Official Title:	A Phase 1/2 Study of the Safety, Pharmacokinetics and Anti-Tumor Activity of the Oral KIT Inhibitor THE-630 in Patients with Advanced Gastrointestinal Stromal Tumors (GIST)
NCT Number:	NCT05160168
Document Date:	09 Jan 2024

Statistical Analysis Plan

Title: A Phase 1/2 Study of the Safety, Pharmacokinetics and Anti- Tumor Activity of the Oral KIT Inhibitor THE-630 in Patients with Advanced Gastrointestinal Stromal Tumors (GIST)

Protocol Number: THE630-21-101

Protocol Version: Version 3.0/25FEB2022

SAP Version 3.0

SAP Issue Date: 09-JAN-2024

SAP Author: PPD , MS.

Previous SAP Versions

1.0, 05-AUG-2022

2.0, 26-OCT-2023

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REVIEW / APPROVAL SIGNATURES

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Plan Approver, Sponsor Clinician PPD MD, Consultant for Theseus Pharmaceuticals, Inc. Signature: PPD *Electronically signed by: PPD* *Reason: I approve this document* *Date: Jan 10, 2024 09:17 EST*	

SAP Amendments prior to database lock

Version	Issue Date	Section	Revision / Addition
2.0	26-OCT-2023	1	Removed unnecessary text given in original version. Added details regarding why there is an amendment
2.0	26-OCT-2023	3,4,5 (Original)	Removed Phase 2 endpoints, sample size and randomization section (Captured in SAP V1.0)
2.0	26-OCT-2023	Multiple	Removed sections referring to phase 2, Dose Expansion (EXP). Removed displays and other details that reference phase 2 or EXP.
2.0	26-OCT-2023	Multiple	The follow populations, subgroups, endpoints and/or displays were dropped due to the reduction in scope for the terminated study (eg, removal of Prior SACT subgroup analyses, reduction in number of analysis sets, and descriptions of response): -Response-Evaluable Analysis Set - Prior SACT Subgroup - Best Overall Response (BOR) and ORR, Confirmed and unconfirmed - Duration of Response (DOR), Confirmed responders-displays - Displays: - Table and/or figures referencing above were dropped or amended not to reflect said data. - OS: Table display - Labs: Table display (e.g., descriptive summaries, CTCAE grade increases) - Tissue/Blood Samples: All displays - Figures: labs, vital signs, and Spider Plots
3.0			Reduction in the number of TFLs required (the following displays/endpoints are dropped): -All listings except for listings referenced as a table. -PFS, OS and time to response -Vital Signs/ECG/ Prior/Concomitant medications (e.g., Descriptive summaries) -several AE displays by preferred term

1 INTRODUCTION

This is a Phase 1/2, open-label, multicenter trial to evaluate the safety, pharmacokinetics, and antitumor activity of THE-630 in patients with advanced GIST. The plan was to conduct the study in two parts: a dose escalation phase (Phase 1) and a subsequent expansion phase (Phase 2).

Enrollment was stopped after 32 patients were enrolled in Phase 1. Phase 2 will not be initiated.

Due to the termination of this study, the scope of reporting has changed. This amendment documents the updates to planned analyses due to the reduction in scope of the study. All details regarding the original study objectives, planned statistical displays and analysis components are detailed in SAP version 1.0. In general, the analyses planned have remained consistent with those defined in SAP version 1.0, but the scope has been reduced due to the lack of an expansion phase, and shorter follow-up of the study.

2 STUDY OBJECTIVES

Below objectives are as defined in the protocol. However, due to the termination of the study, certain objectives (e.g., Phase 2) are no longer applicable.

2.1 Primary Objectives

The primary objectives for the study are as follows:

- Dose Escalation (Phase 1): To determine the safety profile of oral THE-630, including the DLTs, MTD, and RP2D
- Expansion Cohorts (Phase 2): To determine the antitumor activity of oral THE-630 in patients with advanced GIST

2.2 Secondary Objectives

The secondary objectives for the study are as follows:

- Dose Escalation (Phase 1):
  - To determine the PK profile of oral THE-630 and its active metabolite THE-973
  - To document preliminary evidence of antitumor activity of oral THE-630 in patients with advanced GIST
- Expansion Cohorts (Phase 2):

- To evaluate the safety profile of oral THE-630
- To further characterize the PK profile of oral THE-630 and its active metabolite THE-973

2.3 Exploratory Objectives

The exploratory objective for both phase 1 and phase 2 of the study is as follows:

- To explore associations between tumor and plasma biomarkers and THE-630 efficacy and safety

3 ENDPOINTS

3.1 Primary Endpoint

3.1.1 Phase 1

The primary endpoint of the dose escalation phase of the study is the safety profile of THE-630, including identification of DLTs and MTD, and determination of the RP2D.

3.2 Secondary Endpoints

3.2.1 Phase 1

Secondary endpoints of the dose escalation phase include:

- Plasma PK parameters of THE-630 and its active metabolite THE-973 after single oral dose and at steady state after multiple oral doses
- Efficacy assessments, according to modified RECIST 1.1 for patients with GIST including: confirmed objective response rate (ORR), best overall response, best target lesion response, time to response, disease control rate (DCR), Clinical Benefit Rate (CBR) at 16 weeks, PFS and OS

4 PLANNED ANALYSES

4.1 Analysis Sets

4.1.1 Screened Set

The Screened Set includes all patients who signed informed consent and were allocated a patient number.

4.1.2 Enrolled Set

The Enrolled Set includes all screened set patients who meet eligibility criteria.

4.1.3 Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled patients who receive at least one dose of THE-630. Unless otherwise stated, all primary efficacy and safety analyses will be conducted on the Full Analysis Set.

4.1.4 DLT-evaluable Analysis Set (phase 1 only)

The DLT-evaluable Analysis Set (Phase 1 only) will include patients enrolled in the Phase 1 dose escalation portion who completed at least 75% of the planned total dose during Cycle 1 (DLT evaluation period, i.e. 21 of 28 days) and patients who have experienced a protocol-defined DLT, regardless of dosing adherence in Cycle 1. Patients who do not receive study drug for at least 21 of 28 days (at least 75% of planned doses; not necessarily consecutively) during the first cycle for reasons not considered to be a DLT will be excluded from the DLT-evaluable Analysis Set. Additionally, patients who were enrolled as backfill enrollment will be excluded from the DLT-evaluable Analysis Set.

4.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

4.2.1 Age

Age is defined as the age in years at time of informed consent as collected in the CRF.

The follow age groups (categorical) will be created for summary purposes:

Age group 1 (years): 18-64, ≥ 65

Age Group 2 (years): 18-49, 50-64, 65-74, ≥ 75.

4.2.2 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) collected prior to first dose date and time of study drug for a given patient.

4.2.3 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

4.2.4 Prior Systemic Anticancer Therapy (SACT)

Prior TKIs (tyrosine kinase inhibitor) will be identified programmatically and through manual review of the data by the sponsor on an on-going basis. Final identification will be approved by the Sponsor before database lock. Additionally, for reporting purposes, prior SACTs that have different versions (e.g., salt vs no salt) and hence coded to different codes but will be considered the same SACT. These will be identified programmatically and through a manual review by the sponsor. Final identification will be approved by the Sponsor before database lock.

4.2.5 Conventions for Missing and Partial Dates

All rules explained below for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual patient listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

4.2.6 Missing / Partial Start / Stop Date of Adverse Events (AE) and Concomitant Medications

Missing and partial start and stop date will be imputed for analysis purposes as follows.

Partial or missing stop date will be imputed as follows:

If the stop date is completely missing and the event has resolved, or the patient has stopped taking the concomitant medication, the stop date will be imputed as the date of the patient's last clinic visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the patient's last clinic visit in the study if in the same year.

- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the patient's last clinic visit in which case the date of patient's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the patient's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as "01-Jan" of the same year or the date of the first dose of study drug whichever is latest. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug,
  - the start date of the concomitant medication will be imputed as the "01-Jan" of the same year.
  - the start date of the event will be imputed as the "01-Jan" of the same year or patient's screening date, whichever is latest.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date unless this partial start date is same month as patient's screening visit in which case the date of screening will be used.

4.2.7 Missing Last Dates of Study Drug Dosing

If the date of last dose of study drug is completely missing, then the date of last dose of study drug will be taken for analysis purposes as the date of patient's last clinic visit in the study or has been

indicated to have discontinued treatment or has died whichever is earlier but no earlier than the date of first dose.

If only the month and year of the last dose was recorded, then the date of last dosing will be taken for analysis purposes as, the last day of the month of the recorded last dose or the date of patient's last clinic visit in the study or has been indicated to have discontinued treatment or has died whichever is earlier but no earlier than date of first dose.

4.2.8 Missing Diagnosis Dates

If the month and year are present but the day is missing, the diagnosis date will be set to first day of the relevant month. If only the year is recorded the diagnosis date will be set as "01-Jan" for that year.

4.2.9 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

4.2.10 Exposure to Study Drug

Duration of exposure to study drug will be calculated as follows from the date of last dosing minus the first day of dosing + 1. The duration of exposure calculation will not take into account interruptions in therapy/missed doses. Duration of exposure to study drug will be reported in months. Patients will also be assigned to a duration of exposure category (< 1 month, 1 to < 3 months, 3 to < 6 months, 6 to < 12 months, ≥12 months) based on their exposure. Additionally actual number of days dosed will be calculated taking into account interruptions and missed doses.

Cumulative dose taken (mg) will be the sum of all doses taken by a patient taking into account any interruptions/missed doses, dose reductions or dose increases as recorded in the eCRF

$$\sum_{1}^{j} dose\ (mg)_j * (end\ date_j - start\ date_j + 1)$$

Dose intensity (mg/day) is calculated as cumulative dose taken (mg)/duration of exposure (days).

Relative dose intensity is calculated as 100* (dose intensity/expected dose intensity). Expected dose is based on assigned dose level and duration of exposure not adjusted for prescribed interruptions, dose reduction or increases.

4.2.11 Compliance

Treatment compliance for Cycle 1 will be calculated as follows: ([cumulative] amount of treatment actually taken [mg] during Cycle 1)/Total [cumulative] amount of treatment that should have been taken [mg]) during Cycle 1 x 100. Total (cumulative) amount taken for cycle 1, similar to calculation in Section 6.2.10 limiting to Cycle 1. Total (cumulative) amount of treatment that should have been taken (mg) during Cycle 1 will be calculated for each dose level prescribed within Cycle 1*(end date of that dose level -start date of dose level+1) and summed across dosing records within Cycle 1 for a given patient. Patients will also be categorized by Cycle 1compliance based on the following compliance levels (<50%, 50 to <75%, 75 to <90%, ≥ 90%).

4.2.12 Body Mass Index (BMI)

BMI at screening will be derived based on screening height and weight.

BMI = weight (kg) divided by height (m) squared (unit=kg/m^2).

4.2.13 Safety Endpoints

4.2.13.1 Electrocardiogram (ECG) Data

Triplicate ECGs should be taken on Cycle 1, Day 1 (pre-dose and 8 hrs post-dose) and Day 15 (pre-dose and following hrs post-dose: 1, 2, 4, 8); otherwise, single ECGs are required at specific time points per protocol schedule of events.

For triplicate ECG data recorded on continuous scales, the mean value rounded to the integer will be presented. For overall interpretation if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

4.2.13.2 Dose Limiting Toxicities (DLT)

DLTs during Phase 1 (dose escalation phase) are defined as any treatment-emergent adverse event (AE) that meets the following criteria within the first 28 days of treatment (e.g, occurring during Cycle 1) and for which the relationship to THE-630 cannot be ruled out:

- Non-hematologic toxicities
    - Any ≥ Grade 3 non-hematologic toxicity, with the exception of:

- Self-limiting or medically controllable toxicities (e.g., nausea, fatigue, electrolyte disturbances) lasting ≤3 days
- Grade 3 vomiting or diarrhea lasting ≤ 3 days
- Grade 3 elevations of creatine kinase (CK) that are asymptomatic, i.e., not accompanied by muscle pain or worsening renal function or other signs of rhabdomyolysis or cardiac muscle damage (such as abnormal CK-MB, Troponin) and recovered to ≤Grade 1 or baseline in <72 hours
- Grade 3 hypertension that recovers to Grade 2 or below within 5 days
- Alopecia

- Hematologic toxicities
  - Febrile neutropenia (fever, >101°F [>38.3°C]; ANC <0.5 × 109/L)
  - Prolonged Grade 4 neutropenia (≥7 days)
  - Neutropenic infection: ≥ Grade 3 neutropenia with ≥ Grade 3 infection
  - Thrombocytopenia ≥ Grade 3 with bleeding or Grade 4 without bleeding lasting ≥7 days

- Missed ≥25% of planned doses of THE-630 (in the aggregate, not necessarily consecutive) over 28 days due to AEs for which the relationship to THE-630 cannot be ruled out in the first cycle[note the treatment-related AE(s) included should not have met other DLT criteria]

DLTs will be reported as AEs and identified as a DLT in the database.

4.2.13.3 Unscheduled Visits

Only scheduled post-baseline laboratory, vital signs, ECHO/MUGA and ECG values will be tabulated by visit. Certain summaries may have any time, post-baseline/worst post-baseline/minimum post-baseline/maximum post-baseline which would include post-baseline scheduled/repeat/ unscheduled assessments. All post-baseline assessments will be listed in the relevant appendices to the CSR.

4.2.14 Efficacy endpoints

4.2.14.1 Best Overall Response (BOR), Confirmed

BOR is defined as the best response achieved at any time point on the study where response refers to the overall response at a given time point (e.g., overall visit response; (derived; see Appendix 1)) according to the following hierarchy:

- Complete Response (CR),
- Partial Response (PR),
- Stable disease (SD)
- Progressive disease (PD)
- Not Evaluable (NE)

per modified RECIST version 1.1 for patients with GIST.

CR or PR responses must be confirmed by repeat imaging at no less than 4 weeks after the date of the initial response (See Appendix 1). To be assigned SD, patient must have met the SD criteria once after first dose at a minimum of 6 weeks. It should be noted that patients with no measurable disease at baseline should have overall visit response(s) of Non-CR/Non-PD. In these cases, for analysis purposes, BOR will be set to NE. Additionally, if a patient does not have any post-baseline overall visit response assessments, then the patient will be assigned BOR of NE.

4.2.14.2 Confirmed Objective Response Rate (ORR)

Confirmed ORR is defined as the proportion of the patients who were confirmed to have achieved CR or PR per modified RECIST version 1.1 for patients with GIST (confirmed ≥4 weeks after initial response with a subsequent scan) after initiation of study drug. Patients with no measurable disease at baseline or no evaluable post-baseline response assessment (e.g., RECIST) will be considered non-responders.

4.2.14.3 Clinical Benefit Rate (CBR) at 16 Weeks

CBR at 16 weeks is defined as the proportion of patients remaining on study who have not met criteria for progressive disease (PD) on or prior to the 16-week assessment (i.e., patients with an objective response or stable disease (SD) lasting 4 cycles from the start of treatment (defined as at least 109 days from start of treatment). Patients with no tumor assessments (e.g., scans) for Week 16 and later timepoints would not be counted as having clinical benefit.

4.2.14.4 Disease Control Rate (DCR)

DCR is defined as the proportion of patients who have achieved confirmed BOR of CR, PR, or SD (in the case of SD, measurements must have met the SD criteria at least 6 weeks after the initiation of study drug).

4.2.14.5 Best Percent change from baseline in sum of the longest diameter of target lesions

The percentage change in the sum of longest diameter for the target lesions by visit will be calculated. Best percent change in the sum of the longest diameter (SLD) of target lesions will be identified. This is defined as the biggest percent reduction from baseline or in the scenario where patient does not have any reduction then no change or smallest increase.

That said post-baseline visits where the longest diameter of one or more of the identified target lesions(s) were not measured and the target lesion response for said visit is NE will be excluded for purposes of analysis (Appendix 1).

4.2.14.6 Duration of Follow-up

Duration of follow-up is defined as time (months) from first dose until death, lost to follow-up (ltfu) or withdraw from study, whichever is earliest.

Duration of follow-up (months)= (earliest of date of death/ltfu/withdraw from study- date of first dose + 1)/30.4375.

4.3 Conventions

All data listings, summaries, figures, and statistical analyses will be generated using SAS version 9.3 or higher[1].

Dose Escalation (Phase 1) [DE]:

DE or DE cohort refers subjects participating in the Phase 1 dose escalation part of this study. Cohort for DE phase refers to dose level.

Summaries will be presented by dose escalation phase cohorts (dose levels) and overall.

3 mg QD (N=XX)	<Dose 2 level> (N=XX)	<Dose 3 level> (N=XX)	<Dose 4 level> (N=XX)	<Dose X level> (N=XX)	All Patients (N=XXX)

Listings will be sorted in the following order: Cohort number, patient (if applicable, backfill patients should be listed after non-backfill patients), parameter, and visit unless otherwise stated. All data will be listed.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

4.3.1 Decimal Places

Decimal places for derived data described in section 4.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer for example day, month, year, number of days and total scores (for rating scales) will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

4.4 Patient Disposition

Patient disposition will be summarized as follows:

- The number of patients, who are in the Screened Set, Enrolled Set, Full Analysis Set and DLT-Evaluable Set will be summarized by cohort and overall.
- The number of patients who failed screening and the reasons for failure will be tabulated for the Screened Set
- The number and percentage of patients who discontinued study drug along with the reason for discontinuing drug and those who discontinued the study along with the reason for discontinuing the study will be tabulated by cohort and overall for the Full Analysis Set.

- Duration of follow-up will be summarized by cohort and overall for the Full Analysis Set.

4.5 Protocol Deviations

Number (percent) of patients with Major Deviations by deviation category will be presented by cohort and overall for Full Analysis Set.

4.6 Baseline Comparability

The comparability of cohorts with respect to patient demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

The following baseline demographic variables will be summarized by cohort and overall for the Full Analysis Set using standard continuous or categorical variable summaries: Age at informed consent (years), gender, ethnicity, race, height, weight and BMI.

4.7 Medical History

Medical history conditions (prior and on-going) and previous surgical procedures reported at screening will be presented together for Full Analysis Set. Terms will be coded by Medical Dictionary of Regulated Activities (MedDRA) primary system organ class (SOC) and preferred term.

4.8 Baseline Characteristics

Reported mutation status history (e.g, presence of any kit mutation, type of kit Exon mutation, presence of any PDGRA mutation, type of PDGRFA Exon Mutation, Kit and PDGRFA wild-type status) will be summarized by cohort and overall for Full Analysis Set.

Details regarding GIST history (initial diagnosis: time from first diagnosis of GIST to first dose of study drug (years), stage at initial diagnosis, current stage, primary tumor location, histology, any prior surgery related to GIST, any prior radiation therapy related to GIST and any Systemic Anticancer Therapy (SACT) related to GIST; current stage and location of sites of disease at screening) will be summarized by cohort and overall for the Full Analysis Set.

The ECOG performance status scale measures a patient's level of daily functioning (scale ranges from grades 0-5). Descriptive statistics of baseline ECOG score will be presented by cohort and overall.

Details regarding SACT related to GIST (any prior SACT, number of prior therapies, number of prior regimens, number of prior TKIs, type of SACT) will be summarized by cohort and overall for Full Analysis Set.

Details regarding prior surgery and radiation therapy will not be summarized or listed.

4.9 Prior and Concomitant Medications

Data will not be summarized or listed.

4.10 Non-Pharmacological Procedures

Data will not be summarized or listed.

4.11 Exposure to Study Drug

Extent of exposure (number of days of exposure to study), actual number of days dosed, the cumulative amount of administered treatment, dose intensity, and relative dose intensity will be summarized by cohort and overall for Full Analysis Set. Additionally, the number (percent) of patients that had an interruption lasting 3 days or more, duration of longest interruption for those subjects with an interruption lasting at least 3 days, number (percent) of patients that had an interruption due to an AE, number (percent) of patients that had a dose reduction due to an AE or dose increase will also be summarized by cohort and overall.

4.12 Treatment Compliance

Compliance for Cycle 1 will be summarized by cohort and overall for the Full Analysis Set.

4.13 Efficacy Analyses

No statistical comparisons between cohorts are planned for this study. All efficacy analyses will be conducted on the full analysis set unless otherwise stated.

4.13.1 Efficacy Analysis

- ORR

ORR (confirmed) will be summarized by each cohort and overall along with corresponding exact binomial 2-sided 95% CI.

Descriptive summaries will be provided for the confirmed best overall response (BOR) and time to response (confirmed) by cohort and overall.

A waterfall plot of the best percentage change in the target lesion sum of longest diameters from baseline will be produced by cohort. Additionally, swimmer's plots of the duration of treatment overlayed with overall timepoint response will be produced.

- DCR and CBR

DCR and CBR at 16 weeks will be summarized by each cohort and overall along with corresponding exact binomial 2-sided 95% CI.

4.14 Pharmacokinetic Analyses

Pharmacokinetic analyses will be analyzed and reported in a separate report.

4.15 Safety Analyses

The safety analyses will be presented by the treatment received for the Full Analysis Set.

4.15.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug and before last dose + 30 days
- Any pre-existing AE or medical history finding that has worsened in severity on or after the first dose of study drug

A post-treatment AE is Any AE that has an onset greater than 30 days after last dose of study drug.

If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

If a toxicity grade is missing, then the toxicity grade will be reported as missing.

The following tables will be presented for AEs:

- Overall incidence and number of TEAE, TEAEs ≥ Grade 3, Treatment-Related TEAEs, Treatment-Related TEAEs ≥ Grade 3, Serious Treatment Emergent Adverse Events (Treatment-Emergent SAEs), Serious Treatment-Related TEAEs (Treatment Emergent,

Treatment-Related SAEs), TEAEs leading to Study Drug discontinuation, TEAEs leading to interruption of study drug, TEAEs leading to dose reduction of study drug and Fatal TEAEs.

- TEAEs by system organ class and preferred term, incidence and number of events.
- Treatment related TEAE by system organ class and preferred term, incidence and number of events.
- TEAEs ≥ Grade 3 by system organ class and preferred term, incidence and number of events.
- Treatment-related TEAEs ≥ Grade 3 by system organ class and preferred term, incidence and number of events.
- Serious TEAE by system organ class and preferred term, incidence and number of events.
- Serious Treatment related TEAE by system organ class and preferred term, incidence and number of events.
- TEAEs Leading to Discontinuation of Study Drug b system organ class and preferred term
- TEAEs Leading to Interruption of Study Drug by system organ class and preferred term, incidence and number of events.
- TEAEs Leading to dose reduction of Study Drug by system organ class and preferred term, incidence and number of events.
- TEAE by system organ class, preferred term and maximum toxicity, incidence.
- Treatment-Related TEAE by system organ class, preferred term and maximum toxicity, incidence.
- Fatal TEAEs by system organ class and preferred term, incidence
- Post-Treatment Adverse Events by system organ class and preferred term, incidence and number of events.
- Adverse Events, Dose Limiting Toxicities during Cycle 1 By Preferred Term and maximum toxicity, incidence (Phase 1 only; DLT-Evaluable Analysis Set)
- Listing of Serious TEAEs
- Listing of Fatal TEAEs
- Listing of All Deaths
- Listing of DLTs

All AEs will be listed.

4.15.2 Laboratory Data

Laboratory samples will be analyzed by local laboratories. For reporting purposes, lab parameters will be reported using SI units.

Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) will be used to assign grades for select laboratory parameters where applicable (See Appendix 4). A shift table representing two-way frequency tabulation for baseline and the worst post-baseline value according to the CTCAE grade, by cohort and overall, will be provided. For analysis purpose, patients with a lab parameter value that does not meet CTCAE criteria (e.g., value is within normal range) at baseline or any time post-baseline, will be assigned a Grade of 0 for said visit.

The incidence of patients meeting Hy's law criteria will be summarized for any time, post-baseline (See Appendix 5).

A listing of any abnormal laboratory measurements recorded throughout the study will be presented.

4.15.3 Vital Signs

To identify vital signs values of potential clinical importance, the following criteria will be used for the following vital signs parameters: systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Parameter	Category (levels)
SBP (mmHg)	<120 mmHg 120-139 mmHg 140-159 mmHg ≥ 160 mmHg
DBP (mmHg)	<80 mmHg 80-89 mmHg 90-99 mmHg ≥ 100 mmHg

For systolic and diastolic blood pressure, a shift table representing two-way frequency tabulation for baseline and the maximum post-baseline value according to the above criteria, by cohort and overall, will be provided along with summary of any increases in category level.

4.15.4 Echocardiogram/MUGA

Standard continuous and categorical summaries will be presented for each visit by cohort and overall for the following parameters:

- Test type
- Left ventricular ejection
- Fraction (LVEF) % value (observed; change from baseline)
- If LVEF was clinically significant

4.15.5 ECOG Performance Status

Baseline ECOG performance status scale scores will be summarized by cohort and overall (Section 4.8).

4.15.6 Electrocardiogram Data

The number (%) of patients meeting the following criteria at any time, post-baseline will be summarized by cohort and overall:

- QT interval (ms)
  - >500 & baseline ≤500
- QTcF maximum increase (on treatment defined as any assessment on or after first dose up to last dose + 30 days)
  - No increase
  - >0 to <30 ms
  - 30 to 60 ms
  - >60 ms
- QTcF (ms)
  - >500 & baseline ≤500
  - >480 & baseline ≤480
  - >450 & baseline ≤450
- Heart Rate (bpm)
  - <60 bpm
  - <50 bpm
  - >100 bpm
  - >100 bpm and 25% increase from baseline
  - < 50 bpm and 25% decrease from baseline

4.15.7 Physical Examination

Data will not be summarized or listed.

4.15.8 Tissue/Blood Samples for Biomarkers

Data will not be summarized or listed.

5 INTERIM ANALYSIS

No formal pre-specified interim analyses are planned as this is a single arm, open-label, phase 1/2 study, however data may be summarized periodically throughout the study based on a separate plan(s).

6 DATA SAFETY MONITORING BOARD ANALYSIS

No data safety monitoring board (DSMB) analyses are planned.

7 CHANGES TO PLANNED PROTOCOL ANALYSIS

Due to the termination of this study, the scope of reporting has changed. This amendment documents the analyses to be performed, which are generally consistent with the protocol, but reflects the reduction in the scope of reporting.

8 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA

9 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Phase 1 (Dose escalation (DE)) versions of displays will be created. Please note that in titles where text "<phase>" appears, this text should be replaced with "(Phase 1)".

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1 DE	Analysis Sets – Screened Set <Phase>	IP	
14.1.1.2 DE	Screen Failures – Screened Set <Phase>	IP	
14.1.1.3 DE	Inclusion/Exclusion Violations– Screened Set <Phase>	IP	
14.1.1.4 DE	Discontinuation – Full Analysis Set <Phase>	IP	
14.1.1.5 DE	Duration of Follow-Up (months)– Full Analysis Set <Phase>	IP	
14.1.1.6 DE	Major Deviations-Full Analysis Set <Phase>	IP	
14.1.2	**Demographics**		

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.1.2 DE	Demographics – Full Analysis Set <Phase>	IP	
14.1.3	**Baseline Characteristics**		
14.1.3.1 DE	Medical or Surgical History – Full Analysis Set <Phase>	IP	
14.1.3.2 DE	Reported Mutation Status History- Full Analysis Set <Phase>	IP	
14.1.3.3 DE	Baseline Characteristics -Full Analysis Set <Phase>	IP	
14.1.3.4 DE	Prior Systemic Anticancer Therapy Related to GIST-Full Analysis Set <Phase>	IP	
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.1.1 DE	Confirmed ORR, BOR and Time to Response-Full Analysis Set <Phase>	Stat IP/IP	
14.2.2	**Secondary Efficacy Endpoints**		
14.2.2.1 DE	DCR and CBR-Full Analysis Set <Phase>	Stat IP/IP	
14.2.3	**Exploratory Endpoints**		
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1 DE	Adverse Events, Overall Summary of Treatment-Emergent Adverse Events (TEAEs) – Full Analysis Set <Phase>	IP	
14.3.1.2 DE	Adverse Events, TEAEs by System Organ Class and Preferred Term – Full Analysis Set <Phase>	IP	
14.3.1.3 DE	Adverse Events, TEAEs ≥ Grade 3 by System Organ Class and Preferred Term – Full Analysis Set <Phase>	IP	14.3.1.2
14.3.1.4 DE	Adverse Events, Treatment-Related TEAEs by System Organ Class and Preferred Term – Full Analysis Set <Phase>	IP	14.3.1.2
14.3.1.5 DE	Adverse Events, Treatment-Related TEAEs ≥ Grade 3 by System Organ Class and Preferred Term – Full Analysis Set <Phase>	IP	14.3.1.2

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.6 DE	Adverse Events, Serious TEAEs by System Organ Class and Preferred Term –Full Analysis Set <Phase>	IP	14.3.1.2
14.3.1.7 DE	Adverse Events, Serious Treatment-Related TEAEs by System Organ Class and Preferred Term – Full Analysis Set <Phase>	IP	14.3.1.2
14.3.1.8 DE	Adverse Events, TEAEs Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term-Full Analysis Set <Phase>	IP	14.3.1.2
14.3.1.9 DE	Adverse Events, TEAEs Leading to Interruptions of Study Drug by System Organ Class and Preferred Term-Full Analysis Set <Phase>	IP	14.3.1.2
14.3.1.10 DE	Adverse Events, TEAEs Leading to Dose Reductions of Study Drug by System Organ Class and Preferred Term-Full Analysis Set <Phase>	IP	14.3.1.2
14.3.1.11 DE	Adverse Events, TEAEs by System Organ Class, Preferred Term, and Maximum Toxicity-Full Analysis Set <Phase>	IP	
14.3.1.12 DE	Adverse Events, Treatment-related TEAEs by System Organ Class, Preferred Term, and Maximum Toxicity-Full Analysis Set <Phase>	IP	14.3.1.17
14.3.1.13 DE	Adverse Events, Fatal TEAEs by System Organ Class and Preferred Term- Full Analysis Set <Phase>	IP	14.3.1.2
14.3.1.14 DE	Adverse Events, Post-Treatment Treatment Related SAEs by System Organ Class and Preferred Term-Full Analysis Set <Phase>	IP	14.3.1.2
14.3.1.15 DE	Adverse Events, Dose Limiting Toxicities During Cycle 1 by Preferred Term and Maximum Toxicity- DLT Evaluable Analysis Set <Phase>	IP	14.3.1.2
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1 DE	Fatal TEAEs, Listing – Full Analysis Set <Phase>	IP	
14.3.2.2 DE	All Deaths, Listing – Full Analysis Set <Phase>	IP	
14.3.2.3 DE	SAE, Listing – Full Analysis Set <Phase>	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.2.4 DE	TEAEs Reported as Dose Limiting Toxicity, Listing – Full Analysis Set <Phase>	IP	
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1 DE	Laboratory, Listing of Abnormal Values – Full Analysis Set <Phase>	IP	
14.3.4.2 DE	Hematology, CTCAE Grade Shifts from Baseline to Worst Post-Baseline Grade – Full Analysis Set <Phase>	IP	
14.3.4.3 DE	Chemistry, CTCAE Grade Shifts from Baseline to Worst Post-Baseline Grade – Full Analysis Set <Phase>	IP	14.3.4.2
14.3.4.4 DE	Coagulation, CTCAE Grade Shifts from Baseline to Worst Post-Baseline Grade – Full Analysis Set <Phase>	IP	14.3.4.2
14..3.4.5 DE	Potential Hepatotoxicity based on Hy's law – Full Analysis Set <Phase>	IP	
14..3.4.6 DE	Laboratory, Listing of Patients with Potential Hepatotoxicity based on Hy's law -Full Analysis Set <Phase>	IP	
14.3.5	**Extent of Exposure, Dosage Information, And Compliance**		
14.3.5.1 DE	Exposure to Study Drug- Full Analysis Set <Phase>	IP	
14.3.5.2 DE	Compliance to Study Drug During Cycle 1 -Full Analysis Set <Phase>	IP	
14.3.6	**Vital Signs and Physical Examination**		
14.3.6.1 DE	Vital Signs: Blood Pressure Shifts from Baseline to Maximum Post-baseline Value – Full Analysis Set <Phase>	IP	
14.3.7	**Other Safety**		
14.3.7.1 DE	Echocardiogram/MUGA, Descriptive Statistics-Full Analysis Set <Phase>	IP	
14.3.7.2 DE	ECG, QTcF values of Potential Clinical Concern Any Time, Post-baseline by Category-Full Analysis Set <Phase>	IP	
14.3.8	**Concomitant Medication**		
14.4	**PK Tables**		

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.5	**PD Tables**		
14.6	**Other Data**		

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.2.1.3 DE	Best % Change from Baseline in Sum of the Longest Diameter of Target Lesion -Full Analysis Set <Phase>	IP	
14.2.1.4 DE	Swimmers Plot, Duration of treatment -Full Analysis Set <Phase>	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Patient Data Listings**		
16.2.1	**Discontinued Patients**		
16.2.2	**Protocol Deviations**		
16.2.3	**Patients Excluded from The Efficacy Analyses**		
16.2.4	**Demographic Data**		
16.2.5	**Compliance and / or Drug Concentration Data**		
16.2.6	**Individual Efficacy Response Data**		
16.2.7	**Adverse Event Listings**		
16.2.8	**Individual Laboratory Measurements and Other Safety**		

10 APPENDIX 1: RECIST

In this study, the overall RECIST response at a given time point (overall visit response) is determined by investigator based on RECIST 1.1 guidelines modified for GIST. It is based on investigator reported target lesion response, non-target lesion response and presence of any new lesions. For analysis purposes, overall visit response will be derived via programming based on

- deriving target lesion response (via programming),
- non-target lesion response (as collected)
- presence of new lesions (as collected).

10.1 Target Lesion Response

For purposes of analysis, target lesion response will be derived via programming.

Target lesion response is based on the sum of the longest diameters (SLD) of the target lesions.

Target Lesion Response	Criteria
Complete Response (CR)	Disappearance of all target lesions.
Partial Response (PR)	At least a 30% decrease in the SLD of target lesions from baseline (e.g., reference baseline SLD).
Progressive Disease (PD)	• At least a 20% increase in the SLD taking as reference the smallest SLD on the study (including baseline sum if that is the smallest on the study; reference referred to as nadir) • and SLD must also demonstrate an absolute increase of at least 0.5 cm from nadir (i.e., change from nadir in SLD>/=0.5cm). Or • Any re-appearance of one or more target lesions after an overall visit response (see 12.2) of complete response (CR) had been achieved at a prior visit.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Non-Evaluable (NE)	One or more lesions cannot be evaluated because of missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (e.g., PD based on other findings).

Sum of the longest diameter of target lesions

Target lesions (up to 5 lesions) are identified at baseline. The longest diameter (LD) of a target lesion is measured in cm. The sum of the longest diameter (SLD) of all target lesions measured at a given tumor assessment will be calculated by summing the measurements together. At post-baseline tumor assessments, the same target lesions identified at baseline should be assessed using the same method of scan. An indicator flag will be created to flag post-tumor assessments where one or more identified target lesions were not assessed or marked as not evaluable and thus the LD measurement is missing (e.g., MTLFLG=1 for yes). An indicator flag will also be created to flag post-tumor assessments where the scan method does not match baseline scan method.

For purposes of determining target lesion response, SLD, percent change from baseline, and percent change from nadir for post-baseline tumor assessments will be calculated regardless of missing target tumor LD measurements. That said SLD results from assessments with missing target lesion measurements will be excluded from other analyses (e.g., best percent change from baseline) if the derived target lesion response at said visit is NE. Change in method of scan of target lesions will not be taken into account when calculating SLD.

Percent change from baseline in SLD/Percent change from Nadir in SLD

The following calculations for post-baseline tumor assessments at a given visit will help with assigning target tumor response at given visit:

Percent change from baseline in SLD = (SLD at a given post-baseline visit – baseline SLD)/(baseline SLD) x 100.

Percent change from nadir in SLD = (SLD at a given post-baseline visit – nadir SLD)/(nadir SLD) x 100 where nadir represents the smallest SLD prior to the current post-baseline visit.

Note the nadir should only be identified from assessments where all the identified target lesions have a LD measurement. Furthermore, the nadir may (or may not) change at every visit where tumor assessment occurs.

Percentages should be rounded to 1 decimal place prior to assigning target lesion response. For example, 19.84% should be rounded to 19.8%.

Assigning Target lesion response for a given visit

The target lesion response will be either CR, PR, SD or PD based on what criteria is met. If the patient's SLD at a given visit meets the criteria of both PR and PD (based on percent change from baseline and percent change from nadir respectively) then the target lesion response is PD.

If the current tumor assessment has at least one missing target lesion LD measurement (e.g., MTLFLG=1) then assign the target lesion response to PD if the criteria for PD (target lesion) is met based on percent change from nadir. This is the only situation where it can be shown that the contribution of the missing lesion measurement would not change the assigned response. Otherwise, assign the target lesion response to NE.

10.2 Overall Visit Response

Overall visit response will be derived based on

- target lesion response (derived, 10.1),
- nontarget lesion response -(based on [investigator reported] non-target lesion response on the eCRF Modified RECIST v1.1 Response page, RSP01.RSPNTR)
- presence of new lesions (based [investigator reported] "Any new lesions present?" (yes/no) CRF page Modified RECIST v1.1 response page, RSP01.RSNLYN).

The following table will be used:

Target Lesion	Nontarget Lesion	New Lesion (presence)	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD (e.g. CR, Non-CR/non-PD) or NE	No	PR
SD	Non-PD (e.g. CR, Non-CR/non-PD) or NE	No	SD

Not all evaluated (NE)	Non-PD (e.g., CR, Non-CR/non-PR) or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10.3 BOR-confirmation of CR and PR required

BOR is calculated based on the overall visit responses obtained up until objective disease progression (i.e., RECIST response = PD). In the absence of objective disease progression, the BOR is determined using visit responses up until the last evaluable overall visit response.

CR : Overall visit response of CR confirmed at least 4 weeks later by another overall visit response of CR

PR : Overall visit response of PR confirmed at least 4 weeks later by another overall visit response of at least PR (i.e., CR/PR)

SD (≥ 6 weeks): Stable disease recorded at least 6 weeks after the date of first dose (with no prior evidence of progression)

PD: Progression in the absence of CR/PR or SD

NE: Not evaluable.

Overall response first time point	Overall response subsequent time point	Best overall response
CR	CR	CR (if subsequent time point≥ 4 weeks after first time point)
CR	PR	SD, PD or PR[a]
CR	SD	SD-provided minimum criteria for SD duration are met. Otherwise, PD
CR	PD	SD-provided minimum criteria for SD duration are met. Otherwise, PD
CR	NE	SD-provided minimum criteria for SD duration are met. Otherwise, NE

PR	CR	PR
PR	PR	PR (if subsequent time point≥ 4 weeks after first time point)
PR	SD	SD -provided minimum criteria for SD duration are met. Otherwise, PD
PR	PD	SD-provided minimum criteria for SD duration are met. Otherwise, PD
PR	NE	SD-provided minimum criteria for SD duration are met. Otherwise, NE
NE	NE	NE

[a]If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met.

Other considerations

There may be cases where a patient has one or more visits that are not evaluable (NE). These visits may fall in between evaluable visits. This should be taken into account. Thus, subsequent timepoint/visit does not literally mean next time point when NE visit may be involved.

For example, in a case where a patient had PR, NE, PR then as long as the time between the two visits of PR is at least 4 weeks and there is no evidence of PD between the visits with PR, the patient should be assigned a BOR of PR.

Another example is where a patient has NE, NE, SD, SD, the patient can be assigned a BOR of SD as long as the visits with SD occur at least 6 weeks after first dose.

Lastly, if a patient has only NE visits then BOR of NE.

11 APPENDIX 3: SAS CODE

11.1 ORR

CCI

12 APPENDIX 4: LABORATORY TESTS

12.1 Select Laboratory Parameters-CTCAE Grades

The following lab parameters will have CTCAE grades assigned based on numeric criteria listed for CTCAE v5.0 or v4.03. It should be noted that several parameters may have different set of grades based on the CTCAE term of interest (e.g., Sodium (decreased [CTCAE term: hyponatremia] and increased [CTCAE term: hypernatremia]), These CTCAE terms will be summarized separately.

Grades will be derived based on numeric criteria listed in CTCAE v5.0 (or v4.03 in cases where categorization for a laboratory assessment based on numerical value was not possible using CTCAE v5.0) and will not take into consideration clinical signs or symptoms. The below table lists numeric criteria used to determine a grade for a given a parameter value in this study. Note, a semi-colon indicates 'or' within the description of the grade.

Hematology

Parameter	CTCAE Term	Directionality	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	Anemia	Decrease	Hemoglobin(Hgb) <LLN-10.0 g/dL; <LLN-6.2 mmol/L; <LLN-100 g/L	Hgb <10.0-8.0 g/dL; <6.2-4.9 mmol/L; <100-80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80g/L	N/A
White Blood Cells (WBC)	White Blood Cell Decreased	Decrease	<LLN-3000/mm3; <LLN-3.0 x 10e9/L	<3000-2000/mm3; <3.0-2.0 x 10e9/L	<2000-1000/mm3; <2.0-1.0 x 10e9/L	<1000/mm3; <1.0 x 10e9/L

Parameter	CTCAE Term	Directionality	Grade 1	Grade 2	Grade 3	Grade 4
Platelet count	Platelet Count Decreased	Decrease	<LLN-75,000/mm3; <LLN-75.0 x 10e9/L	<75,000-50,000/mm3; <75.0-50.0 x 10e9/L	<50,000-25,000/mm3; <50.0-25.0 x 10e9/L	<25,000/mm3; <25.0 x 10e9/L
Neutrophil count (absolute)	Neutrophil Count Decreased	Decrease	<LLN-1500/mm3; <LLN-1.5 x 10e9/L	<1500-1000/mm3; <1.5-1.0 x 10e9/L	<1000-500/mm3; <1.0-0.5 x 10e9/L	<500/mm3; <0.5 x 10e9/L
Lymphocyte count (absolute)	Lymphocyte Count Decreased	Decrease	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L

ULN=Upper limit of normal
Values in table are based on CTCAE v5.0.

Chemistry

Parameter	CTCAE Term	Directionality	Grade 1	Grade 2	Grade 3	Grade 4
Sodium	Hyponatremia	Decrease	<LLN-130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 mmol/L
Sodium	Hypernatremia	Increase	>ULN-150 mmol/L	>150-155 mmol/L	>155-160 mmol/L	>160 mmol/L

Parameter	CTCAE Term	Directionality	Grade 1	Grade 2	Grade 3	Grade 4
Potassium	Hypokalemia	Decrease	<LLN-3.0 mmol/L	N/A (for purpose of this study)	<3.0-2.5 mmol/L	<2.5 mmol/L
Magnesium	Hypomagnesemia	Decrease	<LLN-1.2 mg/dL; <LLN-0.5 mmol/L	<1.2-0.9 mg/dL; <0.5-0.4 mmol/L	<0.9-0.7 mg/dL; <0.4-0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Magnesium	Hypermagnesemia	Increase	>ULN-3.0 mg/dL; >ULN-1.23 mmol/L	>3.0-8.0 mg/dL; >1.23-3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L	N/A
Phosphorous (based on CTCAE v4.03 criteria)	Hypophosphatemia	Decrease	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L
Calcium (Total) (correct calcium numeric criteria will be applied)	Hypocalcemia	Decrease	Corrected serum calcium of <LLN-8.0 mg/dL; <LLN-2.0 mmol/L	Corrected serum calcium of <8.0-7.0 mg/dL; <2.0-1.75 mmol/L	Corrected serum calcium of <7.0-6.0 mg/dL; <1.75-1.5 mmol/L	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L

Parameter	CTCAE Term	Directionality	Grade 1	Grade 2	Grade 3	Grade 4
Calcium Total) (correct calcium numeric criteria will be applied)	Hypercalcemia	Increase	Corrected serum calcium of >ULN-11.5 mg/dL; >ULN-2.9 mmol/L	Corrected serum calcium of >11.5-12.5 mg/dL; >2.9-3.1 mmol/L	Corrected serum calcium of >12.5-13.5 mg/dL; >3.1-3.4 mmol/L	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L
ALT	Alanine Aminotransferase Increased	Increase	>ULN-3.0 x ULN if baseline was normal; 1.5-3.0 x baseline if baseline was high abnormal (> ULN)	>3.0-5.0 x ULN if baseline was normal; >3.0-5.0 x baseline if baseline was high abnormal (> ULN)	>5.0-20.0 x ULN if baseline was normal; >5.0-20.0 x baseline if baseline was high abnormal (> ULN)	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was high abnormal (> ULN)
AST	Aspartate Aminotransferase Increased	Increase	>ULN-3.0xULN if baseline was normal; 1.5-3.0x baseline if baseline was high abnormal (i.e., > ULN)	>3.0-5.0xULN if baseline was normal; >3.0-5.0x baseline if baseline was high abnormal (i.e., > ULN)	>5.0-20.0xULN if baseline was normal; >5.0-20.0x baseline if baseline was high abnormal (i.e., > ULN)	>20.0xULN if baseline was normal; >20.0x baseline if baseline was abnormal high abnormal (i.e., > ULN)
Total bilirubin	Blood Bilirubin Increased	Increase	>ULN-1.5 x ULN if baseline was normal; > 1.0-1.5 x baseline if baseline was high abnormal (i.e., > ULN)	>1.5-3.0 x ULN if baseline was normal; >1.5-3.0 x baseline if baseline was high abnormal (i.e., > ULN)	>3.0-10.0 x ULN if baseline was normal; >3.0-10.0 x baseline if baseline was high abnormal (i.e., > ULN)	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was high abnormal (i.e., > ULN)
Albumin	Hypoalbuminemia	Decrease	<LLN-3 g/dL; <LLN-30 g/L	<3-2 g/dL; <30-20 g/L	<2 g/dL; <20 g/L	
Creatinine	Creatinine Increased	Increase	>ULN-1.5 x ULN	>1.5-3.0 x baseline; >1.5-3.0 x ULN	>3.0 x baseline; >3.0-6.0 x ULN	>6.0 x ULN

Parameter	CTCAE Term	Directionality	Grade 1	Grade 2	Grade 3	Grade 4
Amylase (based on CTCAE v4.03 criteria)	Serum Amylase Increased	Increase	>ULN-1.5 x ULN	>1.5-2.0 x ULN;	>2.0-5.0 x ULN	>5.0 x ULN
Lipase (based on CTCAE v4.03 criteria)	Lipase Increased	Increase	>ULN-1.5 x ULN	>1.5-2.0 x ULN	>2.0-5.0 x ULN	>5.0 x ULN
CK (Creatinine Kinase)	CPK Increased	Increase	>ULN-2.5 x ULN	>2.5 x ULN-5 x ULN	>5 x ULN-10 x ULN	>10 x ULN
Alkaline phosphatase	Alkaline Phosphatase increased	Increase	>ULN-2.5xULN if baseline was normal; 2.0-2.5x baseline if baseline was high abnormal (i.e., > ULN)	>2.5-5.0xULN if baseline was normal; >2.5-5.0x baseline if baseline was high abnormal (i.e., > ULN)	>5.0-20.0xULN if baseline was normal; >5.0-20.0x baseline if baseline was high abnormal (i.e., > ULN)	>20.0xULN if baseline was normal; >20.0x baseline if baseline was high abnormal (i.e., > ULN)
Alkaline phosphatase	Alkaline Phosphatase increased	Increase	>ULN-2.5xULN if baseline was normal; 2.0-2.5x baseline if baseline was high abnormal (i.e., > ULN)	>2.5-5.0xULN if baseline was normal; >2.5-5.0x baseline if baseline was high abnormal (i.e., > ULN)	>5.0-20.0xULN if baseline was normal; >5.0-20.0x baseline if baseline was high abnormal (i.e., > ULN)	>20.0xULN if baseline was normal; >20.0x baseline if baseline was high abnormal (i.e., > ULN)
Glucose (based on CTCAE v4.03 criteria)	Hyperglycemia	Increase	glucose value >ULN - 160 mg/dL; glucose value >ULN - 8.9 mmol/L	glucose value >160 - 250 mg/dL; glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L	>500 mg/dL; >27.8 mmol/L
Glucose	Hypoglycemia	Decrease	<LLN-55 mg/dL; <LLN-3.0 mmol/L	<55-40 mg/dL; <3.0-2.2 mmol/L	<40-30 mg/dL; <2.2-1.7 mmol/L	<30 mg/dL; <1.7 mmol/L

Coagulation

Parameter	CTCAE Term	Directionality	Grade 1	Grade 2	Grade 3	Grade 4
INR	INR Increased	Increase	>1.2-1.5; >1-1.5 x baseline if on anticoagulation**	>1.5-2.5; >1.5-2.5 x baseline if on anticoagulation**	>2.5; >2.5 x baseline if on anticoagulation**	
aPTT	Activated Partial Thromboplastin time prolonged	Increase	>ULN-1.5 x ULN	>1.5-2.5 x ULN	>2.5 x ULN	

**A subject who is taking a medication assigned WHODrug ATC3 level code "B01A" (antithrombotic agents) will be considered to be on an anticoagulation.

13 APPENDIX 5: CRITERIA BASED ON HY'S LAW

The following criteria for potential Hepatoxicity are based on Hy's law. For criterion which requires multiple parameters to have a certain value (e.g., ALT>3x ULN and TBIL (total bilirubin)> 2xULN), all lab parameters values must be from samples with the same sample collection date.

ALT exceeds thresholds

- ≥3x ULN to <5x ULN
- ≥5x ULN to <8x ULN
- ≥8x ULN to <10x ULN
- ≥10x ULN

AST exceeds thresholds

- ≥3x ULN to <5x ULN
- ≥5x ULN to <8x ULN
- ≥8x ULN to <10x ULN
- ≥10x ULN

ALT or AST exceeds thresholds

- ≥3x ULN to <5x ULN
- ≥5x ULN to <8x ULN
- ≥8x ULN to <10x ULN
- ≥10x ULN

Other criteria

- Total Bilirubin (TBIL) >2x ULN
- ALP> 1.5x
- (ALT or AST> 3x ULN) and (TBIL> 2x ULN or INR >1.5)*
- (ALT or AST >3x ULN) and TBIL ≥ 2x ULN and ALP <2x ULN*

*Criterion which requires multiple parameters to have a certain value (e.g., "and"), it is assumed that all lab parameter values are from the same sample.

80046695-study-11.01.01-20240109-sap_v3.0

Final Audit Report 2024-01-10

Created:	2024-01-09
By:	PPD
Status:	Signed
Transaction ID:	PPD

"80046695-study-11.01.01-20240109-sap_v3.0" History

Document created by PPD
2024-01-09 - 10:33:30 PM GMT

Document emailed to PPD) for signature
2024-01-09 - 10:34:24 PM GMT

Document emailed to PPD for signature
2024-01-09 - 10:34:25 PM GMT

Document emailed to PPD for signature
2024-01-09 - 10:34:25 PM GMT

PPD authenticated with Adobe Acrobat Sign.
2024-01-09 - 10:34:57 PM GMT

Document e-signed by PPD
Signing reason: I am the author of this document
Signature Date: 2024-01-09 - 10:34:58 PM GMT - Time Source: server

Email viewed by PPD
2024-01-09 - 10:50:46 PM GMT

PPD authenticated with Adobe Acrobat Sign.
Challenge: The user opened the agreement.
2024-01-09 - 10:51:02 PM GMT

PPD authenticated with Adobe Acrobat Sign.
2024-01-09 - 10:52:41 PM GMT

Document e-signed by PPD
Signing reason: I am the reviewer of this document
Signature Date: 2024-01-09 - 10:52:43 PM GMT - Time Source: server

Email viewed by PPD

2024-01-10 - 2:16:46 PM GMT

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2024-01-10 - 2:17:35 PM GMT

Document e-signed by PPD

Signing reason: I approve this document

Signature Date: 2024-01-10 - 2:17:36 PM GMT - Time Source: server

Agreement completed.

2024-01-10 - 2:17:36 PM GMT