Statistical Analysis Plan

CLR_15_03: Parts B and C

Version 2.0

A Two-Part Phase 1/2 Study to Determine Safety, Tolerability, Pharmacokinetics, and Activity of K0706, a Novel Tyrosine Kinase Inhibitor (TKI), in Healthy Subjects and in Subjects with Chronic Myeloid Leukemia (CML) or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

[redacted]

Version Number and Date of Protocol: V12, A12, 12Sep2019

Statistical Analysis Plan Signature Page

Statistical Analysis Plan V2.0 (Dated 02 Feb 2024) for Protocol CLR_15_03 Part B and C.

[redacted]

Upon review of this document, the undersigned approve this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

[redacted]

Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1	12 Dec 2021	[redacted]	Not Applicable – First Version
2	07 Jul 2024	[redacted]	This SAP is revised to include both Part B and Part C of the study.

TABLE OF CONTENTS

1. INTRODUCTION

[redacted]

2. STUDY OBJECTIVES

2.1 PART B

Primary Objectives

- To determine the maximum tolerated dose (MTD) or recommended Phase 2 dose [RP2D] of K0706 (Vodobatinib) administered orally.
- To evaluate the safety of Vodobatinib.

Secondary Objectives

- To evaluate the therapeutic activity of Vodobatinib.
- To evaluate the PK of Vodobatinib after multiple oral doses.

Exploratory Objectives

- To evaluate the correlation of therapeutic activity of Vodobatinib in the context of different baseline BCR-ABL mutation profiles.
- To evaluate the BCR-ABL mutation profile at disease progression (should it occur) for possible mechanisms of resistance.

2.2 PART C

Primary Objective

- To evaluate the anti-leukemic efficacy of Vodobatinib in subjects with CML-CP by cytogenetic outcomes and in subjects with CML-AP and BP by hematologic outcomes who have failed ≥3 TKIs, one of which includes ponatinib.

Secondary Objectives

- Anti-leukemic efficacy of Vodobatinib by molecular outcomes.
- Anti-leukemic efficacy of Vodobatinib by hematological outcomes in CML-CP.
- Anti-leukemic efficacy of Vodobatinib by cytogenetic outcomes in CML-AP and BP.
- Time to response.
- Duration of response.
- Progression free survival (PFS) and Overall survival (OS).
- Population PK of Vodobatinib.
- Safety of Vodobatinib.

Exploratory Objectives

- To evaluate the correlation of therapeutic activity of Vodobatinib in the context of different baseline BCR-ABL mutation profiles.
- To evaluate the BCR-ABL mutation profile at disease progression (should it occur) for possible mechanisms of resistance.

3 STUDY DESIGN

3.1 PART B

This is an open-label, dose-ranging, single-agent, multicenter, multidose, dose escalation study initiated in subjects with Ph+ CML (Ph + CML include CML-CP, AP and BP; [without the BCR-ABL T315I mutation until sufficient plasma levels found to be active preclinically in the T315I clone are achieved]) and Ph+ ALL. Eligible subjects will be treated in [redacted] cycles of a once-daily self-administered Vodobatinib.

To determine the MTD and/or the RP2D, the study will initiate with an accelerated titration dose-escalation design and transition to a 3+3 design when the first subject enrolled in the initial accelerated titration dose escalation cohort develops a Grade [redacted] or higher adverse event (AE) that is not clearly and incontrovertibly related to the underlying disease or concomitant medications.

The initial dose escalation cohorts can enroll at least 1 and up to 3 subjects into each cohort. Subject(s) enrolled into each cohort following the accelerated design of the initial escalation steps will receive the initial dose of Vodobatinib, and continue to receive Vodobatinib at the

same dose daily (unless the subject qualifies for intra-subject escalation as described in the dose escalation schema).

If more than one subject has been entered in the accelerated titration component of the study, only the first subject will be evaluable unless the Sponsor and Investigator deem otherwise. If the first subject enrolled in this cohort does not experience Grade [redacted] or higher AEs or DLTs during Cycle 1 of his/her study treatment (i.e., each cycle, including Cycle 1, consists of daily Vodobatinib dosing and an observation period of [redacted]), the dose for the next subject(s) will be escalated to the next dose level. Enrollment into subsequent cohorts will proceed only after the current cohort has completed Cycle 1 of study treatment. When more than 1 subject is enrolled, enrollment may occur concurrently.

If this first subject enrolled in the initial accelerated titration dose escalation cohort experiences a Grade [redacted] or higher AE that is not clearly and incontrovertibly related to the underlying disease or concomitant medications, then that cohort and all subsequent cohorts will follow the standard 3+3 design.

For the cohorts where the 3+3 design applies, 3 subjects will be enrolled initially. Further, if there are no Dose Limiting Toxicities (DLTs) in the first 3 subjects, dose-escalation to the next higher dose level may proceed. If 1 of the 3 subjects experiences a DLT, that dose level will be expanded to 6 subjects (3 additional subjects will be enrolled).

If 2 subjects at a given dose level experience a DLT, the MTD will have been exceeded. The next lower dose level will then be expanded to 6 subjects, or if 6 subjects have already been enrolled and no more than 1 of the 6 subjects experienced a DLT, then this lower dose level will be considered the MTD. Additional subjects may be enrolled in dose escalation cohorts for further assessment of safety and efficacy of Vodobatinib at doses that have been tolerated (i.e.: doses which have <2 DLTs in 6 enrolled subjects or <1 DLT in 3 enrolled subjects).

Once the MTD or recommended Phase 2 dose (RP2D) is established, the study initially planned to enroll up to 12 additional subjects in each of the subgroups as expansion cohorts (i.e., CML-CP, CML-AP, CML-BP, T315I CML-CP, and Ph+ ALL) using the modified toxicity probability interval design starting at the MTD or RP2D for each subset of subjects. [redacted] Subjects with T315I mutations will not be enrolled in any part of the study.

Subject(s) in the subgroup expansion cohorts will start at MTD or RP2D achieved in the dose escalation cohorts. Initially, three subjects will be enrolled into each of the subgroup expansion cohort and monitored for DLTs. An internal Data Monitoring Committee (iDMC) will be convened

after the 3 subjects have completed the DLT observation period. The iDMC may recommend enrolling subsequent subjects at the same dose level if escalation criteria are met (e.g. DLTs in ≤1/3 subjects) depending on emerging safety-efficacy profile. The second set of up to 9 subjects will be enrolled if stopping rule is not met after review of data from first 3 subjects.

During the study conduct, the study team has decided to enroll only subjects from CML-CP subgroup in the expansion cohort and limited to the sites in India only.

Dose Escalation Schema:

In the study, the decision to advance to the next dose level will only occur after the careful evaluation of all available safety and tolerability data for a given dose level by an internal Data Monitoring Committee (iDMC) after completion of Cycle 1; data from later cycles of treated subjects may be taken into consideration in this decision. Progression to the next higher dose will only occur if the previous dose level was deemed to be safe and well tolerated by the Principal Investigators and the Sponsor.

An appropriate interval (usually 7 days between IMP administrations, that is after the completion of the preceding cohort's first cycle and the next cohort's first IMP administration) will separate the investigation of dose levels to permit a timely review and evaluation of safety data prior to proceeding to the next higher dose level.

When it is not appropriate to escalate the dose then the same dose, a previous dose or an intermediate dose may be given following discussion between the Principal Investigators and Sponsor. Additional dose levels may also be investigated depending upon the results of the safety data from the previous dose levels and consideration of the preclinical toxicology data.

If more than 1 subject has been entered in the accelerated titration component of the study, only the first subject will be evaluable unless the Sponsor and Investigator deem otherwise. If the first subject enrolled in a cohort does not develop Grade 2 or higher AEs or DLTs during Cycle 1 of his/her study treatment (i.e., each cycle, including Cycle 1, consists of daily IMP dosing and an observation period of [redacted]), the dose for the next subject(s) will be escalated to the next dose level. Enrollment into subsequent cohorts will proceed only after the current cohort has completed Cycle 1.

A subject administered a dose lower than the highest studied dose may have his/her dose increased up by 1 dose level at a time or to a dose that is 1 dose level below the highest studied dose, as per Investigator's discretion provided that:

1. The dose cohort to which the subject is being escalated has been completed (e.g., 1 cycle has been completed for all subjects).

2. The subject has not previously experienced a DLT.
3. The subject has no residual Vodobatinib-related toxicity that is greater than Grade [redacted]

Any results from intra-subject dose escalations will not affect inter-subject dose escalations unless the Investigator and Sponsor agree that intra-subject escalation information reasonably alters the potential benefit-risk ratio for subsequently treated subjects.

Dose escalations should occur at the beginning of a new cycle. Safety findings from intra-subject escalations will not be used for determination of the MTD of a regimen.

A DLT is defined as the occurrence of any of the following unless clearly and incontrovertibly related to the underlying disease. The hematological DLTs have been defined as per the Phase of CML:

- [redacted]

Hematological DLT, as per the Phase of the CML:

- Hematological DLTs for subjects in CML-Chronic Phase
- Grade [redacted] off the Vodobatinib treatment or [redacted] off the Vodobatinib (i.e.: after treatment interruption)

Hematological DLTs for Subjects in CML-Accelerated Phase

Grade [redacted] and/or [redacted] for [redacted] off Vodobatinib treatment or Grade [redacted] off Vodobatinib (i.e.: after treatment interruption) in the absence of features of accelerated phase (except cytogenetic changes) such as persistent increase in blasts or basophils.

Hematological DLTs for Subjects in CML-Blast Phase

Grade [redacted] and/or [redacted] in the absence of [redacted] or [redacted] with a bone marrow cellularity showing [redacted] blasts.

Subjects who experience a DLT and/or have a treatment delay may continue treatment in the absence of disease progression as long as the toxicity has recovered to the baseline value or

lower.

Subjects who experience a DLT and recover, may be treated (at the Investigator's and subject's discretion) at the next lower dose level until disease progression or other events requiring dose reduction exist. For cohorts at Dose Level 2 or higher, a further dose reduction [redacted] may be implemented in the case of a further DLT or other non-DLT events requiring a dose reduction, if and when the event leading to dose reduction returns to Grade [redacted] or lower in severity.

The reduced dose may be re-escalated to the original or higher dose (i.e.: dose for which safety has been established in the dose escalation cohort) at Investigator's discretion considering subject safety and response to Vodobatinib and in consultation with Sponsor's medical monitor. Subjects experiencing a Grade [redacted] toxicity attributable to Vodobatinib will undergo dose reduction and dose delays as per guidance provided in protocol Section 6.4.2.1. [redacted]

Once 2 subjects experience a Grade [redacted] or a Grade [redacted] (unless the AE is clearly and incontrovertibly related to underlying disease), further dose escalation steps will be reduced to [redacted] increments.

The study design schema is illustrated in Figure 1:

[redacted]

3.2 PART C

Part C is a multicenter, phase 2, single arm, open-label study of oral Vodobatinib in subjects with Ph+ CML (CP, AP and BP) who have resistance and/or intolerance to ≥ 3 prior TKIs one of which includes ponatinib. Subjects must have documented evidence of intolerance and/or primary (never had a response) or secondary resistance (loss of a response) following standard or high dose TKI therapy (refer Inclusion Criteria # 3).

Eligible subjects will enter the study center [redacted] on Day 1 to receive the first administration of Vodobatinib ([redacted] and will complete the required assessments and sample collections, [redacted]. [redacted] Subjects may be admitted a day prior to Cycle 1 Day 1 dosing and if required stay overnight at the study center on Cycle 1 Day 1, based on Investigator's discretion. Subjects will complete the assessments on Cycle 1 Day 2 and may remain in the study center overnight for observation, at the discretion of the Investigator. Subjects will return for follow-up assessments ([redacted]) in Cycle 1 [redacted].

Cycle 2 will have similar [redacted] sample collections on Day 1, and subjects will be required to return to the study center [redacted] for [redacted] follow- up assessments. From Cycle 3 onwards, subjects will only be required to return to the study center once every [redacted] months ([redacted]. Note: The last observation/evaluations for each cycle may coincide with the Day 1 of next cycle e.g., Cycle 6 Day [redacted] observation may coincide with Cycle 7 Day 1). [redacted] samples will be collected on the day of the study visit from Cycle 3 onwards.

Subjects will remain on study treatment for approximately 60 months (i.e.: 5 years from 1st Vodobatinib dosing), or until intolerance, subject withdraws from the study, or progression of disease. Subjects who discontinue the study will be followed up for survival (survival assessment includes information about subject survival and anticancer therapies) every [redacted] (± 2 weeks) after the Vodobatinib discontinuation till 60 months from their first dose of Vodobatinib or until death, withdrawal of consent, or the end of the study, whichever comes first. Subjects enrolled in Part C at [redacted] of Vodobatinib ([redacted]) will remain in the study, but will not be considered for the statistical analysis for Part C.

Treatment beyond 60 months will be considered, provided the Investigator considers that the subject is benefiting from Vodobatinib therapy. Subjects who continue to receive Vodobatinib beyond 60 months will be followed up for safety, survival and response assessment. Information

about subject's survival and disease response will be collected at the follow up visits every [redacted] (± 2 weeks) in these subjects.

A subject experiencing any Vodobatinib associated toxicities may continue on therapy at the same dose if disease control is achieved or with a reduced dose of Vodobatinib at the Investigator discretion. Subjects who experience a toxicity and recover, may be treated, at the Investigator's discretion, at the same dose or next lower dose level until disease progression or occurrence of other events requiring further dose reduction. The subject will be permitted [redacted] Additional dose reductions can be implemented upon consultation between Sponsor's medical monitor, treating investigator and the subject. [redacted] For additional details on the study conduct please refer to the applicable protocol sections and schedule of assessments.

A DSMB will be established for periodic review of safety data for this study. The composition and responsibilities of the DSMB will be described in detail within the DSMB Charter separately.

4 [redacted]

[redacted]

5 ANALYSIS SETS

5.1 ALL ENROLLED SET

The All Enrolled (ENR) set will contain all subjects who signed an informed consent for this study. This analysis set will be used to summarize subject disposition.

5.2 Safety Analysis Set

The Safety analysis set will include all subjects who received at least one dose of Vodobatinib.

5.3 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PAS) will include all subjects in the safety analysis set who provide at least one evaluable PK concentration with no important protocol deviations, violations or events thought to significantly affect the PK of the drug.

5.4 Efficacy Analysis Set

The Efficacy analysis set will include all subjects who received at least 1 dose of Vodobatinib.

5.5 Protocol Deviations

Protocol deviations will be documented separately in a stand-alone document before database lock which include deviation category (e.g., violation of inclusion and exclusion criteria at screening, use of excluded concomitant medications, received the incorrect dose), deviation description, severity (minor/major), visit/time point for each deviation. Major protocol deviations are defined as those deviations from the protocol that threaten the integrity of the data, adversely affect subjects and/or could influence/affect the outcome of the efficacy endpoints (or part of it).

6 General Aspects for Statistical Analysis

6.1 General Considerations

Continuous data will be summarized [redacted]. Categorical variables will be summarized [redacted]

For all percentage calculations, the denominator will be the number of subjects in the analysis set, unless otherwise stated. Time-to-event data will be summarized [redacted]

[redacted]

[redacted]

7 DISPOSITION AND ANALYSIS SETS

The subject disposition table will be based on all enrolled subjects who are consented to participate in the study. The following summaries will be included in the disposition table: total number of subjects screened in the study, number of subjects who failed screening, number of subjects received treatment, number of subjects who discontinued treatment with reason for treatment discontinuation, number of subjects on the treatment, number of subjects under survival follow-up or have completed survival follow-up. In addition, the number of subjects included in each of the analysis sets will be presented. [redacted] A by-subject listing of disposition will be provided for the ENR set. The data may be furthur presented by dosing groups, disease types or other subgroups of interest.

8 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The safety analysis set will be used to summarize the subjects' demographics and baseline characteristics. Continuous variables (e.g., age and weight) will be summarized [redacted] Qualitative variables (e.g., sex, race, and ethnicity) will be summarized [redacted].

The demographic parameters will include age category (<65 and ≥65 years), gender, race, ethnicity. Age will also be summarized as a continuous variable. The baseline parameters include, EOCG performance status, weight, height, body mass index, ECOG performance status, baseline cardiovascular and metabolic co-morbidities. Also included will be baseline TKI status (Refractory, intolerant and resistant), history of bone marrow transplantation, baseline Ph+ cells, number of prior TKIs received, prior ponatinib treatment, prior ponatinib and asciminib treatment, baseline mutation status, extramedullary involvement (Yes/No) and baseline cytogenetic (i.e: complete or partial) and molecular responses (by BCR::ABL1 transcript %). Additionally, data will be separately presented by disease type and dosing cohorts.

By-subject listings of demographic and other baseline characteristics will be provided for safety analysis set.

9 MEDICAL AND SURGICAL HISTORY

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized by system organ class (SOC) and preferred term (PT) overall and by dose group using safety analysis set. Subjects with more than one of the same PTs within

an SOC will be counted only once. Medical histories will be coded using a central coding dictionary, the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

10 MEDICATIONS

Prior, concomitant, and post-therapies will be coded using the latest available version of the Anatomical Therapeutic Chemical (ATC) classification text from the World Health Organization Drug Dictionary (WHO DD) and summarized using safety analysis set. Surgical and medical procedures will be coded by primary system organ class (SOC) and preferred term (PT) according to MedDRA coding dictionary.

Prior therapy:

Prior therapies are therapies which started and stopped before the first dose of Vodobatinib. Any changes to prior medications (dose, regimen, etc.) during the study will be considered a new concomitant medication.

The number and percentage of subjects who received any prior including anti-neoplastic medications will be summarized by the dose group for the safety analysis set. The number and percentage of subjects who received any prior including anti-leukemic medications will be summarized by the dose group for the safety analysis set. The prior medications will be summarized for the lowest anatomical therapeutic classification (ATC) class and preferred name.

Concomitant therapies:

Concomitant therapies are defined as all interventions (medications and procedures) other than the study treatment administered to a subject coinciding with the study treatment period. Concomitant therapies include medications and medical procedures starting on or after the first dose of study treatment or starting prior to the first dose of study treatment and continuing after the first dose of study treatment. Concomitant medication will be summarized by the lowest ATC class and preferred name using frequency counts and percentages. Surgical and medical procedures will be summarized by SOC and PT. A listing will also be provided.

[redacted]

Hematological Response:

Hematological response is a normalization of the blood counts, particularly WBC counts and is evaluated by peripheral blood assessments and clinical assessments of extramedullary disease.

[redacted]

[redacted]

[redacted]

Cytogenetic Response:

Cytogenetic response is assessed by the ratio of number of Ph+ cells seen to the number of cells analyzed on Karyotyping done by the central laboratory. In cases where karyotyping was not performed then the central laboratory florescence in situ hybridization (FISH) results will be

used. When central laboratory data is not available, then data from the local laboratory will be used for the analysis. [redacted]

[redacted]

Molecular Response:

Molecular response is assessed using quantitative PCR (qPCR) based on the amount of BCR-ABL protein in the blood and is presented below in Table 2.

[redacted]

Cytogenetic, molecular, and hematologic responses will be summarized [redacted]

Criteria for Molecular Responses

[redacted]

Cytogenetic, molecular, and hematologic responses will be summarized [redacted]

Cytogenetic, molecular and hematological responses [redacted] will be presented [redacted]. The response rate at a specific time point is defined as the number of subjects who achieved the response at that time point divided by the total number of subjects in the treatment group. [redacted] The hematological

response will be summarized only for subjects with CML-AP and BP.

A separate summary will be provided for the best cytogenetic and molecular responses by achived and maintained resposes during the study period. The assessment for the achived response includes all subjects who entered the study without the specific response. The assessment for the maintained response includes subjects who entered the study with the specific response.

By-subject listings of phytodynamic parameters will be provided for the safety analysis set. A by-subject listings will be provided for subjects who had disease progression.

Time to CCyR/MMR (in weeks), defined as the date of first documented CCyR/MMR - date of randomization + 1 divided by 7 will be summarized descriptively using number of subjects, mean, SD, median, minimum, maximum and quartiles.

Duration of CCyR/MMR, defined as the time between the date of the first documented MMR to the earliest date of confirmed loss of MMR or progression to accelerated phase (AP)/BP, or CML-related death will be summarized descriptively. The duration of CCyR/MMR (in weeks) is calculated as (end date or censoring date of CCyR/MMR - date of first CCyR/MMR + 1)/7.

All analysis will be conducted separately for all CML subjects and CML-CP subjects.

Furthur analyses for efficacy may be performed by dose group, stage of CML, resistance or intolerance, and mutational status.

13 SURVIVAL

Overall survival is defined as the time from date of first dose to the date of death from any cause. Subjects who are alive at the time of the analysis data cut-off will be censored at the date of last contact.

Progression free survival is defined as the time from date of first dose to the date of earliest occurrence of documented disease progression requiring withdrawal from the study or death from any cause. Any subject who has neither progressed nor died will be censored on the date of his/her last response assessment (hematological, cytogenetic or molecular).

Overall survival and progression-free survival rates will be summarized [redacted]

14 PHARMACOKINETIC OUTCOMES

PK sampling will include [redacted] sampling on Day 1 of Cycle 1 and Cycle 2 to

characterize single and multiple dose PK in subjects. The sampling scheme will be as follows:

[redacted]

Vodobatinib plasma concentration results will be summarized by dose. Descriptive summaries [redacted] for Vodobatinib concentration will be presented for each scheduled time point. [redacted]

PK analysis will be performed [redacted]. Any missing samples due to lack of collection, loss during shipping, or other events will be reported as 'Missing' and will not be included for pharmacokinetic analysis, including descriptive statistics at nominal timepoints.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]

15 SAFETY ANALYSIS STRATEGY

All analyses described in this section will be performed on the Safety Analysis set and will be presented by dose. The results will be descriptive in nature. All data will be summarized and listed.

Safety will be assessed based on exposure, adverse events (AEs/SAEs), laboratory assessments (hematology, chemistry and urinalysis), vital signs, 12-Lead electrocardiograms (ECGs) and physical examination.

15.1 EXTENT OF EXPOSURE

Duration of exposure, actual cumulative dose, average daily dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized descriptively by the dose. Counts and percentages of subjects who have dose reductions, interruptions and dose esclation will be summarized by dose. In addition, counts and percentage of subjects who received the assigned dose will be presented. The calculations will be performed to include both the mean and median for the parameters and their respective interquartile ranges.

[redacted]

[redacted]

Cumulative Dose:

Cumulative dose of a study treatment is defined as the total dose (mg) given during the study treatment exposure. The planned cumulative dose for a study treatment refers to the total planned dose as per the protocol up to the last date of study treatment administration. The actual cumulative dose refers to the total actual dose administered, over the duration for which the subject is on the study treatment as document in the DAR eCRF. It is the sum of the non-zero total daily doses recorded over the dosing period.

[redacted]

[redacted]

[redacted]	[redacted]

[redacted]

15.2 Adverse Events

Adverse events will be collected and recorded from the time a subject sign the informed consent to the end of study period. All AEs will be classified by primary system organ class (SOC) and preferred term (PT) according to MedDRA coding dictionary. A treatment-emergent adverse event (TEAE) is an AE that begins after the first administration of Vodobatinib or any existing AEs that worsens after then first dose of Vodobatinib. All reported AEs will be listed, but only TEAEs will be summarized in tables. The reporting period for TEAE begins from the date of first dose of Vodobatinib until 30 days after the last dose of Vodobatinib. Any AE which occurs 30 days after the last dose will be reported if it is considered related to Vodobatinib by the investigator.

An overall summary of TEAEs presenting number and percentage of subjects reporting at least one TEAE for the categories presented below:

- Subjects with at least one TEAE
- Subjects with at least one TEAE related to Vodobatinib
- Subjects with at least one serious TEAE
- Subjects with at least one serious TEAE related to Vodobatinib
- Subjects with at least one TEAE leading to premature discontinuation of Vodobatinib
- Subjects with at least one TEAE leading to death
- TEAEs by highest relationship to Vodobatinib
- TEAEs by highest severity

The following summaries will be tabulated

- TEAEs overall and by SOC and PT
- Study Vodobatinib-related TEAEs, overall and by SOC and PT
- TEAEs by maximum severity, overall and by SOC and PT
- Study Vodobatinib-related TEAEs by maximum severity, overall and by SOC and PT
- Serious TEAEs, overall and by SOC and PT
- Vodobatinib-related Serious TEAEs, overall and by SOC and PT
- CTCAE grade 3 or higher TEAEs
- Vodobatinib-related CTCAE grade 3 or higher TEAEs
- TEAEs leading to discontinuation of Vodobatinib, overall and by SOC and PT

- Vodobatinib related TEAEs leading to discontinuation of Vodobatinib, overall and by SOC and PT
- TEAEs leading to death, overall and by SOC and PT
- Vodobatinib related TEAEs leading to death, overall and by SOC and PT
- TEAE leading to dose interruption/adjustment, overall and by SOC and PT
- Vodobatinib related TEAEs leading to dose interruption/adjustment, overall and by SOC and PT
- Dose Limiting Toxicities
- Summary of CVAEs
    - Subjects with at least one CVAE
    - Subjects with at least one CVAE related to Vodobatinib
    - Subjects with at least one grade 3 or higher TEAEs
    - Subjects with at least one grade 3 or higher TEAEs related to Vodobatinib
    - Subjects with at least one serious CVAE
    - Subjects with at least one serious CVAE related to Vodobatinib
    - Subjects with at least one CVAE leading to premature discontinuation of Vodobatinib
    - Subjects with at least one CVAE related to Vodobatinib leading to premature discontinuation of Vodobatinib
    - Subjects with at least one CVAE leading to death
    - Subjects with at least one CVAE leading to death due to Vodobatinib

- CVAEs by PT all Grades and Grade 3 or higher
- CVAEs related to Vodobatinib by PT all Grades and Grade 3 or higher

For summaries by SOC and PT, a subject will be counted only once at the SOC level and once at each PT within the SOC level, even if the subject experienced more than one AE within a specific SOC and PT. For summaries by SOC, PT, and maximum severity, a subject will be counted only once at the maximum severity level for which the event occurred at the SOC level and at the maximum severity level for which the event occurred for each unique PT within that SOC level. Therefore, subjects will contribute to only one severity level within a PT or SOC.

Summaries presenting frequency of TEAEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT. Summaries presenting TEAEs by PT only will be ordered by overall descending frequency of PT.

Subject listings of all adverse events will be provided. Deaths and other serious or clinically significant non-fatal adverse events will be listed separately.

15.3 Laboratory Evaluations

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) latest version based on the observed values. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by CTCAE latest version, results will be categorized as low/normal/high based on the laboratory normal ranges. Both central and local laboratory results are used for the analysis of laboratory data. The following summaries will be generated on the safety set for hematology and biochemistry parameters by dose.

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline in the on-treatment period.

The following listings will be generated separately for hematology and biochemistry parameters:

- Listing of all CTCAE grade 3 or 4 laboratory toxicities.

15.4 12-Lead Electrocardiogram Evaluations

The following 12-lead ECG will be obtained for each subject during the study period

- Heart Rate (bpm)
- RR interval (msec)
- QRS Interval (msec)
- PR Interval (msec)
- QT interval (msec)
- QTcF Interval (msec)
- Overall Interpretation

[redacted]

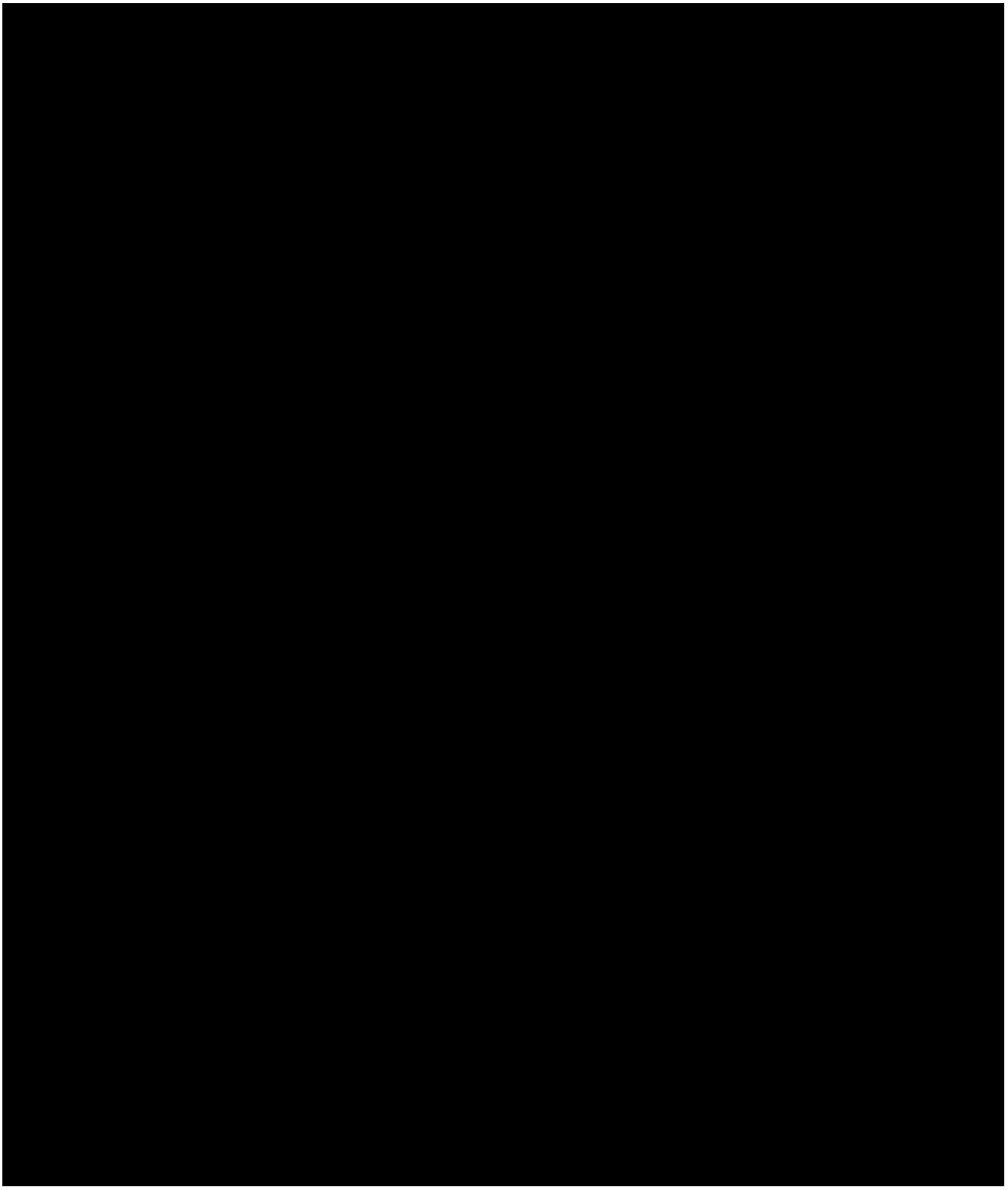
15.5 VITAL SIGNS

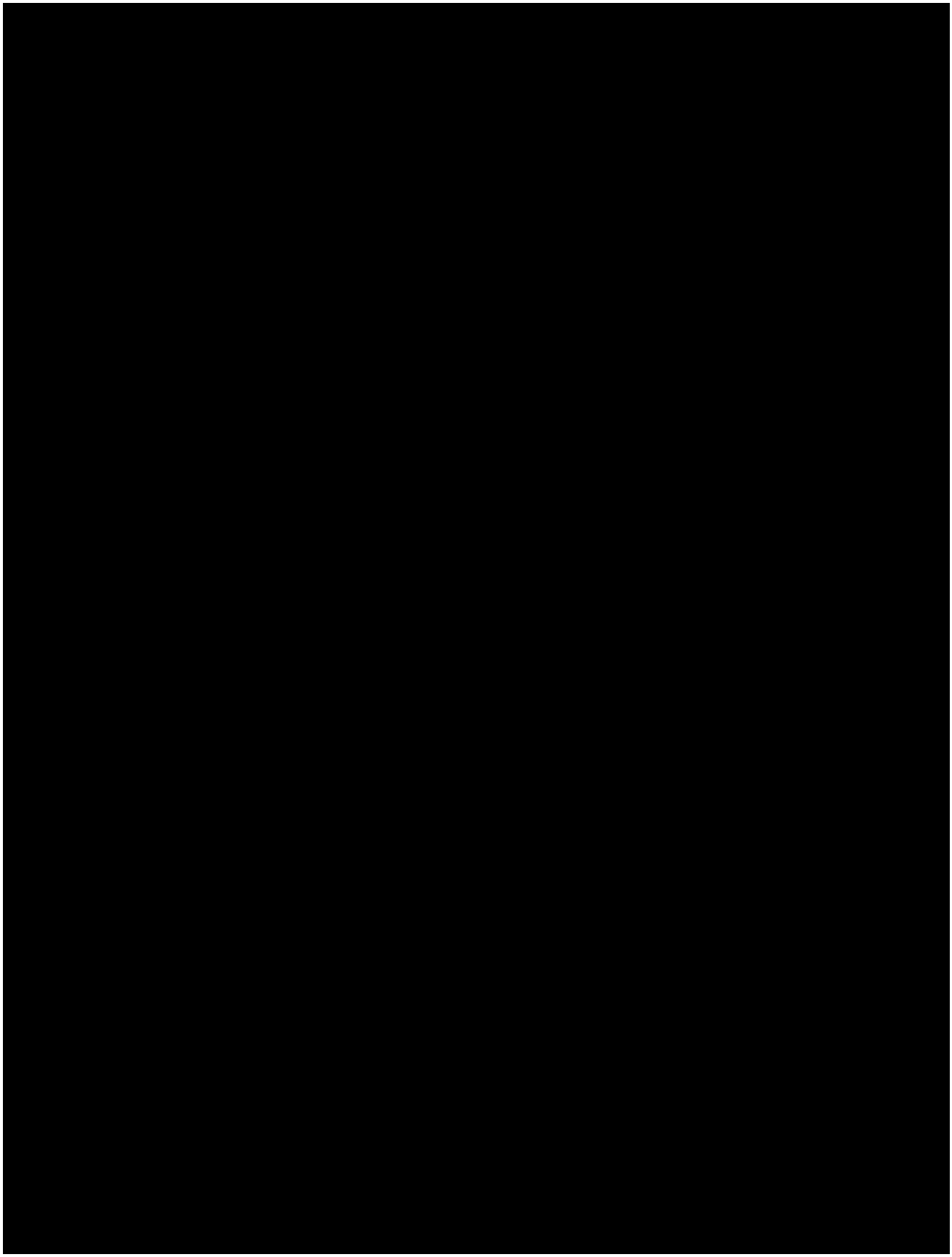
Vital signs including height (cm), weight (kg), systolic and diastolic blood pressure (mmHg), heart rate (bpm), body temperature and respiratory rate will be collected at the scheduled study visits. Any notable changes compared to the screening visit will be recorded as AEs.

15.6 PHYSICAL EXAMINATION

A detailed physical examination will be performed at the Screening visit and targeted physical examination at scheduled visits as well as at the EOT where applicable. Any notable changes compared to the screening visit will be recorded as AEs.

[redacted]





[redacted]