sponsor.

Following the completion of reinduction and consolidation treatment blocks or early discontinuation from treatment, the patient is required to complete the EOT1 visit 25 to 30 days after the last dose of ponatinib (or earlier, if the patient is proceeding to alternate therapy or optional ponatinib continuation therapy) and proceed to follow-up. If a patient is eligible to receive optional ponatinib continuation treatment, they will have another EOT visit (EOT2) 30 to 40 days following this regimen's last dose of ponatinib (or earlier, if the patient is proceeding to alternate therapy) and subsequently proceed to follow-up. Patients will have follow-up visits, starting at 6 months and occurring at 1 year, 18 months, 2 years and then yearly until the end of the study. All patients are to be followed for at least 3 years from EOT1, or until lost to follow-up, study termination by the sponsor, or death, whichever occurs first, to obtain survival status from approximately 80% of all patients in the safety population.

See Appendix A, Table 1 for a detailed SOE.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The end of study will occur upon completion of the last patient's 36-month follow-up visit (post-EOT1) or study termination by the sponsor, whichever is earlier.

Study results will be reported in a CSR.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

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

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
PHASE 1		
Primary: RP2D	--	End of reinduction block (at approximately 4 weeks)
Secondary: CR	CR meeting all the following criteria: • No circulating blasts and <5% blasts in the BM. • Normal maturation of all cellular components in the BM. • No extramedullary disease. • ANC >1000/µL (or >1.0 × 10^9/L). • Platelets >100,000/µL (or >100 × 10^9/L).	End of reinduction block (at approximately 4 weeks)

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
PK: Ponatinib C_{max}, t_{max}, AUC_{last}	C_{max}: maximum observed plasma concentration; t_{max}: time of first occurrence of C_{max}; AUC_{last}: area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration.	End of reinduction block (at approximately 4 weeks)
PHASE 2		
Primary: CR	CR meeting all the following criteria: • No circulating blasts and <5% blasts in the BM. • Normal maturation of all cellular components in the BM. • No extramedullary disease. • ANC >1000/μL (or >1.0 × 10^9/L). • Platelets >100,000/μL (or >100 × 10^9/L).	End of reinduction block (at approximately 4 weeks)
Secondary (Ph+ ALL only): Proportion of patients who achieved CR	--	End of consolidation block (at approximately 8 weeks)
Secondary (Ph+ ALL only): Proportion of patients with MRD-negative status (<0.01%) among those who achieved CR	--	End of reinduction block and consolidation block (at approximately 4 and 8 weeks)
Secondary: Proportion of patients who relapsed or progressed	--	End of reinduction block and consolidation block (at approximately 4 and 8 weeks)
Secondary: EFS	From date of enrollment until one of the following: • Death due to any cause. • Refractory to treatment, defined as failure to achieve CR by end of the consolidation block. • Relapse from CR.	36 months

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
PHASE 2		
Secondary: PFS	From date of enrollment until one of the following: • Death related to disease under study. • Disease progression, defined as an increase from baseline of at least 25% in the absolute number of circulating or BM blasts or development of new extramedullary disease. • Relapse from CR.	36 months
Secondary: OS	From first dose of study drug until death due to any cause.	36 months
Secondary: Duration of response	The interval between the first assessment at which the criteria for CR are met until the time at which relapse from CR occurs.	36 months
Secondary: Proportion of patients with HSCT	Proportion of patients with HSCT following protocol treatment.	36 months

ALL: acute lymphoblastic leukemia; ANC: absolute neutrophil count; BM: bone marrow; CR: complete remission; EFS: event-free survival; HSCT: hematopoietic stem cell transplantation; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival; Ph+: Philadelphia chromosome positive; PK: pharmacokinetic; RP2D: recommended phase 2 dose.

6.3.4 Total Study Duration

Duration of study will be approximately 80 months: approximately 41 months of enrollment, approximately 3 months of study treatment, and at least 36 months of follow-up.

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 meaningful 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

Patients (aged ≥1 year to ≤21 years and weighing at least 5 kg) with Ph+ ALL, Ph+ MPAL, or Ph-like ALL with targetable kinase-activating lesions must have BM involvement and either (i) or (ii) as follows:

(i) **For non-US sites**: patients who have relapsed or are resistant or intolerant to at least one prior therapy that contained a BCR-ABL1–targeted TKI; OR

For US sites: patients who have relapsed or are resistant or intolerant to at least one prior therapy that contained a second-generation BCR-ABL1–targeted TKI; OR

(ii) Have a BCR-ABL1 T315I mutation. Referring institutions laboratory results will be accepted for enrollment; however, the mutation needs to be confirmed by the central laboratory. If the mutational status is not concordant, the patient will be withdrawn from the study and excluded from analyses.

In phase 1 cohort 1, only patients with a body weight of ≥30 kg and able to swallow solid oral dosage forms were enrolled because the AAF was not available. As of protocol amendment 3, patients weighing at least 5 kg or who are unable to swallow solid oral dosage forms are eligible for enrollment as the AAF is available.

7.1 Inclusion Criteria

Phase 1 cohort 1 (enrollment and treatment completed) eligibility criteria at the time of enrollment:

- Patients must have a body weight ≥30 kg.
- Patients must be able to swallow solid oral dosage forms.

Phase 1 cohort 2 eligibility criteria at the time of enrollment:

- Patients must be aged ≥1 year and have a body weight of at least 5 kg.

Each patient must meet all the following inclusion criteria to be enrolled in the study for phase 1 and phase 2:

1. **Diagnosis:** Patients must have a diagnosis of Ph+ ALL, Ph+ MPAL, or Ph-like ALL with:
   a) **Involvement of BM with ALL, including one of the following:**
      i. **M2 BM (5%-24% lymphoblasts):** by morphology with confirmatory testing consisting of at least one of the following: flow cytometry lymphoblasts ≥5%, or BCR-ABL1 fluorescence in situ hybridization, or $\geq 10^{-2}$ leukemic clone identified by immunoglobulin heavy chain–T-cell receptor polymerase chain reaction, OR
      ii. **M3 BM (≥25% lymphoblasts):** by morphology, OR
      iii. **Patients with combined BM (as defined above) and extramedullary disease.**

b) **Evidence of Ph+ ALL, MPAL, or Ph-like ALL:**

i. Definite evidence of BCR-ABL1 fusion (Ph) for Ph+ ALL and MPAL, OR

ii. Definite evidence of Ph-like ALL with targetable kinase-activating lesions involving any of the following kinase genes: *ABL1*, *ABL2*, *CSF1R*, and *PDGFRB*.

Ph-like ALL diagnosis requires the identification of specified targetable kinase-activating lesions preferably by RNA sequencing or by alternative accredited method used by the site. Referring institution's laboratory results will be accepted for diagnosis and study enrollment. No confirmation by a sponsor central laboratory is required.

c) **Disease status:**

i. **For non-US sites:** patients who have relapsed (post 0 or 1 HSCT) or are resistant or intolerant to at least 1 prior therapy that contained a BCR-ABL1–targeted TKI, OR

For US sites: patients who have relapsed (post 0 or 1 HSCT) or are resistant or intolerant to at least 1 prior therapy that contained a second-generation BCR-ABL1-targeted TKI (ie, dasatinib, nilotinib, and bosutinib); OR

ii. Have a BCR-ABL1 T315I mutation irrespective of relapse, resistance/intolerance, or transplant status and irrespective of any prior TKI use. Referring institution's laboratory results will be accepted for study enrollment; however, the mutation needs to be confirmed by the central laboratory. If the mutational status is not concordant, the patient will be withdrawn from the study and excluded from analyses for RP2D and efficacy, but included for safety.

Notes:

A patient will be defined as intolerant if they had a Grade ≥3 nonhematologic toxicity or a Grade 4 hematologic toxicity considered related to the last TKI and lasting for >2 weeks, and led to discontinuation of therapy.

2. **Age and weight:** Patients must be ≥1 and ≤21 years of age and weighing at least 5 kg at the time of enrollment.
3. **Performance Status:** Karnofsky performance status ≥50% for patients ≥16 years of age or Lansky Play Scale ≥50% for patients <16 years of age.

Prior Therapy

4. Patients must have recovered to less than Grade 2 NCI CTCAE Version 5.0, or to baseline, from any nonhematologic toxicities (except alopecia) due to previous therapy.
5. Patients must meet the following criteria related to prior therapies:

Cytoreduction with hydroxyurea: Hydroxyurea can be initiated and continued for up to 24 hours before the start of protocol therapy.

Patients who relapsed while receiving cytotoxic therapy: At least 14 days must have passed since the completion of the last dose of chemotherapy before the first dose of ponatinib can be given except for the following: intrathecal (IT) chemotherapy and/or maintenance therapy such as vincristine, mercaptopurine, methotrexate, or glucocorticoids. There is no waiting period for those relapsing on maintenance-like therapy.

HSCT: Patients who have experienced relapse after a HSCT are eligible, provided they have no evidence of acute or chronic graft-versus-host disease (GVHD), are not receiving GVHD prophylaxis or treatment, and are at least 90 days posttransplant at the time of enrollment.

Hematopoietic growth factors: Before the first dose of ponatinib, at least 7 days must have passed since completion of therapy with granulocyte colony-stimulating factor or other growth factors, and at least 14 days must have passed since completion of therapy with pegfilgrastim.

Biologics and targeted therapies: Before the first dose of ponatinib, at least 7 days must have passed since the last dose of a biologic agent. For agents that have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the sponsor's medical monitor/designee.

Monoclonal antibodies: After the last dose of monoclonal antibody, at least 3 half-lives of the administered antibody must have passed before the first dose of ponatinib.

Immunotherapy: Before the first dose of ponatinib, at least 30 days must have passed after the completion of any type of immunotherapy (eg, tumor vaccines, chimeric antigen receptor T-cell [CAR-T-cell]).

Immunosuppressive therapy: Before the first dose of ponatinib, at least 14 days must have passed after the completion of immunosuppressive therapy (including regimens following stem cell transplant).

Radiotherapy: No washout period is necessary for radiation given to any extramedullary site other than central nervous system (CNS); ≥90 days must have passed if patient received prior total body irradiation or craniospinal or cranial radiotherapy.

Anthracyclines: Patients must have had a lifetime exposure of <400 mg/m^2 of doxorubicin equivalents of anthracyclines.

Organ Function Requirements

6. Patients must have adequate renal and hepatic function as indicated by the following laboratory values:

   a) **Adequate renal function defined as:** Estimated glomerular filtration rate (eGFR) using the Schwartz formula, OR radioisotope glomerular filtration rate (GFR)

≥70 mL/min/1.73 m^2, OR a normal serum creatinine based on age and sex as in Table 7.a:

Table 7.a Maximum Serum Creatinine Value (mg/dL) by Age and Sex

Age (years)	Male	Female
1 to <2	0.6	0.6
2 to <6	0.8	0.8
6 to <10	1	1
10 to <13	1.2	1.2
13 to <16	1.5	1.4
≥16	1.7	1.4

The threshold creatinine values were derived from the Schwartz formula for estimating glomerular filtration rate (Schwartz and Gauthier 1985) using child length and stature data published by the Centers for Disease Control and Prevention.

Schwartz formula: eGFR (mL/min/1.73 m^2) = (k × L) / Pcr

k: proportional constant (see Table 7.b); L: height (cm); Pcr: plasma creatinine (mg/dL)

Table 7.b Mean Values of k by Age

Age Group	k (mean value)
Low birth weight infants ≤1 year	0.33
Full-term infants ≤1 year	0.45
Children >1-12 years	0.55
Females 13-21 years	0.55
Males 13-21 years	0.70

Source: (Schwartz et al. 1987).

b) **Adequate liver function defined as:** Direct bilirubin ≤1.5 times the upper limit of normal (ULN) for age AND ALT ≤5 times the ULN for age.

7. No clinical, radiological or laboratory evidence of pancreatitis, including:
   a) Serum lipase must be <2 times the ULN, AND
   b) Serum amylase must be <2 times the ULN.
8. Adequate cardiac function defined as shortening fraction ≥27% by echocardiogram (ECHO) OR left ventricular ejection fraction of ≥50% by ECHO or multigated acquisition scan (MUGA).
9. Normal QT interval with Fridericia correction method (QTcF) on screening ECG, defined as QTcF of ≤450 ms.

10. Voluntary written informed consent and assent (as dictated by the institutional review board (IRB)/independent ethics committee (IEC) and required by applicable local regulations) 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 (if of the age of consent) or the patient's parent or legal guardian at any time without prejudice to future medical care.

Prevention of Pregnancy

11. Female patients who:
    a) Are surgically sterile, OR
    b) 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/assent through at least 6 months after end of therapy, OR
    c) 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.)
12. 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 at least 6 months after end of therapy, 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 for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. A history or current diagnosis of Burkitt leukemia/lymphoma or mature B-cell leukemia.
2. A history or current diagnosis of CML.
3. Diagnosis of ALL, MPAL, or Ph-like ALL with targetable kinase-activating lesions after treatment with cytotoxic therapy for another cancer.
4. Diagnosis of another concurrent primary malignancy.
5. Clinically significant cardiovascular disease, including but not limited to:
    a) Any history of myocardial infarction (MI) or unstable angina.

b) History of or presence of heart block, and/or clinically significant ventricular or atrial arrhythmias.

c) Uncontrolled hypertension, defined as persistent elevation of systolic and/or diastolic blood pressures to ≥95th percentile based on age, sex, and height percentiles despite appropriate antihypertensive management.

6. Current systemic use of drug(s) that are known to have a risk of causing prolonged corrected QT interval (QTc) or torsades de pointes unless drug(s) can be changed to acceptable alternatives (ie, an alternate class of agents that do not affect the cardiac conduction system) or the patient can safely discontinue the drug(s).
7. Uncontrolled hypertriglyceridemia (triglycerides ≥450 mg/dL).
8. Current systemic use of any medications or herbal supplements that are known to be strong inhibitors or strong inducers of CYP3A within 7 days before the first dose of study drug.
9. Previous treatment with ponatinib.
10. Planned non-protocol chemotherapy, radiation therapy, another investigational agent, or immunotherapy while patient is on study treatment.
11. Known allergy or contraindications to any of the drugs (active or excipient) used in the study.
12. Known gastrointestinal disease or gastrointestinal procedure that could interfere with the oral absorption of ponatinib.
13. Patients with DNA fragility syndromes, such as Fanconi anemia and Bloom syndrome.
14. Patients with Down syndrome.
15. Patients with uncontrolled systemic infection, or known laboratory and/or clinical evidence of active infection with HIV, hepatitis B, or hepatitis C.
16. Patients with pre-existing significant CNS pathology, including history of severe brain injury, dementia, cerebellar disease, organic brain syndrome, psychosis, coordination/movement disorder, or autoimmune disease with CNS involvement, are not eligible.
17. Patients with a history of cerebrovascular ischemia/hemorrhage with residual deficits are not eligible. (Patients with a history of cerebrovascular ischemia/hemorrhage remain eligible provided all neurologic deficits and causative factor(s) have resolved.)
18. Uncontrolled seizure disorder. (Patients with seizure disorders that do not require antiepileptic drugs or are well controlled with stable doses of antiepileptic drugs are eligible.)
19. History of severe coagulopathy or cardiovascular or peripheral vascular events.
20. Any condition or illness that, in the opinion of the investigator or sponsor, would compromise patient safety or interfere with the evaluation of the safety or efficacy of ponatinib.
21. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

22. Pregnancy and breastfeeding exclusions:
    a) Female patients who are pregnant are excluded since fetal toxicities and teratogenic effects have been noted for several of the study treatments. A pregnancy test is required for female patients of childbearing potential.
    b) Lactating women who plan to breastfeed their infants.
23. Treatment with live attenuated vaccinations within 30 days prior to initiation of study treatment regimen.

8.0 STUDY TREATMENT

Investigational therapy: Ponatinib

Chemotherapy backbone (see Table 8.b)

Treatment blocks (ponatinib plus chemotherapy backbone):

- Reinduction phase: One 35-day cycle (29 days study treatment, 6 days rest consisting of daily ponatinib only).
- Consolidation phase: One 35-day cycle (29 days study treatment, 6 days rest consisting of daily ponatinib only). Consolidation can start on or after Day 36 when peripheral counts recover and the patient has recovered from chemotherapy-related toxicities. Ponatinib therapy will not be interrupted during this period unless the patient has toxicity suspected to be related to ponatinib.

Optional continuation therapy (see Table 8.d).

8.1 Study Treatment Administration

8.1.1 Investigational Therapy: Ponatinib

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).

Prior to protocol amendment 3, ponatinib was available as immediate-release tablets at dosage strengths of 10 mg, 15 mg, and 30 mg. To match adult exposures at the phase 1 cohort 1 starting dose (30 mg adult exposures) and to allow for dose reductions (15 mg adult exposures), the tablet strengths were sufficient only for patients weighing ≥30 kg (Section 8.1.1.1). Upon implementation of protocol amendment 3, an AAF of ponatinib minitab capsules is available to enable administration of ponatinib to pediatric patients weighing <30 kg or unable to swallow solid oral dosage forms.

In phase 1 cohort 1, only patients weighing ≥30 kg and able to swallow the tablets were enrolled as the AAF was not available. At the time of protocol amendment 3, the AAF is available at dose strengths of 2.5 mg and 5 mg. In phase 1 cohort 2, ponatinib treatment will be assigned at the starting dose (15 mg adult exposures) and dose reductions will be allowed according to the dose

levels defined in Table 8.a. Additional details regarding administration of the AAF are provided in the study/pharmacy manual.

If the patient is not hospitalized, ponatinib will be administered by the patient's parent or legal guardian or will be self-administered by the patient on a daily schedule at the assigned dose level in phase 1 or at the RP2D in phase 2 by mouth (PO) QD. Each 35-day dosing period is referred to as one block. Each block consists of 29 days of study treatment (ponatinib in combination with chemotherapy) followed by a rest period from chemotherapy for a minimum of 6 days. Ponatinib will be administered QD during the treatment block including the rest period. Any change with the schedule should be discussed with the sponsor's medical monitor/designee.

Each patient or the patient's parent or legal guardian will be provided a diary or equivalent where the date and time of each administration will be recorded; complete instructions will be provided with the site operations manual.

Patients should receive ponatinib at approximately the same time each day. Patients who fail to take their daily ponatinib dose within 6 hours of when it is due should not make up the missed dose. Any missing doses should be recorded, and subsequent training of the patient or patient's parent or legal guardian 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.

8.1.1.1 Tablet Formulation

For eligible patients assigned to ≥10 mg doses and who are able to swallow solid oral dosage forms, ponatinib will be supplied by the sponsor as 10 mg (oval-shaped) and 15 mg and 30 mg (round-shaped), white, film-coated tablets.

Patients and their parents or legal guardians should be instructed to take/administer 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.

8.1.1.2 Age-Appropriate Formulation

For eligible patients who are unable to swallow solid oral dosage forms or require doses <10 mg, an AAF of ponatinib will be provided by the sponsor as round-shaped, film-coated mini-tablets filled into an opaque white capsule as 2.5 and 5 mg capsules (ie, minitab capsules).

Patients and their parents or legal guardians should be instructed to take/administer the prescribed number of minitab capsules at approximately the same time each day, continuously throughout the study, and not to take more than the prescribed dose at any time. Minitab capsules should be taken/administered either swallowed whole with water, with or without food, or, if needed, the capsule contents sprinkled in applesauce or yogurt and swallowed. Additional details regarding administration of the AAF are provided in the study/pharmacy manual.

Patients and/or their parents/legal guardians will be administered a questionnaire to assess the palatability of the ponatinib AAF (during the reinduction block only).

8.1.2 Study Treatment Regimen

Phase 1 will determine the RP2D of ponatinib. A rolling 6 design (Skolnik et al. 2008) will be followed for both phase 1 cohort 1 and phase 1 cohort 2 (details are provided in Section 6.1).

In phase 1 cohort 1, pediatric patients received fixed doses of ponatinib based on body weight ranges (tablet formulation only) with chemotherapy (Table 8.b).

In phase 1 cohort 2, patients will also receive fixed doses of ponatinib based on body weight ranges provided in Table 8.a (both tablet formulation or AAF) with chemotherapy (Table 8.b).

Throughout each block of therapy (ie, reinduction, consolidation, and monthly optional continuation) patients should receive the weight-based dose of ponatinib as assigned based on body weight at Day 1 of each block.

Table 8.a Phase 1 Cohort 2 Ponatinib Doses

	Body Weight			
	≥45 kg	**30 kg to <45 kg**	**15 kg to <30 kg**	**5 kg to <15 kg**
Cohort 2 Dose Level 1	15 mg	10 mg	7.5 mg	5 mg
Cohort 2 Dose Level -1	10 mg	7.5 mg	5 mg	2.5 mg

The following chemotherapy treatment regimen is adapted from the ALL R3 study (Parker et al. 2010) with a modified reinduction block by the replacement of mitoxantrone/idarubicin with daunorubicin, use of conventional dexamethasone regimen, and the addition of daily ponatinib to both treatment blocks (Table 8.b). Additional details are provided in Table 8.c.

Table 8.b Phase 1 and Phase 2 Treatment Regimen for the Reinduction and Consolidation Blocks

	Dose	Days/Frequency
Reinduction Block (Weeks 1-4)		
Ponatinib PO	See Table 8.a (cohort 2) for phase 1 dose; RP2D in phase 2	Daily (Days 1-35)
Vincristine IV	1.5 mg/m^2	1, 8, 15, 22
Dexamethasone PO/IV [a]	10 mg/m^2	1-15
PEG-asparaginase IV/IM [b]	2500 IU/m^2	2
Daunorubicin IV	30 mg/m^2	1, 2
Initial IT chemotherapy [c]	See Table 8.c	1
CNS-1/2: IT methotrexate chemotherapy [d]	See Table 8.c	15 and 29
CNS-3: ITT chemotherapy [e]	See Table 8.c	8, 15, 22, and 29
Consolidation Block (Weeks 5-8) [f]		
Ponatinib PO	See Table 8.a (cohort 2) for phase 1 dose; RP2D in phase 2	Daily (Days 1-35)
Dexamethasone PO/IV [a]	6 mg/m^2	1-5
Vincristine IV	1.5 mg/m^2	3
Methotrexate IV [g]	1000 mg/m^2	8
PEG-asparaginase IV/IM [b]	2500 IU/m^2	9
Cyclophosphamide IV	440 mg/m^2	15-19
Etoposide IV	100 mg/m^2	15-19
CNS-1/2: IT methotrexate chemotherapy [d]	See Table 8.c	8
CNS-3: ITT chemotherapy [e]	See Table 8.c	8

ALT: alanine aminotransferase; ANC: absolute neutrophil count; CNS: central nervous system; IM: intramuscularly; IT: intrathecal; ITT: triple intrathecal; IU: international units; IV: intravenously; PEG: polyethylene glycol; PO: by mouth (orally); RP2D: recommended phase 2 dose.
See Table 8.c or Table 5 for additional administration details.
Note: 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] Dexamethasone will be given as 2 divided doses with a maximum daily dose of 40 mg.
[b] In cases where PEG-asparaginase is not available or where patients are allergic to PEG-asparaginase, *Erwinia*-asparaginase can be used as an alternative. If there are supply issues with PEG-asparaginase at the site, the dosing of PEG-asparaginase can occur over a range of ± 4 days.
[c] May include IT methotrexate or ITT chemotherapy. Omit initial IT chemotherapy on Day 1 if patient received IT chemotherapy within 7 days before study enrollment as part of diagnostic lumbar puncture procedure.
[d] IT methotrexate is for CNS-1/2 patients only. Dose is defined by age; see Table 8.c.
[e] ITT chemotherapy is for CNS-3 patients only. Dose is defined by age; see Table 8.c.
[f] To start the consolidation block, the following criteria must be met: ANC ≥750/µL, platelets ≥50,000/µL (untransfused) (van Veen et al. 2010), and toxicity considered to be related to treatment with ponatinib must have resolved to Grade 1 or baseline or to a level considered acceptable by the physician.
[g] Intermediate-dose methotrexate administered IV over 36 hours. The 1000 mg/m^2/dose should be given as a 100 mg/m^2 bolus over 30 minutes followed by 900 mg/m^2 over 35.5 hours. Note: Be certain that the methotrexate infusion is completed in the 36-hour period. See Table 8.c for IV hydration and leucovorin rescue therapy.

Table 8.c Details of Phase 1 and Phase 2 Treatment Regimens for the Reinduction and Consolidation Blocks

Reinduction Block (Weeks 1-4)
Ponatinib: PO on Days 1-35, dose assigned per protocol
Vincristine: IV push over 1 minute or infusion via minibag as per institutional policy Days: 1, 8, 15, and 22 Dose: 1.5 mg/m^2/dose (max 2 mg)
Dexamethasone: PO or IV Days: 1 through 15 Dose: 10 mg/m^2/day, divided BID, ie, 5 mg/m^2/dose BID
PEG-asparaginase: IV over 1 to 2 hours, or IM Day: 2 Dose: 2,500 IU/m^2/dose Patients with an allergic reaction to PEG-asparaginase can be given *Erwinia* asparaginase IM/IV 25,000 IU/m^2/dose on Monday/Wednesday/Friday (or every other day per institutional standard) × up to 6 doses for each dose.
***Erwinia* asparaginase: for patients with an allergic reaction to PEG-asparaginase or in cases where PEG-asparaginase is not available** IM/IV Dose: 25,000 IU/m^2/dose
Daunorubicin: IV over 15 minutes Days: 1 and 2 Dose: 30 mg/m^2
Initial IT chemotherapy: Day 1; may include methotrexate (CNS-1/2), or triple IT (ITT) chemotherapy (CNS-3) (see Appendix G for definitions)
IT methotrexate: for CNS-1/2 patients only Days: 15 and 29 Omit IT methotrexate on Day 1 if patient received IT chemotherapy within 7 days before study enrollment as part of diagnostic lumbar puncture procedure. Dose: Defined by age: Age 1 through 1.99 years: 8 mg Age 2 through 2.99 years: 10 mg Age 3 through 8.99 years: 12 mg Age ≥9 years: 15 mg

Table 8.c Details of Phase 1 and Phase 2 Treatment Regimens for the Reinduction and Consolidation Blocks

ITT chemotherapy: for CNS-3 patients only
Days: 8, 15, 22, and 29
Dose: Defined by age in the following table:

Age (years)	Methotrexate	Hydrocortisone	Cytarabine
1 – 1.99	8 mg	8 mg	16 mg
2 – 2.99	10 mg	10 mg	20 mg
3 – 8.99	12 mg	12 mg	24 mg
≥9	15 mg	15 mg	30 mg

Consolidation Block (Weeks 5-8) [a]

Ponatinib:
PO on Days 1-35, dose assigned per protocol

Dexamethasone:
PO or IV
Days: 1 through 5
Dose: 6 mg/m^2/day, divided BID, ie, 3 mg/m^2/dose BID

Vincristine:
IV push over 1 minute or infusion via minibag as per institutional policy
Day: 3
Dose: 1.5 mg/m^2/dose (max 2 mg)

Intermediate-dose methotrexate:
IV over 36 hours.
Day: 8
Dose: 1000 mg/m^2/dose, given as a 100 mg/m^2 bolus over 30 minutes followed by 900 mg/m^2 over 35.5 hrs.
Note: Be certain that the methotrexate infusion is completed in the 36-hour period.

Suggested hydration and alkalinization:
Start hydration at least 6 hours prior to the start of methotrexate. Hydrate with 5% dextrose in water 1/4 normal saline with 30 mEq $NaHCO_3$/L at 125 mL/m^2/h to achieve a urine specific gravity ≤1.010 and pH between 7 and 8. Ringers lactate maybe used as initial fluid if a bicarbonate-containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 min) may be given to raise the urine pH relatively quickly. A normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout methotrexate infusion after its completion until the last dose of leucovorin has been given.

Leucovorin:
PO/IV
Days: 10 and 11
Dose: 15 mg/m^2/dose every 6 hours beginning 48 hours after the START of methotrexate infusion.
If 48-hour methotrexate level is ≤0.5 µM, do not give more than 2 doses of leucovorin (48 and 54 hours).
If methotrexate level at 48 hours is >0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose PO/IV every 6 hours until methotrexate level is <0.1 µM.
Hold trimethoprim/sulfamethoxazole, any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors, or aspirin-containing medications on the day of intermediate-dose methotrexate infusion and for at least 72 hours after the start of the intermediate-dose methotrexate infusion and until the methotrexate level is ≤0.5 µM.

Table 8.c Details of Phase 1 and Phase 2 Treatment Regimens for the Reinduction and Consolidation Blocks

PEG-asparaginase:
IV over 1 to 2 hours, or IM
Day: 9 or 10, administer 4 hours after completion of Day 8 IV methotrexate
Dose: 2,500 IU/m^2/dose
Patients with an allergic reaction to PEG-asparaginase can be given *Erwinia* asparaginase IM/IV 25,000 IU/m^2/dose on Monday/Wednesday/Friday (or every other day per institutional standard) × up to 6 doses for each dose.

***Erwinia* asparaginase: in case of unavailability of PEG-asparaginase or for patients with an allergic reaction to PEG-asparaginase**
IM/IV
Dose: 25,000 IU/m^2/dose

Cyclophosphamide:
IV over 15-30 minutes.
Days: 15 through 19
Dose: 440 mg/m^2/dose

Etoposide:
IV over 1-2 hours.
Days: 15 through 19
Dose: 100 mg/m^2/dose

IT methotrexate: for CNS-1/2 patients only
Day: 8
Dose: Defined by age:
Age 1 through 1.99 years: 8 mg
Age 2 through 2.99 years: 10 mg
Age 3 through 8.99 years: 12 mg
Age ≥9 years: 15 mg

ITT chemotherapy: for CNS-3 patients only
Day: 8
Dose: Defined by age in the following table:

Age (years)	Methotrexate	Hydrocortisone	Cytarabine
1 – 1.99	8 mg	8 mg	16 mg
2 – 2.99	10 mg	10 mg	20 mg
3 – 8.99	12 mg	12 mg	24 mg
≥9	15 mg	15 mg	30 mg

BID: twice daily; CNS: central nervous system; IM: intramuscularly; IT: intrathecal; ITT: triple intrathecal; IU: international units; IV: intravenously; PEG: polyethylene glycol; PO: by mouth (orally); ULN: upper limit of normal.
Note: 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] To start the consolidation block, the following criteria must be met: ANC ≥750/µL, platelets ≥50,000/µL (untransfused) (van Veen et al. 2010), and toxicity considered to be related to treatment with ponatinib must have resolved to Grade 1 or baseline or to a level considered acceptable by the physician.

Ponatinib will be administered QD as part of the study treatment regimen (Table 8.b). For phase 1 cohort 1, dose level 1 targeted adult exposures achieved at 30 mg QD as determined by simulations from an allometrically scaled adult population PK model. For phase 1 cohort 2, dose level 1 is expected to achieve systemic exposures that approximately match adult exposures after administration of 15 mg QD. Pediatric patients received fixed doses of ponatinib based on weight ranges for phase 1 cohort 1 and will receive fixed doses of ponatinib based on the weight ranges provided in Table 8.a for phase 1 cohort 2. Patients experiencing TEAEs that require a dose reduction will have their ponatinib dose reduced as per Table 8.a.

Patients achieving documented clinical benefit have the option to continue to receive ponatinib monotherapy or ponatinib in combination with maintenance-type chemotherapy regimen (Table 8.d) on investigator decision and with agreement by the sponsor, with the intent to avoid further intensive multiagent chemotherapy in combination with ponatinib. Also, no experimental agent is allowed to be incorporated in the optional continuation ponatinib/ponatinib-containing therapy. If electing the optional continuation therapy, the patient will continue on the same dose he/she was on and tolerated during the consolidation block. If the patient had a dose reduction during consolidation block, subsequent dose re-escalation may only occur to the reintroduction dose if criteria stated in Section 8.4.2.4 are met. Once the RP2D dose is known, and if it is different from the dose the patient is receiving, it will be at the discretion of the investigator to alter the dose of ponatinib. This optional treatment is to allow patients to continue ponatinib therapy until they are able to receive HSCT or other alternative therapy(ies). Once patients discontinue the optional ponatinib/ponatinib-containing therapy, they will have to complete the EOT2 evaluation. At this time, patients may receive further therapy(ies) at the discretion of the investigator.

Patients who complete protocol therapy (reinduction and consolidation block) and EOT1 evaluation, and do not proceed to an optional continuation ponatinib-containing therapy, are considered to have completed protocol therapy. At this time, patients may receive further therapy(ies) at the discretion of the investigator.

Patients who discontinue ponatinib early in the reinduction block or consolidation block will be discontinued from study treatment and proceed to the EOT1 visit. At this time, patients may receive further therapy(ies) at the discretion of the investigator.

Table 8.d Optional Continuation Therapy With Ponatinib: Recommended Combination Regimen Following Consolidation

Therapeutic Agent	Days/Frequency
Ponatinib	Daily
Vincristine	Every 4 weeks
Dexamethasone or prednisone	5 days every 4 weeks
Mercaptopurine	Daily
Methotrexate (PO)	Once a week
Methotrexate (IT)	Once every 3 months

IT: intrathecal; PO: by mouth (orally).

Note: 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.

8.2 Definitions of Dose-limiting Toxicities

DLTs will be graded according to NCI CTCAE Version 5.0 and the causality will be assigned by the investigator. The DLT observation period for each formulation will be up to the first 35 days on treatment in phase 1 unless there are residual hematologic toxicities on Day 35, in which case the patient will be followed for up to an additional 7 days for DLT evaluation.

Events considered DLTs will be defined as any of the following phase 1 events occurring during the first 35 days on treatment (reinduction block) that are assessed by the investigator as **possibly, probably, or definitely related** to ponatinib and must be reported as related:

- Any Grade ≥3 nonhematologic toxicity that occurs after the first dose of ponatinib and is possibly, probably, or definitely related to ponatinib, with the following exceptions:
  - Fever or infection with or without hospitalization.
  - Fatigue and gastrointestinal symptoms (anorexia, vomiting, dehydration, mucositis).
  - Hypofibrinogenemia.
  - Metabolic/laboratory abnormalities, including ALT, that resolve to ≤Grade 2 within 7 days.
- Grade ≥3 elevation of ALT concurrent with an elevation of direct bilirubin >2 × ULN.
- Any Grade 4 pancreatitis, or Grade 3 pancreatitis which does not resolve within 7 days.
- Any Grade 4 skin rash, or Grade 3 skin rash which does not resolve within 7 days.
- Hematologic toxicities: Failure to recover a peripheral ANC ≥0.5 × 10^9/L and a platelet count ≥50 × 10^9/L due to documented BM hypoplasia (cellularity <10% to 20%) within 42 days

after the beginning of systemic chemotherapy without evidence of active disease by BM evaluation or active infection.

- Any delay or interruption of therapy of ≥4 weeks due to suspected treatment-related toxicity unless otherwise specified.

Patients will be evaluated for DLTs in phase 1 during the reinduction block. Patients who meet DLT criteria will discontinue study treatment and proceed to the EOT1 visit.

When there is ambiguity about whether an AE is related to the underlying disease or the chemotherapy backbone, as opposed to ponatinib, the most conservative approach will be taken and the AE will be considered as study drug–related.

8.3 Criteria for Beginning a Consolidation Block or Optional Continuation Therapy

Treatment with ponatinib will use a block length of 35 days (29 days of study treatment followed by a rest period from chemotherapy for a minimum of 6 days). Ponatinib will be administered QD during the treatment block including the rest period. For a new treatment block to begin, the patient must meet the following criteria:

- ANC must be ≥750/µL.
- Platelet count must be ≥50,000/µL (van Veen et al. 2010).
- For therapy to resume, toxicity considered to be related to treatment with ponatinib must have resolved to Grade 1 or baseline or to a level considered acceptable by the physician. The physician may consult with the sponsor's medical monitor to determine levels that are acceptable based on the overall clinical status of the patient to continue therapy.

If the patient does not meet the above-cited criteria for retreatment, initiation of the next treatment block should be delayed for 1 week. During a period of treatment delay, patients should be closely monitored for recovery and resumption of treatment. Should the start of consolidation need to be delayed for more than 3 weeks because of incomplete recovery from treatment-related toxicity, the dose will be reduced by 1 dose level when treatment resumes. If further treatment is delayed for more than 3 weeks at the reduced dose level and further reductions are not permitted per the guidelines (see Section 8.4) then the patient will discontinue study treatment and proceed to the EOT1 visit.

8.4 Dose Modification Guidelines for Safety

8.4.1 Early Safety Stopping Rules

Due to concerns regarding vaso-occlusive events and pancreatitis resulting from the combination of ponatinib with the multiagent chemotherapy backbone, the sponsor may suspend enrollment for the following events:

- If ≥4 patients in the first 15 patients accrued develop Grade ≥3 veno-occlusive event regardless of the presence or absence of a central vascular access device.

- Any major adverse cardiac event (MACE) including but not limited to:
  - Any grade arteriothrombotic event.
  - Any grade cardiovascular event.
- If ≥3 patients in the first 15 patients accrued develop Grade ≥3 pancreatitis.

A recommendation to reopen enrollment might be made if causes other than therapy are thought to be the primary cause of the event(s). Any decision to restart enrollment after the stopping rules have been met will require prior approval of a substantial amendment by the applicable Health Authorities, such as the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor may suspend further enrollment if more than one patient dies for reasons other than disease progression.

8.4.2 Dose Reduction for Treatment-related Toxicity

8.4.2.1 Nonhematologic Treatment-Related Toxicity: Ponatinib

Dose reduction guidelines for ponatinib are summarized in Table 8.e, and AEs should be graded according to NCI CTCAE Version 5.0.

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 must be communicated with the medical monitor/designee, ideally prior to implementation but no later than 72 hours, 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 8.4.2.4.

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 from the toxicity or toxicities in question to Grade 1 or to baseline values.

Doses may be interrupted for study drug–related toxicities for up to 3 weeks; longer interruptions need to be discussed with the sponsor's medical monitor/designee.

See Section 8.4.2.4 for dose re-escalation guidelines after the resolution of adverse drug reactions.

Table 8.e Dose Modifications for Nonhematologic Treatment-Related Toxicity: Ponatinib

General Toxicities	**Modification**
Grade 1 or transient Grade 2	No dose modification
Grade 2	Dose modification per investigator's discretion
Grade 3 or 4	Occurrence [a] at initial dose: Hold until event is Grade 1, or has returned to baseline Resume at dose level -1 Occurrence [a] at dose level -1: Discontinue ponatinib
Pancreatitis and Elevation of Lipase	**Modification [c]**
Serum lipase >1 to 1.5 × ULN	Consider interrupting ponatinib until resolution, then resume at same dose
Serum lipase >1.5 to 2 × ULN, asymptomatic serum lipase 2 to 5 × ULN, or asymptomatic radiologic pancreatitis	Interrupt ponatinib until Grade 1 (<1.5 × ULN) or baseline, then resume at next lower dose
Symptomatic serum lipase >2 to 5 × ULN, symptomatic Grade 3 pancreatitis, or asymptomatic serum lipase >5 × ULN	Interrupt ponatinib until complete resolution of symptoms and after recovery of lipase elevation to Grade 1 or baseline, then resume at next lower dose
Symptomatic pancreatitis and serum lipase >5 × ULN	Discontinue ponatinib
Hepatic Toxicity	**Modification**
Grade ≥3 elevation of ALT	Occurrence [a] at initial dose: Hold until event is Grade 1, or has returned to baseline Resume at dose level -1 Occurrence [a] at dose level -1: Hold until event is Grade 1, or has returned to baseline: Discontinue ponatinib
Grade ≥3 elevation of ALT concurrent with an elevation of direct bilirubin ≥2 mg/dL	Discontinue ponatinib
Direct bilirubin >2 mg/dL	Hold until <1.5 × ULN Resume at dose level 1 (full dose) Occurrence [a] at dose level 1: Wait until <1.5 × ULN Resume at dose level -1 Occurrence [a] at level -1: Discontinue ponatinib
LVEF/CHF [d]	**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 dose level -1 Occurrence [a] at dose level -1: Discontinue ponatinib

Table 8.e Dose Modifications for Nonhematologic Treatment-Related Toxicity: Ponatinib

Grade 3	Discontinue ponatinib
Grade 4	Discontinue ponatinib
Skin Rash	**Modification**
Grade 1	No dose modification
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 previous dose: Hold until event is Grade 1, or has returned to baseline Resume at dose level -1 Occurrence [b] at dose level -1: Discontinue ponatinib
Skin Rash	**Modification**
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 dose level -1 Occurrence [a] at dose level -1: Discontinue ponatinib
Grade 4	Discontinue ponatinib

AE: adverse event; ALT: alanine aminotransferase; CHF: congestive heart failure; ECHO: echocardiogram; LVEF: left ventricular ejection fraction; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; 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] Also see asparaginase guidance in Section 8.4.3.1; if a patient has pancreatitis, discontinue asparaginase.

[d] See Section 8.4.3.2 for dose modification guidance for daunorubicin-related cardiac toxicity.

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

Patients discontinuing ponatinib will discontinue study treatment and proceed to the EOT visit.

8.4.2.1.1 Peripheral Neuropathy

Peripheral neuropathy will be closely monitored during reinduction and toxicities graded. A complete neurologic examination should be documented before the start of therapy, including a minimum assessment of cranial nerve function; deep tendon reflexes of the brachioradialis, patellar, and Achilles tendons; balance; gait; and general sensation. All dose modifications should be based on the worst preceding toxicity.

Since vincristine can also cause peripheral neuropathy, dose modification will be performed as follows in Table 8.f. Modifications should be made any time peripheral neuropathy is noted.

Table 8.f Dose Modifications for Peripheral Neuropathy and Neuropathic Pain Per Modified "Balis" Pediatric Scale

Grade 1 with pain [a] or Grade 2	Hold ponatinib and vincristine until neuropathy has resolved to Grade 1. When symptoms subside, restart ponatinib and vincristine at full dose.
Grade 2 with pain [a] or Grade 3	Hold ponatinib and vincristine until neuropathy has resolved to ≤Grade 2. When symptoms subside, restart ponatinib at dose level -1 and vincristine at full dose.
Grade 4	Discontinue ponatinib and vincristine.

[a] Pain uncontrolled by nonsteroidal anti-inflammatory drugs or narcotics.
See text below for Modified "Balis" Pediatric Scale.

Modified ("Balis") Pediatric Scale of Peripheral Neuropathies

Peripheral Motor Neuropathy

- Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.
- Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.
- Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.
- Grade 4: Paralysis.

Peripheral Sensory Neuropathy

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.
- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).

8.4.2.2 Dose Modifications for Arterial Occlusive Events and Venous Thrombotic/Embolic Events: Ponatinib

If an AOE or VTE occurs, treatment should be interrupted or discontinued. 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. The sponsor will periodically look at the safety data and inform the site if any AE qualifies for AOEs/VTEs as per these criteria.

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

8.4.2.2.1 Arterial Occlusive Events

In patients suspected of developing any serious or clinically significant AOE requiring urgent intervention or hospitalization AOE, ponatinib should be immediately interrupted, and may be discontinued at the discretion of the treating physician.

Patients should be discontinued from ponatinib in the event of MI, unstable angina, cerebrovascular accident, transient ischemic attack (TIA), or revascularization procedures. For all other AOEs, dose modification guidelines are outlined in Table 8.g.

Table 8.g Dose Modifications for Arterial Occlusive Events: 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 initial dose: 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: Discontinue ponatinib
Grade 3	Discontinue ponatinib
Grade 4	Discontinue ponatinib

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.

8.4.2.2.2 Venous Thrombotic/Embolic Events

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

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

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

VTEs	
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 dose level -1
	Occurrence [a] at dose level -1: Discontinue ponatinib
Grade 3	Occurrence [a] at any dose level: Discontinue ponatinib
Grade 4	Discontinue ponatinib

VTE: venous thrombotic/embolic event.

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

8.4.2.3 Hypothyroidism

If a patient develops evidence of hypothyroidism, a consultation with a pediatric endocrinologist should be initiated for thorough evaluation, follow-up plan and assessment for replacement therapy.

8.4.2.4 Dose Re-escalation After Resolution of Adverse Drug Reactions

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 the following criteria is met:

- All Grade ≥2 and Grade 3 nonhematologic toxicities have recovered to Grade 1 or baseline.

Patients may receive a dose escalation up to the starting dose level if the above criteria continue to be met. In no circumstances should a patient receive a ponatinib dose higher than their starting dose level.

Note: Patients with Grade ≥3 left ventricular dysfunction, congestive heart failure (CHF), arterial occlusion, and Grade ≥2 pancreatitis are not eligible for dose re-escalation after resolution of their symptoms.

8.4.2.5 Criteria for Discontinuation of Ponatinib

Grade 4 nonhematologic toxicities will in general require that treatment with ponatinib be permanently discontinued. If, in the opinion of the investigator and the project clinician, it is in the patient's best interest to continue treatment with ponatinib, then the dose of ponatinib should be reduced to dose level -1 if the patient is receiving the first dose level after recovery of the toxicity or toxicities in question to Grade 1 or to baseline values.

8.4.3 Chemotherapy Backbone

It is the investigator's responsibility to refer to the study/pharmacy manual or the most current individual package insert (local approved label or relevant summary(ies) of product characteristics [SmPC]) for specific information related to the chemotherapy backbone side effects, preparation, reconstitution, dispensation, storage, and handling. Local approved labels or Section 4.8 of the relevant SmPC will serve as the reference safety information (RSI) for determining expectedness of serious adverse reactions (SARs) that occur with these chemotherapy agents. The following are general practice guidelines.

8.4.3.1 Asparaginase (Polyethylene Glycol-Asparaginase or Erwinia *Asparaginase)-Related Toxicities)*

8.4.3.1.1 For Allergy

Local allergic reactions (inflammation at injection site or swelling): Continue asparaginase administration in the presence of Grade 1 allergy (transient flushing or rash; drug fever <38ºC). Note: These recommendations only apply when asparaginase is administered intramuscularly (IM).

Systemic allergic reactions: Discontinuation may be considered for severe Grade 2 or higher allergic reactions as defined by NCI CTCAE version 5.0.

Note: Premedication with antihistamines to decrease the risk of overt allergy symptoms is strongly discouraged since antihistamine use may mask the appearance of systemic allergy. Systemic allergy is frequently associated with the presence of asparaginase-neutralizing antibodies, which render asparaginase therapy ineffective. In the event of severe systemic or recurrent local allergic reaction, *Erwinia* asparaginase should be substituted.

Anaphylaxis: Discontinue polyethylene glycol (PEG)-asparaginase if the patient develops Grade 3 anaphylaxis as defined by NCI CTCAE version 5.0 (symptomatic bronchospasm, with or without urticaria, parenteral intervention indicated; allergy-related edema/angioedema; hypotension). If this occurs, *Erwinia* asparaginase should be substituted.

The FDA initially approved *Erwinia* asparaginase for use following allergy to PEG-asparaginase, at a dose of *Erwinia* asparaginase 25,000 IU/m^2 × 6 doses IM on a Monday/Wednesday/Friday schedule substituted for a single dose of PEG-asparaginase. In December 2014, the FDA expanded its approval to include intravenous (IV) as well as IM administration.

If a patient develops a Grade 3 or higher anaphylaxis to *Erwinia* asparaginase, discontinue future asparaginase therapy. Consider discontinuation for severe Grade 2 or higher allergic reactions.

In the event that a PEG-asparaginase infusion is discontinued for an allergic reaction, regardless of amount received, substitution with *Erwinia* asparaginase should begin approximately 48 hours after PEG-asparaginase has been discontinued and preferably to coincide with the recommended Monday/Wednesday/Friday administration schedule previously detailed in patients who are clinically stable. Up to 6 doses of *Erwinia* asparaginase may be administered, as tolerated, to replace the incomplete IV PEG-asparaginase dose. Of note, *Erwinia* asparaginase is

recommended only for PEG-asparaginase hypersensitivity reactions and not for pancreatitis, hepatitis, coagulation abnormalities, or other nonhypersensitivity toxicities associated with PEG-asparaginase. To best suit the needs of each individual patient, additional modifications to these recommendations may be made at the discretion of the treating physician.

Treating physicians may elect to discontinue PEG-asparaginase and switch to *Erwinia* asparaginase, at their discretion, on the basis of laboratory evidence of silent inactivation of asparaginase activity in the absence of clinical symptoms of hypersensitivity.

8.4.3.1.2 For Coagulopathy

If the patient is symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement (with fresh frozen plasma, cryoprecipitate, or factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.

8.4.3.1.3 For Hyperbilirubinemia

Asparaginase may need to be withheld in patients with elevated direct bilirubin, since asparaginase has been associated with hepatic toxicity. No specific guidelines are available.

8.4.3.1.4 For Hyperglycemia

Do not modify dose. Treat hyperglycemia as medically indicated.

8.4.3.1.5 For Hyperlipidemia

Do not modify dose. Treat hyperlipidemia as medically indicated.

8.4.3.1.6 For Ketoacidosis

Hold asparaginase until the blood glucose level is regulated with insulin.

8.4.3.1.7 For Pancreatitis

Discontinue asparaginase in the presence of Grade 3 or 4 pancreatitis. In the case of asymptomatic Grade 2 pancreatitis (enzyme elevation or radiologic findings only), asparaginase should be held until symptoms and signs subside and amylase/lipase levels return to normal and then resumed. Grade 3 or 4 pancreatitis is a contraindication to additional asparaginase administration.

8.4.3.1.8 For Thrombosis

Withhold asparaginase until resolved, and treat with appropriate antithrombotic therapy, as indicated. Upon resolution of symptoms, consider resuming asparaginase while continuing low-molecular-weight heparin or antithrombotic therapy.

Do not withhold dose for abnormal laboratory findings without a clinical correlate. For significant thrombosis, not central line–related, consider evaluation for inherited predisposition to thrombosis.

8.4.3.1.9 For Central Nervous System Events

For CNS events (bleed, thrombosis, or infarction): Hold asparaginase. Treat with fresh frozen plasma, factors, or anticoagulation therapy as appropriate. Resume at full dose when all symptoms have resolved (and there is evidence of recanalization, in the case of thrombosis by computerized tomography [CT]/ magnetic resonance imaging [MRI]). Consider evaluation for inherited predisposition to thrombosis.

8.4.3.2 Daunorubicin (Anthracycline)-Related Toxicities

8.4.3.2.1 For Cardiac Toxicity

Discontinue for clinical or echocardiographic evidence of cardiomyopathy (shortening fraction <27% or ejection fraction <50%) or Grade 3 or 4 left ventricular systolic dysfunction per NCI CTCAE Version 5.0.

8.4.3.2.2 For Hyperbilirubinemia

The recommended doxorubicin dose reduction algorithm for hyperbilirubinemia is presented in Table 8.i.

Table 8.i Daunorubicin Dose Reduction Algorithm for Hyperbilirubinemia

Direct Bilirubin	% Dose Reduction
<1.2 mg/dL	0% (full dose)
1.2-3.0 mg/dL	50%
3.1-5.0 mg/dL	75%
>5.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved

8.4.3.2.3 For Extravasation

In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines.

8.4.3.3 Intrathecal Methotrexate/Triple Intrathecal Chemotherapy-Related Toxicities

8.4.3.3.1 For Systemic Toxicity

The dosage for IT methotrexate will not be reduced for systemic toxicity (eg, myelosuppression, mucositis). Instead, leucovorin may be used at a dose of 5 mg/m^2/dose every 12 hours × 2 doses, beginning 48 hours after the IT chemotherapy has been delivered. This may reduce the risk of worsening already existent myelosuppression (ANC <0.5 × 10^9/L) or mucositis. Do not administer leucovorin solely to prevent myelosuppression.

8.4.3.3.2 For Acute Neurotoxicity

Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies. These toxicities are poorly understood, and currently it is impossible to predict who will suffer these complications. In addition, there are no data clearly linking the occurrence of an acute neurotoxic event with an increased risk of long-term neurocognitive dysfunction, nor do the changes present on MRI at the time of an acute event clearly correlate with or predict outcome.

The following guidelines are offered for consideration following an acute event, but it must be recognized that there are little data to support these approaches or any others. Thus, the treating physician must evaluate the patient and, with the family, make the best possible decision with respect to the relative risk and benefit of continued therapy.

Following an acute neurotoxic event, a history and physical examination should guide the differential diagnosis. A neurology consult may be of value and should be considered. Seizures and other transient events may be linked to fever, infection, encephalitis, meningitis, hypertension, electrolyte disturbance, hypoglycemia, trauma, intracranial hemorrhage or thrombosis, narcotic withdrawal, illicit drug use, or other causes in addition to the direct side effects of chemotherapy. Appropriate laboratory studies may include, but are not limited to, blood cultures, a complete blood cell count, electrolytes (eg, calcium, magnesium, and phosphorus), glucose levels, renal and liver function studies, and/or an examination of the cerebrospinal fluid (CSF). Imaging studies may include a CT scan and/or an MRI. The CT is commonly normal in the absence of stroke, but if calcifications are present, this finding may be indicative of a more severe mineralizing leukoencephalopathy. MRI abnormalities may be pronounced but transient. Posterior reversible encephalopathy may be present on MRI with extensive diffusion abnormalities, but these do not appear to correlate with subsequent demyelination or gliosis. Additional studies, including magnetic resonance angiography and/or venogram should be considered, if clinically indicated (eg, if there are focal deficits).

Many acute events, seizures or episodes of transient hemiparesis, are temporally related to the administration of IT chemotherapy, commonly occurring 9 to 11 days postadministration. For patients who return to their "pre-event" status, without residual deficits of physical or neurologic examination, there are few data to support or guide therapeutic interventions. It is reasonable to hold the next dose of IT chemotherapy, or, substitute IT cytarabine for 1 dose of IT methotrexate, or triple IT chemotherapy. It is also reasonable to include leucovorin rescue at a dose of 5 mg/m^2 every 12 hours × 2 doses beginning 48 hours after the lumbar puncture. This pattern of rescue was associated with a clear diminution in the incidence of acute neurotoxicity in 1 case series. There have been questions about potential interference of leucovorin with the efficacy of the IT methotrexate, but there are little data to support or refute this position. Moreover, the administration 48 hours later would minimize any potential interference. If the event does not recur, resumption of standard therapy should be considered, following 1 modified or omitted IT dose. In the face of multiple recurrent events, or evidence of progressive encephalopathy, another evaluation is warranted, and the treating physician may consider a more prolonged or definitive change in therapy. These decisions are extremely difficult and may hinge

on an individual's view of the importance of quality of life versus an increase in the risk of relapse. Since the greatest impact of CNS prophylaxis occurs early in therapy, the timing of these events may also influence clinical decisions. Cranial radiation has been suggested as an alternative to continued IT chemotherapy though much of the literature on long-term neurocognitive dysfunction supports a more deleterious effect from cranial radiation therapy than IT chemotherapy. Cranial radiation is not allowed during protocol therapy.

The use of dextromethorphan has been suggested as a neuroprotectant, capable of preventing *N*-methyl-d-aspartate (NMDA)-mediated neurotoxicity without prohibitive toxicity. Low-dose therapy has been recommended, in part, based on data suggesting that dextromethorphan is concentrated in brain relative to serum. However, the literature on the use of dextromethorphan supports a tight dose-response relationship, with the likelihood of sparing an initially unaffected area, following ischemic damage, linked to dose, in both clinical trials and animal models of CNS ischemia. At doses thought to be therapeutic, side effects have included nystagmus, nausea and vomiting, distorted vision, ataxia, and dizziness. In addition, Hollander et al have raised concerns about the potential deleterious effects of long-term NMDA receptor blockade on memory because hippocampal long-term potentiation is dependent on the activation of the NMDA receptor (Hollander et al. 1994). Thus, in the absence of a clinical trial there are few data to support the addition of dextromethorphan.

8.4.3.3.3 For Hydrocephalus, Microcephaly, or Known Abnormality of Cerebrospinal Fluid Flow Precluding Intrathecal Chemotherapy via Lumbar Puncture

Intraventricular chemotherapy via Ommaya catheter may be used in place of IT chemotherapy delivered by lumbar puncture. IT chemotherapy should be given according to the same schedule, but at **50% of the corresponding age-based doses** that would be given by lumbar puncture.

NOTE: Obstruction to CSF flow may be a contraindication to IT and/or intraventricular therapy.

8.4.3.3.4 For Viral, Bacterial, or Fungal Meningitis

Omit until resolved.

8.4.3.4 Dexamethasone-Related Toxicities

8.4.3.4.1 For Hypertension

Dose should not be reduced. Sodium restriction and antihypertensives should be employed in an effort to control hypertension. Avoid calcium channel blockers due to their potential prohemorrhagic effect.

8.4.3.4.2 For Hyperglycemia

Dose should not be reduced for hyperglycemia. Rather, insulin therapy should be employed to control the blood glucose level.

8.4.3.4.3 For Pancreatitis

Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis.

8.4.3.4.4 For Osteonecrosis

Do not modify corticosteroid therapy for osteonecrosis (NCI CTCAE Version 5.0 term: avascular necrosis).

8.4.3.4.5 For Varicella

Steroids should be held during active infection unless being taken as per protocol therapy guidelines. Do not hold during incubation period following exposure.

8.4.3.4.6 For Severe Infection

Do not hold or discontinue steroids without serious consideration, as this is a critical period in the treatment of ALL.

8.4.3.4.7 For Severe Psychosis

Dexamethasone dose may be reduced by 50% for severe psychosis. If symptoms persist, switch to prednisone.

8.4.3.5 Vincristine-Related Toxicities

In this protocol, it may be difficult to determine if peripheral neuropathy is due to vincristine or ponatinib. Both agents can cause peripheral neuropathy, and there is some overlap in their presentation. Ponatinib is commonly associated with painful sensory peripheral neuropathy. Vincristine neuropathy, in contrast, is commonly associated with motor or mixed neuropathy, including distal extremity weakness.

8.4.3.5.1 For Severe Neuropathic Pain (Grade 3 or Greater)

Please use "Balis" Scale for grading neuropathy (see Section 8.4.2.1.1).

Hold dose(s). When symptoms subside, resume at 50% previous calculated vincristine dose (maximum dose: 1 mg), then escalate to full dose as tolerated. Note: Neuropathic pain can be not only severe but also difficult to treat. However, because vincristine is an important component of curative therapy and most neuropathies are ultimately reversible, vincristine therapy may be given at full dose at investigator's discretion. Severe peripheral neuropathies, with or without a family history, might suggest the need for a molecular diagnostic evaluation to rule out Charcot-Marie-Tooth disease (CMT), type 1A or hereditary neuropathy with liability to pressure palsies. Drugs such as gabapentin may be of value.

8.4.3.5.2 For Vocal Cord Paralysis

Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated. See above for comment on CMT.

8.4.3.5.3 For Foot Drop or Paresis

Should be ≥Grade 3 to consider holding or decreasing dose. These toxicities are largely reversible but over months to years. Accordingly, holding doses of vincristine and/or lowering the dose may not result in rapid resolution of symptoms and may compromise cure. See above for comment on CMT. Physical therapy may be beneficial to maintain range of motion and provide ankle foot orthosis and other forms of support. Drugs such as gabapentin may be of value.

8.4.3.5.4 For Jaw Pain

Treat with analgesics; do not modify vincristine dose.

8.4.3.5.5 For Hyperbilirubinemia

The recommended vincristine dose reduction algorithm for hyperbilirubinemia is presented in Table 8.j. See also Table 8.e for modifications of ponatinib for hepatic toxicity.

Table 8.j Vincristine Dose Reduction Algorithm for Hyperbilirubinemia

Direct Bilirubin	Dose Reduction
<3.1 mg/dL	Full dose (maximum dose: 2 mg)
3.1-5.0 mg/dL	50% of calculated dose (maximum dose: 1 mg)
5.1-6.0 mg/dL	75% of calculated dose (maximum dose: 0.5 mg)
>6.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

8.4.3.5.6 For Constipation, Ileus (≥Grade 3), or Typhlitis

Hold dose(s); institute aggressive regimen to treat constipation if present. When symptoms abate, resume at 50% of calculated dose (maximum dose: 1 mg) and escalate to full dose as tolerated.

8.4.3.5.7 For Extravasation

In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines.

8.4.3.6 Etoposide (VP-16)

8.4.3.6.1 For Allergic Reaction

Premedicate with diphenhydramine (1-2 mg/kg slow IV push, maximum dose is 50 mg). If symptoms persist, add hydrocortisone 100-300 mg/m^2. Continue to use premedication before etoposide in future. Also consider substituting an equimolar amount of etoposide phosphate, in the face of significant allergy and/or hypotension. Etoposide phosphate is a water-soluble prodrug that does not contain polysorbate 80 and PEG, the solubilizing agent in etoposide that may induce allergic reactions and hypotension. Etoposide phosphate is rapidly converted to etoposide in vivo and provides total drug exposure that is statistically indistinguishable from that measured for etoposide at equimolar doses.

8.4.3.6.2 For Hypotension

If diastolic or systolic blood pressure falls 20 mm Hg during infusion, reduce infusion rate by 50%. Start a simultaneous infusion of normal saline (NS) 10 mL/kg if blood pressure fails to recover or falls further. Stop infusion if blood pressure does not recover, continue NS. If the patient has had any episode of hypotension, prehydrate with 0.9% sodium chloride at 10 mL/kg/h for 2 hours prior to any subsequent infusion.

8.4.3.6.3 For Renal Insufficiency

If renal function decreases, adjust etoposide as follows: creatinine clearance (CrCl) 10-50 mL/min/1.73 m^2, decrease dose by 25%; if CrCl <10 mL/min/1.73 m^2, decrease dose by 50%.

8.4.3.6.4 For Hyperbilirubinemia

If direct bilirubin is >2 mg/dL, decrease dose by 50%. If direct bilirubin is >5 mg/dL, hold etoposide.

8.4.3.7 Intermediate-Dose Methotrexate Infusion Guidelines and Dose Modifications for Toxicity

When IT therapy and intermediate-dose methotrexate are scheduled for the same day, it is strongly recommended to deliver the IT therapy within 6 hours of beginning of the IV methotrexate infusion (hour -6 to +6, with 0 being the start of the methotrexate bolus).

Hold trimethoprim/sulfamethoxazole, any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of intermediate-dose methotrexate infusion and for at least 72 hours after the start of the intermediate-dose methotrexate infusion and until the methotrexate level is less than 0.5 μM for intermediate-dose methotrexate. *In the presence of delayed clearance continue to hold these medications until methotrexate level is less than 0.1 μM.*

Recommended prehydration: to start at least 6 hours prior to commencement of IV methotrexate. **Fluid:** 5% dextrose in water 1/4 NS with 30 to 50 mEq $NaHCO_3$/L at

125 mL/m^2/hour. Ringers lactate may be used as the initial fluid if a bicarbonate-containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity ≤1.010 and pH between 7 and 8. A bicarbonate bolus (25 mEq/m^2 over 15 min) may be given to raise the urine pH relatively quickly; a NS bolus may also be helpful in facilitating hydration.

Hour 0: Methotrexate 100 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by methotrexate 900 mg/m^2 given by continuous IV infusion over 35.5 hours. Be certain that the intermediate-dose methotrexate infusion is completed in the 36-hour period. **Note, even if the infusion is not complete at this time point, it must be stopped.**

Recommended posthydration: Continue hydration using 5% dextrose in water 1/4 NS with 30-50 mEq $NaHCO_3$/L at 125 mL/m^2/hour (3 L/m^2/day) throughout intermediate-dose methotrexate infusion until the last dose of leucovorin has been given. In patients with delayed methotrexate clearance, continue hydration until the plasma methotrexate concentration is below 0.1 µM.

Leucovorin rescue: 15 mg/m^2 PO/IV at 48 and 54 hours after the start of the methotrexate infusion. If 48-hour methotrexate level is ≤0.5 µM, then only 2 doses of leucovorin are administered (at 48 and 54 hours). If methotrexate level at 48 hours is >0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose PO/IV every 6 hours until methotrexate levels are <0.1 µM.

Hour 48: Check plasma methotrexate level at 48 hours after start of the methotrexate infusion. If the level is ≤0.5 µM, then do not give more than 2 doses of leucovorin (48 and 54 hours). If methotrexate level at 48 hours is >0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose PO/IV every 6 hours until methotrexate levels are <0.1 µM.

For methotrexate levels that exceed these expected values, modify the rescue regimen as noted below and increase hydration to 200 mL/m^2/h. Monitor urine pH to assure a value ≥7.0 and monitor urine output to determine if volume is ≥80% of the fluid intake, measured every 4 hours. If serum creatinine rises significantly, at any time point (>100% in 24 hours), assure appropriate urine pH and urine volume as above and consider glucarpidase. If urine output fails to continue at 80% of the fluid intake, consider furosemide or acetazolamide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G2) (Table 8.k).

Table 8.k Methotrexate Dose Reduction Algorithm for Toxicity

48 h methotrexate level	Leucovorin Rescue
≤0.5 µM	Continue 15 mg/m^2 IV/PO q 6 hours for 2 doses.
0.5 – 1 µM	Increase to 15 mg/m^2 q 6 hours until methotrexate level <0.1 µM (draw q 6-24 hours).
1 – 5 µM	Increase to 15 mg/m^2 q 3 hours until methotrexate level <0.1 µM (draw q 6-24 hours).
5 – 10 µM	Increase to 100 mg/m^2 q 6 hours until methotrexate level <0.1 µM (draw q 6-24 hours).
>10 µM	Increase to 1000 mg/m^2 q 6 hours until methotrexate level <0.1 µM (draw q 6-24 hours). Consider glucarpidase.

IV: intravenous; PO: by mouth (orally); q: every.

8.4.3.7.1 For Nephrotoxicity

Postpone course if pretreatment (methotrexate) serum creatinine is >1.5 × baseline or GFR CrCl <65 mL/minute/1.73m^2. If there is a rising creatinine (>100% in 24 hours) or the 48-hour methotrexate level is >10 µ/L consider using glucarpidase. If renal function does not recover, omit methotrexate. Do not give intermediate-dose methotrexate to a patient with this degree or renal impairment, assuming that prolonged excretion can be managed with glucarpidase.

NOTE: For patients who have markedly delayed methotrexate clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G2, Voraxaze). To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at 855-786-7292. Additional information can be found at btgplc.com/products/specialty-pharmaceuticals/voraxaze regarding product availability through ASD Healthcare, Cardinal, and McKesson. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300-046-774 (local) or medicalinformationAUS@hospira.com. Patients requiring glucarpidase rescue will remain on study.

Stop leucovorin 2 hours before administering glucarpidase as it is a competitive substrate and may compete with methotrexate for glucarpidase binding sites.

Dose of glucarpidase: 50 units/kg administered by IV bolus over 5 minutes. Reconstitute each vial with 1 mL sodium chloride 0.9% (do not further dilute). Each vial contains 1000 units/mL (after reconstitution) and round dose up to vial size. No further dose is required.

Maintaining alkalinization of urine with sodium bicarbonate is essential to maintain urinary pH >7.

It is essential that patients are NOT co-prescribed the following medicines which reduce methotrexate excretion: nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, ciprofloxacin, co-trimoxazole, penicillin, probenecid, omeprazole.

Two hours after administration of glucarpidase, leucovorin should be administered at a dose of 250 mg/m^2 every 6 hours by IV bolus (maximum rate: 160 mg/min) for up to 48 hours and then

decreased based on plasma methotrexate concentrations to 15 mg/m^2 IV or PO every 6 hours until the plasma methotrexate concentration is <0.2 μM.

8.4.3.7.2 For Liver dysfunction

Samples for the determination of ALT value must be drawn within 72 hours, PRIOR to a course of IV methotrexate. Blood samples for ALT should not be drawn following the start of methotrexate infusions as methotrexate causes significant short-term elevation in ALT levels.

Hold IV methotrexate for direct hyperbilirubinemia of >2.0 mg/dL.

8.4.3.7.3 For Mucositis

For Grade 3-4 mucositis, withhold IV methotrexate until resolved.

8.4.3.8 Cyclophosphamide

8.4.3.8.1 For Hematuria

Omit in the presence of macroscopic hematuria. If there is a history of previous significant hematuria, hydrate before cyclophosphamide until specific gravity is <1.010 and hydrate at 125 mL/m^2/h for 24 hours after dose. Monitor for adequate urine output as per institution guidelines. Give IV mesna at a total dose that is 60% of the cyclophosphamide dose divided to 3 doses (eg, if the cyclophosphamide dose is 1000 mg/m^2, the total mesna dose is 600 mg/m^2 or 200 mg/m^2/dose). Give the first mesna dose 15 minutes before or at the same time as the cyclophosphamide dose and repeat 4 and 8 hours after the start of cyclophosphamide. This total daily dose of mesna can also be administered as IV continuous infusion. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of cyclophosphamide infusion.

8.4.3.8.2 For Renal Dysfunction

If CrCl or radioisotope GFR is <10 mL/min/1.73m^2, reduce dose of cyclophosphamide by 50%. Prior to dose adjustment of cyclophosphamide, the CrCl should be repeated with good hydration.

8.4.4 Supportive Care

Best supportive care and treatment will be given as appropriate to each patient (antiemetics, antibiotics, transfusions, oxygen therapy, nutritional support, palliative treatment for pain or cough, etc.). Patients may experience profound myelosuppression and immune suppression during this time. Parents/legal guardians must also be made aware that patients may experience very rapid clinical deterioration. This suggests the need for a supportive care network that can recognize and respond to sudden changes in a patient's condition.

Hospitalization is strongly recommended until the absolute phagocyte count (sum of the neutrophils, bands, and monocytes) is rising for 2 successive days, and the patient is afebrile and clinically stable. An additional discharge criterion of an ANC of at least 200/μL is also suggested.

Aggressive supportive care improves outcome. The following guidelines are intended to give general health direction for optimal patient care and to encourage uniformity in the treatment of this patient population. Notify the study clinician (or designee) of any unexpected or unusually severe complications.

8.4.4.1 Concurrent Therapy

8.4.4.1.1 Chemotherapy or Investigational Therapy

Patients must not receive any non-protocol chemotherapy, investigational therapy, or immune modulating agents.

8.4.4.1.2 Cranial Irradiation for Central Nervous System Disease

Cranial irradiation for CNS disease is NOT allowed during protocol therapy.

8.4.4.1.3 Radiotherapy to Chloroma

Radiotherapy for chloroma is NOT allowed.

8.4.4.1.4 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes, and general supportive care are to be used as necessary.

8.4.4.1.5 Hydroxyurea

Patients may have received hydroxyurea to keep WBC count below 50,000/μL prior to beginning protocol therapy, but hydroxyurea must be discontinued 24 hours prior to starting systemic protocol therapy.

8.4.4.1.6 Cardiac Protectants

Patients can receive cardiac protectants such as dexrazoxane while treated on this protocol per treating physician's decision.

8.4.4.1.7 Alternative Medication

Use of alternative medications (eg, herbal or botanical for anticancer purposes) is not permitted during the entire study period.

8.4.4.2 Blood Products

Investigators should follow institutional guidelines regarding the administration of blood products.

8.4.4.3 Infection Control

8.4.4.3.1 Pneumocystis Prophylaxis

All patients are to receive prophylaxis with trimethoprim/sulfamethoxazole for pneumocystis for 2 sequential days each week at a dose of 2.5 mg/kg/dose trimethoprim/sulfamethoxazole (maximum dose of 160 mg) twice daily (BID) or according to institutional policy, unless they have a documented sulfa allergy. Patients with sulfa allergy should receive dapsone 2 mg/kg PO QD with a maximum dose of 100 mg/day, or monthly pentamidine (IV or aerosolized). Pneumocystis prophylaxis should be continued throughout the entire study period.

8.4.4.3.2 Bacterial, Fungal, and Viral Prophylaxis

Secondary to the high risk of serious invasive bacterial and fungal infection in patients with relapsed ALL, prophylaxis for bacterial and fungal infections is **MANDATED** on this protocol. Patients should receive levofloxacin at a dose based on each institution's formulary (but as a recommendation, levofloxacin could be dosed at 10 mg/kg/dose [maximum 750 mg/dose] IV or PO BID if <5 years old and at 10 mg/kg/dose [maximum 750 mg/dose] IV or PO QD if ≥5 years old).

All patients MUST receive antifungal prophylaxis during each course of therapy. Antifungal prophylaxis may be given per each institution's standards. It is strongly encouraged to use a drug with antimold activity such as caspofungin or micafungin. The doses used should be in the treatment range more so than prophylactic as that is when colonization and infection may occur in patients at high risk for fungal infection.

For patients with a history of documented or suspected herpes simplex virus or varicella zoster virus infection, it is recommended for them to receive prophylactic acyclovir at 750 mg/m^2/day divided BID.

It is strongly recommended that patients have quantitative immunoglobulins checked per institutional policy. Those with quantitative immunoglobulin G level below the normal range for age should receive IV immunoglobulin monthly.

Bacterial, fungal, and viral prophylaxis should be initiated on Day 8 of reinduction and continued at least until the post-nadir ANC is >500/µL.

8.4.4.3.3 Fever and Neutropenia

All patients with a fever ≥38.5°C on a single occasion, or ≥38°C on 2 occasions within 12 hours, and an ANC <500/µL are to be hospitalized and treated immediately with IV broad-spectrum antibiotics after obtaining appropriate cultures. The specific choice of antibiotics to be used in empiric treatment of febrile neutropenia is dependent on each institution's experience regarding the type of infecting organisms, and their antibiotic sensitivity patterns. Duration of therapy should be determined by site of infection, culture results, and response to treatment. Antifungal treatment is to be considered for the persistence of fever, or emergence of a new fever in neutropenic patients after 3 days of broad-spectrum antibiotic coverage. Radiographic imaging

surveillance for sites of infection should also be performed as clinically indicated. When severe mucositis or a sepsis syndrome is present in patients with febrile neutropenia, or a patient has a history of prior alpha hemolytic sepsis, consider inclusion of vancomycin in the empiric antibiotic regimen.

8.4.4.3.4 Empiric Management of Pulmonary Infiltrates

Pulmonary infiltrates should be evaluated in the context of the patient's clinical and laboratory profile as well as institutional infection patterns. If the patient is not neutropenic, and the pulmonary lesions on CT scan are not particularly suggestive of a fungal infection (*Aspergillus*, mucor), consider using broad-spectrum antibiotics. If the patient develops progressively worsening clinical or laboratory features, or if, the pulmonary lesions on CT scan are suggestive of a fungal infection (*Aspergillus*, mucor), then more aggressive diagnostic measures should be undertaken. Pulmonary infiltrates may be evaluated with bronchoscopy and biopsy, lavage, or open lung biopsy. If a procedure cannot be tolerated, and/or if there is high clinical suspicion consider beginning empiric treatment with amphotericin B given the high likelihood of fungal disease. It is advisable to seek an infectious disease consult under these circumstances. Empiric coverage may include treatment of gram-negative and positive bacteria, Legionella (erythromycin), Pneumocystis (trimethoprim/sulfamethoxazole), and fungi (amphotericin) pending culture results.

If fungal pulmonary disease is documented, surveillance radiographic imaging studies of the sinuses, abdomen/pelvis are indicated. Surgical excision of pulmonary lesions should be considered at the discretion of the treating physician. Treatment of fungal infections with amphotericin B and/or other antifungal agents will be at the discretion of the treating physician.

8.4.4.3.5 Management of Mucositis/Perirectal Cellulitis

Mucositis should be managed with IV hydration and hyperalimentation (if indicated), effective analgesia, broad-spectrum gram-positive and gram-negative antibiotic therapy, and empiric antiviral and antifungal therapy, as indicated. Management of perirectal cellulitis should include broad-spectrum antibiotic therapy with dual gram-negative coverage as well as anaerobic coverage (ie, ceftazidime + aminoglycoside + metronidazole; or piperacillin-tazobactam + aminoglycoside), sitz baths, a strong barrier technique, and effective analgesia.

8.4.4.3.6 Use of Granulocyte Colony-Stimulating Factor

The routine use of granulocyte colony-stimulating factor or other hematopoietic growth factors are not generally recommended but may be used at the discretion of the investigator in situations such as serious infection with neutropenia.

8.4.4.4 Safety Monitoring for Cardiac Toxicity

Elevation of cardiac biomarkers in the first 3 months of anthracycline therapy suggests possible pathological left ventricular remodeling and the need for long-term follow-up. Dexrazoxane therapy has been associated with lower elevation of these biomarkers (Lipshultz et al. 2012).

Additionally, cardiotoxicity has been observed with ponatinib in adult studies but the effects in pediatric population is not known. Please refer to section 8.4.2.2 for guidance on ponatinib dose modifications for these events.

Cardiac function and biomarkers will be followed in all patients enrolled on study, according to the following schedule:

1. **Biomarkers of cardiotoxicity**
   a) Cardiac troponin T or I.
   b) NT-proBNP.

Both will be assessed prior to first dose of ponatinib and daunorubicin and 2 weeks, 1 month, 2 months, and 3 months from the second daunorubicin dose.

2. **Cardiac function**

   ECHO or MUGA will be performed in the following schedule:

   a) Baseline - prior to initiating therapy.
   b) At the end of reinduction block.
   c) At the end of consolidation block.
   d) At EOT1.
   e) Yearly until end of study follow-up.

8.5 Excluded Concomitant Medications and Procedures

Systemic treatment with any of the following drug-metabolizing enzyme inhibitors or inducers should be avoided during the study:

- Strong CYP3A inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit-containing products including grapefruit juice, idelalisib, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole.
- Strong CYP3A inducers: carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, primidone, rifampin, rifapentine, rifabutin, and St. John's wort.

Because the above lists are not exhaustive, the investigator should consult the package insert for any medication under consideration for use to assess if it is a strong CYP3A inhibitor or strong CYP3A inducer.

Medications that prolong the QT interval but are not associated with a known risk of torsades de pointes 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. Discuss with the medical monitor a possibility of study drug discontinuation if any possible cardiac changes are noted.

The investigator should refer to the most current package insert for the agents in the chemotherapy backbone for their drug-drug interaction information (Table 8.b and Table 8.c).

The following concurrent medications and treatments are also prohibited:

- Other anticancer therapies.
- Chemotherapy, radiation therapy, another investigational agent, or immunotherapy.
- Herbal preparations or related over-the-counter preparations containing herbal ingredients.
- All live vaccines during the study treatment period and for at least 6 months after the last dose of the study treatment regimen.

8.6 Permitted Concomitant Medications and Procedures

All treatments/therapies 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 EOT1 visit (or EOT2 visit, for patients who receive optional ponatinib continuation therapy) (either the last dose of ponatinib 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 of childbearing potential (ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile; a postmenopausal state

is defined as no menses for 12 months without an alternative medical cause) 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.

Given the preclinical findings of phototoxicity in rats (see current version of the investigator's brochure), particularly with regard to eye sensitivity, it is recommended that patients minimize exposure to direct sunlight and take precautions, such as using sunscreen, sunglasses with 100% UV protection, or wearing a broad-brimmed hat along with the sunglasses, when outdoors.

Smoking/e-cigarettes/vaping are strongly discouraged due to unknown effects of smoking on cardiovascular disease.

8.8 Management of Clinical Events

Although the study excludes patients with active hepatitis B at the time of screening, ponatinib and chemotherapeutic agents 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 a high tumor burden such as WBC count ≥100,000/μL or diffuse organ involvement are considered high risk. Pre-existing uremia or hyperuricemia, decreased urinary flow or acidic urine, dehydration, 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, CHF, 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.

Refer to the current local ponatinib package insert for details on management of patients who have or who develop the following conditions: AOEs, VTEs, hypertension, 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, TLS, posterior reversible encephalopathy syndrome, compromised wound healing, or gastrointestinal perforation.

For all other therapies to be administered per this protocol, investigators should refer to the current local package insert for specific drugs for management of clinical events. See also Section 8.4.3 and Section 8.4.4.

8.9 Blinding and Unblinding

This is an open-label, unblinded study.

8.10 Description of Investigational Agents

The tablet formulation of the ponatinib investigational drug product is supplied as white, oval or round, film-coated tablets for oral administration. Each tablet contains 10, 15, 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 PEG, talc, polyvinyl alcohol, and titanium dioxide.

An AAF of ponatinib (minitab capsules) was developed for pediatric patients unable to swallow solid oral dosage forms and for patients requiring doses less than 10 mg. Ponatinib minitab size 2 opaque white hydroxypropyl methylcellulose (HPMC) capsules are filled with 2-mm, round, film-coated mini-tablets. The formulation of the core mini-tablets contains ponatinib HCl, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate. The 5 and 2.5 mg strengths capsules contain 10 and 5 minitabs (0.5 mg), respectively. These mini-tablets are coated with an aqueous film coating composed of PEG, talc, polyvinyl alcohol, and titanium dioxide. The coated mini-tablets are then encapsulated in a capsule containing HPMC and titanium dioxide.

8.11 Preparation, Reconstitution, and Dispensation

Ponatinib tablets should be swallowed whole with water and should not be crushed or dissolved in liquid (Iclusig (ponatinib) Tablets for Oral Use 2022).

Ponatinib minitab capsules should be either swallowed whole with water, or the capsule contents sprinkled in applesauce or yogurt and swallowed.

Additional details regarding administration of the AAF are provided in the study/pharmacy manual.

8.12 Packaging and Labeling

Upon receipt of drug supply, contents must be verified promptly, and the proper contacts notified of any discrepancies or damages as described in the study/pharmacy manual.

8.12.1 Ponatinib Tablets

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 (only provided for phase 1 cohort 1): 30 count in white HDPE bottles with foil induction seal and cap.

Bottle labels for ponatinib tablets 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 Ponatinib Age-Appropriate Formulation (AAF)

The ponatinib AAF (mini-tablet filled into capsules, ie minitab capsules) will be supplied as follows:

- 2.5 mg capsules: 35 count in white HDPE bottles with induction seal and cap.
- 5 mg capsules: 35 count in white HDPE bottles with induction seal and cap.

Bottle labels for ponatinib AAF 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 minitab capsules, and lot number.

8.12.3 Chemotherapy Backbone

The chemotherapy backbone may be sourced by the clinical study sites when local regulations allow.

8.13 Storage, Handling, and Accountability

8.13.1 Storage

All investigational supplies are to be kept in a secure area with controlled access.

Ponatinib should be stored as described on the study drug labels.

The chemotherapy backbone should be stored and handled as described in the study/pharmacy manual or, if locally sourced, the most current drug label (eg, US Package Insert, EU Summary of Product Characteristics), as applicable.

8.13.2 Handling and Accountability

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/minitab capsule strength, the number of tablets/minitab capsules 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.

During the coronavirus disease 2019 (COVID-19) public health emergency, alternative study drug delivery to trial participants may be necessary to avoid unnecessary patient visits to sites while providing needed study drug. Additional study drug may be dispensed during a scheduled study visit or study drug may be shipped directly from investigative sites to participants' residences by a contracted logistics provider or distributor (direct-to-patient [DTP] shipment) in compliance with national laws or temporary national emergency measures and Takeda processes.

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 standard practice at each study site (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

Refer to the pharmacy manual for any other protocol-specified materials to be used in the study.

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 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 IRB/IEC and Takeda (or designee).

9.3 Study Procedures

Refer to the SOEs (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.

All possible measures should be taken to reduce pain and discomfort (eg, use of local anesthesia before venipunctures, noninvasive measure should be preferred and timing coordinated with daily activities as far as possible). Physical pain and discomfort intensity must be assessed and regularly monitored and treated according to local appropriate guidance (eg, ethical considerations for clinical studies on medicinal products conducted with minors), particularly in neonates and children who cannot express it verbally. In order to minimize pain, discomfort, and fear, facilities should be appropriate to childcare, and the personnel should be trained to look after children and supervised by experienced health care professionals. The investigative site's staff should be trained to communicate with both the parents or legal guardian and the children.

The degree of burden and risk threshold will be constantly monitored by the investigator.

9.3.1 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 enrollment, patients must continue to maintain laboratory values within eligibility parameters. Any patient who is rescreened 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. See the SOE in Appendix A, Table 1 for all screening procedures.

For patients diagnosed with Ph-like ALL the site must provide the methodology used and the accredited laboratory performing the test for diagnosis (eg, RNA sequencing, fluorescence in situ hybridization [FISH]) and document in the eCRF.

Patients who discontinued from screening or run-in period due to COVID-19–related factors but were otherwise qualified to participate in the study may be rescreened if the sponsor's medical monitor agrees.

9.3.2 Informed Consent/Assent

Each patient or patient's parent or legal guardian must provide written informed consent/assent 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 and, if applicable, the patient's parent or legal guardian of all elements of informed consent. Adequate time must be allowed for questions and for the patient to make a voluntary decision.

9.3.3 Demographics and Medical/Surgical History

During the screening period, demographic data and a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 9.3.10.

9.3.4 Physical Examination and Vital Signs

A complete physical examination (including height and weight) will be completed as specified in the SOEs (Appendix A, Table 1 and Table 2).

Sites should calculate body surface area (BSA) from the weight and height measured at baseline and prior to each block of therapy as specified in the SOEs.

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Vital sign measurements will be assessed as specified in the SOEs.

9.3.5 Growth and Development

Growth will be assessed using growth charts. Developments will be assessed with Tanner staging. Growth and development will be assessed as indicated in the SOEs (Appendix A, Table 1 and Table 2).

9.3.6 Performance Status

The Karnofsky performance status scale (patients ≥16 years of age) or Lansky Play Scale performance status (patients <16 years of age) should be evaluated during each complete physical examination, as specified in the SOEs (Appendix A, Table 1 and Table 2). These performance score scales are available in Appendix D (Karnofsky and Burchenal 1949; Lansky et al. 1987). Patients must have a Karnofsky or Lansky Play Scale performance status ≥50% to be eligible for this study. Additional details on assessing performance status are provided in the site operations manual.

9.3.7 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 pregnancy testing (urine or serum) will be performed according to local standard of care while patient is on ponatinib continuation therapy (Appendix A, 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.

9.3.8 Cardiovascular Risk Assessments

9.3.8.1 12-Lead Electrocardiogram

All ECGs must be 12-lead ECGs, performed as specified in the SOEs (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 blood draw coincides with the timing of an ECG, the ECG should be performed first, followed by the blood draw.

9.3.8.2 Echocardiogram or Multigated Acquisition Scan

An ECHO or MUGA for assessment of left ventricular ejection fraction must be performed as specified in the SOEs (Appendix A, Table 1 and Table 2).

9.3.9 Ophthalmological Examination

An ophthalmological examination will be performed to screen for corneal and retinal vascular pathology at the time points outlined in the SOE (Appendix A, Table 1).

9.3.10 Concomitant Medications and Procedures

All relevant medications/therapies and therapeutic procedures used/completed by the patient 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 informed consent form (ICF) until the EOT1 visit (or the EOT2 visit, for patients who receive optional ponatinib continuation therapy) will be recorded in the eCRF as concomitant medications, as specified in the SOEs (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.

9.3.11 Adverse Events

Monitoring of AEs will be conducted throughout the study, starting on the date of signed ICF, and continuing until the EOT1 visit (or the EOT2 visit, for patients who receive optional ponatinib continuation therapy) as specified in the SOE (Appendix A, Table 1 and Table 2). Monitoring of SAEs will be conducted throughout the study, starting on the date of signed ICF, and continuing through 30 days after administration of the last dose of ponatinib.

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 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.

9.3.12 Enrollment

A patient is considered to be enrolled in the study at the time of initiation of the first dose of study drug. Procedures for completion of the enrollment information are described in the site operations manual.

9.3.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed as specified in the SOEs (Appendix A, Table 1 and Table 2). Local laboratory test results should be assessed before dosing.

9.3.13.1 Hematology and Chemistry

Blood samples for complete blood cell count with differential will be obtained as specified in the SOEs (Appendix A, Table 1 and Table 2) including on Day 35 of the reinduction block and consolidation block for disease assessment, or more frequently as clinically indicated. The full chemistry panel must be obtained as specified in the SOE, or more frequently as clinically indicated.

9.3.13.2 Coagulation

A blood sample for a coagulation panel will be obtained as specified in the SOE (Appendix A, Table 1).

9.3.13.3 Troponin and NT-proBNP

Assessment can be performed with either troponin T or troponin I, but ensure the same type of testing is used throughout the study. A blood sample for troponin testing (either troponin T or I) and another sample for NT-proBNP will be obtained as specified in the SOE (Appendix A, Table 1).

9.3.13.4 Free T4 and Thyroid Stimulating Hormone

Blood samples for free T4 and thyroid stimulating hormone will be obtained as specified in the SOEs (Appendix A, Table 1 and Table 2).

9.3.13.5 Hepatitis B and C

At the time of screening, hepatitis is testing is mandatory in countries with regulatory requirements and is optional in countries without regulatory requirements for testing. Blood is to be tested for hepatitis B and C surface antigen, hepatitis B and C core antibody, and hepatitis B and C surface antibody, at minimum, as specified in the SOE (Appendix A, Table 1).

9.3.13.6 HIV

At the time of screening, HIV testing is mandatory in countries with regulatory requirements, and clinical assessment with HIV testing is optional in countries without regulatory requirements for testing (Appendix A, Table 1).

9.3.14 Disease Assessment

9.3.14.1 Evaluation of CR

BM samples (aspirate and/or biopsy) and complete blood cell count will be needed to assess CR status at the time points indicated in the SOE (Appendix A, Table 1). CR status will be confirmed by the investigator upon review of blasts in the BM morphology report from the local laboratory, extramedullary disease, neutrophil, and platelet recovery as well as blasts in peripheral blood, if applicable.

After EOT1, complete blood cell count and BM evaluation for CR assessment may be performed at other times when clinically indicated. Results from the local laboratory testing of any BM sample (aspirate and/or biopsy), whether scheduled or unscheduled, must be recorded in the patient's eCRF.

If a BM sample (aspirate and/or biopsy) is used for the diagnosis of recurrence, a complete blood cell count should also be performed. If relapse from CR is confirmed, results of the assessments used to confirm the relapse, including peripheral blood, BM, CSF, or radiologic assessment, and their dates must be provided in the electronic data capture (EDC). If relapse from CR is confirmed, a peripheral blood sample must be collected for molecular mutation analysis.

9.3.14.2 Cerebrospinal Fluid

CSF will be needed to assess CR status at the time points indicated in the SOEs (Appendix A, Table 1 and Table 2). CR status will be assessed by CSF for cell count and cytospin cytology.

9.3.15 Biomarkers and Pharmacokinetic Measurements

Table 9.a includes information on the primary specimens to be collected for this study. Blood, BM, and plasma samples will be collected at the time points detailed in Appendix A, Table 1. Details on sample handling, storage, shipment, and analysis are provided in the laboratory manual.

MRD will be evaluated once CR assessment is performed and only for patients with CR status reported by the investigator by the end of the consolidation block.

Table 9.a Primary Specimen Collection

#	Specimen Name	Primary Specimen	Primary Specimen Derivative 1	Description of Intended Use	Sample Collection
1	Fresh BM aspirate sample for MRD (Ph+ ALL only)	BM	DNA RNA	MRD measurements	Mandatory
2	Peripheral blood sample for MRD (Ph+ ALL only)	Blood	DNA RNA	MRD measurements	Mandatory if BM sample cannot be obtained [a]
3	Blood samples for molecular mutations (Ph+ ALL only)	Blood	RNA	Confirm T315I mutation/ potential sensitivity/ resistance mutation	Mandatory
4	Plasma sample for ponatinib PK	Plasma		PK measurements	Mandatory

ALL: acute lymphoblastic leukemia; BCR-ABL1: breakpoint cluster region Abelson 1; BM: bone marrow; MRD: minimal residual disease; Ph+: Philadelphia chromosome positive; PK: pharmacokinetic(s); WBC: white blood cell.

[a] For initial screening, if a BM aspirate cannot be obtained, peripheral blood may be substituted to send for MRD probe development as long as there are at least 1000 circulating blasts/µL (ie, a WBC count of 10,000/µL with 10% blasts or a WBC count of 5000/µL with 20% blasts).

9.3.15.1 Bone Marrow Samples for MRD Assessment

MRD will be evaluated (only in patients with Ph+ ALL and only those who achieve CR by end of consolidation as reported by the investigator) as specified in the SOE (Appendix A, Table 1). The optimal sample for MRD assessment is the first pull or early pull of the BM aspirate. BM aspirate samples for MRD evaluation will be sent to a central laboratory.

For initial screening, if a BM aspirate cannot be obtained, peripheral blood may be substituted to send for MRD probe development as long as there are at least 1000 circulating blasts/µL (ie, a WBC count of 10,000/µL with 10% blasts or a WBC count of 5000/µL with 20% blasts).

For MRD assessment, BM evaluation 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.

9.3.15.2 Peripheral Blood Samples for Molecular Mutations

Peripheral blood samples will be collected only from Ph+ ALL patients as specified in the SOEs (Appendix A, Table 1 and Table 2). Baseline samples will be tested immediately to confirm T315I mutation for patients requiring enrollment eligibility confirmation and communicated to the investigator. All other enrolled patients will have baseline samples tested to identify T315I mutation along with the other screening of molecular mutations to be conducted by sponsor for

exploratory analysis and will not be communicated to the investigator. Other samples both prior and following ponatinib treatment will be tested to characterize biomarkers of sensitivity and resistance to ponatinib-containing therapy (eg, *BCR-ABL1*, *IKZF1*, *CDKN2A*/2B) (Table 9.a). Peripheral blood samples for molecular mutations analysis will be sent to a central laboratory.

9.3.15.3 PK Measurements

Blood samples for the measurement of plasma concentrations of ponatinib will be collected from all patients at multiple time points as specified in Appendix A, Table 3 and Table 4. These data will be used to characterize the PK of ponatinib. A sparser sampling scheme will be used for patients weighing <20 kg because of potential blood volume loss limitations.

The exact date and time of each PK sample collection should be recorded in the eCRF. In addition, the exact date and time of dosing for the 2 preceding doses of ponatinib before all PK sample collections, and on the day of PK sample collection, should be recorded (at a minimum) in the eCRF.

Details regarding the preparation, handling, and shipping of the PK samples are provided in the site operations manual.

9.3.16 Palatability and Acceptability of Ponatinib Age-Appropriate Formulation

Patient acceptance of medication (acceptability) can be defined as the overall ability of the patient to use the medicine as intended. Acceptability of an oral medication is an important consideration in patients, particularly children, since it has a significant impact on patient compliance (Mistry et al. 2017; Van Riet-Nales et al. 2017). Palatability tests have been performed for several pediatric medications using different measurement scales (Davies and Tuleu 2008). This study will incorporate a questionnaire with questions related to the taste and smell using a 5-point facial hedonic scale. This scale allows for indication of preference by pointing at a pictorial scale of facial expressions that has been commonly used in palatability studies (Davies and Tuleu 2008; Mulla et al. 2016).

After each dose of ponatinib on Days 1, 8, 15, and 22 during reinduction, a questionnaire will be provided to the patient and parent/legal guardian. At the investigator's/designee's discretion, if the patient is too young to complete the survey, only the parent/legal guardian will be surveyed. In each case, a nurse or research staff member will record the verbal responses to the questions. When facial hedonic scale is used, the child or parent/legal guardian will be asked to indicate their preference by circling the pictorial scale of facial expression. The palatability study questionnaire is provided in Appendix E.

9.3.17 Follow-up Assessments

All patients will be followed for survival, recurrence, progression, growth and development, and subsequent treatments for at least 3 years from EOT1. Any disease assessments completed as clinically indicated need to be recorded in the EDC as indicated in Section 9.3.14.

Patients will be evaluated for alternative therapy, safety, and survival after EOT1 at 6 months, 1 year, 18 months, 2 years, and every year thereafter for a total of at least 3 years after EOT1.

If a patient refuses to return to the clinic for scheduled long-term follow-up study visits, information can be collected via telephone contact reports at the time of the regularly scheduled study visits; however, this is not preferred. If any concerns relating to study treatment are identified by the investigator during this telephone consultation with the patient, the investigator should request that the patient attend an in-person clinic visit to complete the assessments outlined in the SOEs (Appendix A, Table 1 and Table 2) for the long-term follow-up visits, or alternatively, have the patient visit their personal physician/other medical care provider for appropriate follow-up. Any results generated outside of the investigative site must be obtained by the investigator and recorded in the eCRF.

Efforts will be made to avoid any patient being lost to follow-up during the conduct of the study. Before patients are considered lost to follow-up, a minimum of 2 documented telephone contact attempts must be made, and 1 certified letter must be sent within 6 weeks of the most recent planned study visit in an effort to contact patients.

If a patient has been documented as lost to follow-up or if the site staff becomes aware of a patient's death between scheduled visits, then the date of death must also be obtained and recorded in the eCRF.

9.3.18 Changes to Study Procedures Due to COVID-19 Public Health Emergency

The following information provides guidance regarding changes to the study procedures that could be implemented for patients or study sites affected by the COVID-19 public health emergency. 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 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 principal investigator in consultation with the study team and the medical team as needed, while maintaining patient safety and confidentiality as the priority.

Procedural changes due to COVID-19 public health emergency may include the following:

- Informed consent procedure: If necessary, informed consent from a potential or current patient may be obtained via electronic informed consent (eIC) capabilities, or an electronic face-to-face consent interview when these patients are unable to travel to the site.
- All patient visits from screening/baseline through to and including the EOT1 visit must be done with the patient present at the investigative site. This includes, but is not limited to, visits containing PK assessments, lumbar punctures, BM evaluations, or chemotherapy dosing. The optional continuation therapy visits should be done at the investigative site.

Every effort should be made to conduct patient visits at the investigative site. However, follow-up visits may be conducted by home health care visits in cases where flexibility is needed due to the COVID-19 public health emergency. Home health care visits will be documented in the study records and eCRF. 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).

- 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 site staff who can visit the patient's residence.
- Missed clinic visits or patient withdrawals due to COVID-19 must be recorded on the eCRF. (Section 9.6).
- 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.
- Allow transfer of patients to investigative sites away from risk zones or closer to their home to sites already participating in the study or new ones.
- Deviations from the protocol-specified procedures (eg, not collecting a protocol-specified specimen, such as postdose blood work) will be recorded as related to COVID-19 (Section 14.2).
- Alternative study drug deliveries may include dispensing additional ponatinib at clinic visits or DTP delivery of ponatinib from the investigative site to patients in compliance with national laws or temporary national emergency measures (Section 8.13.2).
- Alternative monitoring approaches may include remote source data verification or remote source data review (Section 14.1).

9.4 Completion of Study Treatment

All patients will be considered to have completed study treatment when they have completed the reinduction and consolidation blocks and the EOT1 visit and did not discontinue study treatment early or meet any of the criteria listed in Section 9.5, and if the patients received optional continuation therapy then after completing the EOT2 visit.

9.5 Reasons for Discontinuation of Treatment

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

Study drug must be immediately discontinued for patients who become pregnant. Depending on the outcome of the pregnancy (spontaneous or elective abortion), the sponsor/investigator may decide the patient can continue in the study.

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

- AE.
- Protocol deviation and noncompliance.
- Progressive disease.
- Symptomatic deterioration.
- Initiation of non-protocol therapy.
- Study terminated by sponsor.
- Withdrawal by patient or, if applicable, patient's parent or legal guardian.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the EOT1 visit will be completed as specified in the SOE (Appendix A, Table 1). The primary reason for study drug discontinuation will be recorded on the eCRF including unavoidable circumstances such as the COVID-19 public health emergency.

In the case of study termination by the sponsor, eligible patients may have continued access to ponatinib as described in Section 6.3.5.

9.6 Withdrawal of Patients From Study

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 or, if applicable, patient's parent or legal guardian.
- Lost to follow-up.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

9.7 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.

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

9.8 Criteria for Premature Termination or Suspension of the Study

Study participation by individual sites or the entire study may be prematurely terminated if 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.

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of ponatinib that indicates a change in the known safety profile such that the benefit-risk is no longer acceptable for patients participating in this study.
- The independent data monitoring committee (IDMC) recommends that the study should be suspended or terminated.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Study-specific criteria for terminating the study (eg, study meets predefined rule for futility or benefit).
- Emergence of events that meet the criteria for early safety stopping rules as in Section 8.4.1.
- Insufficient recruitment rate.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A 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 Adverse Event Definition

AE 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. AE relationship should be assessed as related (includes attribution of possibly, probably, or definitely) or not related.

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 Serious Adverse Event Definition

SAE 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, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one 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 considered an AE, will be determined using the NCI CTCAE Version 5.0. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 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 (Grade 3 or 4) does not necessarily need to be considered serious. For example, a WBC 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 Adverse Events of Special Interest Definitions

AOEs and VTEs have been identified as AESIs for ponatinib. These include arterial and VTE and occlusive AEs that meet the criteria for SAEs, as defined in Section 10.1.3.

The sponsor has determined that the events in the following list should be considered AESIs:

- MI: The Third Universal Definition of Myocardial Infarction (Thygesen et al. 2012) is used 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) with at least 1 value above the 99th percentile upper reference limit (URL) and with at least 1 of the following:
    - Symptoms of ischemia.
    - 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 cardiac troponin values (>5 × 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cardiac troponin 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 cardiac troponin 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).

- Coronary artery disease (CAD) (newly diagnosed or worsening of existing CAD) or symptoms that may reflect cardiovascular disease (Thygesen et al. 2012).
- 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 (Easton et al. 2009).
- 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.
- 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 these criteria. Dose modification guidelines for AOEs/VTEs are presented in Section 8.4.2.2.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient or parent/legal guardian 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. This will be done by transmitting an 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. 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 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).

10.3 Monitoring of Adverse Events 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 the EOT visit (EOT1 or EOT2, as applicable) 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 progressive disease 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 ponatinib 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).

The safety and response data from phase 1 will be continuously reviewed by the sponsor and the medical monitor. At the cohort review meeting, the safety and response data will be reviewed by the sponsor together with participating investigators and a decision will be made either to proceed to the next phase of the study, evaluate a lower dose, or terminate the study.

Prior to proceeding with the phase 2 enrollment for each formulation (tablet and AAF), an end of phase 1 meeting will be conducted and all factors impacting safety, including protocol deviations will be evaluated. These data and decisions will be provided to the IDMC for their review and feedback and an end of phase 1 summary will be sent to all participating sites. After the determination of the RP2D and commencing phase 2 enrollment at the RP2D, the sponsor's team will continue to monitor all available safety data and hold safety review meetings on a regular basis. At any time, if the IDMC raises any important safety concerns, these will be communicated to the sites and when appropriate, the informed consents may be amended. Further details on the IDMC are provided in Section 11.2.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a patient becomes pregnant or suspects pregnancy while participating in this study, the patient 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. The pregnancy must be followed for the final pregnancy outcome.

If a patient impregnates a partner during 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. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Reporting details and contact information are provided in the site operations manual.

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 address provided in the site operations manual.

A medication error is a preventable event that involves an identifiable patient and 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 address provided in the site operations manual.

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.

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 EU EMA, investigators, and IRBs and 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 expedited reports 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 trial. The investigative site also will forward a copy of all expedited reports to its IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Sponsor Liaison Team

The Sponsor Liaison Team (SLT) or their respective delegates consists of key representatives from the ponatinib development team who have knowledge of the day-to-day activities of the study. The SLT should consist of, at a minimum, the following individuals:

- Ponatinib global clinical lead.
- Project clinician.
- Lead project statistician.
- Ponatinib global safety lead.

The team will attend the open meeting sessions to answer any questions proposed by the IDMC relevant to study/program scientific and clinical issues. The SLT may request that the IDMC addresses specific issues related to the study. The committee will also liaise with the pediatric consortia study committees regarding important issues and developments related to the study.

11.2 IDMC

An IDMC comprised of a pediatric oncologist, pediatric hematologist, and a statistician will review safety and efficacy data at the planned primary analysis and at regular intervals outlined in the charter. The IDMC will review study data according to the IDMC charter.

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 Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), Preferred Term (PT), 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. Additionally, the IDMC will receive regular listing updates on all SAEs and immediate notification of any deaths.

Details of the IDMC (scope of functions and schedule) will be captured in its charter before the start of the study. Further details will be provided in the IDMC charter.

A cardiovascular endpoint adjudication process may be implemented at any time throughout the study to determine if an AOE meets the definition for a MACE.

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 MedDRA. Drugs will be coded using the World Health Organization (WHO) Drug Dictionary (01 March 2018).

12.1 eCRFs

Completed eCRFs are required for each patient who signs, or whose parent or legal guardian 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, contract research organization (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 the 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.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor (or 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 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, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the

audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or 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 or electronic medical record to ensure long-term legibility. Furthermore, ICH E6 (GCP) 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 for record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical Analysis Plans

A SAP will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, patient evaluability, and appropriateness of the planned statistical methods.

In general, summary tabulations will be presented by study phase and dose cohort 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 database lock for the interim analysis as defined in Section 13.2. Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final CSR.

13.1.1 Analysis Sets

The populations used for analysis will include the following:

- Safety population: Patients who receive at least 1 dose of ponatinib. The safety population will be used for all safety analyses.

- PK analysis population: Patients in the phase 1 portion of the study who have sufficient ponatinib dosing data and concentration–time data to permit the calculation of ponatinib PK parameters.
- DLT-evaluable population: Patients in the phase 1 portion of the study who receive at least 1 dose of ponatinib in the reinduction block; to confirm no DLT was observed, the patient must have received at least 70% of the planned ponatinib dosing. The DLT-evaluable population will be used to determine the maximum tolerated dose.

  Patients who are withdrawn from treatment during the reinduction block for reasons other than DLTs will be replaced.
- Response-evaluable population: Ph+ ALL patients at RP2D who receive at least 1 dose of ponatinib and complete at least 1 postbaseline disease assessment will be used for efficacy analyses.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized, including sex, age, race, ethnicity, weight, height, BSA, primary diagnosis, and other parameters as appropriate.

13.1.3 Efficacy Analysis

Patients with Ph-like ALL and Ph+ MPAL will not be included in efficacy analyses. These patients will be included in safety and other descriptive analyses.

13.1.3.1 Primary Efficacy Endpoint Assessment

Primary efficacy endpoint will be analyzed in the phase 2 portion of the study. Primary data analysis for this study will be conducted when all patients have been assessed for their primary endpoint and been on study for approximately 6 months after the last patient has been enrolled.

The response-evaluable population will be assessed for the phase 2 primary endpoint. The phase 2 primary endpoint is CR at the end of the reinduction block. The estimate of the primary endpoint will be presented with 2-sided 90% Wilson Score CI.

13.1.3.2 Secondary Efficacy Endpoint Assessment

Secondary efficacy endpoints will be summarized descriptively, with 2-sided 95% CIs provided. Time-to-event analysis will be conducted to obtain point estimates and 95% CIs for duration of response and the EFS, PFS, and OS rates at 6 months, 1 year, 18 months, 2 years, and 3 years.

13.1.3.3 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
CR	CR meeting all the following (ie, no recurrence): • No circulating blasts and <5% blasts in the BM. • Normal maturation of all cellular components in the BM. • No extramedullary disease. • ANC >1000/µL (or >1.0 × 10^9/L). • Platelets >100,000/µL (or >100 × 10^9/L).
Duration of response	The interval between the first assessment at which the criteria for CR are met until the time at which relapse from CR occurs.
EFS	From date of enrollment until one of the following: • Death due to any cause. • Refractory to treatment, defined as failure to achieve CR by end of the consolidation block. • Relapse from CR.
MRD negative (Ph+ ALL only)	MRD status <0.01%
OS	The interval between the first dose date of study drug and death due to any cause.
PFS	From date of enrollment until one of the following: • Death related to disease under study. • Disease progression, defined as an increase of at least 25% in the absolute number of circulating or BM blasts or development of new extramedullary disease. • Relapse from CR.
Relapse from CR [a]	Reappearance of blasts in the blood or BM (≥5%) or in any extramedullary site after a CR.

ALL: acute lymphoblastic leukemia; ANC: absolute neutrophil count; BM: bone marrow; CR: complete remission; EFS: event-free survival; MRD: minimal residual disease; OS: overall survival; Ph+: Philadelphia chromosome positive; PFS: progression-free survival.

[a] If a bone marrow sample (aspirate and/or biopsy) is used for the diagnosis of recurrence, a complete blood cell count should also be performed.

13.1.4 Exploratory Analyses

Exploratory endpoints will be summarized descriptively, with 95% CIs provided where appropriate.

13.1.5 PK Analysis

Ponatinib PK parameters will be calculated, as permitted by the data, for individual phase 1 patients in the PK analysis population using the ponatinib plasma concentration–time data. The calculated parameters will include ponatinib C_{max}, t_{max}, and AUC_{last}. PK parameters will be summarized using descriptive statistics. Individual ponatinib plasma concentration–time data and

individual PK parameters will be presented in listings. Individual and mean ponatinib plasma concentration–time profiles will be plotted.

The sparse PK data collected in the phase 2 portion of the study will be listed and summarized by time point. The PK data collected in both phase 1 and phase 2 of the study will contribute to population PK and exposure-response analyses of ponatinib in the pediatric patient population. These analyses may include data collected in other ponatinib studies. The analysis plan for the population PK and exposure-response analyses will be separately defined, and the results of these analyses will be reported separately.

13.1.6 Safety Analysis

The safety analysis will cover short-term AE, SAE, and AESI rates and changes from baseline in laboratory values.

AEs will be summarized using the safety population. The DLT-evaluable population will be used for the analysis of DLT.

All AEs will be coded using the MedDRA. Data will be summarized using PT and primary SOC.

The safety analysis will be carried out at interim, primary and final analyses.

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. 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.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters. In addition, urinalysis results will be listed.

A summary of ECG abnormalities will be presented by visit. ECG parameters (QT, QTc, PR, and QRS intervals and ventricular rate) will be summarized at each scheduled time point, along with the mean change from baseline to each posttreatment time point. Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE Version 5.0 grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the ponatinib safety profile.

All concomitant medications collected from screening through the study period will be classified to PTs according to the WHO Drug Dictionary (01 March 2018).

13.2 Interim Analysis and Criteria for Early Termination

There will be 1 interim analysis performed when 20 patients at the RP2D have completed reinduction. Enrollment will not be stopped while the interim analysis data is reviewed by the IDMC (Section 11.2). Following the interim analysis results and application of the prespecified rules, the IDMC may recommend stopping the trial for futility or recommend continuing the trial with or without modifications. The sponsor's Executive Committee will make final decisions based on the IDMC's recommendations. The analysis will be performed as defined in Section 13.1.3.1.

13.3 Determination of Sample Size and Justification of Control Rate Assumption

The Wilson Score CI approach will be used for the sample size determination. The Wilson Score interval is an improvement over the normal approximation interval in that the actual coverage probability is closer to the nominal value. Based on the Wilson Score CI approach and assuming N = 68 patients to reject the null hypothesis of a 67% CR rate, a 2-sided type I error of 0.1, and that under the alternative hypothesis the ponatinib CR rate is 80% based on simulations with 1,000,000 iterations, the power of the trial equals 81.5%. This simulation also demonstrated that under the null hypothesis, the type I error is controlled at a nominal level of 0.1 (2-sided).

The null hypothesis of a 67% CR rate is based on the following justification from 2 studies. In the first study, 87 adult patients with Ph+ ALL were treated with imatinib plus chemotherapy (Lim 2017). Of the 87 patients, 44 experienced a relapse, and of those, 19 (43.2%) achieved a second CR (CR2). Based on these results, we assume that the prior distribution control rate follows $\beta(a, b)$, mean = $a/(a + b) = 19/(19 + 25) = 0.432$. The outcomes of imatinib plus chemotherapy were also evaluated in a study of 92 pediatric patients with Ph+ ALL (Schultz et al. 2014). Among those who relapsed, follow-up data were available on 34 patients, of which 24 (70.6%) achieved a CR2 (personal communication, 11 June 2019). Based on those results, we assume that a CR2 event, x, follows a binomial (n, p) distribution, where x = 24, n = 34, and the estimated rate $p = 24/34 = 0.71$. The CR2 posterior distribution follows $\beta(a + x, n – x + b)$.

Thus, the mean CR2 rate from the posterior distribution = $(a + x)/(n + a + b) = 0.5513$. The 95% credible interval of the CR2 rate = (0.44, 0.66) = (44%, 66%).

Because our prior distribution control rate uses adult data, we take a conservative approach and assume that the control rate is no less than the 95% upper credible limit, ie, 67%.

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 including, but not limited to, the investigator's site file, 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.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 public health emergency, 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. Such alternative approaches must adhere to any applicable local laws and guidances.

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. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

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 EC, 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 the primary study assessment.

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 investigator should document each protocol deviation and report to the IRB/IEC each deviation that the IRB/IEC requires to be reported. For COVID-19–related protocol deviations, the specific protocol deviation and the reason for the deviation should be documented.

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 US FDA, the UK MHRA, and the EU EMA). 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 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 Harmonised Tripartite 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 because of privacy and conflict of interest concerns should instead provide a Federalwide 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 advertisements and other documents required by all applicable laws and regulations must be submitted to a central and/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 its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. 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 the 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 patients, 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 designee).

Patient incentives should not exert undue influence for participation. Payments to patients 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 guideline for GCP and will be in accordance with all applicable laws and regulations. The ICF, assent form (if applicable), subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's 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, and 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 and, if applicable, the subject authorization form. The ICF, assent form (if applicable), subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, assent form (if applicable), subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject's parent or legal guardian (or the prospective subject, if the subject is of the age of consent). It is the responsibility of the investigator to explain the detailed elements of the ICF, assent form (if applicable), subject authorization form (if applicable), and subject information sheet (if applicable) to the subject or the subject's parent or legal guardian. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the subject is not capable of rendering adequate written informed consent, then the subject's parent or legal guardian may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's parent or legal guardian, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject, or the subject's parent or legal guardian, determines that he or she will participate in the study, then the ICF and assent form (if applicable) must be signed and dated at the time of consent and before the subject enters into the study. The subject or the subject's parent or legal guardian should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF, assent form (if applicable), and subject authorization (if applicable) 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, subject authorization form (if applicable), and subject information sheet (if applicable) 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. Copies of the signed ICF, the signed assent form (if applicable), the signed subject authorization form (if applicable), and the subject information sheet (if applicable) shall be given to the subject.

All revised ICFs and assent forms must be reviewed and signed by relevant subjects or the relevant subject's parent or legal guardian 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.

During the COVID-19 public health emergency, informed consent and assent from a potential or current trial participant and parent/legal guardian may be obtained via eIC capabilities, or an electronic face-to-face consent/assent interview when these individuals are unable to travel to the site.

For patients who would have to travel long distances to the study site, remote consenting and assenting is allowed if permitted by local regulations (eg, IRB or IEC).

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 be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or subject initials, may be used to verify the subject's identity and accuracy of the subject's unique identification number.

To comply with ICH guideline 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), 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 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 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 by Takeda policy/standards. 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 in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/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 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, clinicaltrialsregister.eu, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

15.4.4 Data Sharing

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 Schedules of Events

Table 1 Schedule of Events

35-Day Cycles	**Screening/ Baseline [a]**	**Reinduction Block**						**Consolidation Block**						**EOT1 [b]**	**Follow-up [c]**
Cycle Days		**1**	**8**	**15**	**22**	**29**	**35**	**1**	**8**	**15**	**22**	**29**	**35**	**25-30 Days After Last Dose**	
Window (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±14**
Study Procedures															
Informed consent/pediatric assent	X														
Enrollment		X													
Demographics	X														
Prior therapy	X														
Medical/surgical history	X														
Hematology and chemistry [d]	X [d]	X [d]	X	X	X	X	X [z]	X	X	X	X	X	X [z]	X	X [e]
Hepatitis B and C testing [f]	X														
HIV testing [g]	X														
Coagulation panel [h]	X					X						X			
Troponin and NT-proBNP [i]	X	X		X				X				X		X	
Free T4, TSH	X					X								X	X
Pregnancy test [j]	X	X						X						X	
Vitals, including height, weight, BSA [k]	X	X						X						X	X
Physical examination including neurological assessment [l]	X	X						X						X	X
Growth and development assessment [m]	X											X			X
Performance status (Karnofsky/Lansky score, Appendix D)	X	X						X						X	X
12-lead ECG [n]	X	X		X				X		X				X	X
ECHO or MUGA	X					X						X		X	X [o]
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1 Schedule of Events

35-Day Cycles	Screening/ Baseline [a]	Reinduction Block						Consolidation Block						EOT1 [b]	Follow-up [c]
Cycle Days		**1**	**8**	**15**	**22**	**29**	**35**	**1**	**8**	**15**	**22**	**29**	**35**	**25-30 Days After Last Dose**	
Window (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±14**
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lumbar puncture [p]	X	X	X [q]	X	X [q]	X			X			X			
Bone marrow aspirate assessed locally and/or biopsy for morphology, cytogenetics, and flow cytometry [r]	X					X						X			
Fresh bone marrow aspirate sample assessed centrally for MRD [s, t, v]	X					X						X			
Peripheral blood samples for molecular mutations [u, v]	X [aa]	X												X	X (relapse only)
Administration of study treatment [w]		X	X	X	X	X	X	X	X	X	X	X	X		
Palatability questionnaire of ponatinib [x]		X	X	X	X										
Ophthalmological examination [y]	X					X						X			
Plasma sample for ponatinib PK	See Table 3 for phase 1 and Table 4 for phase 2 PK sampling schedules.														
Investigator's assessment of disease							X						X		X [bb]
Alternative therapy (anticancer therapy)															X

AE: adverse event; ALL: acute lymphoblastic leukemia; BCR-ABL1: breakpoint cluster region Abelson 1; BSA: body surface area; CNS: central nervous system; COVID-19: coronavirus disease 2019; ECG: electrocardiogram; ECHO: echocardiogram; EOT: end of treatment; IT: intrathecal; MPAL: mixed phenotype acute leukemia; MRD: minimal residual disease; MUGA: multigated acquisition scan; NT-proBNP: N-terminal pro-brain natriuretic peptide; Ph-like: Philadelphia chromosome-like; PK: pharmacokinetic; PT: prothrombin time; QTcF: QT interval corrected per Fridericia method; TSH: thyroid stimulating hormone; WBC: white blood cell.

Note: Other studies or more frequent monitoring may be indicated for good clinical care. Initial IT chemotherapy: Day 1; may include methotrexate for CNS-1/2 patients, or triple IT chemotherapy for CNS-3 patients. All patient visits from screening/baseline through to and including the EOT1 visit must be done with the patient present at the investigative site. Every effort should be made to conduct patient visits at the investigative site. However, follow-up visits may be conducted by home health care visits in cases where flexibility is needed due to the COVID-19 public health emergency.

[a] The screening visit must occur within 10 days before the day of the first dose of study drug (Day -10 to Day 0).

[b] All patients will proceed to EOT (EOT1) 25 to 30 days after last dose of study treatment in the consolidation block or earlier, if the patient is proceeding to alternate therapy or optional ponatinib continuation therapy; EOT1 should be completed before alternative anticancer therapy(ies) are given. For patients with an early EOT1, the ECHO or MUGA

Table 1 Schedule of Events

35-Day Cycles	Screening/ Baseline [a]	Reinduction Block						Consolidation Block						EOT1 [b]	Follow-up [c]
Cycle Days		1	8	15	22	29	35	1	8	15	22	29	35	25-30 Days After Last Dose	
Window (days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±14

does not need to be repeated if done within 25 days and the ECG does not need to be repeated if done within 7 days prior to the visit. Only patients who receive optional continuation therapy containing ponatinib will undergo a second EOT visit (EOT2). See Table 2. Patients who discontinue ponatinib early in the reinduction block or consolidation block will be discontinued from study treatment and proceed to the EOT1 visit.

[c] Each patient will be followed for a minimum of 36 months after the EOT1 visit or until patient withdrawal from study, whichever occurs first. Follow-up visits will occur after EOT1 at 6 months, 1 year, 18 months, 2 years, and then annually until the end of the study. If a patient refuses to return to the clinic for the scheduled long-term follow-up visits, information can be collected via telephone contact reports; however, this is not preferred (see Section 9.3.17).

[d] The hematology and chemistry blood samples for Day 1 may be collected within 4 days before dosing to ensure patient eligibility on study Day 1. If screening clinical laboratory testing was performed within 4 days before the Day 1 dose, it need not be repeated on Day 1. Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBCs), differential WBC count, and platelets. Machine counts are acceptable. The chemistry panel consists of the following: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen or urea, creatinine, direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, gamma-glutamyl transferase, triglycerides, lipase, amylase, albumin, glucose, urate, calcium, phosphate, and magnesium.

[e] To follow organ function and detect relapse.

[f] Hepatitis testing is mandatory in countries with regulatory requirements and is optional in countries without regulatory requirements for testing.

[g] HIV testing is mandatory in countries with regulatory requirements, and clinical assessment with HIV testing is optional in countries without regulatory requirements for testing.

[h] Coagulation panel includes platelets [with hematology], activated partial thromboplastin time and PT, fibrinogen degradation products or D-dimer, factor FVII, and antithrombin level.

[i] Troponin testing can be performed with either troponin T or troponin I, but ensure the same type of testing is used throughout the study. Blood sample can be collected either at the screening visit or on Day 1 before ponatinib and daunorubicin dosing. Additional evaluations may be done if clinically indicated.

[j] A pregnancy test will be performed only for female patients of childbearing potential according to local standard of care. At screening, the results must be negative within 3 days before the first dose of ponatinib is administered. Monthly pregnancy testing (urine or serum) will be performed according to local standard of care while patient is receiving ponatinib.

[k] Height and weight needed to assess growth.

[l] The neurological assessment can be performed by the pediatric oncologist and includes the Modified "Balis" Pediatric Scale for peripheral neuropathy.

[m] Growth charts and Tanner staging will be used for growth and development assessments. Other tests may be needed as clinically indicated.

[n] ECGs must all be 12-lead ECGs. The baseline ECG should be performed at screening/baseline, or on Day 1, before ponatinib dosing. On Day 1, and thereafter as per the schedule in the reinduction and consolidation period, the ECG should be performed 4-6 hours after ponatinib administration. 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. On days when both an ECG and a blood draw is performed, the ECG should be done before the blood draw.

[o] During follow-up, ECHO or MUGA will be performed yearly until end of study follow-up.

Table 1 Schedule of Events

35-Day Cycles	Screening/ Baseline [a]	Reinduction Block						Consolidation Block						EOT1 [b]	Follow-up [c]
Cycle Days		1	8	15	22	29	35	1	8	15	22	29	35	25-30 Days After Last Dose	
Window (days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±14

[p] Lumbar puncture for cell count and cytospin cytology will be performed with every IT therapy and when clinically indicated.

[q] For CNS-3 patients only.

[r] For initial screening, if a bone marrow aspirate cannot be obtained, peripheral blood may be substituted for initial diagnosis as long as there are at least 1000 circulating blasts/µL (ie, a WBC count of 10,000/µL with 10% blasts or a WBC count of 5000/µL with 20% blasts). Flow cytometry, cytogenetics, fluorescence in situ hybridization, or molecular studies can be used to confirm the type and subtype of acute leukemia. If a bone marrow sample (aspirate and/or biopsy) is used for the diagnosis of recurrence, a complete blood cell count should also be performed.

[s] At screening, at the end of each treatment block and when clinically indicated. Bone marrow aspirate for MRD evaluation will be performed by a central laboratory (not applicable for patients with Ph-like ALL and MPAL).

[t] For initial screening, if a bone marrow aspirate cannot be obtained, peripheral blood may be substituted to send for MRD probe development as long as there are at least 1000 circulating blasts/µL (ie, a WBC count of 10,000/µL with 10% blasts or a WBC count of 5000/µL with 20% blasts).

[u] Submission of peripheral blood samples to central laboratory to assess molecular mutations (eg, *BCR-ABL1*, *IKZF1*, *CDKN2A/2B*). Only 1 evaluation is needed before starting therapy: blood sample can be taken either at the screening/baseline visit or on Reinduction Block Day 1 prior to dosing, but not both. Blood samples should be taken post-protocol treatment at EOT1 before alternative therapy(ies) are given. For patients with Ph+ ALL for whom the investigator reports a relapse from complete remission, a peripheral blood sample should also be taken before alternative therapy(ies) are given and submitted to central laboratory to assess molecular mutations.

[v] Not applicable for patients with Ph-like ALL and MPAL.

[w] Administration of study treatment will also include diary review and study treatment verification. Ponatinib will be administered once daily throughout each 35-day block (Days 1-35). See Table 5 for details of study treatment administration.

[x] Age-appropriate formulation only: After each dose of ponatinib taken on Days 1, 8, 15, and 22 of the reinduction block, a questionnaire will be provided to patient and parent/legal guardian. If the patient is too young to complete the survey, only the parent/legal guardian will be surveyed. In each case, site staff will record the verbal responses to the questions.

[y] Ophthalmological examination to screen for corneal and retinal vascular pathology.

[z] Hematology at Day 35 (±3 days) includes platelets and neutrophils to complete the investigator's disease assessment for determination of complete remission prior to initiation of the consolidation block. (This assessment may be used as the same assessment for Day 1 of the consolidation block). Chemistry assessment at Day 35 is not required.

[aa] Baseline samples will be tested immediately to confirm T315I mutation for patients requiring enrollment eligibility confirmation and communicated to the investigator.

[bb] If relapse from complete remission is confirmed, results of the assessments used to confirm the relapse, including bone marrow assessment, and their date must be provided in the electronic data capture.

Table 2 Schedule of Events for Ponatinib

28-Day Cycles	**Optional Continuation Regimen**		**EOT2** [a]	**Follow-up** [b]
Cycle Days	**1** [c]	**Every 3 Months**	**30-40 Days After Last Dose**	
Window (days)	**±3**	**±7**		**±14**
Hematology and chemistry [d]	X		X	X [e]
Pregnancy test [f]	X		X	
Vitals, including height, weight, BSA [g]	X		X	X
Physical examination and neurological assessment [h,i]	X		X	X
Growth and development assessment [j]			X	X
Performance status (Karnofsky/Lansky score, Appendix D)	X		X	X
12-lead ECG [k]		X	X	X
ECHO or MUGA [l]		X	X	X
Free T4, TSH	X			X
Concomitant medications and procedures	X		X	
AE reporting	X		X	
Lumbar puncture [m]		X [m]		
Peripheral blood samples for molecular mutations [n]	Only required if relapse occurs. (Not applicable for Ph-like ALL and MPAL).			
Administration of study treatment [o]	X			
Investigator's assessment of disease			X	X [p]
Alternative therapy (anticancer therapy)				X

AE: adverse event; BCR-ABL1: breakpoint cluster region Abelson 1; BSA: body surface area; COVID-19: coronavirus disease 2019; ECG: electrocardiogram; ECHO: echocardiogram; EOT: end of treatment; MUGA: multigated acquisition scan; TSH: thyroid stimulating hormone; WBC: white blood cell.

Note: Other studies or more frequent monitoring may be indicated for good clinical care. The optional continuation therapy should be done at the investigative site. Every effort should be made to conduct patient visits at the investigative site. However, follow-up visits may be conducted by home health care visits in cases where flexibility is needed due to the COVID-19 public health emergency.

Table 2 Schedule of Events for Ponatinib

28-Day Cycles	Optional Continuation Regimen		EOT2 [a]	Follow-up [b]
Cycle Days	**1 [c]**	**Every 3 Months**	**30-40 Days After Last Dose**	
Window (days)	**±3**	**±7**		**±14**

[a] EOT2 is 30 to 40 days after the last dose of ponatinib, or earlier, if the patient is proceeding to alternate therapy; EOT2 should be completed before alternative anticancer therapy(ies) are given.

[b] Each patient will be followed for a minimum of 36 months after EOT1 visit or until patient withdrawal from study, whichever occurs first. For patients eligible to receive optional ponatinib continuation treatment, follow-up visits after EOT2 will occur at 6 months, 1 year, 18 months, 2 years, and then annually. If a patient refuses to return to the clinic for the scheduled long-term follow-up visits, information can be collected via telephone contact reports; however, this is not preferred (see Section 9.3.17).

[c] For the first cycle of optional ponatinib continuation therapy only: Day 1 assessments need to be performed ONLY if 10 days or more have elapsed since the EOT1 visit.

[d] The hematology and chemistry blood samples will be collected on Day 1 as well as at EOT2 and Follow-up. Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBCs), differential WBC count, and platelets. Machine counts are acceptable. The chemistry panel consists of the following: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen, creatinine, direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, gamma-glutamyl transferase, triglycerides, lipase, amylase, albumin, glucose, urate, calcium, phosphate, and magnesium. A local bone marrow aspirate and biopsy for morphology, cytogenetics, and flow cytometry should be done if clinically indicated.

[e] To follow organ function and detect relapse.

[f] A pregnancy test will be performed only for female patients of childbearing potential according to local standard of care. At initiation of therapy, the results must be negative within 3 days before the first dose of ponatinib is administered. Monthly pregnancy testing (urine or serum) will be performed according to local standard of care while patient is on ponatinib continuation therapy.

[g] Height and weight needed to assess growth.

[h] The neurological assessment can be performed by the pediatric oncologist and includes the Modified “Balis” Pediatric Scale for peripheral neuropathy.

[i] The neurological assessment should be performed once a month during continuation therapy.

[j] Growth charts and Tanner staging will be used for growth and development assessments. Other tests may be needed as clinically indicated.

[k] ECGs must all be 12-lead ECGs. 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. On days when both an ECG and a blood draw is performed, the ECG should be done before the blood draw. During the optional ponatinib continuation therapy, ECGs may be performed more frequently if clinically indicated. During follow-up, ECGs will be performed yearly until the end of study follow-up.

[l] During the optional continuation therapy, ECHOs or MUGAs may be performed more frequently if clinically indicated. During follow-up, ECHO or MUGA will be performed yearly until the end of study follow-up.

[m] Lumbar puncture for cell count and cytospin cytology to be performed every 3 months while the patient is receiving optional continuation combination

Table 2 Schedule of Events for Ponatinib

28-Day Cycles	Optional Continuation Regimen		EOT2 [a]	Follow-up [b]
Cycle Days	**1 [c]**	**Every 3 Months**	**30-40 Days After Last Dose**	
Window (days)	**±3**	**±7**		**±14**

therapy with intrathecal chemotherapy.

[n] Submission of peripheral blood samples to central laboratory to assess molecular mutations including T315I (eg, *BCR-ABL1*, *IKZF1*, *CDKN2A/2B*) if relapse from complete remission is reported by the investigator.

[o] Administration of study treatment will also include diary review and study treatment verification. Ponatinib will be administered once daily. See Table 6 for details of recommended combination regimen for optional ponatinib continuation therapy. Patients may receive ponatinib as monotherapy or in combination with maintenance-type chemotherapy until more definitive therapy is initiated.

[p] Bone marrow and other pertinent investigations are to be performed as clinically indicated. If relapse from complete remission is confirmed, results of the assessments used to confirm the relapse, including bone marrow assessment, and their date must be provided in the electronic data capture.

Table 3 Phase 1 PK Sampling Schedule

Blood samples will be collected from all patients for the measurement of plasma concentrations of ponatinib. A sparser PK sampling schedule will be used for patients weighing <20 kg because of potential blood volume loss limitations. The exact date and time of each PK sample collection should be recorded in the eCRF.

Note: If ponatinib is not administered on Day 22 of the reinduction block, then the Day 22 and Day 23 PK samples should be collected on the next ponatinib dosing day.

Time Point	Reinduction Block Day 1	Reinduction Block Day 2	Reinduction Block Day 22	Reinduction Block Day 23
For Patients <20 kg				
Predose (within 1 hour prior to dosing)			X	
2 hours postdose (±15 minutes)			X	
4 hours postdose (±15 minutes)	X			
6 hours postdose (±15 minutes)			X	
24 hours postdose (±1 hour)		X [a]		X [a]
For Patients ≥20 kg				
Predose (within 1 hour prior to dosing)			X	
1 hour postdose (±10 minutes)	X		X	
2 hours postdose (±15 minutes)	X		X	
4 hours postdose (±15 minutes)	X		X	
6 hours postdose (±15 minutes)	X		X	
8 hours postdose (±30 minutes)	X		X	
24 hours postdose (±1 hour)		X [a]		X [a]

PK: pharmacokinetic.

[a] The 24 hours postdose sample should be collected prior to the Day 2 or Day 23 dose of ponatinib.

Table 4 Phase 2 PK Sampling Schedule

Blood samples will be collected from all patients for the measurement of plasma concentrations of ponatinib. A sparser PK sampling schedule will be used for patients weighing <20 kg because of potential blood volume loss limitations. The exact date and time of each PK sample collection should be recorded in the eCRF.

Note: If ponatinib is not administered on Day 22 of the reinduction block, then the Day 22 PK samples should be collected on the next ponatinib dosing day.

Time Point	Reinduction Block Day 1	Reinduction Block Day 2	Reinduction Block Day 22
For Patients <20 kg			
Predose (within 1 hour prior to dosing)			X
1 to 2 hours postdose	X		
3 to 4 hours postdose			X
6 to 8 hours postdose	X		X
24 hours postdose (±1 hour)		X [a]	
For Patients ≥20 kg			
Predose (within 1 hour prior to dosing)			X
1 to 2 hours postdose	X		X
3 to 4 hours postdose	X		X
6 to 8 hours postdose	X		X
24 hours postdose (±1 hour)		X [a]	

PK: pharmacokinetic.

[a] The 24 hours postdose sample should be collected prior to the Day 2 dose of ponatinib.

Table 5 Schedule of Drugs

Days	**1**	**2**	**3**	**5**	**8**	**9**	**15**	**19**	**22**	**29**	**35**
Reinduction Block											
Ponatinib PO [a]	→	→	→	→	→	→	→	→	→	→	→
Vincristine IV (1.5 mg/m^2) [b]	X				X		X		X	Bone marrow	
Dexamethasone PO/IV (10 mg/m^2) [c]	→	→	→	→	→	→					
PEG-asparaginase IV/IM (2500 IU/m^2) [d]		X									
Daunorubicin IV (30 mg/m^2) [e]	X	X									
CNS-1/2: IT methotrexate chemotherapy [g]	X [f]						X			X	
CNS-3: ITT chemotherapy [h]	X				X		X		X	X	
Consolidation Block [i]											
Ponatinib PO [a]	→	→	→	→	→	→	→	→	→	→	→
Dexamethasone PO/IV (6 mg/m^2) [j]	→	→	→	→						Bone marrow	
Vincristine IV (1.5 mg/m^2) [b]			X								
Methotrexate IV (1000 mg/m^2) [k]					X						
PEG-asparaginase IV/IM (2500 IU/m^2) [l]						X					
Cyclophosphamide IV (440 mg/m^2) [m]							→	→			
Etoposide IV (100 mg/m^2) [n]							→	→			
CNS-1/2: IT methotrexate chemotherapy [g]					X						
CNS-3: ITT chemotherapy [h]					X						

ANC: absolute neutrophil count; BID: twice daily; CNS: central nervous system; IM: intramuscularly; IT: intrathecal (therapy); ITT: triple intrathecal (therapy); IU: international units; IV: intravenous(ly); PEG: polyethylene glycol; PO: orally (by mouth); RP2D: recommended phase 2 dose.

[a] Dose assigned per protocol: In phase 1, dose is as described in Table 8.a; in phase 2, dose is RP2D.

[b] IV push over 1 minute or infusion via minibag as per institutional policy. Maximum dose is 2 mg.

[c] 10 mg/m^2/day divided BID, ie, 5 mg/m^2/dose BID.

[d] IV over 1 to 2 hours or IM. In cases where PEG-asparaginase is not available or where patients are allergic to PEG-asparaginase, *Erwinia*-asparaginase can be used as an alternative. If there are supply issues with PEG-asparaginase at the site, the dosing of PEG-asparaginase can occur within 4 days of due date.

[e] IV over 15 minutes.

Table 5 Schedule of Drugs

[f] May omit initial IT chemotherapy on Day 1 if patient received IT chemotherapy within 7 days before study enrollment as part of diagnostic lumbar puncture procedure.
[g] IT methotrexate is for CNS-1/2 patients only. Dose is defined by age as follows: age 1 through 1.99 years: 8 mg; age 2 through 2.99 years: 10 mg; age 3 through 8.99 years: 12 mg; age ≥9 years: 15 mg.
[h] ITT chemotherapy is for CNS-3 patients only. Dose is defined by age in the following table:

Age (years)	Methotrexate	Hydrocortisone	Cytarabine
1 – 1.99	8 mg	8 mg	16 mg
2 – 2.99	10 mg	10 mg	20 mg
3 – 8.99	12 mg	12 mg	24 mg
≥9	15 mg	15 mg	30 mg

[i] To start the consolidation block, the following criteria must be met: ANC ≥750/µL, platelets ≥50,000/µL (untransfused) (van Veen et al. 2010), and toxicity considered to be related to treatment with ponatinib must have resolved to Grade 1 or baseline or to a level considered acceptable by the physician.
[j] 6 mg/m^2/day divided BID, ie, 3 mg/m^2/dose BID.
[k] Intermediate-dose methotrexate administered IV over 36 hours. The 1000 mg/m^2/dose should be given as a 100 mg/m^2 bolus over 30 minutes followed by 900 mg/m^2 over 35.5 hours. Note: Be certain that the methotrexate infusion is completed in the 36-hour period. See Table 8.c for IV hydration and leucovorin rescue therapy.
[l] IV over 1 to 2 hours or IM on Day 9 or 10; administer 4 hours after completion of Day 8 IV methotrexate. In cases where PEG-asparaginase is not available or where patients are allergic to PEG-asparaginase, *Erwinia*-asparaginase may be given IM/IV on Monday/Wednesday/Friday (or every other day per institutional standard) × up to 6 doses for each dose of PEG-asparaginase at 25,000 IU/m^2/dose.
[m] IV over 15-30 minutes.
[n] IV over 1-2 hours.

Table 6 Optional Continuation Therapy With Ponatinib: Recommended Combination Regimen Following Consolidation

Therapeutic Agent	Days/Frequency
Ponatinib	Daily
Vincristine	Every 4 weeks
Dexamethasone or prednisone	5 days every 4 weeks
Mercaptopurine	Daily
Methotrexate (PO)	Once a week
Methotrexate (IT)	Once every 3 months

IT: intrathecal; PO: by mouth (orally).

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 investigator agrees to assume the following responsibilities:

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 (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential patients 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 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 patients. 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 ICH and local regulations, are met.
9. Obtain valid informed consent from each patient who participates in the study, and document the date of consent in the patient'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 patient'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 patient or the patient's parent or legal guardian.
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 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.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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 the 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.

Appendix D Performance Score Scales

Karnofsky Performance Status Scale (patients ≥16 years of age)		Lansky Play Scale (patients <16 years of age)	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Source: (Karnofsky and Burchenal 1949) and (Lansky et al. 1987).

Appendix E Acceptability and Palatability Questionnaire for the Ponatinib AAF (Reinduction Only)

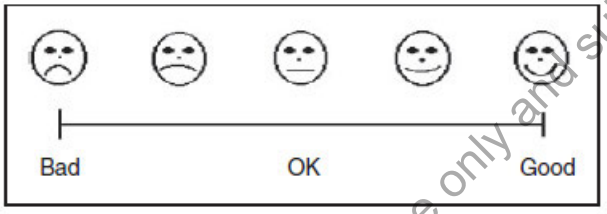
Acceptability/Palatability Questionnaire for Ponatinib AAF (Reinduction only)

Patient ID #: _____ **Date:** _____

Dose Day: Day 1____ Day 8____ Day 15____ Day 22____

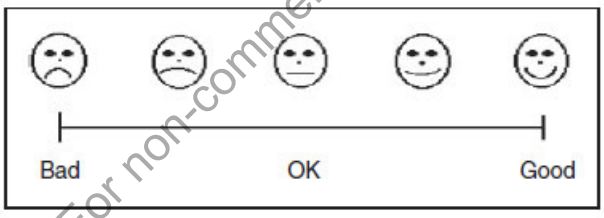
Who completed the form? Parent/Guardian____ Child____

1. How was ponatinib AAF administered?
   ____ Whole minitablet capsule(s) with water
   ____ Opened capsule with minitablets sprinkled on applesauce
   ____ Opened capsule with minitablets sprinkled on yogurt
2. Did you (or your child) swallow the dose? Yes____ No____
3. What do you think of the smell?



1 2 3 4 5

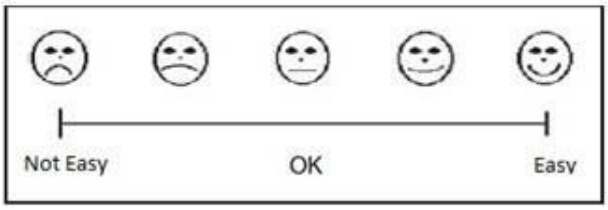
4. What do you think of the taste?



1 2 3 4 5

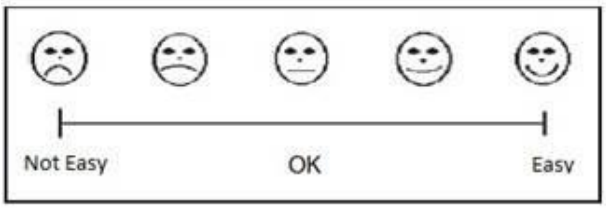
5. Any aftertaste? Yes____ No____

6. How easy is it for you (your child) to take ponatinib?



1 2 3 4 5

7. How easy is it to take other oral medications?



1 2 3 4 5

Appendix F Tanner Scale

Criteria for Distinguishing Tanner Stages 1 to 5 During Female Pubertal Maturation

Stage	Breast	Pubic Hair
1 (prepubertal)	No palpable glandular tissue or pigmentation of areola; elevation of areola only	No pubic hair; short, fine vellus hair only
2	Glandular tissue palpable with elevation of breast and areola together as a small mound; areolar diameter increased	Sparse, long, pigmented terminal hair chiefly along the labia majora
3	Further enlargement without separation of breast and areola; although more darkly pigmented, areola still pale and immature; nipple generally at or above midplane of breast tissue when individual is seated upright	Dark, coarse, curly hair, extending sparsely over mons
4	Secondary mound of areola and papilla above breast	Adult-type hair, abundant but limited to mons and labia
5 (adult)	Recession of areola to contour of breast; development of Montgomery's glands and ducts on areola; further pigmentation of areola; nipple generally below midplane of breast tissue when individual is seated upright; maturation independent of breast size	Adult-type hair in quantity and distribution; spread to inner aspects of the thighs in most racial groups

Source: Data from Ross GT: Disorders of the ovary and female reproductive tract. In Wilson JD, Foster DW (eds): Textbook of Endocrinology, 7th ed. Philadelphia, WB Saunders, 1985, p 206.

Criteria for Distinguishing Tanner Stages 1 to 5 During Pubertal Stages in Boys

Stage	Pubic Hair	Genital
1	Absence of pubic hair	Childlike penis, testes, and scrotum (testes 2 mL)
2	Sparse, lightly pigmented hair mainly at the base of the penis	Scrotum enlarged with early rugation and pigmentation; testes begin to enlarge (3–5 mL)
3	Hair becomes coarse, darker, and more curled and more extensive	Penis has grown in length and diameter; testes now 8–10 mL; scrotum more rugated
4	Hair adult in quality, but distribution does not include medial aspect of thighs	Penis further enlarged with development of the glans; scrotum and testes (10–13 mL) further enlarged
5	Hair is adult and extends to thighs	Penis and scrotum fully adult; testes 15 mL and greater

Source: Modified from Marshall WA, Tanner JM: Variation in pattern of pubertal changes in boys. Arch Dis Child 1970;45:13–23.

Appendix G Definition of CNS- 1/2/3 in CSF

CNS-1: In CSF, absence of blasts on cytospin preparation, regardless of the number of WBCs.

CNS-2: In CSF, presence <5/µL WBCs and cytospin positive for blasts, or ≥5/µL WBCs but negative by Steinherz/Bleyer^ algorithm in traumatic lumbar punctures.

CNS-3: In CSF, presence of ≥5/µL WBCs and cytospin positive for blasts and/or clinical signs of CNS leukemia.

Method of Evaluating Initial Traumatic Lumbar Punctures:

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥5 WBC/µL and blasts, the following algorithm should be used to distinguish between CNS-2 and CNS-3 disease:

If CSF WBC ÷ CSF RBC >2 × blood WBC ÷ blood RBC, then patient has CNS-3 disease

If CSF WBC ÷ CSF RBC <2 × blood WBC ÷ blood RBC, then patient has CNS-2 disease

Example: CSF WBC = 60/µL; CSF RBC = 1500/µL; blood WBC = 46000/µL; blood RBC = 3.0×10^6/µL: 0.04 >2× 0.015: Patient has CNS-3 disease.

Appendix H Protocol History

Date	Amendment Number	Amendment Type	Region
02 November 2023	Amendment 4	Substantial	Global
23 May 2023	Amendment 3	Substantial	Global
23 February 2021	Amendment 2	Substantial	Global
09 April 2020	Amendment 1	Substantial	Global
25 July 2019	Initial Protocol	Not applicable	Global

Protocol Amendment 3 Summary and Rationale:

This section describes the changes to the protocol incorporating Amendment 3. The primary reasons for this amendment are to:

- Modify inclusion Criterion 1 and exclusion Criterion 3 relating to diagnosis to allow globally the inclusion of patients with Philadelphia chromosome–like acute lymphoblastic leukemia (Ph-like ALL). Patients with Ph-like ALL will not be included in efficacy analyses.
- Define the second cohort (cohort 2) of the phase 1 portion of the study, including information on the composition of each weight group and the ponatinib dose assignment.
- Revise the disease assessment at end of reinduction and consolidation blocks to add a visit at Day 35 (±3) for hematology assessment (for recovery of platelets and neutrophils).
- Include administration and dosing information for the age-appropriate formulation that is now available.
- Modify the medical management of elevated alanine aminotransferase.
- Clarify the definition for dose-limiting toxicities (DLT) for liver toxicities given the liver toxicities observed in phase 1 cohort 1.

In addition, the protocol was updated to:

- Change a secondary objective ("to characterize BCR-ABL1 domain mutations both prior to and following ponatinib treatment") to an exploratory objective and update the corresponding endpoint and analyses of molecular mutations to be performed.
- Divide a secondary objective ("to describe the proportion of patients in continued complete remission (CR) or who achieve CR at the end of consolidation and the proportion of patients with minimal residual disease (MRD) status <0.01% at the end of each treatment block") into 2 objectives for clarity.
- Revise the optional ponatinib continuation to extend beyond 12 months under specified conditions, remove the optional continuation phase monthly Day 14 visit, and add an investigator's assessment of disease at the second end of treatment (EOT2) visit.
- Provide information on clinical experience for phase 1 cohort 1.
- Add the possibility that some study-related activities may be performed remotely.

- Correct in the schedule of events (SOEs) on which days the study treatment is administered.
- Provide additional guidance to sites regarding: enrollment under T315I mutation eligibility criterion; method of disease diagnosis in patients with Ph-like ALL; study treatment; use of concomitant medications; mandatory/non-mandatory hepatitis testing and HIV testing; nature of bone marrow (BM) samples (aspirate and/or biopsy); timing of complete blood cell count and BM evaluation for CR assessment; timing of peripheral blood samples for molecular mutations during follow-up; results of the assessments used to confirm the relapse from CR and completed as clinically indicated; necessity to perform a complete blood cell count; chemistry parameters to be assessed; testing of baseline samples; threshold of platelet counts to start the consolidation block or optional continuation therapy; assessment of adverse event (AE) relationship; hospitalization or surgical procedures not considered as AEs; SAE follow-up; reporting of drug exposure during pregnancy and birth events; method to assess the left ejection fraction; samples of BM not to be centrally assessed; patient population to be administered the palatability questionnaire; management of nonhematologic treatment-related toxicities; frequency of follow-up visits for patients eligible to receive optional ponatinib continuation treatment; and timings of pharmacokinetic sample collection.
- Clarify that the required number of patients in phase 1 of the study corresponds to DLT-evaluable patients.
- Clarify that patients with Ph-like ALL and Philadelphia chromosome-positive mixed phenotype acute leukemia will not be included in efficacy analyses.
- Update the definition of progression-free survival event for death.
- Correct or clarify the patients' age for Karnofsky performance status scale and Lansky play scale.
- Clarify that lumbar puncture for cell count and cytospin cytology is to be conducted while patient is receiving optional ponatinib continuation therapy if done in combination with intrathecal chemotherapy.

In this amendment, minor grammatical, editorial, formatting (including bibliographic references format), and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only and may not be listed in the summary of changes below.

Protocol Amendment 3			
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.	Throughout the document.	Changed "caregivers" to "parents/legal guardians".	Administrative change for consistency across the document.

Protocol Amendment 3			
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 1.1 Contacts	Added text with regards to contact information.	To provide additional guidance to sites, consistently with the sponsor protocol template.
3.	Section 1.2 Approval	Updated the list of approvers.	Administrative change.
4.	Section 4.1.3 Ponatinib Nonclinical Data	Removed the investigator's brochure version and the section number of the investigator's brochure.	Administrative change: the investigator's brochure being updated each year, version and section numbers may not be up-to-date.
5.	Section 4.2.4.1 Cohort 1 of the Phase 1 Portion of the Study	Revised to provide dosing information for pediatric patients <30 kg due to availability of the AAF.	The AAF is available for use as of protocol amendment 3.
6.	Section 2.0 STUDY SUMMARY (and Figure 2.a) Section 4.2.4.1 Cohort 1 of the Phase 1 Portion of the Study Section 6.1 Overview of Study Design (and Figure 6.a) Section 7.0 STUDY POPULATION Section 8.1.1 Investigational Therapy: Ponatinib Section 8.1.2 Study Treatment Regimen Section 8.12.1 Ponatinib Tablets	Modified language and updated study design schema as enrollment to cohort 1 of the phase 1 portion of the study is completed.	To update the section and indicate phase 1 cohort 1 status.

Protocol Amendment 3			
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***
7.	Section 2.0 STUDY SUMMARY (and Figure 2.a, Table 2.a) Section 4.2.4.2 Safety Data from Cohort 1 of the Phase 1 Portion of the Study Section 4.2.4.3 Cohort 2 of the Phase 1 Portion of the Study Section 6.1 Overview of Study Design (and Figure 6.a) Section 7.0 STUDY POPULATION Section 8.1.1 Investigational Therapy: Ponatinib Section 8.1.2 Study Treatment Regimen (and Table 8.a) Section 8.4.2.4 Dose Re-escalation After Resolution of Adverse Drug Reactions Section 8.10 Description of Investigational Agents Section 8.11 Preparation, Reconstitution, and Dispensation Section 8.12.2 Ponatinib Age-Appropriate Formulation (AAF) Section 8.13.2 Handling and Accountability	Added 2 new sections (Sections 4.2.4.2 and 4.2.4.3). Added clinical experience from phase 1 cohort 1. Added rationale and text relative to the opening of second cohort (cohort 2) to the phase 1 portion of the study. Included the minimum number of patients in each weight group in phase 1 cohort 2, and related requirements with regards to patients' age and weight. Modified text related to the AAF that is now available. Provided further information on the AAF and the doses for phase 1 cohort 2. Modified study design schema: • Changed "to confirm RP2D for 2 formulations" to "to confirm RP2D" in phase 1 box. • Removed arrow between phase 1 box and phase 2 box. • Added that enrollment to phase 1 cohort 1 is complete. • Added phase 1 cohort 2.	To indicate phase 1 cohort 1 status, add information related to phase 1 cohort 2 and clarify.

Protocol Amendment 3			
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***
8.	Section 4.3 Age-Appropriate Formulation for Ponatinib	Added a new section with conclusions of Study INCB 84344-103 that assessed the relative bioavailability of the AAF versus the tablet formulation.	To provide information regarding the relative bioavailability of the AAF versus the tablet formulation to support use of the AAF in this pediatric study.
9.	Section 2.0 STUDY SUMMARY Section 5.1.2.1 Phase 1 Secondary Objectives Section 5.1.2.2 Phase 2 Secondary Objectives Section 5.1.3 Exploratory Objectives	Changed a secondary objective ("to characterize BCR-ABL1 domain mutations both prior to and following ponatinib treatment") to an exploratory objective ("Ph+ ALL only: To characterize biomarkers of sensitivity and resistance to ponatinib-containing therapy, which may include molecular mutations (eg, *BCR-ABL1*, *IKZF1*, *CDKN2A/2B*) in samples both prior to and following ponatinib treatment"). Clarified that this objective is only for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).	To allow flexibility with the sites, to prioritize the samples for MRD assessment, and to broaden the analyses of molecular mutations.

Protocol Amendment 3			
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***
10.	Section 2.0 STUDY SUMMARY Section 5.1.2.2 Phase 2 Secondary Objectives	Divided the secondary objective relating to CR and MRD ("to describe the proportion of patients in continued CR or who achieve CR at the end of consolidation and the proportion of patients with MRD status <0.01% at the end of each treatment block") into 2 objectives to clarify the assessment based on patients' CR status. ("to describe the proportion of patients who achieved CR at the end of consolidation" and "to describe the proportion of patients with MRD status <0.01% among those who achieved CR at the end of each treatment block")	To clarify.
11.	Section 2.0 STUDY SUMMARY Section 5.1.2.2 Phase 2 Secondary Objectives Appendix A, Schedules of Events (Table 1 and Table 2)	Clarified that the secondary objectives relating to CR and MRD are only for patients with Ph+ ALL.	To clarify as MRD cannot be followed for patients with Ph-like ALL or MPAL due to heterogeneity of underlying molecular mutations and challenges in finding assays for them with adequate sensitivity.

Protocol Amendment 3			
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 2.0 STUDY SUMMARY Section 5.2.2.1 Phase 1 Secondary Endpoints Section 5.2.2.2 Phase 2 Secondary Endpoints Section 5.2.3 Exploratory Endpoints Section 9.3.15 Biomarkers and Pharmacokinetic Measurements Section 9.3.15.2 Peripheral Blood Samples for Molecular Mutations Appendix A, Schedules of Events (Table 1 and Table 2)	Grouped a secondary endpoint ("characterization of BCR-ABL1 domain mutations both prior to and following ponatinib treatment") and an exploratory endpoint ("biomarkers of disease sensitivity and resistance to ponatinib and/or biomarkers affecting ponatinib") into a single exploratory endpoint ("Ph+ ALL only: Biomarkers of potential sensitivity and resistance to ponatinib-containing therapy, which may include molecular mutations (eg, *BCR-ABL1*, *IKZF1*, *CDKN2A/2B*) in samples both prior and following ponatinib treatment"). Clarified that this endpoint is only for patients with Ph+ ALL. Updated the intended use of blood samples for molecular mutations at screening and clarify these analyses are only for patients with Ph+ ALL (including Table 9.a).	To allow flexibility with the sites, to prioritize the samples for MRD assessment, and to broaden the analyses of molecular mutations.

Protocol Amendment 3			
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***
13.	Section 2.0 STUDY SUMMARY Section 5.2.2.2 Phase 2 Secondary Endpoints Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures (Table 6.a)	Divided the secondary endpoint relating to CR and MRD ("proportion of patients in continued CR or who achieve CR at the end of consolidation and the proportion of patients with MRD negative status (<0.01%) at the end of each treatment block") into 2 endpoints to clarify the assessments based on the patients' CR status ("proportion of patients who achieved CR at the end of consolidation" and "proportion of patients with MRD negative status (<0.01%) among those who achieved CR at the end of each treatment block").	To clarify.
14.	Section 2.0 STUDY SUMMARY Section 5.2.2.2 Phase 2 Secondary Endpoints Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures (Table 6.a) Section 9.3.15 Biomarkers and Pharmacokinetic Measurements (Table 9.a) Section 9.3.15.1 Bone Marrow Samples for MRD Assessment Section 13.1.3.3 Definitions of Response Criteria (Table 13.a) Appendix A, Schedules of Events (Table 1)	Clarified that the secondary endpoints relating to CR and MRD are only for patients with Ph+ ALL.	To clarify as MRD will not be followed for patients with Ph-like ALL or MPAL.

Protocol Amendment 3			
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***
15.	Section 2.0 STUDY SUMMARY (Figure 2.a) Section 6.1 Overview of Study Design (Figure 6.a) Appendix A, Schedules of Events (Table 1)	Added 1 visit at Day 35 (±3) of both the reinduction and consolidation blocks for assessment of platelets and neutrophils recovery. Added the other following events for these additional visits: concomitant medications and procedures, AE reporting, and administration of study treatment. Updated the study design schema: disease assessment at Day 35 instead of Day 29 of both the reinduction block and the consolidation block.	To assess the disease at a more appropriate timing for peripheral counts recovery. To update the schedule of events and the study design schema for the additional visits.
16.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 7.0 STUDY POPULATION Section 7.1 Inclusion Criteria (inclusion Criterion 1) Section 7.2 Exclusion Criteria (exclusion Criterion 3)	Deleted "United States (US) only".	To include patients with Ph-like ALL globally, based on a specific molecular definition, as these patients will most likely benefit from ponatinib treatment.
17.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 8.1.2 Study Treatment Regimen	Added the minimum of DLT-evaluable patients in each weight group of phase 1 cohort 2 and added the maximum number of patients >16 years of age in each weight group. Grouped information on design, DLTs, and cohorts in Section 6.1 (and deleted them from Section 8.1.2).	To provide information on the composition of each weight group. To clarify.

Protocol Amendment 3			
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***
18.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 13.1.1 Analysis Sets	Updated/added the definition of DLT-evaluable population and clarified the replacement of patients who are not evaluable for DLT (indicated in Section 6.2).	To take into account the percentage of planned dosing to be received for a patient to be included in the DLT-evaluable population and to clarify.
19.	Section 2.0 STUDY SUMMARY (and Figure 2.a) Section 6.1 Overview of Study Design (and Figure 6.a)	Clarified which study treatment (ponatinib and chemotherapy or ponatinib alone) is given.	To clarify that for each treatment block, treatment with ponatinib and chemotherapy for 29 days is followed by a chemotherapy rest period.
20.	Section 2.0 STUDY SUMMARY (and Figure 2.a) Section 6.1 Overview of Study Design (and Figure 6.a) Section 6.3.1 Duration of an Individual Patient's Study Participation	Clarified the extension of the optional continuation treatment with ponatinib beyond 12 months if patients continue deriving clinical benefit.	To clarify that the intention was to allow flexibility, under the protocol, to permit patients who continue to benefit from treatment to continue to receive treatment under the study after 12 months.
21.	Section 6.1 Overview of Study Design Appendix A, Schedules of Events (Table 1) Section 8.1.1.2 Age-Appropriate Formulation	Clarified that the palatability questionnaire of ponatinib is for AAF only.	To provide additional guidance to sites.
22.	Section 6.1 Overview of Study Design Section 9.3.14.1 Evaluation of CR Section 13.1.3.3 Definitions of Response Criteria (Table 13.a) Appendix A, Schedules of Events (Table 1)	Changed "bone marrow aspirate" to "bone marrow sample (aspirate and/or biopsy).	To provide additional guidance to sites, ie when BM aspirate cannot be obtained, a BM biopsy can be used.

Protocol Amendment 3			
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***
23.	Section 2.0 STUDY SUMMARY Section 6.2 Number of Patients	Clarified that the required number of patients in phase 1 of the study (approximately 18 patients) corresponds to DLT-evaluable patients. Clarified the replacement of patients withdrawn from treatment during the reinduction block.	To clarify.
24.	Section 6.3.1 Duration of an Individual Patient's Study Participation	Clarified when the EOT1 visit should be performed.	To clarify.
25.	Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures (Table 6.a)	Deleted "BCR-ABL1 domain mutations" rows (secondary endpoint).	To modify in accordance with the change of secondary to exploratory endpoint.
26.	Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures (Table 6.a) Section 13.1.3.3 Definitions of Response Criteria (Table 13.a)	Updated the definition of death used for progression-free survival endpoint: "death due to any cause" to "death related to disease under study".	To clarify the events that are progression of disease and to not count deaths due to other causes, instead these will be censored (different from event-free survival events).
27.	Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures (Table 6.a)	Clarified that for disease progression definition, the increase of at least 25% in the absolute number of circulating or BM blasts or development of new extramedullary disease is an increase from baseline.	To clarify.
28.	Section 2.0 STUDY SUMMARY Section 7.0 STUDY POPULATION Section 7.1 Inclusion Criteria (inclusion Criterion 2)	Added minimum weight in the age inclusion criterion.	To provide guidance to sites with regards to the patients' minimum weight.

Protocol Amendment 3			
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***
29.	Section 2.0 STUDY SUMMARY Section 7.0 STUDY POPULATION	Clarified that patients must have BM involvement to be eligible.	To clarify.
30.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria (inclusion Criterion 1c)ii))	Updated phase 1 eligibility criteria at the time of enrollment prior to availability of the AAF as the formulation is now available. Added phase 1 eligibility criteria at the time of enrollment for patients to be administered ponatinib as the AAF.	To update as the AAF is now available.
31.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria (inclusion Criterion 1b)ii)) Section 9.3.1 Screening Period Procedures	Added that RNA sequencing or alternative accredited method is required to identify specified targetable kinase-activating lesions for the diagnosis of the disease in patients with Ph-like ALL, and that no confirmation by a sponsor central laboratory is required.	To provide guidance to sites with regards to Ph-like diagnosis for enrollment in the study.
32.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria (inclusion Criterion 1c))	Clarified that the last 2 numbered items relate to disease status by adding a sub-criterion heading (“disease status”).	To clarify.
33.	Section 2.0 STUDY SUMMARY Section 7.0 STUDY POPULATION Section 7.1 Inclusion Criteria (inclusion Criterion 1c)ii))	Added information on the confirmation of T315I mutation eligibility criterion.	To clarify that for patients enrolled under T315I mutation eligibility criterion, the mutation needs to be confirmed by the central laboratory, and to provide additional guidance to sites.

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Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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34.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria (inclusion Criterion 1) Section 9.3.11 Adverse Events	Deleted "at least possibly" in "at least possibly related" as it was clarified in Section 10.1.2 that AE relationship should be assessed as related or not related.	To clarify.
35.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria (inclusion Criterion 3) Section 9.3.6 Performance Status Appendix D, Performance Score Scales	Corrected the inclusion of 16 years old in the age threshold to use Karnofsky performance status scale or Lansky play scale. Clarified the patients' age for Karnofsky performance status scale and Lansky play scale in Appendix D.	To correct and to clarify.
36.	Section 2.0 STUDY SUMMARY (Table 2.b) Section 7.1 Inclusion Criteria (Table 7.a)	Added the source and method for determination of maximum serum creatinine value by age and sex.	To provide source and method.
37.	Section 2.0 STUDY SUMMARY (Table 2.c) Section 7.1 Inclusion Criteria (Table 7.b)	Updated reference for Schwartz formula.	To correct.
38.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria (inclusion Criterion 8)	Added that besides multigated acquisition scan, echocardiogram can be used to assess the left ejection fraction.	To provide guidance to sites.
39.	Section 8.1.1 Investigational Therapy: Ponatinib	Added that any change to the ponatinib administration schedule should be discussed with the sponsor's medical monitor/designee.	To clarify.
40.	Section 2.0 STUDY SUMMARY Section 8.1.2 Study Treatment Regimen	Updated ponatinib doses in the table to include dosing information for patients <30 kg due to availability of the AAF.	To update ponatinib dosing information starting with cohort 2 in the phase 1 portion of the study.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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41.	Section 8.1.2 Study Treatment Regimen (Table 8.b and Table 8.c) Section 8.3 Criteria for Beginning a Consolidation Block or Optional Continuation Therapy Appendix A, Schedules of Events (Table 5)	Decreased the threshold of platelets counts from ≥75,000/µL to 50,000/µL to start the consolidation block or optional continuation therapy.	To avoid treatment delays, while maintaining safe thresholds of peripheral platelet counts.
42.	Section 8.1.2 Study Treatment Regimen (Table 8.c) Section 8.4.3.7 Intermediate-Dose Methotrexate Infusion Guidelines and Dose Modifications for Toxicity	Clarified the meaning of "D5" (5% dextrose in water).	To clarify.
43.	Section 8.1.2 Study Treatment Regimen	Corrected the ponatinib dose during optional continuation therapy and added information in case of dose reduction during consolidation block.	To correct, as patients need to complete consolidation, and to provide additional guidance to sites.
44.	Section 8.2 Definitions of Dose-limiting Toxicities	Updated text relating to events related to ponatinib, ie, "probably", "possibly", and "definitely" removed.	To clarify for consistency with data captured.
45.	Section 8.2 Definitions of Dose-limiting Toxicities	Revised definition of dose-limiting toxicities.	To align with definition in current early-phase pediatric studies.
46.	Section 8.3 Criteria for Beginning a Consolidation Block or Optional Continuation Therapy Section 8.4.2.1 Nonhematologic Treatment-Related Toxicity: Ponatinib (Table 8.e)	Increased thresholds for hepatic toxicity.	To modify in accordance with current pediatric ALL protocols and in line with current pediatric oncology protocols.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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47.	Section 8.3 Criteria for Beginning a Consolidation Block or Optional Continuation Therapy	Clarified study treatment discontinuation in case of treatment delay at a reduced level when further reductions are not permitted.	To clarify and to provide additional guidance to sites.
48.	Section 8.4.1 Early Safety Stopping Rules	Modified the early safety stopping rule if ≥4 patients in the first 15 patients accrued develop Grade ≥3 veno-occlusive event: it applies regardless of the presence or absence of a central vascular access device.	To correct an error.
49.	Section 8.4.2.1 Nonhematologic Treatment-Related Toxicity: Ponatinib (Table 8.e)	Modified medical management of nonhematologic treatment-related toxicities (pancreatitis and elevation of lipase, and alanine aminotransferase elevation).	To align with current early-phase pediatric studies and to provide additional guidance to sites.
50.	Section 8.4.3.3.2 For Acute Neurotoxicity	Clarified the meaning of "Ara-C" (cytarabine).	To clarify.
51.	Section 8.5 Excluded Concomitant Medications and Procedures	To clarify the use of concomitant medications (medication that prolong the QT interval but are not associated with a known risk of torsades de pointes).	To provide additional guidance to sites.
52.	Section 9.3 Study Procedures	Added "and Table 2" where it was missing.	To correct as there are 2 SOEs in the protocol.
53.	Section 9.3 Study Procedures	Removed "Appendix A, Table 1" at several instances in the section and subsequent subsections.	To avoid repetitions.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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54.	Section 9.3.13.5 Hepatitis B and C Appendix A, Schedules of Events (Table 1)	Clarified mandatory/non-mandatory hepatitis testing for countries with/without regulatory requirements for testing.	To provide additional guidance to sites.
55.	Section 9.3.13.6 HIV Appendix A, Schedules of Events (Table 1)	Clarified mandatory/non-mandatory HIV testing for countries with/without regulatory requirements for testing.	To provide additional guidance to sites.
56.	Section 9.3.14.1 Evaluation of CR	Clarified that after EOT1, complete blood cell count and BM evaluation for CR assessment may be performed at other times than that indicated in Appendix A, Table 1. Update the section heading from "Bone Marrow Aspirate and Biopsy/Evaluation of CR" to "Evaluation of CR".	To provide additional guidance to sites.
57.	Section 9.3.14.1 Evaluation of CR Appendix A, Schedules of Events (Table 1)	Added that when relapse from CR is confirmed, results of the assessments used to confirm the relapse and their date must be provided in the electronic data capture.	To provide additional guidance to sites.
58.	Section 9.3.14.1 Evaluation of CR Section 13.1.3.3 Definitions of Response Criteria (Table 13.a) Appendix A, Schedules of Events (Table 1)	Added the necessity of a complete blood cell count should also be performed if a BM sample is used for the diagnosis of recurrence.	To provide additional guidance to sites.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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59.	Section 9.3.15 Biomarkers and Pharmacokinetic Measurements (Table 9.a)	Added a row for peripheral blood sample to be collected at screening for MRD assessment if a BM blood sample cannot be obtained.	To clarify, consistently with the schedules of events.
60.	Section 9.3.15.2 Peripheral Blood Samples for Molecular Mutations Appendix A, Schedules of Events (Table 1)	Added information on testing of baseline samples for patients requiring enrollment eligibility confirmation and other patients.	To provide additional guidance to sites.
61.	Section 9.3.17 Follow-up Assessments Appendix A, Schedules of Events (Table 1)	Added that any disease assessments completed as clinically indicated need to be recorded in the electronic data capture.	To clarify and provide additional guidance to sites.
62.	Section 9.3.17 Follow-up Assessments Appendix A, Schedules of Events (Table 1 and Table 2)	Added the possibility of remote contacts for the scheduled long-term follow-up, and defined a patient lost to follow-up and a patient documented as lost to follow-up.	To allow telephone contact reports and to provide additional guidance to sites.
63.	Section 9.3.18 Changes to Study Procedures Due to COVID-19 Public Health Emergency Section 9.5 Reasons for Discontinuation of Treatment	Changed “pandemic” to “public health emergency”.	Administrative change for consistency across the document.
64.	Section 9.4 Completion of Study Treatment	Updated the requirements for patients to be considered to have completed study treatment with regards to optional continuation therapy.	To correct.
65.	Section 10.1.2 Adverse Event Definition	Added that AE relationship should be assessed as related or not related.	To clarify.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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66.	Section 10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events	Added information relative to follow-up SAE reports. Added that SAEs should be followed until resolution or permanent outcome of the event.	To provide additional guidance to sites, consistently with the sponsor protocol template.
67.	Section 10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events	Clarified that planned hospitalization or surgical procedures are not to be considered AEs.	To provide additional guidance to sites.
68.	Section 10.3 Monitoring of Adverse Events and Period of Observation	Clarified the review of safety and response data by the sponsor, the medical monitor, and participating investigators.	To clarify the review of study data.
69.	Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Updated text with regards to the reporting of drug exposure during pregnancy and birth events.	To provide additional guidance to sites, consistently with the sponsor protocol template.
70.	Section 11.2 IDMC	Deleted duplicated text. Moved text from Section 10.3 Monitoring of Adverse Events and Period of Observation with regards to the reception of listing updates by the IDMC.	Administrative change. To group responsibility of the IDMC within the same section, for consistency.
71.	Section 12.0 DATA HANDLING AND RECORDKEEPING	Added the version of World Health Organization Drug Dictionary used.	Administrative change, for consistency across the document.
72.	Section 12.1 eCRFs	Corrected the meaning of the abbreviation CRO (contract research organization).	To correct.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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73.	Section 2.0 STUDY SUMMARY Section 13.1.3 Efficacy Analysis	Added that patients with Ph-like ALL and Ph+ MPAL will not be included in efficacy analyses (they will be included in safety and other descriptive analyses).	To clarify as there is no clinical evidence showing the 2 subtypes of ALL to have identical response to tyrosine kinase inhibitor therapy.
74.	Section 15.2 Subject Information, Informed Consent, and Subject Authorization	To add the possibility of remote consenting and assenting for patients who would have to travel long distances to the study site, if permitted by local regulations.	To allow remote consenting and to provide additional guidance to sites.
75.	Section 15.4.4 Data Sharing	Added numbered heading.	To correct.
76.	Appendix A, Schedules of Events (Table 1)	Added that for patients with an early EOT1, the echocardiogram or multigated acquisition scan does not need to be repeated if specified circumstances are met.	To clarify and provide additional guidance to sites.
77.	Appendix A, Schedules of Events (Table 1)	Added that during follow-up, peripheral blood samples for molecular mutations are required in case of relapse only.	To clarify and provide additional guidance to sites.
78.	Appendix A, Schedules of Events (Table 1)	Corrected in the SOEs that the study treatment is also administered on Days 1, 15, 22, and 29 of the consolidation block (daily administration).	To correct, consistently with the protocol.
79.	Appendix A, Schedules of Events (Table 1 and Table 2)	Added a row in both SOEs for the investigator's assessment of disease and for collection of alternative therapy (anticancer therapy).	To clarify when the disease is to be assessed and when alternative therapy is collected.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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80.	Appendix A, Schedules of Events (Table 1 and Table 2)	Added that EOT1 (Table 1) and EOT2 (Table 2) should be completed before alternative anticancer therapy(ies) are given.	To clarify and provide additional guidance to sites.
81.	Appendix A, Schedules of Events (Table 1 and Table 2)	Clarified in the chemistry panel of both SOEs that the 'direct' bilirubin is to be assessed.	To provide additional guidance to sites.
82.	Appendix A, Schedules of Events (Table 1 and Table 2)	Added triglycerides in the chemistry panel of both SOEs.	To provide additional guidance to sites.
83.	Appendix A, Schedules of Events (Table 1)	Added that no BM sample is to be shipped for central laboratory MRD assessment for patients with MPAL and for patients with Ph-like ALL.	To provide additional guidance to sites to ensure samples are collected only from patients for whom an analysis can be performed (patients with Ph+ ALL).
84.	Appendix A, Schedules of Events (Table 1)	Clarified than when a relapse from CR is reported for patients with Ph+ ALL, a peripheral blood sample is to be taken before alternative therapy(ies) are given.	To clarify.
85.	Appendix A, Schedules of Events (Table 2)	Removed the optional ponatinib continuation phase monthly Day 14 visit and assessments.	To reduce the patient's burden in the optional treatment phase and align with standard practice in this population.
86.	Appendix A, Schedules of Events (Table 2)	Changed that peripheral blood samples for molecular mutations are only required "if relapse occurs" rather than "if relapse is suspected".	To clarify.
87.	Appendix A, Schedules of Events (Table 2)	Added an investigator's assessment of disease to the EOT2 visit.	To clarify expectation for investigator to record the patient's disease status at the end of study treatment which will support secondary endpoint evaluation of duration of response and/or relapse.

Protocol Amendment 3			
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***
88.	Appendix A, Schedules of Events (Table 2)	Clarified the frequency of follow-up visits for patients eligible to receive optional ponatinib continuation treatment.	To provide additional guidance to sites.
89.	Appendix A, Schedules of Events (Table 2)	Updated when echocardiograms multigated acquisition scans are to be performed.	To harmonize, consistently with Table 1.
90.	Appendix A, Schedules of Events (Table 2)	Clarified the wording of when lumbar puncture for cell count and cytospin cytology is to be performed.	To clarify and provide additional guidance to sites.
91.	Appendix A, Schedules of Events (Table 2)	Added that BM assessment and other pertinent investigations are to be performed as clinically indicated at the follow-up visit and listed data to be collected if relapse from complete remission is confirmed.	To clarify and for consistency with Appendix A, Table 1.
92.	Appendix A, Schedules of Events (Table 3 and Table 4)	Clarified timing of pharmacokinetic sample collection if ponatinib dosing is interrupted or delayed.	To provide additional guidance to sites.
93.	Appendix A, Schedules of Events (Table 5)	Clarified initial intrathecal chemotherapy administered on Day 1 of reinduction block for CNS-1/2 patients and CNS-3 patients.	To provide additional guidance to sites.
94.	Appendix F, Tanner Scale	Updated the table heading for pubertal stages in boys.	To harmonize within Appendix F.

AAF: age-appropriate formulation; AE: adverse event; BCR-ABL1: breakpoint cluster region Abelson 1; BM: bone marrow; CNS: central nervous system; CR: complete remission; DLT: dose-limiting toxicities; EOT1: end of treatment 1; IDMC: independent data monitoring committee; MPAL: mixed phenotype acute leukemia; MRD: minimal residual disease; Ph-like ALL: Philadelphia chromosome–like acute lymphoblastic leukemia; RP2D: recommended phase 2 dose; SAE: serious adverse event; SOE: schedule of events.

Protocol Amendment 2 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 2. The primary reasons for this amendment are:

- To remove a dose of asparaginase therapy given in combination with ponatinib.
- To clarify procedural details for enhanced patient safety.
- To maintain patient safety, confidentiality, and study integrity in the context of health care delivery challenges presented by the coronavirus disease 2019 (COVID-19) pandemic.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 2			
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 4.2.4 Rationale for the Dose of Ponatinib	Added a sentence to the beginning of the section to provide additional context for the design of phase 1 of the study.	To provide additional context for the design of phase 1 of the study.
2.	Section 5.2.3 Exploratory Endpoints	Added endpoint to match last exploratory objective.	To match the exploratory objective with a corresponding endpoint.
3.	Section 6.1 Overview of Study Design and Section 8.1.2 Study Treatment Regimen	Added language to clarify the transition of patients to the optional continuation therapies and expectations of end of treatment visits. Also clarified the dose of ponatinib used in optional continuation therapy.	To provide clarity for investigators on expectations for continuation therapies.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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4.	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 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures Table 6.a Section 6.3.4 Section 9.3.17 Follow-up Assessments, and Appendix A Schedules of Events, Table 1 and Table 2	Clarified the period of follow-up.	To allow for at least 3 years of follow-up.
5.	Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting	Clarified the end of study definition.	To provide clarity.
6.	Section 2.0 Study Summary and Section 6.3.4 Total Study Duration	Clarified the period of evaluation.	To allow for at least 36 months of evaluation.
7.	Section 6.3.4 Total Study Duration	Updated the projected duration of study.	To update based on current projections.
8.	Section 2.0 Study Summary and Section 6.2 Number of Patients	Updated the number of study sites and countries.	To update numbers.

Protocol Amendment 2			
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***
9.	Section 2.0 Study Summary and Section 7.1 Inclusion Criteria	Inclusion Criterion 1 was changed to clarify the eligibility criteria for diagnosis.	To provide further clarity on diagnosis of patients that would be appropriate for the study.
10.	Section 2.0 Study Summary and Section 7.1 Inclusion Criteria	In Inclusion Criterion 6.a, adequate renal function was defined using estimated glomerular filtration rate as calculated by the Schwartz formula.	To provide a formula for characterizing renal function in the pediatric population.
11.	Section 2.0 Study Summary and Section 7.1 Inclusion Criteria	Changed Inclusion Criteria 11 and 12 to require "at least 6 months" of contraception after the end of study therapy for both male and female patients in the study.	This change was made to address contraception requirements for all study treatments.
12.	Section 2.0 Study Summary and Section 7.2 Exclusion Criteria	Deleted the exception from Exclusion Criterion 7 relating to patients with hypertriglyceridemia.	This change was made to ensure patient safety.
13.	Section 2.0 Study Summary and Section 7.2 Exclusion Criteria	Changed Exclusion Criterion 11 to include contraindications to any study drugs.	To ensure patient safety.
14.	Section 2.0 Study Summary and Section 7.2 Exclusion Criteria	Added exclusion criterion for hepatitis B, hepatitis C, and HIV infections.	To ensure patient safety.
15.	Section 2.0 Study Summary and Section 7.2 Exclusion Criteria	Exclusion Criterion #17 was modified in the exception to state that all neurologic deficits and causative factor(s) have resolved.	To ensure patient safety.
16.	Section 2.0 Study Summary, Section 7.2 Exclusion Criteria, and Section 8.5 Excluded Concomitant Medications and Procedures	Added that live vaccines are exclusionary before and during the study.	To ensure patient safety.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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17.	Section 8.1.2 Study Treatment Regimen and Section 8.2 Definitions of Dose-limiting Toxicities	Clarified the dose-limiting toxicity (DLT) observation period to be 35 days on treatment in phase 1 unless there are residual hematologic toxicities on Day 35, in which case the patient will be followed for up to an additional 7 days for DLT evaluation.	This change was made to provide clarity and internal consistency in the document.
18.	Section 8.1.2 Study Treatment Regimen and Appendix A Schedules of Events, Table 5	Deleted the Day 15 dose of polyethylene glycol (PEG)-asparaginase from the reinduction block in Table 8.b and Table 8.c Section 8.1.2.	To mediate the concern about asparaginase therapy in combination with ponatinib.
19.	Section 8.1.2 Study Treatment Regimen	Deleted doses of triple intrathecal chemotherapy on Days 1, 15, 22, and 29 in the consolidation block from Table 8.c to match dosing in Schedule of Events.	For internal consistency in the document (this was a typographical error in the original) and to reflect what was to be dosed.
20.	Section 8.1.2 Study Treatment Regimen Appendix A Schedules of Events, Table 5, Schedule of Drugs	Changed the availability of *Erwinia*-asparaginase as an alternative for PEG-asparaginase in cases where patients are allergic or PEG-asparaginase is not available. Also added language to allow PEG-asparagine dosing over a range of days in case of supply shortage.	To allow for substitution of *Erwinia*-asparaginase for PEG-asparaginase for allergy or availability of PEG-asparaginase.
21.	Section 8.1.2, Table 8.c and Appendix A Schedules of Events, Table 1	Made the following change in Table 8.c and the note in Appendix A, Table 1: **Initial IT chemotherapy:** Day 1; may include methotrexate (CNS-1/2), or triple IT chemotherapy (CNS-3)	To clarify the dosing based on central nervous system (CNS) disease status.
22.	Section 8.4.2 Dose Reduction for Treatment-related Toxicity	Added row for Grade 2 to Table 8.e under General Toxicities	To provide guidance to investigators for dose modifications.
23.	Section 8.7 Precautions and Restrictions	Added a definition for women of childbearing potential.	To clarify restrictions on pregnancy.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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24.	Section 8.13.2 Handling and Accountability	Added text to allow for alternative study drug delivery in case of supply issues caused by coronavirus disease 2019 (COVID-19) public health emergency.	To ensure delivery of investigational product to study participants, to prevent shortages caused by COVID-19–related quarantines, cancellations of on-site visits, or concerns about possible COVID-19 exposure.
25.	Section 9.3.1 Screening Period Procedures	Added text to allow for rescreening (if sponsor agrees) of patients discontinued due to COVID-19–related factors.	To allow for the rescreening of patients with COVID-19 at the discretion of the sponsor.
26.	Section 9.3.13.5 Hepatitis B and C and Section 9.3.13.6 HIV	Added these sections to Section 9.3.13 Clinical Laboratory Evaluations.	To describe the assessment of status of patients for hepatitis B and C and HIV.
27.	Section 9.3.14.2 Cerebrospinal Fluid	Added a section to describe collection of cerebrospinal fluid.	To ensure complete description of assessments in the study.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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28.	Section 9.3.18 Changes to Study Procedures Due to COVID-19 Pandemic, Section 14.1 Study Site Monitoring Visits, and Section 14.2 Protocol Deviations	Added text to address situations that might arise due to the COVID-19 public health emergency.	To ensure patient monitoring and evaluation during the COVID-19 public health emergency. To ensure that only strictly necessary site visits are conducted during the COVID-19 public health emergency. Site visits may be converted to phone or video visits or home health care visits. Some scheduled visits may be canceled or postponed with larger intervals between on-site visits.
29.	Section 9.5 Reasons for Discontinuation of Treatment	Added text to clarify how to capture study drug discontinuation due to COVID-19 public health emergency.	To ensure that patient discontinuation due to COVID-19–related factors are documented in the electronic case report form.
30.	Section 9.8 Criteria for Premature Termination or Suspension of the Study	Added Section 9.8 to describe situations in which the study might be suspended or terminated.	To provide clarity on suspension or termination of the entire study.
31.	Section 10.3 Monitoring of Adverse Events and Period of Observation	A paragraph was added to clarify who is responsible for reviewing the emerging data from phase 1 to make decisions regarding dose and enrollment and how the decisions and any important safety data are communicated to all investigators in a timely manner.	This was added to clarify who was making decisions and communicating important safety data.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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32.	Section 15.2 Subject Information, Informed Consent, and Subject Authorization	Added text to describe potential alternative methods for obtaining informed consent/assent if travel is unavailable due to the COVID-19 public health emergency.	To permit the use of electronic informed consent during the COVID-19 public health emergency.
33.	Appendix A Schedules of Events, Table 1	Added hepatitis B, hepatitis C, and HIV testing to screening tests in the Schedule of Events, Table 1.	To ensure patient safety.
34.	Appendix A Schedules of Events, Table 1	Added timing for electrocardiogram (ECG) assessments in Footnote m.	To clarify when ECGs should be performed.
35.	Appendix A Schedules of Events, Table 1 and Table 2	Added neurological assessments to Table 1 and Table 2. Added footnotes to clarify.	To ensure patient safety and to conform to agreements made in the Paediatric Investigational Plan (PIP).
36.	Appendix A Schedules of Events, Table 1 and Table 2	Added collection of blood samples for BCR-ABL1 mutation status to Table 2 and edited the footnote in both Table 1 and Table 2 to clarify the collection of sample at follow-up visit only if suspicion of relapse.	To ensure patient safety and to comply with the PIP.
37.	Appendix A Schedules of Events, Table 1 and Table 2	Changed "CSF and cytospin cytology" to "Lumbar puncture" and described in the footnote.	To match wording on the case report forms.
38.	Appendix A Schedules of Events, Table 1 and Table 2	Added lipase and amylase to the chemistry panel.	To monitor for pancreatitis during ponatinib administration.
39.	Appendix A Schedules of Events, Table 2	Added the following to the table to be done on Day 1 and follow-up: Free T4 and thyroid stimulating hormone (TSH).	TSH and Free T4 will be assessed for all patients in FU regardless of whether or not the patient received the optional ponatinib continuation therapy.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
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40.	Appendix E	Clarified the questions on how ponatinib age appropriate formulation was administered. Deleted "with juice" and "with other" from choices of how administered. The correct scale was added to Questions 7 and 8 as below. The wording in the 5 point scale was changed to: "Not Easy, OK, Easy".	To correct the scale.
41.	Appendix F	Tanner Scale added to protocol.	To provide this scale in appendices.
42.	Appendix G	Added definitions of CNS-1, CNS-2, and CNS-3 in cerebrospinal fluid.	To provide clarity on the definitions.

Rationale for Amendment 01

This document describes the changes to the protocol incorporating Amendment 01. The primary reasons for this amendment are to incorporate feedback from the Innovative Therapies for Children with Cancer (ITCC), European Consortium and Children's Oncology Group (COG), as well as adjust and clarify timing of assessments and laboratory samples, clarify language for study conduct, include language on precautions (eg, sun protection, smoking, and eye examinations), provide guidance for the administration of ponatinib in a non-hospital setting, include an additional exploratory objective, and update the schedule of events associated with these updates.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 01

1. Update Sponsor name and address.
2. Clarify the timing of BCR-ABL1 domain mutation characterization.
3. Update the timing of event-free survival (EFS), progression-free survival (PFS), and overall survival (OS) assessments.
4. Update the timing of end of treatment 1 (EOT1).
5. Add exploratory objective to determine OS for patients receiving/not receiving hematopoietic stem cell transplantation (HSCT).
6. Add language regarding primary analysis and follow-up time points.

7. Add language for patients in need of additional ponatinib therapy.
8. Add language to clarify posttrial access to ponatinib.
9. Allow patients with a BCR-ABL1 T315I mutation to enroll based on local laboratory results, followed by central confirmation.
10. Add language for patients with Ph-like ALL eligibility (United States [US] only).
11. Remove qualifier for definition of adequate liver function, "(unless related to leukemic involvement)."
12. Update the exclusion criterion for current systemic use of any medications or herbal supplements that are known to be strong inhibitors or strong inducers of cytochrome P450 3A4 (CYP3A).
13. Replace exclusionary language, "History of significant bleeding disorder" with "History of severe coagulopathy or vascular events."
14. Clarify that self-administration or administration of ponatinib by a parent or legal guardian will occur if the patient is not hospitalized.
15. Provide hypothyroidism guidance.
16. Addition of precautions for sun protection.
17. Addition of precautions for smoking/vaping.
18. Addition of ophthalmological examinations.
19. Clarified timeframe for documentation of concomitant medications and procedures.
20. Updated procedures for recording and reporting adverse events and serious adverse events.
21. Updated procedures for reporting drug exposure during pregnancy and birth events.
22. Addition of blood samples for coagulation testing.
23. Addition of blood samples for troponin/ N-terminal pro-brain natriuretic peptide (NT-proBNP).
24. Addition of blood samples for free T4 and thyroid dysfunction.
25. Clarified complete remission (CR) assessment by bone marrow aspirate and/or biopsy.
26. Removed peripheral blood samples for minimal residual disease (MRD).
27. Clarified endpoint assessment timeframes.
28. Added definition of relapse from CR.
29. Clarified timing of peripheral blood samples for BCR-ABL1 domain mutation status.

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