Statistical Analysis Plan

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: Version 3.0, 25 July 2024

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.

STATISTICAL ANALYSIS PLAN

Study Number: Ponatinib-1501

Study 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

Phase: 1/2

Version: 3.0

Date: 25-JUL-2024

Prepared by:

[redacted], MS

Study Statistician

[redacted], Oncology Statistics

Based on:

Protocol Version: Amendment 04

Protocol Date: 02-NOV-2023

Approval Signatures

Study 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**

Approvals: (Electronic signatures can be found at the last page of this document)

[redacted], MPH Clinical Study Lead [redacted], Oncology Clinical Science	Date
[redacted], PhD [redacted], Oncology Statistics	Date
[redacted], MD [redacted], Iclusig	Date
[redacted], PharmD, PhD [redacted], Quantitative Clinical Pharmacology	Date

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
1.0	22-Mar-2021	Initial version
2.0	14-Jul-2023	To make SAP consistent with Amendment 3 of the protocol
3.0	25-Jul-2024	SAP is updated to 1) account for changes in Amendment 4 of the protocol; 2) to include adjustment and clarification based on team feedback received during dry run review.

Statistical Analysis Plan Amendment 2			
Summary of Major 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 1.2.2 Secondary Endpoints	Add text for MRD evaluated population.	To specify MRD evaluated population per Protocol Amendment # 4.
2.	Section 2.0 Study Design	Change the number 18 to 12 of DLT-evaluable patients for Phase 1	Revised per Protocol Amendment # 4.
3.	Section 2.0 Study Design	Revise percentage from 50% to 70% as :"DLT-evaluable patients must have received ponatinib doses on at least 70% of the reinduction block days….."	Revised DLT-evaluable patients' received ponatinib doses requirement per Protocol Amendment # 4.
4.	Section 2.0 Study Design	Remove the paragraph of 2 weight groups in the phase 1 Cohort 2.	Revised per Protocol Amendment # 4.
5.	Section 2.0 Study Design	Added how RP2D will be determined in cohort 2.	Revised per Protocol Amendment # 4.
6.	Section 2.0 Study Design	Add text for Phase 1 results report.	Revised per study's latest status and CSR reporting requirement.
7.	Section 2.0 Study Design	Update the Figure 2.a	Revised per Protocol Amendment # 4.
8.	Section 5.0 ANALYSIS Population	Update the DLT-evaluable and response-evaluable population definition	Revised per Protocol Amendment # 4 and made further clarification for DLT-evaluable population to reflect updated rule for cohort 2.
9.	Section 6	Removed formulation as grouping factor in summary tables	Revised per table shells agreed by study team
10.	Section 6.1, 6.2, 6.3, 6.4	Add text for cohort	Revised per meeting agreement with clinical and clinical pharmacology team.
11.	Section 6.5	Added details for phase 1 efficacy analysis for secondary endpoint (CR at the end of the reinduction block) and additional efficacy endpoints	Revised per discussion with clinical team. Additional summary for laboratory table (bone marrow blast, platelets, ANC) is specified to provide additional support for efficacy.

Statistical Analysis Plan Amendment 2			
Summary of Major 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 6.6 and Section 6.6.1	Remove HLT from the summary table of AE for CSR tables and modified description of AE summary to reflect the summary tables included	Revised based on Takeda TLF standard template with agreement from clinical team
13.	Section 6.6.3	Added test names for safety laboratory results to be summarized	Details added based on discussion and agreement from clinical team
14.	Section 6.6.4	Specify the detailed dose levels displayed in the exposure table according to the revised table shell.	Revised per meeting agreement with clinical and clinical pharmacology team
15.	Section 6.6.4	Added details for summary of backbone chemotherapy	Revised per agreed table shells and agreement from clinical team
16.	Section 6.7.3	Clarified that there is no plan to analyze exploratory biomarker data	Revised per agreement from with clinical and clinical pharmacology team
17.	Section 6.8.1	Clarified that there is currently no plan to summarize patient reported acceptability and palatability of the AAF of ponatinib as part of the CSR analysis"	Removed the summary with agreement with clinical and clinical pharmacology team, given patient reported acceptability and palatability of the AAF of ponatinib considered exploratory for this study
18.	Section 9.1.3	Clarified details for missing date imputation	Clarification made to more accurately reflect imputation algorithm

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AAF	age-appropriate formulation
ABL1	Abelson
AE	adverse event
AESI	adverse events of special interest
ALL	acute lymphoblastic leukemia
ANC	absolute neutrophil count
AOE	arterial occlusive event
AP	accelerated phase
ATC	Anatomical Therapeutic Chemical
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
BM	bone marrow
BP	blast phase
CI	confidence interval
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CP	chronic phase
CR	complete remission
CR2	second complete remission
CSR	clinical study report
DLT	dose-limiting toxicity
DOB	date of birth
ECG	electrocardiogram
EFS	event-free survival
EOT	end of treatment
HSCT	hematopoietic stem cell transplantation
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMDA	*N*-methyl-d-aspartate

NS	normal saline
NT-proBNP	N-terminal pro-brain natriuretic peptide
OS	overall survival
PFS	progression-free survival
Ph+	Philadelphia chromosome-positive
PK	pharmacokinetic(s)
PO	by mouth (orally)
PT	Preferred Term
QTcF	QT interval with Fridericia correction method
RP2D	recommended phase 2 dose
SAE	serious adverse event
SD	standard deviation
SOC	System Organ Class
SOE	schedule of events
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
t_{max}	time of first occurrence of maximum observed plasma concentration
UK	United Kingdom
US	United States
VTE	venous thrombotic/embolic event
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objectives

1.1.1.1 Phase 1 Primary Objective

- To determine the recommended phase 2 dose (RP2D) of ponatinib (tablet and age-appropriate formulation [AAF]) in combination with chemotherapy.

1.1.1.2 Phase 2 Primary Objective

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

1.1.2 Secondary Objectives

1.1.2.1 Phase 1 Secondary Objectives

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

1.1.2.2 Phase 2 Secondary Objectives

- Philadelphia–positive (Ph+) acute lymphoblastic leukemia (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.

1.1.2.3 Phase 1 PK Objective

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

1.1.2.4 Phase 2 PK Objective

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

1.1.2.5 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).

1.1.3 Additional Objectives

1.1.3.1 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.
- To determine OS for patients who receive HSCT and patients who do not receive HSCT.

1.2 Endpoints

1.2.1 Primary Endpoints

1.2.1.1 Phase 1 Primary Endpoint

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

1.2.1.2 Phase 2 Primary Endpoint

- CR at the end of the reinduction block. CR is defined as <5% blasts in bone marrow (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.

1.2.2 Secondary Endpoints

1.2.2.1 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.

1.2.2.2 Phase 2 Secondary Endpoints

- 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. 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.

- 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.

1.2.2.3 Safety Endpoints

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

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

1.2.2.4 Phase 1 PK Endpoints

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}).

1.2.3 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.
- OS for patients who receive HSCT and patients who do not receive HSCT.

1.3 Estimand

Not applicable.

2.0 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+ mixed phenotype acute leukemia, or Philadelphia chromosome–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 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.

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 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.

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. 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 dose-limiting toxicity (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 in combination with the chemotherapy backbone. The ponatinib doses evaluated in the phase 1 portion of the study were selected to target systemic exposures comparable to those achieved in adults receiving 15 (cohort 2) and 30 mg (cohort 1) once daily, based on the results of population PK modeling and simulation. 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 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.

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. 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. 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. Details of the RP2D determination process can be referred to Protocol Section 6.1.

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.

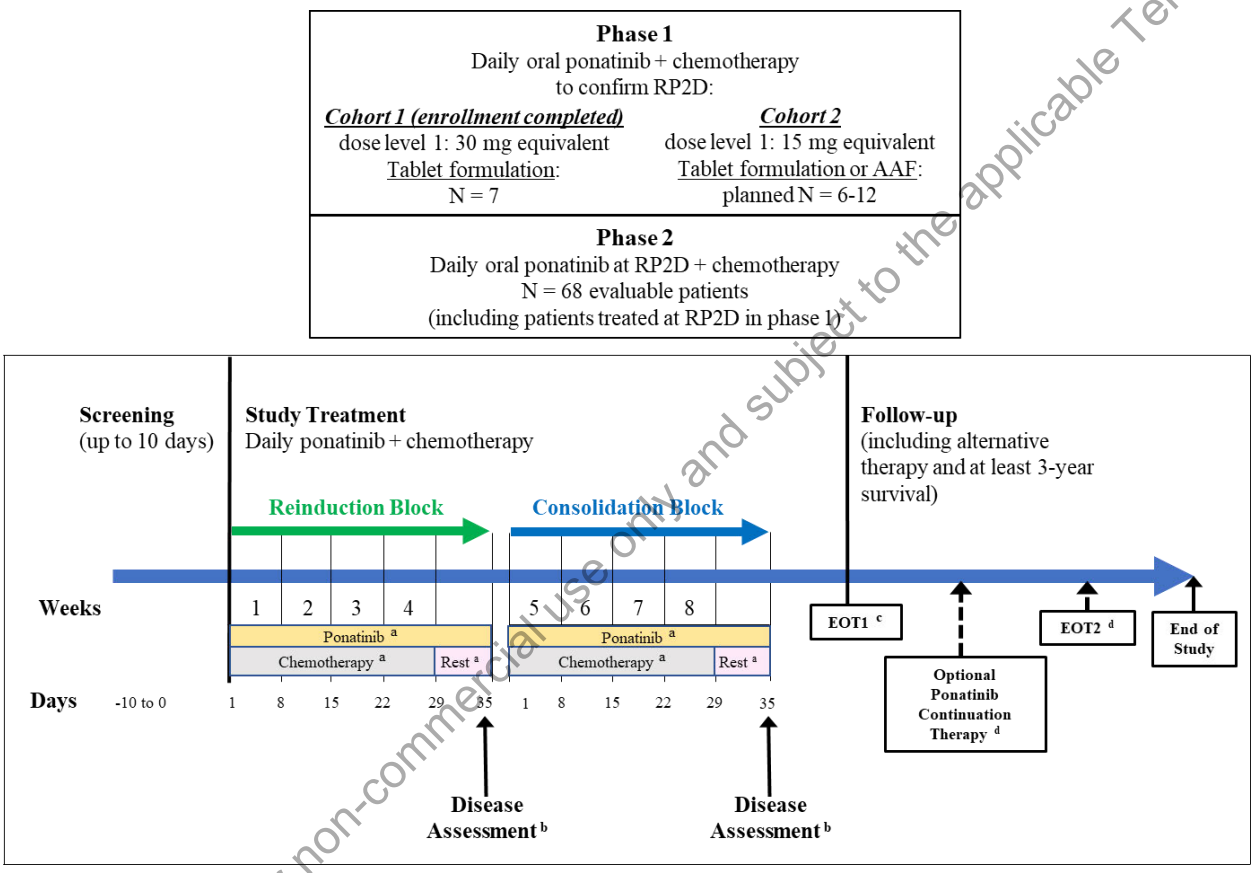
To provide quantitative summary of the clinical data from the patients completing phase 1 for the RP2D determination, a set of tables, listings, and figures (TLFs) will be presented for study team's review. This includes, but not limited to, patient disposition, demographic and baseline characteristics, exposure and compliance, plasma pharmacokinetic parameters, summary of CR at the end of the reinduction block, treatment-emergent adverse events (TEAEs) (drug-related or not), DLTs, TEAEs with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) severity Grade 3 or 4 (drug-related or not), treatment-emergent SAEs (drug-related or not), TEAEs leading to treatment discontinuation, AESIs, signs and symptoms for Grade 3 or above AESIs, etc. The general data handling convention and analysis approach will follow corresponding sections in this SAP.

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.

If RP2D cannot be derived from phase 1 data, study may not proceed to phase 2 and data will be summarized for phase 1 study only.

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. Phase 2 will evaluate the efficacy and safety of ponatinib at the RP2D in combination with chemotherapy in the study population.

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 in protocol amendment 4 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.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

The null hypothesis H_0 and alternate Hypothesis H_a for phase 2 primary endpoint CR rate are:

H_0: CR Rate is equal to 0.67

H_a: CR Rate is not equal to 0.67

The estimate of the CR will be presented with 2-sided 90% Wilson Score confidence interval (CI).

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

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 the null hypothesis for the CR rate =67%, and the alternative hypothesis for the CR rate=80%, based on simulation with 1,000,000 iterations, sample size of 68 patients will provide 81.5% power to reject the null hypothesis with the overall type I error controlled at a nominal level of 0.1 (2-sided).

The null hypothesis of a 67% CR rate is based on the following justifications from 2 studies. In the first study with 87 adult patients (Ph+ ALL) treated with imatinib in combination with chemotherapy [1], 44 patients experienced a relapse, and of those, 19 (43.2%) achieved a second CR (CR2). We assume that the prior distribution control rate follows β (a, b), then the prior control CR2 rate = a/(a + b) = 19/(19 + 25) = 0.432. In another study with a total of 92 pediatric patients (Ph+ ALL) [2], treated with imatinib plus chemotherapy, of 34 relapsed patients with follow up data available, 24 (70.6%) achieved a CR2 (personal communication, 11 June 2019). Assuming that a CR2 event, x, follows a binomial (n, p) distribution, where x = 24, n = 34, then the estimated rate p = 24/34 = 0.71. As the CR2 posterior distribution follows β (a + x, n – x + b), the posterior CR2 rate = (a + x)/(n + a + b) = 0.5513. And the 95% credible interval for the CR2 rate will be (0.44, 0.66) = (44%, 66%). Considering the prior distribution control rate was based on adult data, we will take a conservative approach and assume that the control rate is no less than the 95% upper credible limit, ie, 67%.

5.0 ANALYSIS POPULATION

5.1 Safety Analysis Population

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

5.2 PK Analysis Population

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.

5.3 DLT-Evaluable Population

DLT-evaluable population is defined as following for Cohort 1 (Ponatinib 30 mg adult equivalent group) and Cohort 2 (Ponatinib 15 mg adult equivalent group) in the phase 1 portion of the study:

- Cohort 1: patients who receive at least 1 dose of ponatinib in the reinduction block;
- Cohort 2: patients who receive ponatinib doses on at least 70% of the reinduction block days (e.g. 25 or more of the 35 days) or experience a DLT in the reinduction block.

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.

5.4 Response-Evaluable Population

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.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

In general, summary tabulations will be presented by dose cohort (ponatinib 30 mg adult equivalent and ponatinib 15 mg adult equivalent) in phase 1 and will display the number of observations, mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum for continuous variables, and the number and percent of non-missing values 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 95% CI for time-to-event data.

Unless otherwise specified, the baseline values are defined as the last observed value before the first dose of study drug administration.

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

6.1.1 Handling of Treatment Misallocations

Not applicable.

6.1.2 Analysis Approach for Continuous Variables

In general, summary tabulations will be presented by dose cohort in phase 1 and will display the number of observations, mean, SD, median, first quartile, third quartile, minimum, and maximum for continuous variables. Means, medians, first quartiles and third quartiles will be presented to 1 more decimal place than the recorded data. The SD will be presented to 2 more decimal places than the recorded data.

Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

6.1.3 Analysis Approach for Binary Variables

For the categorical variables, the count and proportions of each possible value will be tabulated based on the number of subjects who provided non-missing responses to the categorical variable by dose cohort in phase 1.

6.1.4 Analysis Approach for Time-to-Event Variables

The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CI for time-to-event data by dose cohort in phase 1.

6.2 Disposition of Subjects

Dispositions of patients will be summarized using the number and percentage of patients by dose cohort in phase 1 (ponatinib 30 mg adult equivalent and ponatinib 15 mg adult equivalent). Patients ongoing study treatment, patients completed study treatment, patients discontinued from treatment, patients discontinued from study, primary reason for discontinuation from treatment, primary reason for discontinuation from study, follow up status will be summarized. All percentages will be based on the number of patients in the safety analysis set.

6.3 Demographic and Other Baseline Characteristics

Baseline demographic and baseline characteristics will be summarized separately by dose cohort in phase 1.

6.3.1 Demographics

Baseline demographic data to be evaluated includes age at informed consent, sex, race, ethnicity, height, weight, body surface area, Karnofsky or Lansky Play Scale Performance status, and other parameters appropriate based on the safety analysis set.

6.3.2 Medical History and Concurrent Medical Conditions

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT) using number of events, number and percentage of patients based on the safety analysis set for each dose cohort. Patients with the same medical history more than once will have that medical history counted only once within each SOC, and once within each PT.

6.3.3 Baseline Characteristics

Baseline characteristics include but not limited to:

- Time from primary initial diagnosis to first dose date (months)
- Prior TKI therapy and anti-cancer regimen
- Resistance or intolerance to prior TKIs
- Mutation status at baseline
- Estimated glomerular filtration rate (eGFR) at baseline
- Best response to prior TKI
- Disease Diagnosis Group

6.4 Medication History and Concomitant Medications

Medications taken within 30 days prior to first dose of study drug and continued through treatment are considered as both prior and concomitant medications.

6.4.1 Prior Medications

All treatments/therapy received before the first dose of study drug will be recorded as prior treatments. Prior medications will be coded using the WHO drug dictionary and the number and percentage of patients taking prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term for each dose cohort in the safety population.

6.4.2 Concomitant Medications

All medications administered from the first dose of study drug until the EOT1 visit (or the EOT2 visit, for patients who receive optional ponatinib continuation therapy) will be recorded in the electronic case report form (eCRF) as concomitant medications.

Concomitant medications will be coded by preferred term using WHO drug dictionary. The number and percentage of patients taking concomitant medications will be summarized by ATC classification pharmacological subgroup and WHO drug generic term for each dose cohort in the safety population.

6.5 Efficacy Analysis

6.5.1 Phase 1: Secondary Endpoint (CR at the end of the reinduction block) and Additional Efficacy endpoints

CR at the end of the reinduction block (RB) will be summarized descriptively with frequency tables by dose cohort. In addition, CR at the end of consolidation block (CB), CR at EOT 1 and CR at EOT 2 will also be summarized.

Time to event analysis will be conducted to obtain point estimates and 95% CIs for 25th, 50th (median), and 75th percentiles for OS. Point estimate and 95% CIs for OS rates at 6 months, 1 year, 18 months, 2 years, and 3 years will also be provided.

Additionally, number and percentage of patients falling in the following laboratory categories at the end of RB and at the end of CB will be summarized by dose cohort:

- <5% blasts in the bone marrow
  - Platelets $>100 \times 10^9$/L and ANC $>1.0 \times 10^9$/L
  - Platelets $\leq 100 \times 10^9$/L or ANC $\leq 1.0 \times 10^9$/L
- ≥5% blasts in the bone marrow
  - Platelets $>100 \times 10^9$/L and ANC $>1.0 \times 10^9$/L
  - Platelets $\leq 100 \times 10^9$/L or ANC $\leq 1.0 \times 10^9$/L

Safety population will be used for phase 1 efficacy analysis.

Individual data listing will also be provided including bone marrow blast, hematology and investigator response assessment.

6.5.2 Phase 2: Primary Endpoints Analysis

The primary analysis will be conducted when all patients have been assessed for primary endpoint and been on study for approximately 6 months after the last patient enrolled. The primary efficacy endpoint will be analyzed in the phase 2 portion of the study. The response-evaluable population will be assessed for the phase 2 primary endpoint.

6.5.2.1 Derivation of Endpoint

The phase 2 primary endpoint is CR at the end of the reinduction block.

6.5.2.2 Main Analytical Approach

The estimate of the primary endpoint will be presented with 2-sided 90% Wilson Score CI.

6.5.2.3 Sensitivity Analysis

Not applicable.

6.5.2.4 Supplementary Analyses

Not applicable.

6.5.3 Phase 2: Secondary Endpoints Analysis

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.

CR, EFS, PFS, OS will be based on response-evaluable population. Duration of response will be analyzed on responders.

6.5.3.1 Definitions of Response Criteria

Definitions of response criteria for the purpose of efficacy analyses are provided in Table 6.a.

Table 6.a Definitions of Efficacy Response Criteria

Term	Definition
CR	Complete remission; 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:

Table 6.a Definitions of Efficacy Response Criteria

Term	Definition
	• Death due to any cause. • Refractory to treatment, defined as failure to achieve CR by end of the consolidation block. The event date will be Day 1 of the study treatment. • Relapse from CR.
MRD negative (Ph+ ALL)	MRD status <0.01%
OS	The interval between the first dose date of study drug and death due to any cause. If death is not observed, overall survival will be censored at the date using all the assessment dates, event start and end dates, intervention start and end dates, the date of contact from Subject Survival status form and get the latest non-missing date.
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 BM sample (aspirate and/or biopsy) is used for the diagnosis of recurrence, a complete blood cell count should also be performed.

6.5.4 Subgroup Analyses

Not applicable.

6.6 Safety Analysis

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.

Safety data will be summarized using the safety population.

All AEs will be coded using the MedDRA. Data will be summarized using SOC and PT unless specified otherwise.

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 electrocardiogram (ECG) abnormalities will be presented by visit. ECG parameters (QT, QT interval with Fridericia correction method [QTcF], 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.

6.6.1 Adverse Events

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. Descriptive statistics will be calculated. TEAEs will be tabulated by SOC and PT unless specified otherwise. 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 and PT. In particular, number and percentage of patients with AE and number of AEs will be tabulated for the following categories:

- TEAEs.by SOC and PT
- TEAEs by SOC, PT and severity
- Serious TEAEs by SOC and PT
- Treatment-related TEAEs by SOC and PT
- Treatment-related Serious TEAEs by SOC and PT
- Frequently Occurring (>=10% of All Subjects) TEAEs by PT
- TEAEs of Hepatotoxicity by PT
- Dose Limit Toxicity (DLT) AEs in Phase 1 by SOC and PT

An overall summary TEAE table will be provided, including number and percentage of patients and number of AEs for the following categories:

- Any TEAE
- Serious TEAE
- TEAEs related to any treatment, ponatinib, backbone therapy
- TEAEs leading to ponatinib dose discontinuation or dose reduction
- TEAEs leading to backbone therapy dose discontinuation, dose interrupted or dose reduced
- Serious TEAEs related to any treatment, ponatinib, backbone therapy
- Grade 3 or higher TEAE
- Grade 3 or higher TEAE related to any treatment, ponatinib, backbone therapy
- TEAEs leading to on-study death

Deaths, AEs, SAEs, grade 3 or higher TEAEs, AOEs, VTEs, TEAEs of Hepatotoxicity, DLTs, TEAE leading to study drug discontinuation, TEAE leading to death (if present), will be presented in separate data listings.

6.6.2 Adverse Events of Special Interest

AOEs and VTEs have been identified as AESIs for ponatinib. These include arterial, venous thrombotic/embolic, and occlusive AEs that meet the criteria for SAEs.

6.6.3 Other Safety Analysis

6.6.3.1 Clinical Laboratory Evaluations

Clinical laboratory data will be summarized for the following selected laboratory tests:

- Chemistry: alanine aminotransferase, aspartate aminotransferase, direct bilirubin, total bilirubin, triglycerides, lipase and amylase.
- Hematology: hemoglobin, leukocytes, neutrophils and platelets.
- Coagulation: activated partial thromboplastin time, d-dimer, fibrin degradation products and prothrombin intl. normalized ratio.

The actual and change from baseline will be summarized at each scheduled timepoints, using descriptive statistics (ie, n, mean, SD, median, minimum, and maximum).

The changes from baseline to maximum CTCAE severity grade during the treatment period will be summarized by frequency and percentage of patients using shift tables for each gradable laboratory test. Maximum CTCAE severity grade will be defined as the highest (worst) CTCAE (version 5.0) severity grade reported for a patient.

Mean laboratory values over time will be plotted for hematology and chemistry results.

In addition, individual data listings will be provided hematology, chemistry, coagulation urinalysis results will be listed.

6.6.3.2 Vital Sign

The actual vital sign values (including systolic, diastolic blood pressure, heart rate, respiratory rate, temperature, height, weight, body mass index) and changes from baseline at all scheduled timepoints will be summarized by descriptive statistics (ie n, mean, SD, median, minimum, and maximum).

6.6.3.3 12-Lead ECG

The actual ECG values and change from baseline will be summarized at each scheduled timepoint using descriptive statistics (ie, n, mean, SD, median, minimum, and maximum). This includes ECG ventricular rate, PR interval, QRS duration, QT interval, and QT interval with Fridericia correction method (QTcF) interval.

QTcF interval will be calculated using Fridericia correction, if necessary. The formulas are:

QTcF (Fridericia) = $QT / (RR^{0.33})$

where RR = 60 / heart rate (bpm)

ECG abnormalities will be presented in a data listing.

6.6.3.4 Other Observations Related to Safety

The Karnofsky or Lansky Play Scale performance status at each scheduled timepoint will be summarized by dose cohort.

The result of echocardiogram for assessment of left ventricular ejection fraction and multiple-gated acquisition scan (MUGA) will be presented in a data listing.

6.6.4 Extent of Exposure and Compliance

Study drug exposure (ie, duration of exposure, number of days dosed, dose intensity, total cumulative dose, an aggregate summary of numbers and percentages of patients who had completed reinduction block, consolidation block, 1 to 3, 4 to 6, 7 to 12, and >12 months of optional treatment continuation) will be summarized separately for each dose group (ponatinib 30 mg, ponatinib 20 mg, ponatinib 15 mg and ponatinib 10 mg) and dose cohort in phase 1 reinduction and consolidation blocks for ponatinib.

Duration of treatment exposure is defined as the time interval from the first dose to the last dose of study treatment (including ponatinib and chemotherapy) (last dose date – first dose date +1) for reinduction/consolidation block respectively.

Total dose expected for ponatinib is the expected daily dose at Day 1 multiplied by the greater of 35 days and duration of treatment for reinduction/consolidation block respectively. For other chemotherapy treatments, total dose expected is defined as the expected daily dose at Day 1

multiplied by the number of days dosed per protocol in reinduction/consolidation block respectively.

Total cumulative dose is the sum of the daily dose received across all days that ponatinib was administered.

Dose intensity (mg/day) is calculated as total cumulative dose in mg divided by duration of treatment exposure in day.

Relative dosing intensity is calculated as (total cumulative dose/total dose expected) multiplied by 100%.

The drug exposure parameters (ie, duration of exposure, number of days dosed, total cumulative dose) during reinduction block and consolidation block will be summarized for other chemotherapy treatments listed below.

- Vincristine
- Dexamethasone
- PEG-asparaginase/ Erwinia-asparaginase
- Daunorubicin
- Methotrexate
- Cyclophosphamide
- Etoposide
- Intrathecal (IT) Methotrexate only for CNS-1/2
- Triple intrathecal (ITT) (Methotrexate/Hydrocortisone/Cytarabine) only for CNS-3
- Prednisone

In addition, patients who received optional ponatinib continuation along with other chemotherapy will also be summarized.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic 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 (at a minimum) ponatinib C_{max}, t_{max}, and AUC_{last}. PK parameters and plasma concentrations will be summarized using descriptive statistics as appropriate. 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. Additional details regarding the PK analyses will be provided in the Clinical Pharmacology Analysis Plan.

The sparse PK data collected in the phase 2 portion of the study will be listed and summarized by timepoint. 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.

6.7.2 Pharmacodynamic Analysis

Not applicable.

6.7.3 Biomarker Analysis

- Change from baseline in laboratory values and cardiovascular outcomes associated with elevated cardiac troponin and NT-proBNP.
- Biomarkers of disease sensitivity and resistance to ponatinib and/or biomarkers affecting ponatinib.

With biomarker data considered exploratory, there is currently no plan to summarize biomarker data as part of the CSR analysis.

6.8 Patient-Reported Outcomes and Health Care Utilization Endpoints Analysis

6.8.1 Patient-Reported Outcomes Analysis

Patient acceptance of medication (acceptability) is defined as the overall ability of the patient to use the medicine as intended. This study will incorporate a questionnaire with questions related to the AAF taste and smell using a 5-point facial hedonic scale. The palatability study questionnaire will be provided to the patient/caregiver after each dose of ponatinib on Days 1, 8, 15, and 22 during reinduction.

With patient reported acceptability and palatability of the AAF of ponatinib considered exploratory, there is currently no plan to summarize this data as part of the CSR analysis.

6.8.2 Health Care Utilization Analysis

Not applicable.

6.9 Interim Analyses

An interim analysis will be conducted when 20 patients at RP2D have completed the reinduction block. Enrollment will not be stopped while the interim analysis data is reviewed by the independent data monitoring committee (IDMC).

No formal statistical test is planned for this interim analysis. The safety and efficacy data will be summarized by descriptive statistics, including overall AE summary, subject incidence rates of AEs (including all SAEs, treatment-related AEs, serious treatment-related events, and events resulting in study drug discontinuation) will be tabulated by MedDRA SOC, HLT, PT, and severity grade. Listings of on-study deaths and other serious and significant AEs, including any early withdrawals because of AEs, will be provided. The CR at the end of reinduction block will also be summarized.

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.

6.10 Data Monitoring Committee

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 MedDRA, SOC, HLT, 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 major adverse cardiac event.

7.0 REFERENCES

1. Lim S. Long-Term Outcome of Relapsed Adult Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia Treated with Continuous Imatinib Plus Combination Therapy. Clinical Lymphoma, Myeloma & Leukemia 2017;17(10S): S1. ALL-008.
2. Schultz K, Carroll A, Heerema N, Bowman W, Aledo A, Slayton W, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: children's oncology group study AALL0031. Leukemia 2014; 28:1467–71.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

NA

9.0 APPENDIX

9.1 Data Handling Conventions

9.1.1 Definition of Study Day

Study Day 1 is defined as the date on which a subject is administered with their first dose of the study drug. Other study days are defined relative to the Study Day 1, as Study Day = Date of event - Date of the first dose + 1 day if date of event is on or after date of the first dose; Study Day=Date of event-Date of the first dose if date of event is before first dose date.

9.1.2 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screening visits.

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.
- If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose date, in which case the date of the first of January will be used, unless other data indicate that the date is earlier.
- If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used, unless other data indicates that the date is earlier.

9.1.3 Missing Adverse Event Dates/Concomitant Therapies/Subsequent Therapies

Every effort should be made to avoid missing/partial dates in on-study date. AEs with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known but day is missing

If month and year are the same as month and year of first dose date, then impute to first dose date

If month and year are different than month and year of first dose date, then impute to first date of the month

- If year is known but day and month are missing

If year is same as year of 1st dose date, then 1st dose date will be used instead

If year is different than year of 1st dose date, then 1st of January of the year will be imputed.

If the start date of an event is completely missing, then it is imputed with 1st dose date.

Imputing missing event start date is mandatory.

AEs with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.

If month and year are known but day is missing, the last day of the month will be imputed

or the data cutoff date whichever is earlier If year is known, but day and month are missing, December 31st will be imputed

If all are missing, then impute date to 31st of December, in the year of last dose.

Imputing missing AE stop date is not mandatory if AE is regarded as ongoing. If subject dies, then use death date for AE stop date.

After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date the same as the start date.

Concomitant medications/therapies with start dates that are completely or partially missing will be analyzed as follows:

If month and year are known, but day is missing, then impute day to first of the month

If year is known, but day and month are missing, then 1st of January of the year will be imputed

- the last day of the month will be imputed ; or the data cutoff date whichever is earlier.
-

If all is missing, then impute date to Date of Birth (DOB)

If DOB is not available but age is available, then estimate DOB by using screening date and age (age = screening date – DOB)

Concomitant therapies with stop dates that are completely or partially missing will be analyzed as follows:

If "ongoing" is checked, no imputation is necessary.

If month and year are known but day is missing, the last day of the month will be imputed

If year is known but day and month are missing, then December 31st will be imputed

If the date is completely missing, then impute date to 31st of December in the year of last dose

If subject dies, then use death date for concomitant therapies stop date. After the imputation, all imputed dates are checked against the start dates to ensure stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date.

Subsequent therapies with start date which is completely or partially missing will be analyzed as follows:

When month and year are present and the day of the month is missing,

If the onset month and year are the same as the month and year of last dose with study drug, the day of last dose + 1 will be imputed.

If the onset month and year are not the same as the month and year of last dose with study drug, the first day of the month is imputed.

When only a year is present,

If the onset year is the same as the year of last dose with study drug, the date of last dose + 1 will be imputed.

If the onset year is not the same as the year of last dose with study drug, the first day of the year is imputed.

If no components of the onset date are present the date of last dose + 1 will be imputed.

Signature Page for Ponatinib-1501_Statistical_Analysis_Plan_V3
Title:

Approval	[redacted] Statistics 26-Jul-2024 14:39:35 GMT+0000
Approval	[redacted] Clinical 26-Jul-2024 14:59:38 GMT+0000
Approval	[redacted] Clinical 27-Jul-2024 14:23:38 GMT+0000
Approval	[redacted] Clinical 30-Jul-2024 13:10:23 GMT+0000

Document Number: TDN-000382581 v1.0