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STUDY TITLE:

**A Phase 1/2 Study of TAS3351 in Patients with Advanced
Non-Small Cell Lung Cancer and EGFR Mutations**

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This clinical study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) Guidelines, and applicable regulatory requirements.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
BOIN	Bayesian optimal interval design
BOR	Best Overall Response
BSA	Body Surface Area
C _{max}	maximum plasma concentration
CNS	central nerve system
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DI	Dose intensity
DLT	Dose-limiting toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFRmt	Epidermal Growth Factor Receptor mutation
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICR	Independent Central Review
IXRS	Interactive Web Response System
LVEF	Left ventricular ejection fraction
MedDRA	medical dictionary for regulatory activities
MUGA	multiple-gated acquisition
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PDI	Planned Dose Intensity
PFS	Progression-Free Survival
PK/PD	Pharmacokinetics/Pharmacodynamics
PR	Partial Response
PT	Preferred Term
QTc	QT interval corrected for heart rate

Abbreviation	Definition
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable Disease
SI Units	International System of Units
SOC	System Organ Class
T _{max}	time to maximum plasma concentration
TEAE	Treatment-Emergent Adverse Event
TRAE	Treatment related Adverse Event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the Clinical Study Report (CSR) for Study 10073010 based on the protocol amendment 2 dated 07JUL2023.

Part A (A1 as dose escalation part, A2 as backfill patients in dose escalation) and Part B (as dose expansion part) will be discussed in this SAP. Biomarker analysis will be described in a separate biomarker analysis plan. Detailed procedures of population PK and exposure-response analyses will be described in a separate SAP as needed.

2. STUDY OBJECTIVES AND ENDPOINTS

The primary, secondary and exploratory objectives and endpoints of this study are shown in [Table 1](#). The definition and detail of each endpoint will be described in section 5.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Phase 1 Dose Escalation	
Primary	
<ul style="list-style-type: none"> To investigate the safety and determine the recommended Phase 2 dose (RP2D) and dosing schedule of TAS3351 	<ul style="list-style-type: none"> Incidence of dose limiting toxicities (DLTs) Adverse Events Clinical laboratory tests Vital signs 12-lead ECGs Echocardiography/MUGA Ophthalmologic assessment Other safety assessments
Secondary	
<ul style="list-style-type: none"> To evaluate the antitumor activity of TAS3351 	<ul style="list-style-type: none"> Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by investigator Duration of response (DoR) by investigator Disease control rate (DCR) by investigator Time on treatment Progression free survival (PFS; Patients in part A2 only) Overall survival (OS; Patients in part A2 only)
<ul style="list-style-type: none"> To characterize the pharmacokinetics (PK) of TAS3351 and its active metabolite (TAS-05-14317) in plasma 	PK parameters including: <ul style="list-style-type: none"> Maximum plasma concentration (C_{max}) Time to maximum plasma concentration (T_{max}) Area under the plasma concentration-time curve (AUC) Terminal elimination half-life ($T_{1/2}$)
Exploratory	
<ul style="list-style-type: none"> To explore the relationship between exposures of TAS3351 and its active metabolite (TAS-05-14317) in plasma and QT prolongation 	<ul style="list-style-type: none"> Time matched plasma exposures of TAS3351 and its active metabolite (TAS-05-14317) and changes from baseline in QTcF
<ul style="list-style-type: none"> To explore biomarkers for TAS3351 including their potential association with antitumor activity 	<u>Described in separate biomarker analysis plan</u> <ul style="list-style-type: none"> Biomarkers

Objectives	Endpoints
<ul style="list-style-type: none"> To explore metabolites of TAS3351 in plasma 	<ul style="list-style-type: none"> Metabolites of TAS3351 in plasma

Phase 1 Dose Expansion	
Primary	
<ul style="list-style-type: none"> To explore the efficacy of TAS3351 	<ul style="list-style-type: none"> ORR per RECIST v1.1 by independent central review (ICR)
Secondary	
<ul style="list-style-type: none"> To confirm the safety and tolerability of TAS3351 at the RP2D and dosing schedule 	<ul style="list-style-type: none"> Adverse Events Clinical laboratory tests Vital signs 12-lead ECGs Echocardiography/MUGA Ophthalmologic assessment
<ul style="list-style-type: none"> To further explore the anti-tumor efficacy of TAS3351 	<ul style="list-style-type: none"> DoR by ICR/investigator PFS by ICR/investigator DCR by ICR/investigator ORR by investigator Intracranial ORR (icORR) by ICR/investigator Intracranial DoR (icDOR) by ICR/Investigator Overall survival (OS)
Exploratory	
<ul style="list-style-type: none"> To explore biomarkers for TAS3351 including their potential association with efficacy 	<u>Described in separate biomarker analysis plan</u> <ul style="list-style-type: none"> Biomarkers
<ul style="list-style-type: none"> To explore the potential exposure-response associations for efficacy and safety 	<u>Described in separate biomarker analysis plan</u> <ul style="list-style-type: none"> Exposures estimated by Population PK model and selected efficacy and safety measures

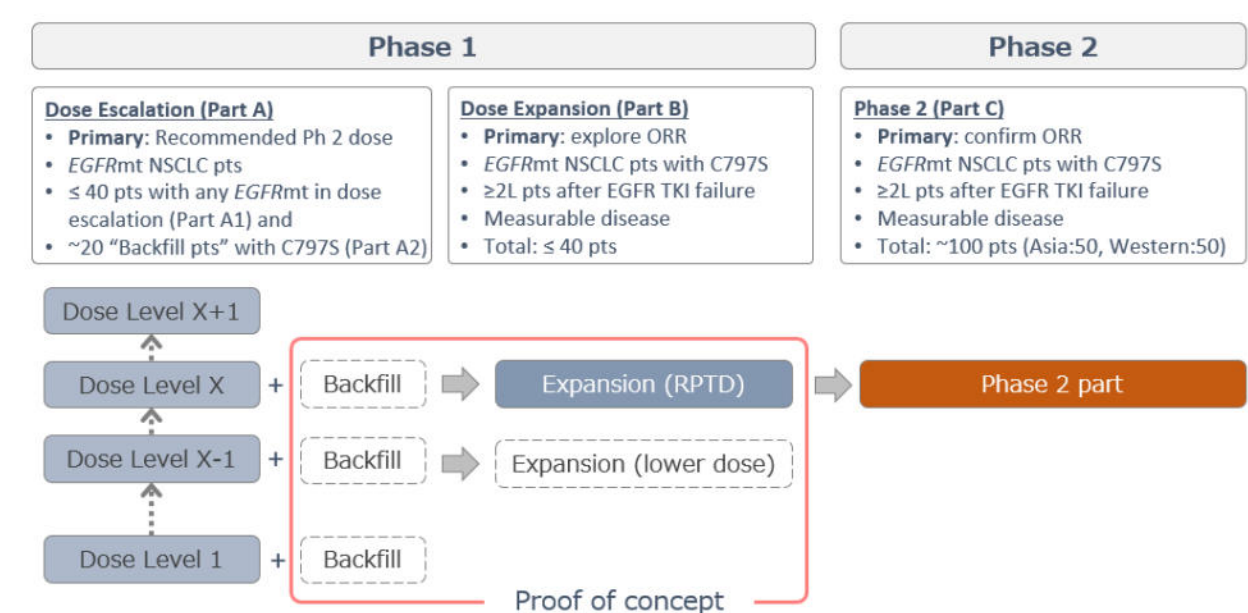
3. STUDY DESCRIPTION

3.1. Summary of Study Design

Study 10073010 is a first-in-human (FIH) Phase 1/2 study designed to determine the recommended Phase 2 dose (RP2D) and efficacy of TAS3351 in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring an acquired C797S epidermal growth factor receptor (EGFR) mutation.

The study design is summarized in Figure 1.

Figure 1: Study Schema



3.2. Treatment Assignment and Blinding/Unblinding

This study will be a single-arm, open-label, phase 1/2 study.

Eligibility must be verified prior to patient enrollment. Upon eligibility verification, patient information will be entered into an Interactive Web Response System (IXRS). The patient should receive the first dose of study therapy within 3 days following entry into the IXRS.

The Phase 1 Dose Escalation is designed to evaluate 6 dose levels of TAS3351 from 50 to 700 mg/day using a Bayesian Optimal Interval (BOIN) design (see Protocol Section 6.1.1).

When a dose level has been determined to be safe in Part A1 and preliminary antitumor activity has been observed, up to 10 further patients may be enrolled at each of such dose levels (“back-fill” patients).

In case a second dose level of TAS3351 might be evaluated in Part B (see Protocol Section 4.2.2), an additional 20 patients with C797S EGFRmt will be enrolled in Part B. A total of 40 patients will be then randomized at a 1:1 ratio between the two treatment arms (i.e., TAS3351 dose levels).

3.3. Determination of Sample Size

Part A:

Part A1: Phase 1 Dose Escalation

There will be up to 40 evaluable patients enrolled using the BOIN (Bayesian optimal interval design) design, [REDACTED] A minimum of 3 patients at each dose level are required.

Part A2: Backfill patients

Approximately 20 patients will be added for “back-fill” cohorts as needed in the Phase 1 Dose Escalation. The additional information from these “back-fill” patients will broaden the amount of safety and preliminary anti-tumor activity data for TAS3351 at a potential active dose levels to inform the selection of the RP2D of TAS3351.

Part B: Phase 1 Dose Expansion

Approximately 40 patients (20 patients per cohort) will be enrolled in the Dose Expansion part of this study. Sample size considerations were based on estimating the proportion of responders with certain precision. If there will be 9 responders, a sample size of 20 patients per cohort would allow to exclude the current standard of care ORR of 25% (90% CI: 27.4%, 68.0%) at 2-sided significance level of 10%.

4. STUDY PERIODS, TREATMENT REGIMENS, AND POPULATIONS FOR ANALYSIS

4.1. Study Periods for Analyses

Study periods are defined in [Table 2](#).

Table 2: Definition of Study Periods for Analysis

Period	Definition
Study Period	From the day of the first ICF signature to the last day of Survival Follow-up Period
Screening Period	From the day of informed consent form (ICF) signature (up to 28 days before first dose) to the day before the first dose
Treatment Period	From the date of first dose of study drug (Day 1/PK lead-in for part A1) to the last day of dosing.
Safety Follow-up Period	30 (+3) days after the last day of dosing
Survival Follow-up Period	From the last day of Safety Follow-up period to death, or study completion, whichever happens first

4.2. Populations for Analysis

The analysis populations in the study are defined in [Table 3](#).

Table 3: Definitions of Analysis Populations

Analysis Population	Definition
All Consenting Population	All patients who signed an informed consent form (ICF).
All Treated Population	All patients who received at least one dose of the study drug. This is the primary population for dosing, efficacy and safety analyses.
DLT Evaluable Population	All patients in the Dose Escalation, except backfill patients, who either experienced a DLT during the 1st cycle of treatment including PK lead-in period, or who completed the 1st cycle without experiencing a DLT and with at least 80% of planned study treatments administered. This is the specific population for DLT summarization.
PK Analysis Population	All patients who received at least one dose of study drug and have at least one post-dose TAS3351 and/or TAS-05-14317 plasma concentration measurement will be evaluated for PK; unless significant protocol

	deviations may have affected the data or if key dosing information is missing. This is the primary population for PK analysis.
PK/ECG Analysis Population	All patients who received at least one dose of study drug, have a baseline and at least one post-dose ECG value, and have time-matched plasma concentrations to at least one post-dose ECG value.
Pharmacodynamic/Biomarker Analysis Population	All patients in the All-Treated Population who have at least one evaluable baseline and one evaluable post-dose pharmacodynamic/biomarker datapoint for analyses.

4.3. Timing of Analysis

4.3.1. Interim Analyses

No interim analysis is planned. Unplanned interim analyses may be performed if required for regulatory purposes or at the Sponsor's discretion.

4.3.2. Primary Analyses

The primary analyses for Phase 1 Dose Escalation (Part A) and Phase 1 Dose Expansion (Part B) will be performed once all patients in each part have completed the Safety Follow-up Period or at least 6 months have passed since the last patient in each part was enrolled, whichever occurs first.

5. STATISTICAL ANALYSIS

5.1. General Methods

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of patients falling into each category, grouped by dose level (with total). Summary table will be separated by part A1, part A2, part A and part B. Total of part A and part B will be added in disposition summary, study drug medication summary and overview of adverse events. All listings will be presented for part A and part B. Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by treatment group (with total) using the mean, standard deviation, median, minimum, and maximum values.

Time to event distribution (i.e., PFS, OS and duration of response) will be estimated using Kaplan Meier techniques. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survivor function $S(t)$. Rates at fixed time-points (e.g., PFS at 6 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function $S(t)$.

5.2. Study Conduct

5.2.1. Accrual

The accrual will be summarized per country and investigational site for informed consent patients. Informed consent date, first dosing date, protocol/amendment ICF version, version, country, investigational site will be presented in a by-patient listing of accruals.

5.2.2. Important Protocol Deviations

Important protocol deviation (ICH E3 Q&A (R1)) is defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect the patient's rights, safety or well-being. These include important informed consent form (ICF) issues, eligibility criteria not met, discontinuation criteria not followed; wrong treatment, incorrect dose/overdose based on protocol definitions, important deviations based on protocol design, and other important Good Clinical Practice (GCP) deviations.

Important protocol deviations will be summarized and listed in the Clinical Study Report (CSR).

According to US Food and Drug Administration (FDA) guidance on conduct of clinical trials of medical products during COVID-19 public health emergency, updated in Aug 2021, protocol deviations related to COVID-19 and COVID-19 impact will be listed in the CSR.

5.2.3. Analysis Populations

The number of patients and percentages in each analysis population (based on all treated population) will be summarized for all treated population. Analysis population assignments for all treated population will also be listed.

5.2.4. Subgroup Analysis

If certain groups of patients (e.g., patients with brain metastases, regional specific analysis) become clinically interesting during the Escalation, subgroup analysis will be performed.

5.3. Study Population

5.3.1. Patient Disposition

Patients may be pre-screened for *EGFR* C797S status prior to the screening. These data will be captured in EDC screening folder. The number of patients who are pre-screened and their gender, *EGFR* status will be summarized and listed.

The total number of patients screened will be presented. Number of screen failures, number of patients not treated with study drug along with reason will be tabulated. Number of patients who discontinued treatment/study along with corresponding primary reason will be tabulated. Number of patients ongoing at time of data cutoff, and for part A1, number of patients who are DLT evaluable per dose level will also be tabulated.

Listings for informed consent patients will be provided showing each patient's informed consent date with protocol amendment version, date of re-consent, if available, reason for not being treated with study drug, first and last dosing date, date of study ending and primary reason for discontinuation of treatment and end of study. A listing to present DLT evaluable patient disposition for patients in DLT evaluable population of part A1 will be provided. A listing for patients not treated will also be provided, showing each patient's race, gender, age, and consent date.

5.3.2. Demographics

The following baseline characteristics will be summarized. Listings will also be provided.

- Age at the time of informed consent
- Age category (< 65, ≥65)
- Sex (Male, Female)
- Race (Caucasian/White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not collected, Other)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino, Unknown, Not collected)
- Country (USA, Japan, Germany, France, Netherlands (for A1); also, Italy, Spain, Korea for A2 and beyond)
- ECOG performance status (0, 1)
- Is/was the patient a tobacco smoker? (Yes/No)
- If the patient is/was a tobacco smoker, Brinkman index (piece/day*year)
- Baseline height

- Baseline weight
- Baseline BMI (= Weight (kg) / (Height (cm) / 100)²)

5.3.3. Baseline Disease Characteristics

The following nature and duration of cancer will be summarized. Listings will also be provided.

- Time since initial diagnosis (years)
= (Year of informed consent) – (Year of initial diagnosis) + 1
- Age at initial diagnosis
= (Age at the time of informed consent) – (Time since initial diagnosis)
- Time since confirmation of first metastasis (years)
= (Year of informed consent) – (Year of the first metastasis confirmed) + 1
- Cancer stage (TNM: I A1 to IV B) at the time of initial diagnosis
- Histology (Adenocarcinoma/Squamous cell carcinoma/Neuroendocrine tumors/Large cell carcinoma/Other)
- Grade of tumor (Well differentiated/Moderately differentiated/Poorly differentiated/Undifferentiated/Unknown)
- Presence and absence of CNS metastases
- New CNS metastases (yes/no)
- CNS metastases progressing after last treatment (yes/no)
- Patient with leptomeningeal disease (yes/no)
- Results of local tumor tissue/cfDNA analysis
 - Type of sample (Tumor tissue, cfDNA from blood sample)
 - Assay method (NGS, PCR, Other)
 - Type of EGFRmt (C797S/ Exon 19 Deletion/ Exon 20 insertion/ E709X/ G719X/ L858R/ L861Q/ L861R/ S768I/ T790M/ Amplification/ Other)

5.3.4. Medical History and Active Symptoms

Medical history (and Active Symptoms) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 25.1 or later. Medical history and active symptoms will be summarized by System Organ Class (SOC) and preferred term (PT) respectively. These will be listed by patient.

5.3.5. Prior Anticancer Therapy

Prior surgery for lung cancer, prior radiotherapy for lung cancer, and prior systemic anticancer therapy will be summarized:

- The number and percentage of patients with at least one surgery for lung cancer will be presented. Outcome of surgery will be summarized. Surgery location, such as brain, will be listed as applicable.
- The number and percentage of patients with at least one prior radiotherapy for lung cancer will be presented. The intent of the radiotherapy (it is "treatment setting") and whether the radiation field includes the thoracic region (ie Yes/No) will be summarized.
- The number and percentage of patients with at least one prior systemic anticancer therapy for lung cancer will be presented. The preferred name of drug name per regimen coded with WHO Drug Dictionary will be summarized. The best response to therapy (CR, PR, SD, PD), the treatment modality (Chemotherapy, EGFR targeted, Immunotherapy, Antibody-drug Conjugate, Other EGFR targeted, other) the treatment setting (Neoadjuvant, Adjuvant, 1st line, 2nd line, 3rd line, 4th line, 5th line, 6th line, 7th line, 8th line, 9th line, 10th line, Other), the reason for the therapy discontinuation, duration of the anticancer therapy, and time from the end date of the anticancer therapy to the first dosing date of study drug will be summarized.

All collected information for prior surgery, prior-radiation therapy, and prior systemic anticancer therapy will be listed.

5.4. Concomitant Medication and Therapy

Medications and therapies taken on or after the first dose of study drug through 30 days after the last dose of study drug are considered concomitant medications and therapies. In addition, medications that started prior to the first dose of study drug and continued into the treatment period are considered concomitant medications and therapies. A medication is considered prior if the stop date of the medication is prior to the study drug start.

Concomitant medications/corticosteroids use for brain metastases will be coded with World Health Organization (WHO) Drug Dictionary (most up-to-date version at the time of analysis). Concomitant medications will be summarized by ATC level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup). Medications will be sorted in descending order of frequency of ATC level 2 and ATC level 4 within ATC level 2 in the total column. A patient will be counted only once within each level of summarization if the patient has taken a medication more than once. Medications will be reported using the generic name.

Concomitant therapies will be coded according to the WHO Drug Dictionary. It will be summarized by ATC level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup).

All concomitant medications and therapies will be listed. Detailed information about corticosteroid uses for brain metastases will be listed and summarized..

5.5. Efficacy Analyses

Unless otherwise specified, all efficacy analyses will be performed based on all treated population. The definition for confirmation and duration of overall response is presented in the protocol Appendix C.

The description of each efficacy endpoint is provided in [Table 4](#).

Table 4: Efficacy Endpoint Definitions

Endpoint	Definition
ORR	The proportion of patients experiencing a best overall response of PR or CR (per RECIST 1.1), based on IRC (and Investigator assessment). (investigator assessment only for part A)
DCR	The proportion of patients experiencing a best overall response of SD, PR, or CR (per RECIST 1.1), based on IRC (and Investigator assessment) (investigator assessment only for A)
DoR	For patients who demonstrated CR or PR as the best overall response, the time from the first documentation of response as CR or PR (per RECIST 1.1 based on IRC and Investigator assessment; investigator assessment only for part A to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. If a patient does not progress or die following a response, then their DoR will use the PFS censoring time. - (Date of PD/death or censoring) – (date of first response of CR/PR(as BOR)) + 1.
PFS (All treated)	Time from date of first dose to the date of documentation of disease progression, or date of death, whichever occurs first - (Date of PD/death or censoring) – (date of first dose) + 1.
OS (All treated)	Measured from the date of first dose until the date of death due to any cause - (Date of death or censoring) – (date of first dose) + 1.

The best overall response (BOR) is determined once all the data for the patient, which are assessments obtained after study treatment discontinuation or starting a subsequent anti-cancer therapy, are known. The following best overall responses are defined based on the timepoint level response.

- Complete Response (CR): Required two timepoint assessments of CR, with the second at least 4 weeks after the initial CR. An intervening timepoint assessment of PR, SD, or PD will not be confirmed as CR.
- Partial Response (PR): Required a first assessment of PR and a second assessment of PR (or CR) at least 4 weeks after the initial PR. An intervening timepoint assessment of SD or PD will not be confirmed as PR.
- Stable Disease (SD): Assessed if the criteria for best overall response of CR, or PR are not met and if in addition, an assessment of SD (or better) has been documented at least once more than 6 weeks from the first dose of study drug.
- Progressive Disease (PD): Defined by any timepoint assessment of PD with no prior response qualifying as SD, PR, or CR.
- Not evaluable (NE): NE refers to patients with post-baseline tumor assessment(s) that are not evaluable.

5.5.1. Objective Response rate (ORR)

Primary Analysis in Part B – ORR by ICR

The following analyses will be performed.

The best overall response will be tabulated, and ORR with 95% CI will be calculated using the Clopper-Pearson method. Confirmed and unconfirmed responses will be listed.

- For Part B, 2-sided 90% CI will also be provided.
- Waterfall plot of target lesion will be provided.

Secondary Analysis in Part A, B – ORR by investigator

The following analyses will be performed.

- The best overall response will be tabulated, and ORR with 95% CI will be calculated using the Clopper-Pearson method.
- Waterfall plot of target lesion will be provided.

5.5.2. Disease Control Rate (DCR)

Secondary Analysis in Part A & B – DCR by investigator

The following analyses will be performed.

- The best overall response will be tabulated, and DCR with 95% CI will be calculated using the Clopper-Pearson method.

5.5.3. Duration of Response (DoR)

Both DoR by ICR and DoR by investigator will be performed. [Table 5](#) summarizes event and censoring rules for DoR.

Table 5: Event and Censoring Rules for DoR

Event/Censor	Decision	Date of event or censor to consider for analysis
Documented first disease progression	Event	Date of 1 st PD scan
Death without disease progression	Event	Date of Death
Patients who not known to have progressed or died at the time of data cut-off	Censor	Date of last evaluable tumor scan (non-NE)
Patient progresses or dies immediately after two or more consecutive missed visits	Censor	Date of last evaluable tumor assessment prior to the two missed visits (non-NE)

For missing data, i.e., patients who were lost to follow-up or who have withdrawn their consent without radiological progression or reached the time point of analysis without a known record of death or disease progression, the DoR will be censored at the date of last evaluable tumor scan.

Secondary Analysis in Part A & B – DoR by investigator

The following analyses will be performed.

- The Kaplan-Meier method will be used to estimate the median and percentile with the 2-sided 95% CI calculated using the Brookmeyer and Crowley method.
- Swimmer plot of treatment duration and response will be provided.

Secondary Analysis in Part B – DoR by ICR

The following analyses will be performed.

- The Kaplan-Meier method will be used to estimate the median and percentile with the 2-sided 95% CI calculated using the Brookmeyer and Crowley method.
- Swimmer plot of treatment duration and response will be provided.

5.5.4. Intracranial ORR (icORR)

Both icORR by ICR and icORR by investigator will be performed.

Secondary Analysis in Part A & B – icORR by investigator

The following analyses will be performed.

- The best overall response in the CNS will be tabulated, and icORR with 95% CI will be calculated using the Clopper-Pearson method.
- Waterfall plot of target lesion will be provided.

Secondary Analysis in Part B – icORR by ICR

The following analyses will be performed.

- The best overall response in the CNS will be tabulated, and icORR with 95% CI will be calculated using the Clopper-Pearson method.
- Waterfall plot of target lesion will be provided.

5.5.5. Intracranial DoR (icDoR)

Both icDoR by ICR and icDoR by investigator will be performed.

Event and censoring rule are the same with DoR event and censoring rule.

Secondary Analysis in Part A & B – icDoR by investigator

- The Kaplan-Meier method will be used to estimate the median and percentile with the 2-sided 95% CI calculated using the Brookmeyer and Crowley method.
- Swimmer plot of treatment duration and response will be provided.

Secondary Analysis in Part B – icDoR by ICR

- The Kaplan-Meier method will be used to estimate the median and percentile with the 2-sided 95% CI calculated using the Brookmeyer and Crowley method.
- Swimmer plot of treatment duration and response will be provided.

5.5.6. Progressive Free Survival (PFS)

Table 6: Event and Censoring Rules for PFS

Event/Censor	Decision	Date of event or censor to consider for analysis
Documented first disease progression	Event	Date of 1st PD scan
Death without disease progression	Event	Date of Death
Patients who not known to have progressed or died at the time of data cut-off	Censor	Date of last evaluable tumor scan (non-NE)
Patient progresses or dies immediately after two or more consecutive missed visits	Censor	Date of last evaluable tumor scan prior to the two missed visits (non-NE)
No baseline or post-baseline tumor assessment unless they die within two visits of baseline (<12 weeks from baseline)	Censor	Date of the first dose

For missing data, i.e., patients who were not known to have progressed or died at the time of data cut-off or who were progressed or died after 2 or more consecutive missed visit, the PFS will be censored at the date of last evaluable tumor scan. If no tumor assessments are performed unless patients die within two visits of baseline visit, PFS will be censored at the time of the first administration.

Secondary Analysis in Part A (Patients in part A2 only), B

The Kaplan-Meier method will be used to estimate the median and percentile with the 2-sided 95% CI calculated using the Brookmeyer and Crowley method.

Kaplan-Meier plot will be provided.

5.5.7. Overall Survival (OS)

Overall survival is defined as the time from the date of first dose to the date of death due to any cause. For patients without documentation of death, the OS will be censored at the last contact date the patient was known to be alive. [Table 7](#) summarizes event and censoring rules for OS.

Table 7: Event and Censoring Rules for OS

Event/Censor	Decision	Date of event or censor to consider for analysis
Death	Event	Date of death
Patient alive without documented death	Censor	Date of last contact*

* Maximum date among completed dates relative to patient's information

In the absence of death confirmation or for patients alive as of the data cut-off date, survival time will be censored at the date of patient last known alive, or the data cut-off date, whichever is earlier. The patient last known alive is defined as the latest among dates recorded on eCRF.

Secondary Analysis in Part A (Patients in part A2 only), B

The Kaplan-Meier method will be used to estimate the median and percentile with the 2-sided 95% CI calculated using the Brookmeyer and Crowley method.

Kaplan-Meier plot will be provided.

End of safety follow-up data, survival follow-up data, and post study treatments data will be presented in by-patient listings.

5.6. Safety Analyses

All safety analyses except DLTs will be performed considering all treated population, summarized by dose level. The DLT analysis will be based on DLT-evaluable Population.

5.6.1. Extent of Exposure

5.6.1.1. Administration of Study Drug

The following parameters will be summarized. These will also be summarized by dose group.

- Duration of treatment
- Number of patients with treatment duration (<1 months, >=1-3 months, >=3-6 months, >=6-9 months, >9 months)
- Cumulative Dose
- Number of Cycles Treated
- Dose intensity
- Relative dose intensity (RDI)

Duration of treatment will be calculated as: (Date of last dose – Date of first dose + 1). For categorical summary, 1 month is set as 30.4375 days.

Cumulative dose

Cumulative dose (mg) is sum of the doses administered to a patient during the treatment period.

Dose intensity

Dose intensity (mg/day) is the cumulative dose (mg) divided by the duration of treatment (days).

Relative dose intensity (RDI)

Relative dose intensity (%) is calculated as cumulative dose (mg) divided by total planned dose (mg), where total planned dose is the treatment duration multiplied by planned dose level.

A by-patient listing of dose of study drug will also be provided.

5.6.1.2. Modification of Study Drug

The following drug modification will be summarized:

- The number and percentage of patients with at least one dose reduction along with reason for the reduction

- The number and percentage of patients with at least one dose interruption and reason for the dose interruption
- The number and percentage of patients with at least one dose error and reason for the dose error
- The number and percentage of patients with at least one dose missed and reason for the dose missed
- Number of dose reductions (1, 2, >2)
- Number of dose interruptions (1, 2, >2)
- Number of dose errors (1, 2, >2)
- Number of doses missed (1, 2, >2)

Listings of dose interruptions and dose reductions will be also provided.

5.6.2. Adverse Events

5.6.2.1. Deaths

Deaths and primary cause of death will be summarized for all deaths, deaths on treatment period, deaths within 30 days of last dose received, and deaths after 30 days of last dose.

A by-patient listing of all deaths/autopsy records will be provided for all treated Patients population.

5.6.2.2. Adverse Events

An AE is any untoward medical condition that occurs in patients while participating in this clinical trial. AEs will be coded according to the MedDRA (Version 25.1 or later) terminology, and the severity of the toxicities will be graded according to NCI CTCAE Version 5.0. Unique instances of all AEs (that is, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (same PT) have been collapsed) will be summarized.

A treatment-emergent AE (TEAE) is defined as an AE that is starting or worsening at the time of or after the first dose of study drug administration and within 30 days after the last dose of study drug and does not necessarily have a causal relationship to the use of the study drug.

The following summary tables will be generated:

- As an overall summary, summary of TEAEs with the number and percentage of patients reporting TEAEs, Grade ≥ 3 TEAEs, Treatment related AEs (TRAEs), Grade ≥ 3 TRAEs, serious adverse events (SAEs), treatment related SAEs, TEAEs leading to study drug discontinuation, dose interruption and dose reduction, and TEAEs with outcome of death.
- Summary of TEAEs (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by SOC and PT.

- Summary of TRAEs (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by SOC and PT.
- Summary of TEAEs (any grade, Grade ≥ 3) presented by dosing cohort and descending frequency of PTs (sorted by any grade PTs)
- Summary of TRAEs (any grade, Grade ≥ 3) presented by dosing cohort and descending frequency of PTs (sorted by any grade PTs)

A by-patient listing of all reported AEs will be provided for all treated Patients population, and non-TEAE will also be provided by listing separately.

5.6.2.3. Adverse Events Leading to Discontinuation/Interruption/Reduction of Study Drug

AEs leading to drug discontinuation/interruption/reduction will be summarized:

- Summary of TEAEs leading to discontinuation of study drug (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of TRAEs leading to discontinuation of study drug (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of TEAEs leading to interruption of study drug (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of TRAEs leading to interruption of study drug (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of TEAEs leading to reduction of study drug (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of TRAEs leading to reduction of study drug (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listings of TEAEs and TRAEs leading to discontinuation/interruption/reduction of study drug will also be provided separately.

5.6.2.4. Serious Adverse Events

Serious adverse events (SAE) will be summarized:

- Summary of Serious TEAEs (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by SOC and PT

- Summary of Serious TRAEs (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listing of SAEs will also be provided.

5.6.2.5. Consolidated AEs

Consolidated terms of AEs will be summarized by treatment group for each category:

- Summary of TEAEs (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by category and PT
- Summary of TRAEs (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by category and PT
- Summary of serious TEAEs (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by category and PT
- Summary of serious TRAEs (50mg cohort, 100mg cohort, 200mg cohort, 300mg cohort, 500mg cohort, any grade, Grade ≥ 3) presented by category and PT

A by-patient listing of consolidated AEs will also be provided.

5.6.3. Dose-Limiting Toxicity (DLT)

Primary Analysis in Part A

Incidence of Dose-limiting Toxicity (DLT) will be summarized by DLT category (hematologic, hepatic, renal, skin, other nonhematologic, other) and DLT event and the analysis will be based on DLT-evaluable Population. The occurrence of any toxicity outlined in Table 8 of Protocol during the DLT evaluation period will be considered a DLT, excluding toxicities clearly related to disease progression or intercurrent illness (See Protocol Section 6.1.2).

A by-patient listing will also be provided.

5.6.4. Clinical Laboratory Evaluations

Clinical laboratory results will be summarized using SI Units. Laboratory measurements will be summarized for each parameter. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for clinical chemistry, hematology, and coagulation parameters at each scheduled visit. Change from baseline will be summarized in a similar manner.

Laboratory test results will be graded by NCI CTCAE (Version 5.0). Shift tables will be presented for each laboratory parameter to display the shift from baseline grade to the worst post-baseline grade. Summary tables will be provided presenting the number and percentage of patients for each laboratory test by baseline grade and worst post-baseline grade. All post-baseline assessments (including unscheduled visits) will be used to determine the worst post-baseline grade.

For qualitative urinalysis parameters and summary tables will be provided presenting the number and percentage of patients for each parameter and scheduled visit. If any quantitative urinalysis parameters will be collected, descriptive statistics will also be presented at each parameter and scheduled visit.

All clinical laboratory data will be presented in by-patient listings.

The laboratory tests of hematology, serum chemistry, coagulation, and urinalysis are listed in [Table 8](#).

Table 8: Laboratory Tests

Assessment	Test Items
Hematology	Red blood cell (RBC) count, hemoglobin, hematocrit, platelets, white blood cell (WBC) count with differential, neutrophils (ANC), lymphocytes, monocytes, eosinophils, basophils
Serum chemistry	AST, ALT, ALP, total bilirubin, direct bilirubin, albumin, lipase, amylase, LDH, triglyceride, total cholesterol, creatinine, BUN, Na, K, Cl, Serum Calcium, Ca (corrected value), Mg, blood glucose, C reactive protein (CRP), creatinine clearance (if there is a measured value, use the measured value) or eGFR. For a calculated CrCl value, use the Cockcroft-Gault formula: Male: $CrCl = \frac{(140 - [insert\ age\ in\ years]) \times [insert\ weight\ in\ kg]}{72 \times [insert\ serum\ creatinine\ in\ mg/dL]}$ Female: $CrCl = [\frac{(140 - [insert\ age\ in\ years]) \times [insert\ weight\ in\ kg]}{72 \times [insert\ serum\ creatinine\ in\ mg/dL]}] \times 0.85$
Coagulation	PT-INR, APTT, and fibrinogen
Urinalysis	Qualitative: Urine protein, sediment, occult blood by dipstick or laboratory. Quantitative: If urine protein is 2+ to 4+, add urinary β 2-microglobulin and proteinuria.

For a calculated creatinine clearance (CrCl) value, use the Cockcroft-Gault formula:

Male CrCl (mL/min) = $\text{weight (kg)} \times (140 - \text{age (years)}) / [72 \times \text{serum creatinine (mg/dL)}]$

Female CrCl (mL/min) = male CrCl \times 0.85

5.6.5. Vital Signs and Body Weight

Vital sign measurements include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (celsius), and body weight (kg). Each vital sign parameter will be summarized with descriptive statistics by scheduled time point. Change from baseline will be summarized in a similar manner.

All vital sign data will be presented in by-patient listings.

5.6.6. Electrocardiograms

ECGs are to be performed using local machines. Additionally, in part A1, ECGs will also be obtained using central ECG machines, according to the schedule of assessments. ECGs are to be performed in triplicate from Cycle 1 Day 1 to Cycle 3 Day 1. Investigators are to review all ECGs, regardless of whether these are from local or central ECG machines, and record findings

in the eCRF and these will be summarized and listed. ECG interpretation (abnormal, clinical significance) is to be performed by the investigator on all ECGs. ECGs performed as part of the time matched exposure/QT analysis will also be read by central cardiologists.

The safety ECG analysis will be done using the All Treated analysis population. Central ECG measurements include HR, RR interval, QT interval and its Fridericia's correction. QTcF (Fridericia's correction) is calculated as $QT/RR^{0.33}$. Screening ECG, performed locally, will have QTcF reported. This parameter will be summarized using descriptive statistics. For central ECGs, each ECG parameter will be summarized with descriptive statistics by scheduled time point. For ECG measurements collected in triplicate at nominal timepoints, the mean of the triplicate measurements will be used in the analysis. Changes from baseline will be summarized in a similar manner. Interpretations based on central cardiologist review will be summarized and listed. Shift tables will present changes from baseline in ECG interpretation based on investigator assessment (categorized as normal, abnormal not clinically significant, abnormal clinically significant) and based on central cardiologist assessment (normal, abnormal significant, abnormal insignificant) to the worst post-baseline result.

Listings will display central and local ECGs with visits/timepoints.

For central ECGs, in addition, the number and percentage of patients with at least one post-baseline abnormal ECG result in QTcF during on-treatment period will be summarized. abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- Maximum Post-baseline Value ≤ 450 msec
- Maximum Post-baseline Value $> 450 - 480$ msec (with baseline QTc interval ≤ 450 msec)
- Maximum Post-baseline Value $> 480 - 500$ msec (with baseline QTc interval < 470 msec)
- Maximum Post-baseline Value > 500 msec

Change from baseline in QTcF interval:

- Maximum Increase from baseline ≤ 30 msec
- Maximum Increase from baseline $30 - 60$ msec
- Maximum Increase from baseline > 60 msec

All ECG data will be presented in by-patient listings.

5.6.7. Time-Matched QTcF versus Plasma Concentration Analysis

Change from baseline QTcF (Δ QTcF) versus time-matched plasma concentration will be plotted for PK Lead-in Day -3 (for QD dosing) or Day 1 (for BID dosing if applicable) and Day 15 (for both QD dosing and BID dosing, if applicable) of Cycle 1 for PK/ECG Analysis Population in the Dose Escalation portion of the study. In addition, the relationship between plasma concentration of TAS3351 and Δ QTcF will be modeled using a linear mixed-effects model where Δ QTcF is the dependent variable, plasma concentration, nominal day (categorical), nominal time post-dose (categorical), and influence of baseline on intercept are independent

variables, and with random effect of patient on the intercept and slope under an unstructured covariance matrix. In case of convergence or estimation issues, model may be fit without random effect for concentration on the slope and/or intercept. Age, sex and body-weight may be included as a covariate. Additional covariates may be explored to be included in the model. Covariates will be added one at a time to the base model described above and compared using Akaike Information Criterion (AIC). If AIC of the model with covariate is less than that of the AIC of base model and p-value for covariate is less than 0.05 then the covariate will be retained in model. The relationship between plasma concentration of active metabolite TAS-05-14317 and Δ QTcF will be modeled using a similar mixed model as parent. Any interaction between TAS3351 and TAS-05-14317 may also be characterized. Note that for QTcF measurements collected in triplicate at nominal timepoints, the mean of the triplicate measurements will be used in the analysis.

The following will be presented in tabular form for TAS3351 and TAS-05-14317 separately:

- Slope of plasma concentration effect on Δ QTcF
- Standard error of plasma concentration effect on Δ QTcF
- P-value of slope of plasma concentration effect
- P-value of overall model fit (from the likelihood ratio test)

In addition, the predicted mean change from baseline QTcF (in milliseconds) will be presented for each dose level using the same linear mixed-effects models as described above, where plasma concentration is specified as the geometric mean C_{\max} for each dose level on a specific visit. The predicted mean change from baseline QTcF (in milliseconds) may also be presented for each dose level using the same linear mixed-effects models as described above, where plasma concentration is specified as the maximal observed concentration at each dose level. A double-sided 90% confidence interval for the predicted mean Δ QTcF will also be presented.

The following model assumptions will be evaluated by the indicated exploratory plots:

- Assumption 1: No drug effect on HR
 - Time course of mean Δ HR effects by dose will be plotted
- Assumption 2: QTcF interval is independent of HR
 - QTcF vs RR will be plotted
 - The adequacy of the correction formula will be assessed by determining the linear relationship of QTcF to RR. Adequacy will be evaluated based on the population QTcF:RR slope. If QTcF is determined to be an inadequate correction, then another fixed-formula rate correction may replace the primary endpoint of QTcF
- Assumption 3: No time delay between drug concentrations and Δ QTcF
 - Time course of mean concentrations and mean Δ QTcF by dose will be plotted
- Assumption 4: Linear C-QTcF relationship
 - Δ QTcF versus concentration will be plotted with a trend line included

If significant hysteresis is found, another model (e.g., Emax model, effect-compartment model) should be explored.

Goodness-of-fit plots, including but not limited to Model predicted vs observed $\Delta Q T c F$, Quartile-Quartile plot of residuals, Concentrations vs residuals, Baseline $Q T c F$ vs residuals, Time vs residuals, and Quantiles of concentrations and $\Delta Q T c F$ overlaid with slope of final model and when relevant for key stages during model development may be presented.

5.6.8. Physical Examination

The physical examination data will be presented in by-patient listings.

5.6.9. ECOG Performance Status

The ECOG PS scores and the grades from 0 to 5 are described in [Table 9](#).

The ECOG performance status score will be summarized by presenting the number and percentage of each score by scheduled time point. A shift table will be presented to display the shift from baseline grade to the worst post-baseline grade. Change from baseline to post-baseline of ECOG performance status at each scheduled visit will be presented in a shift table. A patient level listing will also be presented.

Table 9: Grade Categories of Eastern Cooperative Oncology Group Score

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

5.6.10. Pregnancy Test

If the patient is female and of childbearing potential, a serum or urine human chorionic gonadotrophin (human chorionic stimulating hormone) test will be performed at scheduled time point. For screening, serum test is required. Pregnancy test result will be presented in by-patient listing.

5.6.11. Echocardiography/MUGA

Left ventricular ejection fraction (LVEF) by echocardiography or MUGA will be summarized with descriptive statistics by scheduled time point. Changes from baseline will be summarized in a similar manner. Shift table of echocardiography/MUGA (multiple gated acquisition) is presented by scheduled time point. Also, it will be presented in by-patient listing.

5.6.12. Ophthalmological Examination

The result of ophthalmological examination will be summarized with the number and percentage of each category by scheduled time point, examination, and tested eye (left, right). Also, it will be presented in by-patient listing.

5.7. Pharmacokinetic / Pharmacodynamic Analyses

All PK analyses will be conducted using the PK population. If deviation and/or interruption of study drug administration are considered to affect the PK, the data will be excluded from summary statistics and statistical evaluations.

5.7.1. Plasma Concentration Data

5.7.1.1. Concentration Summarization

The lower limit of quantification (LLOQ) and the upper limit of quantification of TAS3351 and TAS-05-14317 are 0.5 and 1000 ng/mL, respectively in plasma. Individual plasma concentration data and actual time after dose will be listed by study period, dose level, patient, study day, and nominal collection time. The actual time after dose will be calculated as “actual date and clock time of blood collection” – “actual date and clock time of dosing”. Concentrations reported as below or above the quantification limits (BQL or AQL) will be reported as “BQL” or “AQL” in the listing of individual concentration data, respectively.

Plasma concentrations at each PK blood sampling day and time included in the study protocol will be summarized by dose level and treatment period according to nominal collection time. The time of collection of the pre-dose sample will be set to zero. Concentrations reported as BQL or AQL will be treated as missing for the purpose of concentration summarization. When sampling times fall outside a specified window or when sampling times deviate from the nominal time by a specified percentage, concentrations may be excluded from summaries.

Descriptive statistics for plasma concentrations at each PK blood sampling day and time included in the study protocol, including number of observations (n), arithmetic mean, standard deviation (SD), coefficient of variation (CV%), minimum, median, and maximum, will be presented by dose level and treatment period according to nominal collection time. The mean, median, minimum, and maximum will be presented to the same significant digit as the original values. SD will be presented to the same decimal place as the mean. CV% will be presented to 1 decimal place.

If less than half of individual data is available at a time point, summary data will be omitted or flagged. The number of observations is defined as the number of actual, reported values as received from the bioanalytical laboratory, including <LLOQs, before any transformations are made. Any missing value due to causes such as: sample not drawn, sample not received, sample not suitable, result not reported, including possible other reasons why there is no sample analysis result, does not contribute to the count of “number of observations”.

If a patient is treated with dose-modification or dose-interruption, concentrations from this patient on next PK collection date onward may be flagged and excluded from the summary statistics if deemed as appropriate.

The concentration data may also be used for a population PK analysis as appropriate. An analysis plan for the population PK will be provided separately from this SAP.

5.7.1.2. Graphical Presentation

The following plots of individual data will be made:

- The time of collection of the pre-dose sample will be set to zero;
- Actual sampling time will be used for individual graphs as horizontal axes;
- Individual plasma concentration vs. time curves on Day -3 of PK-Lead-in and Day 15 of Cycle 1 will be generated by each dose level on linear scales;
- Individual plasma concentration vs. time curves on Day 1 of Cycle 2 onward will be generated by each dose level on linear scales.

The following plots of summarized data will be made;

- The time of collection of the pre-dose sample will be set to zero;
- Nominal sampling time will be used for mean graphs as horizontal axes.
- Mean plasma concentration (Mean \pm SD) vs. time curves on Day -3 of PK-Lead-in and Day 15 of Cycle 1 will be generated on linear and log-linear scales combining the curves for all dose levels in one plot;
- Mean plasma concentration (Mean \pm SD) vs. time curves on Day 1 of Cycle 2 onward will be generated by each dose level on linear scales;
- The data will be handled for the graphical presentation in the same fashion as for the summary of individual plasma concentrations.

5.7.2. Plasma PK Parameters

5.7.2.1. PK Parameter Calculation

For the Dose Escalation part (Part A1) of the study, PK parameters will be calculated by standard noncompartmental analysis (NCA) on Day -3 of PK Lead-in (for QD dosing) or Day 1 (for BID dosing, if applicable) and Day 15 (for both QD and BID dosing, if applicable) of Cycle 1.

The calculation of PK parameters in plasma will be based on the actual time after the dosing. The time of collection of the pre-dose sample will be set to zero for calculating PK parameters. The plasma concentration data for the calculation of PK parameters will be handled as described in Section 5.7.1.1 except that plasma concentrations below the LLOQ appearing in terminal time-points will be treated as missing.

Plasma PK parameters will be estimated as follows:

- C_{\max} (Maximum observed concentration);
- T_{\max} (Time of maximum observed concentration);

C_{\max} and T_{\max} are obtained from experimental observations. If C_{\max} occurs at 2 or more time points, T_{\max} is assigned to the time of the earliest occurrence. In determining T_{\max} , the actual time of the plasma sample relative to the dosing time will be used.

- AUC_{last} (Area under the curve from the time of dosing to the time of last quantifiable concentration);
- AUC_n (Area under the curve from the time of dosing to time n);

AUCs will be calculated using the linear log trapezoidal rule. AUC_n will be calculated by the program as a partial area depending on the dosing interval. Prior to calculating AUCs and $T_{1/2}$ (terminal elimination half-lives), the individual plasma concentrations by time profiles are evaluated on an individual basis as to their suitability for inclusion in these calculations. In calculating AUCs, plasma concentrations that are listed as BQL are treated as missing, except for the following cases: for single-dose profiles, BQL concentrations prior to the first quantifiable concentration will be set to 0; for multiple-dose profiles, BQL concentrations at the beginning of the profile may be set to 0 or C_{\min} . The pre-dose sampling time will be set to 0. For single-dose profiles, the concentration at pre-dose will be set to 0.

- $T_{1/2}$ (Terminal half-life)
 $T_{1/2}$ is calculated from the terminal log-linear phase of the concentration-time curve which is identified by least-squares linear regression of at least three data points, which yield a minimum mean square error. Visual inspection and improvement in the adjusted square of the coefficient of correlation (RSQ) will be used to determine those time points prior up to but not including C_{\max} . Points included in the estimation of terminal elimination rate constant will be flagged. $T_{1/2}$ is calculated as $\ln(2) / \lambda_z$, where λ_z is the absolute value of the terminal elimination rate constant. A uniform weighting scheme in the regression analysis will be used to calculate the terminal elimination rate constant.

The following PK parameters will be calculated on Day -3 of PK-Lead-in of Cycle 1 in Dose Escalation:

- AUC_{inf} (Area under the plasma concentration-time curve from time of dosing extrapolated to infinity);
 $AUC_{\text{inf}} = AUC_{\text{last}} + C_{\text{last}} / \lambda_z$, where AUC_{last} is the area under the curve from 0 to the last quantifiable concentration, C_{last} is the last measurable plasma concentration and λ_z is the absolute value of the slope of the terminal log-linear phase.

The following PK parameters for only TAS3351 will be calculated on Day -3 of PK-Lead-in of Cycle 1 in Dose Escalation:

- CL/F (Apparent clearance);
CL/F will be calculated as $\text{Dose} / AUC_{\text{inf}}$;
- Vz/F (Apparent volume of distribution base on the terminal phase);
Vz/F will be calculated as $(\text{CL}/F) / \lambda_z$.

- MRT (Mean residence time);
MRT will be calculated as $AUMC_{inf}/AUC_{inf}$ where $AUMC_{inf}$ is the area under the first moment curve (AUMC) extrapolated to infinity

The following items will be calculated using PK parameters:

- RA (Accumulation ratio)
Individual RA of each PK parameter will be calculated as $RA(C_{max}) = C_{max} \text{ on Day 15} / C_{max} \text{ on Day -3}$, $RA(AUC_n) = AUC_n \text{ on Day 15} / AUC_n \text{ on Day -3}$, and $RA(AUC_{last}) = AUC_{last} \text{ on Day 15} / AUC_{last} \text{ on Day -3}$.
 $RA(AUC_{last})$ will not be calculated if the last sample was collected at different nominal timepoint between Day -3 and Day 15.

The following PK parameter will be calculated:

- MR (Metabolic ratio)
Individual MR of each PK parameters will be calculated as $MR(C_{max}) = C_{max} \text{ of TAS-05-14317} / C_{max} \text{ of TAS3351}$, $MR(AUC_n) = AUC_n \text{ of TAS-05-14317} / AUC_n \text{ of TAS3351}$, $MR(AUC_{last}) = AUC_{last} \text{ of TAS-05-14317} / AUC_{last} \text{ of TAS3351}$, $MR(AUC_{inf}) = AUC_{inf} \text{ of TAS-05-14317} / AUC_{inf} \text{ of TAS3351 on day -3 and Day 15}$. $MR(AUC_{inf})$ will be calculated only on Day -3.

5.7.2.2. Criteria to Estimate Elimination Parameters

The following acceptance criteria will be applied to elimination parameters ($T_{1/2}$, AUC_{inf} , CL/F , and Vz/F) to evaluate their reliability based on calculation of λz ;

- Sufficient number of time points (≥ 3) excluding C_{max} is available for calculating λz ;
- Adjusted RSQ is ≥ 0.75 ;
- $AUC_{extrap} \%$ (percentage of AUC_{inf} due to extrapolation from T_{last} [time of last quantifiable concentration] to infinity) is $\leq 30\%$.

If any of the criteria are not met for $T_{1/2}$, AUC_{inf} , CL/F , and Vz/F , they will be flagged in listings and excluded from summary statistics and statistical analyses.

5.7.2.3. PK Parameter Summarization

The plasma PK parameters, C_{max} , AUC_n , AUC_{last} , AUC_{inf} , $T_{1/2}$, CL/F , Vz/F , MRT, $RA(C_{max})$, $RA(AUC_n)$, $RA(AUC_{last})$, $MR(C_{max})$, $MR(AUC_n)$, $MR(AUC_{last})$, $MR(AUC_{inf})$ and others as applicable will be listed by patient and summarized by dose level and treatment period, including number of observations (n), arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean, geometric CV%. T_{max} will be listed by patient and summarized by dose level, and treatment period, including number of observations (n), minimum, median, and maximum.

The arithmetic mean, median, minimum, maximum, and geometric mean will be presented to the same decimal places as the individual values. SD will be presented to the same decimal place as

the mean. CV% and geometric CV% will be presented to 1 decimal place. PK parameters of secondary interest (R-square, R-square adjusted, the number of data points used for estimating λ_z , the upper and lower time point used for estimation of λ_z , λ_z itself, and $AUC_{\text{extrap}}\%$ will be listed by patient to enable verification of the exclusions, if any, of data from the summary statistics of the PK parameters of primary interest.

If a patient is treated with dose-modification or dose-interruption, concentrations from this patient on next PK collection date onward may be flagged and excluded from the summary statistics if deemed as appropriate.

5.7.2.4. Dose-proportionality

Dose-proportionality of TAS3351 and TAS-05-14317 PK parameters on Day -3 and Day 15 will be evaluated based on both power regression analysis and one-way analysis of variance (ANOVA). Dose-proportionality will be assessed in C_{max} , AUC_{last} , AUC_n , AUC_{inf} on Day -3, and C_{max} , AUC_{last} , AUC_n on Day 15.

Regression analysis using power model

The power regression analysis will be performed using the following model:

$$\log(\text{AUCs or } C_{\text{max}}) = \alpha + \beta \times \log(\text{dose})$$

This model will be used to investigate the null hypothesis ($H_0: \beta=1$) with calculating 90% confidence intervals (CIs) for the power constant (β) with insignificance ($p < 0.05$) of testing the lack of fit. For a given parameter, a minimum of 3 values per dose level must be available for that dose level to be included in the power model.

One-way ANOVA

Prior to the analysis, dose-dependent parameters (C_{max} and AUCs) will be normalized with dose. All dose-normalized PK parameters will be log-transformed prior to the analysis, and then the differences in the means of dose levels will be tested by one-way ANOVA.

5.8. Pharmacodynamic and Other Biomarker Analyses

All biomarkers except for C797S EGFRmt in this study are for exploratory purpose. Biomarker data will be investigated on this basis and will not be listed in this SAP.

5.9. Other Analyses

The serum chemistry KL-6, the vital sign SpO_2 , and the viral tests for HBV and HCV will be assessed for patients who are accrued only at sites in Japan. The analyses for these Japan specific assessments are as follows.

KL-6

Descriptive statistics will be presented for KL-6 using SI Units at each scheduled visit. Change from baseline will be summarized in a similar manner. All KL-6 data will be presented in by-patient listings.

SpO_2

SpO₂ will be summarized with descriptive statistics by scheduled time point. Change from baseline will be summarized in a similar manner. All SpO₂ data will be presented in by-patient listings.

Viral Tests

Viral tests include HBc antibody, HBs antibody, HBV DNA, and HCV RNA. The data for all of these viral tests will be presented in by-patient listings.

6. CHANGES IN PLANNED ANALYSIS

All analyses specified in this SAP are consistent with the study protocol (Protocol 10073010 Amendment 2 (07-July-2023)).

SAP Version	Major Updates	Rationale
1.0	Original	
2.0	<ul style="list-style-type: none"> Section 4.1: The definition of the study period was added for clarity for the analysis Section 5.5.1: Unconfirmed response was added Section 5.5.4: The Intracranial ORR analysis for Part A as assessed by investigator was added for clarity Section 5.5.5: The Intracranial DoR statistical method for Part A as assessed by investigator was added for clarity Section 5.6.1.1: Actual Dose intensity per cycle and relative dose intensity per cycle summaries were removed. Cumulative dose calculation was changed to the sum of the doses administered to a patient during the treatment period by removing the division by BSA. Such changes were fit for purposes. Section 5.6.1.2: The number and percentage of patients with at least one dose increase and reason for the dose increase were removed. The number of dose increases (1, 2, >2) was removed. Section 5.6.2.1: Summaries of death were corrected from deaths within (30(+3) days and deaths after 33 days to deaths within 30 days and deaths after 30 days, respectively. This approach is consistent with general practice. Section 5.6.2.2-5: The analysis was changed to by dosing cohorts by grade. Section 5.6.4: Amylase and lipase were added with amendment 2. . Section 5.6.6: Additional details of ECG data collection were added for ease of understanding analysis. Section 5.6.7: Additional details of time-matched QTcF versus plasma concentration analysis methodology were added for ease of understanding analysis. Section 5.7.2.4: The analysis of dose proportionality further specified that for a given parameter, a minimum of 3 values per dose level must be available for that dose level to be included in the power model. 	Added/updated based on protocol amendment 1 & 2, and provided further details to clarify the analysis and removed content that was not applicable

7. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

7.1. Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study drug. Evaluations on the same date and time of the first dose of study drug will be considered as baseline evaluations.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study drug
- Baseline evaluations will be defined as evaluations with a date on or prior to the day of first dose of study drug

If there are multiple valid assessments, the assessment that is closest to the day (and time if collected) of the first dose of study drug will be used as the baseline in the analyses. If multiple assessments are collected on the same date (and time, if collected), the assessment with the latest database entry date (and time, if collected) will be considered as baseline.

7.2. Post-Baseline Period

On-treatment AEs will be defined as AEs with an onset date and time on or after the date of the first dose of study drug (or with an onset date on or after the day of first dose of study drug if time is not collected or is missing). For patients who are off study drug, AEs will be included if event occurred within a safety window of 30 days after the last dose of study drug. No “subtracting rule” will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.

On-treatment evaluations will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study drug. For patients who are off study drug, evaluations should be within a safety window of 30 days after the last dose of study drug.

7.3. Terms of consolidated AEs

Consolidated terms of AEs will be identified by sponsor.

7.4. Other Data Handling Rules

For other data handling rules, such as missing data, please refer to TOI data handling rule document.

8. REFERENCES

Yuan Y, Hess KR, Hilsenbeck SG, and Gilbert MR. Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. Clin Cancer Res (2016); 22(17): 4291–4301.