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

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Clinical Study Protocol

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

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Amendment 2

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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.

**CONFIDENTIAL**

# SUMMARY OF CHANGES

The purpose of this amendment was to address the EMA's comments and clarify existing information. All changes have been incorporated into the study synopsis as appropriate; the Table of Contents has also been updated.

In addition to these substantive changes, minor administrative alterations were made as necessary throughout the protocol, including formatting adjustments and correction of typographical errors. These editorial changes do not affect the rationale or planned conduct of the study or analyses, and therefore are not summarized in the table below.

| **Section #**<br>Section Name | **Description of Change** |
|---|---|
| **Synopsis** | Replaced detailed inclusion/exclusion criteria with a high level summary of patient population by study part. |
| **Section 1.3**<br>Schedule of Events<br>Table 1: Schedule of Events for Phase1 (Parts A and B)<br>Table 2: Schedule of Events for Phase 2 (Part C)<br>Table 3: Schedule of Events – Study Extension Phase | Added direction to physical examination assessment that skin examination should be performed at each timepoint (Table 1, Table 2 and Table 3).<br>Clarified pre-dose collection window timing for hematology, chemistry, coagulation, and urinalysis assessments in alignment with Section 7.1.4 (Table 1 and Table 2).<br>Added MUGA to echocardiography assessment (Table 1) to align with Table 12.<br>Clarified timing of PK assessments in the PK Lead-in period (Table 1).<br>Clarified timing of ECG assessments (Table 1 and Table 2) and timing of triplicate ECGs.<br>Clarified timing of optional tumor tissue biopsy samples (Table 1 and Table 2) |
| **Section 2.1.1**<br>Disease Background and Study Population | Clarified existing information sourced from literature.<br>Added summary of post-osimertinib response in patients with C797S mutation |
| **Section 2.2.3**<br>Overall Benefit/Risk Ratio Evaluation | Corrected references. |
| **Section 3**<br>Objectives and Endpoints | Restructured section to include subheadings for each study part and removed use of Table caption. |
| **Section 3.3**<br>Phase 2 – Part C | Corrected version of PRO assessment to be used. |
| **Section 4.1**<br>Overview of Study Design | Removed study schema and added cross-reference to Section 1.2. |
| **Section 4.2.1**<br>Phase 1 Dose Escalation (Part A) | Clarified that TAS3351 will be administered to patients who harbor any EGFR mutation in Part A1.<br>Added description of safety and efficacy signals to be used in selection of Part A2 dose levels. |
| **Section 4.2.4**<br>Study Stopping Criteria | Modified to include additional stopping criteria. |
| **Section 4.3**<br>Scientific Rationale for Study Design | Added to include more detailed rationale for Phase 1/2 study design. |
| **Section 4.10**<br>Patient Enrollment | Removed requirement regarding timing of first dose.<br>Updated definition of enrolled patient. |
| **Section 4.11**<br>Randomization and Blinding | Added text regarding randomization in Parts A and C, and for no blinding in study.<br>Clarified Part B randomization language. |

| **Section #**<br>Section Name | **Description of Change** |
|---|---|
| **Section 4.12**<br>Data Monitoring Committee | Added section. |
| **Section 5.1**<br>Inclusion Criteria | Reformatted inclusion criteria #4 and #5 to convert bulleted content to alphabetical list.<br>Modified inclusion criterion #4a to remove acceptability of patient declining standard of care prior to study entry.<br>Separated Part A2 from Part B and C in inclusion criteria #4 b and c; criteria remain the same for both parts. |
| **Section 5.2**<br>Exclusion Criteria | Reformatted exclusion criterion #2c and #2d to converted bulleted content to numerical list.<br>Reformatted exclusion criterion #5 to convert bulleted content to alphabetical list.<br>Modified exclusion criterion #5 to allow patients with leptomeningeal disease in Parts A2, B, and C under specified circumstances.<br>Modified exclusion criterion #7b to clarify that screening for HBV, HCV and HIV is not required for consistency with Section 7.1 |
| **Section 6.1**<br>Study Drug Administration | Added explanation of dosing in PK Lead-in period. |
| **Section 6.1.1**<br>Part 1: Dose Escalation | Clarified column header in Table 6.<br>Added waiting period for dosing after first patient in dose levels following the first dosing group. |
| **Section 6.1.2**<br>Dose-limiting Toxicity | Added Sponsor/Investigator DLT communication plan. |
| **Section 6.2.1**<br>Dose Reduction, Interruption, and Resumption | Clarified dose reduction from 50 mg BID. |
| **Section 6.2.1.2**<br>Dose Modifications for Non-hematologic Toxicities | Modified Grade 3 QT prolongation management recommendation to include cardiologist evaluation and clarified that resumption of study drug should be at the next lower dose level. |
| **Section 6.4.4.2**<br>Gastrointestinal Toxicities | Clarified antiemetic guidance language. |
| **Section 6.4.4.4**<br>Amylase or Lipase Elevations | Added section. |
| **Section 6.5.2**<br>Sun Protection | Clarified sun protection language. |
| **Section 7.1**<br>Study Assessments and Procedures | Added race/ethnicity to demographics/medical history assessment.<br>Added direction to physical examination assessment that skin examination should be performed at each timepoint.<br>Added guidance regarding consistency in Echocardiography/MUGA modality used throughout study.<br>Updated serum chemistry assessment to include lipase and amylase.<br>Removed urobilinogen from urinalysis assessment and specified preference for a 24-hour quantitative measurement of proteinuria.<br>Removed viral tests assessment. |
| **Section 7.1.2**<br>12-Lead Electrocardiogram | Clarified timing and need for triplicate ECG assessments. |

| **Section #**<br>Section Name | **Description of Change** |
|---|---|
| **Section 7.1.6**<br>PRO Measurements | Corrected version of PRO assessment to be used. |
| **Section 8.1**<br>Sample Collection | Clarified timing of ECGs with respect to PK sampling on same day.<br>Added ECG timepoints to Table 13 and Table 14 for consistency with Table 1.<br>Clarified timing, use of central vs local, and need for triplicate ECG assessments (Table 13 and Table 14)<br>Clarified timing and conduct of PK sampling. |
| **Section 9.1**<br>Efficacy Criteria | Removed reference to content in Appendix C. |
| **Section 10.1.4.3**<br>Causal Relationship with Study Drug | Clarified criterion #2. |
| **Section 10.2**<br>Laboratory Assessments | Added urine to list of assessments for which normal reference ranges must be provided. |
| **Section 10.3.3**<br>Reporting of Deaths (within 24 hours) | Clarified that all deaths must be recorded on the eCRF death page. |
| **Section 10.4.1**<br>Pregnancy | Added section heading.<br>Clarified existing language. |
| **Section 10.5**<br>Communication of New Information Affecting the Conduct of the Study | Section added. |
| **Section 11**<br>Analysis of Biomarkers | Clarified biomarker sample collection, patient eligibility, and sample storage and disposal language. |
| **Section 12**<br>Statistical Considerations | Added confirmation that SAP will be finalized prior to database lock. |
| **Section 12.3**<br>Estimation of Sample Size | Corrected term “historical ORR” to “the current standard of care ORR” and added reference to supporting literature. |
| **Section 12.5**<br>Analysis Populations | Added All Consenting Population to Table 17.<br>Clarified PK Analysis and Pharmacodynamic/Biomarker Analysis Populations definitions. |
| **Section 12.7.5**<br>Other Analyses | Corrected version of PRO assessment to be used. |
| **Section 13.12**<br>Post-study Provisions | Section removed due to redundancy. |
| **Section 15.3**<br>Institutional Review Board/ Independent Ethics Committee | Updated section heading to include Independent Ethics Committee. |
| **Section 17**<br>Signatures of Sponsor and Investigator | Section removed to align with updated corporate policies. |
| **Section 17**<br>References | Section numbering updated due to removal described above.<br>Added Oken et al, Yin et al, Wages et al, and Yang et al 2021 to reference list.<br>Removed Hesketh et al and Takeda et al. from list. |

| **Section #**<br>Section Name | **Description of Change** |
|---|---|
| **Appendix A**<br>Examples of Clinical Substrates, Inhibitors, and Inducers of CYP Enzymes and Transporters | Added edoxaban to P-gp and BCRP substrates table to align with current version of listed source. |
| **Appendix B**<br>Eastern Cooperative Oncology Group (ECOG) Performance Status | Appendix removed to align with updated corporate policies. |
| **Appendix C**<br>Tumor Definitions and RECIST v1.1 Response Criteria | Appendix removed to align with updated corporate policies. |
| **Appendix D**<br>Supplemental Requirements for Japan | Appendix relocated to a Japan-specific addendum. |

# 1. PROTOCOL SUMMARY

## 1.1. SYNOPSIS

**Name of Sponsor:**
Taiho Pharmaceutical Co., Ltd. and Taiho Oncology, Inc.

**Name of Investigational Product:**
TAS3351

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

**Brief Title:** Phase 1/2 of TAS3351 in *EGFR*mt NSCLC

**Phase of Development:** Phase 1/2

**Study Rationale:**

About 10%–15% of Caucasian patients with non-squamous non-small cell lung cancer (NSCLC) and up to 50% of East-Asian patients with NSCLC have tumors harboring epidermal growth factor receptor (EGFR) activating mutations (eg, L858R or exon 19 deletion mutations).[1] The current standard of care for patients with locally advanced or metastatic NSCLC is treatment with an EGFR tyrosine kinase inhibitor (TKI). Several Phase 3 clinical trials have established the role of first-generation (gefitinib and erlotinib) and second-generation (afatinib and dacomitinib) EGFR TKIs as first-line treatment with similar median response rates of 70%-75% and progression-free survival (PFS) ranging from 10-14 months as first-line treatment, which was a significant improvement compared to platinum-based chemotherapy.[2] The most frequent resistance mechanism to first-and second-generation EGFR TKIs is the emergence of T790M EGFR kinase domain mutations. More recently, the third-generation EGFR TKI osimertinib active against T790M *EGFR*mt showed superior efficacy in first-line *EGF*Rmt NSCLC patients when compared against erlotinib, with improved PFS (18.9 versus 10.2 months) and overall survival (OS) (38.6 versus 31.8 months).[3,4]

Despite third-generation EGFR TKIs being highly effective in advanced *EGFR*mt NSCLC, resistance to EGFR TKIs inevitably occurs leading to disease progression. The current treatment options for *EGFR*mt NSCLC patients progressing on treatment with third-generation EGFR TKIs are limited. Platinum-based chemotherapy combinations with pemetrexed is currently considered standard of care.[5] However, the reported clinical outcome is poor with approximately 25% ORR and median PFS of approximately 4-5 months post osimertinib.[6,7,8,9] One of the prevalent resistance mechanisms to third-generation EGFR TKIs is an acquired C797S *EGFR* mutation which is observed in 10%-25% of NSCLC patients progressing on osimertinib.[10,11,12,13]

TAS3351 is a novel fourth-generation EGFR TKI designed to potently inhibit triple-mutant EGFR in NSCLC patients. In addition to its activity against EGFR sensitizing mutations (eg, L858R or exon 19 deletion mutations) and the acquired T790M resistance *EGFR*mt, TAS3351 also inhibits C797S *EGFR*mt observed in patients progressing on third-generation EGFR TKIs, while sparing EGFR wild-type. In nonclinical studies, TAS3351 demonstrated dose-dependent activity in vitro and in vivo in NSCLC models with co-occurrence of sensitizing *EGFR*mt and T790M/C797S *EGFR*mt (data on file). Furthermore, TAS3351 has been shown to be brain penetrant in nonclinical models. Approximately 25%-40% of patients with NSCLC develop brain metastases and, due to limited treatment options, the prognosis of patients with brain metastases remains poor. Thus, TAS3351

might also provide a new treatment option for patients with EGFR deregulated NSCLC who have brain metastases.

Based on these results, TAS3351 is expected to have antitumor activity in NSCLC patients with tumors harboring an acquired C797S *EGFR*mt, a population with an unmet medical need.

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Phase 1 Dose Escalation** | |
| **Primary** | |
| • To investigate safety and determine the recommended Phase 2 dose (RP2D) and dosing schedule of TAS3351 | • Safety, including (but not limited to) AEs graded by CTCAE v5.0, and incidence of dose limiting toxicities (DLTs). As supplementary data, preliminary antitumor activity and PK/PD results will be considered. |
| **Secondary** | |
| • To evaluate the antitumor activity of TAS3351 | • Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by Investigator<br>• Duration of response (DoR), disease control rate (DCR), and time on treatment<br>• Progression free survival (PFS) and Overall Survival (OS) (Patients in part A2 only) |
| • To characterize the pharmacokinetics (PK) of TAS3351 and its active metabolite (TAS-05-14317) in plasma | • PK parameters including but not limited to maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($T_{max}$), area under the plasma concentration-time curve (AUC), and terminal elimination half-life ($T_{½}$) |
| **Exploratory** | |
| • To explore the relationship between exposures of TAS3351 and its active metabolite (TAS-05-14317) in plasma and QT prolongation | • Time matched plasma exposures of TAS3351 and its active metabolite (TAS-05-14317) and changes from baseline in QTcF |
| • To explore biomarkers for TAS3351 including their potential association with antitumor activity | • Biomarkers from tumor tissue and blood samples, including (but not limited to) DNA/RNA, protein, and cfDNA analysis |
| • To explore metabolites of TAS3351 in plasma | • Metabolites of TAS3351 in plasma will be characterized |

| Objectives | Endpoints |
|---|---|
| **Phase 1 Dose Expansion** | |
| **Primary** | |
| • To explore the efficacy of TAS3351 | • ORR per RECIST v1.1 by independent central review (ICR) |
| **Secondary** | |
| • To confirm the safety and tolerability of TAS3351 at the RP2D and dosing schedule | • AEs, including SAEs, clinical laboratory tests, vital signs, and 12-lead ECGs graded according to CTCAE v5.0 |
| • To further explore the antitumor efficacy of TAS3351 | • DoR, PFS, and DCR by ICR<br>• ORR, DoR, PFS, and DCR by Investigator assessment<br>• Intracranial ORR (icORR) and DoR (icDoR) by ICR and Investigator assessment<br>• Overall survival (OS) |
| **Exploratory** | |
| • To explore biomarkers for TAS3351 including their potential association with efficacy | • Biomarkers from tumor tissue and blood samples, including (but not limited to) DNA/RNA, protein, and cfDNA analysis |
| • To explore the potential exposure-response associations for efficacy and safety | • Exposures estimated by Population PK model and selected efficacy and safety measures |

| Objectives | Endpoints |
|---|---|
| **Phase 2** | |
| **Primary** | |
| • To assess the efficacy of TAS3351 | • ORR per RECIST v1.1 by ICR |
| **Secondary** | |
| • To further assess the efficacy of TAS3351 | • DoR, PFS, and DCR by ICR<br>• ORR, DoR, PFS, and DCR by Investigator assessment<br>• Intracranial ORR (icORR) and DoR (icDOR) by ICR and Investigator assessment<br>• Overall survival (OS) |
| • To evaluate the safety and tolerability of TAS3351 | • AEs, including SAEs, clinical laboratory tests, vital signs, and 12-lead ECGs graded according to CTCAE v5.0 |

| Objectives | Endpoints |
|---|---|
| • To evaluate patient reported outcomes (PROs) | • EORTC QLQ-C30 and EQ-5D-5L |
| **Exploratory** | |
| • To investigate biomarkers of response to TAS3351 and determine their potential association with efficacy | • Biomarkers from tumor tissue and blood samples, including (but not limited to) DNA/RNA, protein, and cfDNA analysis |
| • To explore the potential exposure-response associations for efficacy and safety | • Exposures estimated by Population PK model and selected efficacy and safety measures |

**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 will consist of 3 parts:

- **Part A: Phase 1 Dose Escalation** part to determine the RP2D and dosing schedule of TAS3351 in advanced NSCLC patients. Part A of study 10073010 will consist of a Dose Escalation part (Part A1) and a part for "Backfill" patients (Part A2)
  - **Part A1: Dose Escalation**

    TAS3351 will be administered once daily (QD) on a 21-day cycle at a starting dose of 50 mg QD to patients who harbor any EGFR mutations. The study is designed to escalate TAS3351 up to 700 mg QD based on safety and tolerability, with lower increments considered if clinically relevant toxicities are observed (see Section 6.1.1). The study will use a Bayesian Optimal Interval (BOIN) design [redacted][15] A PK lead-in period will be utilized to assess the terminal elimination phase of TAS3351 and active metabolite TAS-05-14317 in plasma. If PK, pharmacodynamics, and/or safety data indicate, twice daily (BID) dosing of TAS3351 may be explored.
  - **Part A2: Backfill Patients**

    When a dose level has been determined to be safe in Part A1 and either preliminary antitumor activity has been observed or the TAS3351 exposure level is associated with antitumor activity in nonclinical models, up to 10 additional patients may be enrolled at each of such dose levels ("backfill" patients, see also Section 4.2.1). "Backfill" patients enrolled are required to have a tumor harboring a C797S *EGFR*mt. The additional information from these "backfill" patient cohorts will broaden the amount of safety and preliminary antitumor activity data for TAS3351 at potential active dose levels in Part A to inform the selection of the RP2D of TAS3351.

- **Part B: Phase 1 Dose Expansion** part to explore the efficacy of TAS3351 in patients with C797S *EGFR*mt NSCLC.

  The Phase 1 Dose Expansion part of the study will be initiated after an RP2D and dosing scheme have been identified in Part A. Patients with C797S *EGFR*mt NSCLC will be enrolled to explore the efficacy and confirm the safety of TAS3351 at the RP2D in a larger patient population. Moreover, a second dose level of TAS3351 might be evaluated in an additional cohort of patients in Part B if promising antitumor activity is observed at another lower TAS3351 dose level during the Phase 1 Dose Escalation. In such case, patients will be randomized between the two dose levels. The results from the Phase 1 Dose Expansion will confirm the RP2D of TAS3351 and are expected to provide, in combination with the "Backfill" patients, the proof of concept for the efficacy of TAS3351 in patients with C797S *EGFR*mt NSCLC. Based on these results, the Phase 2 part of this study will be initiated.

- **Part C: Single arm Phase 2** part to assess efficacy of TAS3351 in patients with C797S *EGFR*mt NSCLC.

  The Phase 2 part of the study will be an open-label, single-arm Phase 2 study to assess the efficacy of TAS3351 in advanced NSCLC patients with a C797S *EGFR*mt who progressed on a prior treatment with another EGFR inhibitor. Patients will receive TAS3351 at the RP2D and dosing scheme and be evaluated for ORR based on RECIST 1.1 by independent central review (ICR) as the primary endpoint of the Phase 2. A key secondary endpoint of this part of the study will be duration of response by ICR.

**Number of Patients (planned):**
Approximately 200 patients with NSCLC will be enrolled in this study. The total number of patients will depend upon the number of dose levels evaluated and potential patient replacements including:

- **Part A** (Phase 1): Up to 60 NSCLC patients
  - Part A1: Dose escalation in up to 40 patients with any *EGFR*mt status
  - Part A2: "Backfill" cohorts with approximately 20 patients with C797S *EGFR*mt
- **Part B** (Phase 1 Dose Expansion): Up to 40 patients with C797S *EGFR*mt NSCLC
- **Part C** (Phase 2): 100 patients with C797S *EGFR*mt NSCLC.

**Study Population:**

Part A1

The study population for Part A1 includes adult patients with histologically or cytologically confirmed, locally advanced, nonresectable or metastatic NSCLC with any *EGFR*mt. Patients who have received standard of care and no more than 2 lines of prior cytotoxic chemotherapy for locally advanced or metastatic disease are eligible.

Part A2

The study population for Part A2 includes adult patients with histologically or cytologically confirmed, locally advanced, nonresectable or metastatic NSCLC with any sensitizing *EGFR*mt and a confirmed C797S *EGFR*mt. Patients who have progressed on any third-generation EGFR TKI and are not eligible for platinum-based chemotherapies or other targeted therapies (in case of off-target alterations), and have received no more than 2 lines of prior cytotoxic chemotherapy for locally advanced or metastatic disease are eligible.

Parts B and C

The study population for Parts B and C includes adult patients with histologically or cytologically confirmed, locally advanced, nonresectable or metastatic NSCLC with any sensitizing *EGFR*mt and a confirmed C797S *EGFR*mt. Patients who have progressed on any third-generation EGFR TKI and have received no more than 2 lines of prior cytotoxic chemotherapy for locally advanced or metastatic disease are eligible.

**Investigational Product:**
TAS3351 is supplied as 25, 100, and 200 mg tablets. TAS3351 will be administered orally once daily (QD) on a 21-day cycle. If PK, pharmacodynamic, and/or safety data indicate that splitting the TAS3351 dose into 2 daily doses might be preferable, twice daily (BID) dosing of TAS3351 may be explored.

**Reference and/or Control Therapy, Dosage, and Mode of Administration:**
Not applicable.

**Duration of Treatment:**
Patients will receive TAS3351 study medication until documentation of progressive disease (PD), unacceptable toxicity, or any other discontinuation or withdrawal criterion is met.

**Criteria for Evaluation:**

Efficacy:
Efficacy will be evaluated based on tumor assessments (including CT]/magnetic resonance imaging [MRI) performed by Investigator/local radiologist according to RECIST v1.1 guideline.

Safety:
Safety and tolerability will be assessed based on the incidence of treatment-emergent adverse events (TEAEs, including serious adverse events [SAEs] and DLTs), dose modifications, clinical laboratory parameters, 12-lead electrocardiograms (ECGs), measurement of ejection fraction, ophthalmologic abnormalities, and vital signs. Grading of TEAEs will be performed based on CTCAE, Version 5.0.PK matched central ECG will be performed as triplicates for patients enrolled in Part A1.

Pharmacokinetics
The plasma concentrations of TAS3351 as well as its active metabolite, TAS-05-14317, will be measured by a validated LC/MS/MS method. The PK data obtained in the Dose Escalation phase will be analyzed by non-compartmental analysis to derive key PK parameters including but not limited to $C_{max}$, $T_{max}$, AUC, and $T_{1/2}$. The concentration data by time and study day obtained in the Expansion phase and/or Phase 2 will be summarized descriptively.

Biomarkers
For patient eligibility, the *EGFR*mt status has to be determined by a CLIA certified (US), locally certified (outside of the US), or the study central laboratory based on tumor tissue or plasma cfDNA. For patients enrolled based on local results, *EGFR*mt status will be confirmed at the Sponsor's designated study central laboratory post-enrollment.

For exploratory biomarker analysis, changes in circulating free tumor DNA (cfDNA) from blood samples collected at baseline and on-treatment may be assessed retrospectively for any change of genomic variants following TAS3351 treatment and any association with clinical outcomes. Changes in biomarkers from optional tumor samples (eg, pEGFR) collected

on-treatment may be analyzed relative to baseline expression, if paired tumor samples are available.

Patient Reported Outcome
Patients' health-related quality of life, symptoms, functioning, and general well-being will be captured using the EORTC QLQ-C30 and EQ-5D-5L questionnaires.

**Statistical Methods:**

Sample Size Calculation:

- Part A: Phase 1 Dose Escalation

  There will be up to 40 evaluable patients enrolled using the BOIN design, [redacted]. Up to approximately 20 patients may be added for backfill cohorts as needed in the Phase 1 Dose Escalation (up to 60 patients total).

- Part B: Phase 1 Dose Expansion

  Approximately 40 patients in 2 cohorts may be enrolled in the Phase 1 dose expansion in Part B of this study. Beside the RP2D, an additional lower dose level may be evaluated in the Phase 1 expansion. Sample size considerations for each cohort were based on estimating the proportion of responders with certain precision. If there are 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%).

- Part C: Phase 2

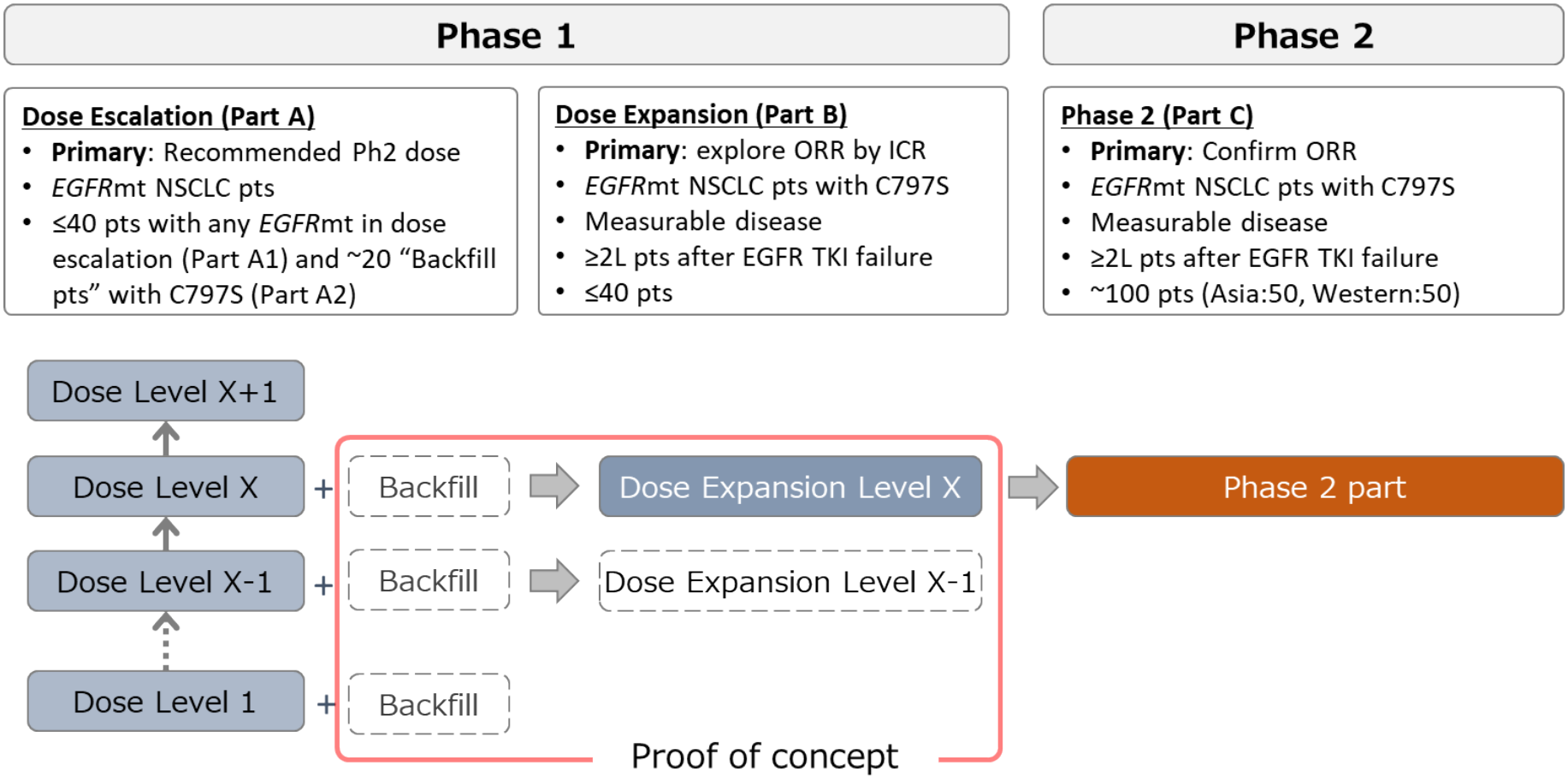
  Approximately 100 patients will be enrolled in the Phase 2 part of this study. Sample size considerations were based on estimating the proportion of responders with certain precision. The 95% exact CI for ORR would exclude the current standard of care ORR of 25% if the overall ORR is 35% or higher. With 100 patients, if there are 35 responses, the 95% exact CI is (25.7 to 45.2%) to exclude the current standard of care ORR of 25%.

Efficacy Analysis

Descriptive statistics and summaries will be presented. Two-sided 95% CI will be estimated using the Clopper–Pearson method. For time to event endpoints, 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.

Safety Analysis
Safety data will be summarized descriptively.

## 1.2. STUDY DIAGRAM




**Abbreviations:** 2L=second line; *EGFR*mt=epidermal growth factor receptor mutation; ICR=independent central review; NSCLC=non-small cell lung cancer; ORR= overall response rate; pts=patients; TKI=tyrosine kinase inhibitor

## 1.3. SCHEDULE OF EVENTS

**Table 1: Schedule of Events for Phase 1 (Parts A and B)**

| Procedure | Screening Period<br><br>Within 28 Days prior to first dose | Treatment Period | | | | | | | Follow-up Period | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PK Lead-in[a] | Cycle 1 (21 days) | | | Cycle 2 (21 days) | | Cycles ≥3 (21 days) | Safety Follow-up[b] | Survival Follow-up | |
| | | Day -3 | Day 1 | Day 8 (±1 day) | Day 15 (±3 days) | Day 1 (±3 days) | Day 8 (±3 days) | Day 1 (±3 days) | 30 (+3) days after last dose | | |
| *EGFR* C797S status (pre-screening informed consent) | See Notes | | | | | | | | | | Only if central pre-screening done. Can be done any time prior to screening. |
| Written informed consent (main study) | X | | | | | | | | | | To be obtained prior to any study related procedures. |
| Review inclusion / exclusion criteria | X | | | | | | | | | | All patients in Part A2 and B must have documented C797S *EGFR*mt. See Section 4.1 and Section 4.2 |
| Demographics/ Medical history | X | | | | | | | | | | Including prior antitumor treatment |
| Physical examination | X | X | X | X | | X | | X | X | | Within 24 hours prior to dosing. May be symptom directed during treatment period. Examination of skin should be performed at each timepoint. See Section 7.1 |
| Ophthalmological examination | X | As clinically indicated | | | | | | | X | | See Section 7.1.5 |
| Height and weight | X | X | X | | | X | | X | X | | Height at screening only |
| Vital signs | X | X | X | X | X | X | X | X | X | | Heart rate, blood pressure, and body temperature. See Section 7.1 |
| Hematology | X | X | X | X | X | X | X | X | X | | Assessment prior to first day of dosing may be done up to 72 hours prior to dosing |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | (Section 7.1.4)<br>All other assessments may be done within 24 hours prior to dosing<br>See Section 7.1 |
| Chemistry | X | X | X | X | X | X | X | X | X | | Assessment prior to first day of dosing may be done up to 72 hours prior to dosing (Section 7.1.4)<br>All other assessments may be done within 24 hours prior to dosing<br>See Section 7.1 |
| Coagulation | X | X | X | | | X | | X | X | | Assessment prior to first day of dosing may be done up to 72 hours prior to dosing (Section 7.1.4)<br>All other assessments may be done within 24 hours prior to dosing<br>See Section 7.1 |
| Urinalysis | X | X | X | | | X | | X | X | | Assessment prior to first day of dosing may be done up to 72 hours prior to dosing (Section 7.1.4)<br>All other assessments may be done within 24 hours prior to dosing. See Section 7.1 |
| Pregnancy test | X | X | (X) | | | X | | X | | | For WOCBP only: Serum pregnancy test required at screening only. See Section 7.1<br>(X) not required for patients in Part A1 |
| Adverse events | X | X | X | | | | | | X | (X) | From signing ICF through 30-day safety follow-up or until start of new anticancer therapy, whichever is earlier. See Section 10.1<br>(X) only related SAE Investigator becomes aware of |
| Concomitant medications | X | X | X | | | | | | X | | From signing ICF through 30-day safety follow-up or until start of new anticancer therapy, whichever is earlier. See Section 6.4 |
| ECOG Performance Status | X | | X | | | X | | X | X | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| PK sampling | | See Table 13 / Table 14 | | | | | | | | Table 13 for QD dosing /Table 14 for BID |
| Central ECG | | See Table 13 / Table 14 | | | | | | | | To be performed as triplicates. For patients in Part A1 only. See Section 7.1.2 |
| Local ECG[c] | X | | X | | | X | | X | X | 12-lead ECG. Not needed if central ECG done the same day. Additional ECG monitoring as clinically indicated. See Section 7.1.2 |
| Echocardiography/ MUGA | X | | | | | | | X | | From Cycle 4 onwards, every 4 cycles or as clinically indicated. See Section 7.1.3 |
| cfDNA blood samples | | | X | | | X | | X | X | From Cycle 3 onwards, every other cycle. After 12 months, every 3 cycles. |
| Tumor tissue samples | X | | | | | (X) | | | (X) | Baseline sample optional for patients in Part A1. See Section 11.2<br>(X) On-treatment biopsy optional; can be done at one of these timepoints |
| Radiologic tumor assessment | X | | X | | | | | | (X) | Every 6 weeks (±7 days) from C1D1 irrespective of cycle. After 12 months, every 9 weeks (±7 days).<br>(X) Patients who discontinue study treatment without radiographic PD will continue every 9 weeks (±7 days) until radiographic PD. See Section 7.1 |
| Survival status | | | | | | | | | X | Every 3 months (±2 weeks); collect also further anticancer therapies. See Section 7.1. For patients in Part A2 and B only |
| Administration of TAS3351 | | X | X | | | | | | | Continuous dosing<br>See Section 6.1 |

[a] PK lead-in period applies to Part A1 only: During PK lead-in period, patients will receive a single dose of TAS3351 3 days prior to the start of multiple TAS3351 dosing in Cycle 1 with subsequent PK blood collection. The PK blood sample collection times during the PK lead-in period may be found in Table 13. For these patients, 72-hour post-dose assessments occur on C1D1, prior to C1D1 dosing.

[b] The 30-day Safety Follow-up visit should be performed 30 days (+3 days) following the last dose of study therapy. If the patient starts new anticancer therapy within 30 days of the last dose of study medication, the 30-day Safety Follow-up visit should be performed before the start of new anticancer therapy. Only if the patient is unable to return to the study site, a follow-up phone call can be made by the study site to collect any new safety information that occurred during the Safety Follow-up period.

[c] ECG assessment for C1D1, and D1 of C2 and beyond should be conducted pre-dose (up to 30 minutes prior to dosing). ECG should be performed on D1 of every cycle. All ECGs should be performed in triplicate on Day 1 of Cycles 1 to 3 for all patients. After C3D1, ECGs are not required to be performed in triplicate unless clinically indicated.

**Abbreviations:** AE=adverse event; C=cycle; cfDNA=cell-free DNA; D=day; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of therapy; ICF=informed consent form; MUGA=multi-gated acquisition scan; PD=progressive disease; PK=pharmacokinetics; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; WOCBP=women of childbearing potential
**Note:** (X) = See notes for details.

**Table 2: Schedule of Events for Phase 2 (Part C)**

| Procedure | Screening Period<br><br>Within 28 Days prior to first dose | Treatment Period | | | Follow-up Period | | Notes |
|---|---|---|---|---|---|---|---|
| | | Cycle 1 (21 days) | | Cycle ≥2 (21 days) | Safety Follow-up[a] | Survival Follow-up | |
| | | Day 1 | Day 8 (±1 day) | Day 1 (±3 days) | 30 (+3) days after last dose | | |
| *EGFR* C797S status (pre-screening informed consent) | See Notes | | | | | | Only if central pre-screening done. Can take place any time prior to screening |
| Written informed consent (Main study) | X | | | | | | To be obtained prior to any study related procedures. Can take place any time before Day 1 |
| Review inclusion / exclusion criteria | X | | | | | | All patients must have documented C797S *EGFR*mt |
| Demographics/Medical history | X | | | | | | Including prior antitumor treatment |
| Physical examination | X | X | | X | X | | Within 24 hours prior to dosing. May be symptom directed during treatment period. Examination of skin should be performed at each timepoint. |
| Ophthalmological examination | X | As clinically indicated | | | X | | See Section 7.1.5 |
| Height and weight | X | X | | X | X | | Height at screening only |
| Vital signs | X | X | X | X | X | | Heart rate, blood pressure, body temperature |
| Hematology | X | X | X | X | X | | Assessment prior to first day of dosing may be done up to 72 hours prior to dosing (Section 7.1.4)<br>All other assessments may be done within 48 hours prior to dosing, See Section 7.1 |
| Chemistry | X | X | X | X | X | | Assessment prior to first day of dosing may be done up to 72 hours prior to dosing (Section 7.1.4)<br>All other assessments may be done within 48 hours prior to dosing. See Section 7.1 |

| Procedure | Screening Period<br><br>Within 28 Days prior to first dose | Treatment Period | | | Follow-up Period | | Notes |
|---|---|---|---|---|---|---|---|
| | | Cycle 1 (21 days) | | Cycle ≥2 (21 days) | Safety Follow-up[a] | Survival Follow-up | |
| | | Day 1 | Day 8 (±1 day) | Day 1 (±3 days) | 30 (+3) days after last dose | | |
| Coagulation | X | X | | X | X | | Assessment prior to first day of dosing may be done up to 72 hours prior to dosing (Section 7.1.4)<br>All other assessments may be done within 48 hours prior to dosing. See Section 7.1 |
| Urinalysis | X | X | | X | X | | Assessment prior to first day of dosing may be done up to 72 hours prior to dosing (Section 7.1.4)<br>All other assessments may be done within 48 hours prior to dosing. See Section 7.1 |
| Pregnancy test | X | X | | X | | | For WOCBP only: Serum pregnancy test required at screening only. See Section 7.1 |
| Local ECG[b] | X | X | | X | X | | 12-lead ECG. Additional ECG monitoring as clinically indicated. See Section 7.1 |
| Adverse events | X | X | | | X | (X) | From signing ICF through 30-day safety follow-up.<br>(X) only related SAE Investigator becomes aware of |
| Concomitant medications | X | X | X | X | X | | From signing ICF through 30-day safety follow-up. |
| ECOG Performance Status | X | X | | X | X | | |
| Patient reported outcomes | X | | | X | X | | During treatment period, to be assessed as close as possible to the tumor assessments. |
| PK sampling | | See Table 13 | | | | | |
| cfDNA blood samples | | X | | X | X | | From C3D1 onwards, every other cycle. After 12 months, every 3 cycles |
| Tumor tissue samples | X | | | (X) | (X) | | (X) On-treatment biopsy optional; can be done at one of these timepoints |

| Procedure | Screening Period<br><br>Within 28 Days prior to first dose | Treatment Period | | | Follow-up Period | | Notes |
|---|---|---|---|---|---|---|---|
| | | Cycle 1 (21 days) | | Cycle ≥2 (21 days) | Safety Follow-up[a] | Survival Follow-up | |
| | | Day 1 | Day 8 (±1 day) | Day 1 (±3 days) | 30 (+3) days after last dose | | |
| Radiologic tumor assessment | X | X | | | (X) | (X) | Every 6 weeks (±7 days) from C1D1 irrespective of cycle. After 12 months, every 9 weeks (±7 days).<br>(X) Patients who discontinue study treatment without radiographic PD will continue every 9 weeks (±7 days) until radiographic PD. See Section 7.1 |
| Survival status | | | | | | X | After discontinuation of treatment, survival follow-up should occur every 3 months (±2 weeks), collection of further anticancer therapies. See Section 7.1 |
| Administration of TAS3351 | | X | | | | | Continuous dosing. See Section 6.1 |

[a] The 30-day Safety Follow-up visit should be performed 30 days (+3 days) following the last dose of study therapy. If the patient starts new anticancer therapy within 30 days of the last dose of study medication, the 30-day Safety Follow-up visit should be performed before the start of new anticancer therapy. Only if the patient is unable to return to the study site, a follow-up phone call can be made by the study site to collect any new safety information that occurred during the Safety Follow-up period.

[b] ECG assessment for C1D1, and D1 of C2 and beyond should be conducted pre-dose (up to 30 minutes prior to dosing). ECG should be performed on D1 of every cycle. All ECGs should be performed in triplicate on Day 1 of Cycles 1 to 3 for all patients. After C3D1, ECGs are not required to be performed in triplicate unless clinically indicated.

**Abbreviations:** AE=adverse event; C=cycle; cfDNA=cell-free DNA; D=day; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of therapy; ICF=informed consent form; PD=progressive disease; PK=pharmacokinetics; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; WOCBP=women of childbearing potential

**Table 3: Schedule of Events – Study Extension Phase**

| | Treatment Period | Safety Follow-up | Notes |
|---|---|---|---|
| | At Least Every 3 Cycles[a] | 30 (±7) Days After Last Dose | |
| Physical examination | X | X | May be symptom directed during treatment period. Examination of skin should be performed at each timepoint. |
| Vital signs | X | X | Heart rate, blood pressure, and body temperature |
| Local ECG | X | X | 12-lead ECG |
| Weight | X | X | |
| Hematology | X | X | See Section 7 |
| Chemistry | X | X | See Section 7 |
| Pregnancy test | X | | Serum or urine pregnancy test |
| Concomitant medications, AE assessments | X | X | Collect from the time main informed consent is signed through 30 days after administration of the last dose of study therapy or until the start of new anticancer therapy, whichever is earlier. See Section 6.4.1 and Section 10.1 |
| Tumor assessments / scans | X | | Tumor assessments may be performed as necessary to determine continued benefit from treatment, every 3 cycles (±14 days), or as clinically indicated, until clinical or radiographic PD. See Section 7.1.1 |
| Administer TAS3351 | X | | Continuous dosing. See Section 6.1 |

**Abbreviations:** AE=adverse event; ECG=electrocardiogram; PD=progressive disease

[a] More frequent visits/assessments may be performed as per local practice.

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## LIST OF TABLES

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| APTT | Activated partial thromboplastin time |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase |
| AUC | Area under the plasma concentration-time curve |
| $AUC_{0-24}$ | Area under the plasma concentration-time curve from 0 to 24 hours |
| $AUC_{inf}$ | Area under the plasma concentration-time curve to infinity |
| $AUC_{last}$ | Area under the plasma concentration-time curve up to the last observable concentration |
| BCRP | Breast cancer resistance protein |
| BID | Twice daily (or 2 times a day) |
| BOIN | Bayesian optimal interval design |
| BUN | Blood urea nitrogen |
| cfDNA | Circulating free DNA |
| CHF | Congestive Heart Failure |
| CI | Confidence interval |
| CLIA | Clinical laboratory improvement amendments |
| CL/F | Apparent clearance of drug from plasma after extravascular administration |
| $C_{max}$ | Maximum plasma concentration |
| CNS | Central nervous system |
| CONSORT | Consolidated Standards of Reporting Trials |
| CR | Complete response |
| CrCl | Creatinine clearance |
| CRP | C reactive protein |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | Cytochrome P450 |
| DCR | Disease control response |
| DLT | Dose-limiting toxicity |
| DMC | Data monitoring committee |
| DNA | Deoxyribonucleic acid |

| Abbreviation | Definition |
|---|---|
| DoR | Duration of response |
| DRESS | drug rash with eosinophilia and systemic symptoms |
| $EC_{50}$ | 50% effective concentration |
| ECG | Electrocardiogram |
| ECHO | Echocardiography |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EGFR | Epidermal growth factor receptor |
| EGFRmt | Epidermal growth factor receptor mutation |
| eGFR | Estimated glomerular filtration rate |
| $E_{max}$ | Maximum induction ratio |
| EORTC | European Organization for Research and Treatment of Cancer |
| FIH | First-in-human |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte colony-stimulating factor |
| HBs | Hepatitis B surface |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HED | Human equivalent dose |
| hERG | Human ether-a-go-go related gene |
| HIV | Human immunodeficiency virus |
| HNSTD | highest non-severely toxic dose |
| HRCT | High-resolution computed tomography |
| HSA | Human serum albumin |
| $IC_{50}$ | Half maximal inhibitory concentration |
| icDOR | Intracranial duration response |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| icORR | Intracranial overall response rate |
| ICR | Independent central review |
| IEC | Independent ethics committee |
| ILD | Interstitial lung disease |
| IRB | Institutional review board |
| IXRS | Interactive voice/web response system |
| $K_{p, brain}$ | Brain to plasma concentration ratio |
| $K_{inact}$ | Inactivation rate constant |

| Abbreviation | Definition |
|---|---|
| LVEF | Left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| MRT | Mean residence time |
| MTD | Maximum tolerated dose |
| MUGA | Multi-gated acquisition scan |
| NSCLC | Non-small cell lung cancer |
| ORR | Overall response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PFS | Progressive free survival |
| P-gp | P-glycoprotein |
| PGx | Pharmacogenomics |
| PK | Pharmacokinetics |
| PO | Oral |
| PRO | Patient reported outcomes |
| PT-INR | Prothrombin time - international normalized ratio |
| QD | Once daily |
| QTc | QT interval corrected |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| RBC | Red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RP2D | Recommended Phase 2 dose |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Stable disease |
| SOC | Standard of care |
| SOP | Standard operating procedure |
| SPE | Sun protection factor |
| STD10 | Severely toxic dose in 10% |
| SUSAR | Suspected unexpected serious adverse reaction |
| $T_{1/2}$ | Terminal elimination half-life |
| TEAE | Treatment-emergent adverse event |
| TKI | Tyrosine-kinase inhibitor |
| $t_{max}$ | Time to maximum plasma concentration |
| ULN | Upper limit of normal |
| US or USA | United States or United States of America |

| Abbreviation | Definition |
|---|---|
| Vz/F | Apparent volume of distribution during the terminal ($\lambda_z$) phase |
| WBC | White blood cell |
| WOCBP | Women of childbearing potential |

# 2. INTRODUCTION

## 2.1. Background and Study Rationale

### 2.1.1. Disease Background and Study Population

About 10%-15% of Caucasian patients with non-small cell lung cancer (NSCLC) and up to 50% of East-Asian patients with NSCLC have tumors harboring an epidermal growth factor receptor (*EGFR*) activating mutation (ie, L858R or exon 19 deletion mutations).[1] The current standard of care for these patients with locally advanced or metastatic NSCLC is treatment with an EGFR tyrosine kinase inhibitor (TKI). Several Phase 3 clinical trials have established the role of first-generation (gefitinib and erlotinib) and second-generation (afatinib and dacomitinib) EGFR TKIs as first-line treatment with a similar median response rate of 70%-75% and progression-free survival (PFS) ranging from 10-14 months, which was a significant improvement compared to platinum-based chemotherapy.[2] The most frequent resistance mechanism to first-and second-generation EGFR TKIs is the emergence of T790M *EGFR* kinase domain mutations. More recently, the third-generation EGFR TKI osimertinib active against T790M *EGFR*mt showed superior efficacy when compared against erlotinib, with improved PFS (18.9 versus 10.2 months) and overall survival (OS) (38.6 versus 31.8 months).[3,4]

Despite third-generation EGFR TKIs being highly effective in treatment of advanced *EGFR*mt NSCLC, resistance to EGFR TKIs inevitably occurs leading to disease progression. The current treatment options for patients with *EGFR*mt NSCLC progressing on treatment with third-generation EGFR TKIs are limited. Platinum-based chemotherapy combinations with pemetrexed are currently considered standard of care.[5] However, the reported clinical outcome is poor with approximately 25% ORR (range: 20.7% to 34.1%) and median PFS of approximately 4-5 months post osimertinib.[6,7,8,9] One of the prevalent resistance mechanisms to third-generation EGFR TKIs is an acquired C797S *EGFR* mutation which is observed in 10%-25% of patients with NSCLC progressing on osimertinib.[10,11,12,13] A study of patients with C797S mutations after treatment with osimertinib showed 1 tumor response out of 23 patients (4%) treated with chemotherapy.[14]

### 2.1.2. Overview of TAS3351

TAS3351 is a novel fourth-generation EGFR TKI designed to potently inhibit triple-mutant EGFR in patients with NSCLC. In addition to its activity against *EGFR* sensitizing mutations (ie, L858R or exon 19 deletion mutations) and acquired T790M resistance *EGFR*mt, TAS3351 also inhibits C797S *EGFR*mt while sparing wild-type EGFR. In nonclinical studies, TAS3351 demonstrated dose-dependent activity in in vitro and in vivo models with co-occurrence of a sensitizing *EGFR*mt and T790M/C797S *EGFR*mt (data on file). Furthermore, TAS3351 has been shown to be brain penetrant in nonclinical models. Approximately 25%-40% of patients with NSCLC develop brain metastases and, due to limited treatment options, the prognosis of patients with brain metastases remains poor.[15] Thus, TAS3351 might also provide a new treatment option for patients with EGFR deregulated NSCLC who have brain metastases.

Based on these results, TAS3351, is expected to have antitumor activity in patients with NSCLC harboring an acquired C797S *EGFR*mt, a population with an unmet medical need.

### 2.1.2.1. Nonclinical Experience

#### 2.1.2.1.1. Pharmacology

TAS3351 is a novel and highly potent and selective inhibitor of *EGFR*mt. In biochemical assays, TAS3351 and its active metabolite TAS-05-14317 inhibited EGFR enzymes harboring T790M and/or C797S mutation in addition to exon 19 deletion (ex19del) or L858R point mutation with mean half-maximal inhibitory concentration ($IC_{50}$) values ranging from 0.28 to 1.1 nmol/L, while sparing WT EGFR enzyme (mean $IC_{50}$: 3.9 nmol/L).

In cellular assays, TAS3351 inhibited autophosphorylation of EGFR in *EGFR*mt cell lines with mean $IC_{50}$ values ranging from 12 to 465 nmol/L and showed potent inhibition of cell viability with mean $IC_{50}$ values ranging from 2.84 to 241 nmol/L regardless of the presence of co-occurring EGFR T790M and/or C797S resistance mutations, while sparing autophosphorylation of WT EGFR. The cell viability mean $IC_{50}$ values ranged from 6.55 to 241 nM in cell lines with C797S mutation. Similar results were observed for TAS3351 active metabolite TAS-05-14317 in cellular assays.

In vivo, TAS3351 demonstrated antitumor activity in models with sensitizing *EGFR*mt and co-occurring EGFR resistance mutations following oral administration at doses from 10 to 80 mg/kg/day. In xenograft tumor models harboring L858R and T790M *EGFR* mutations, TAS3351 inhibited phosphorylation of downstream proteins AKT and ERK, in addition to EGFR in a dose-dependent manner. Furthermore, TAS3351 treatment led to potent tumor growth inhibition and/or tumor regression in the NIH/3T3-EGFR (ex19del/T790M/C797S) allograft model and the HCC827 and NCI-H1975 xenograft models, both of which express EGFR with ex19del or L858R/T790M mutation, respectively. In addition to these subcutaneously transplanted tumor mouse models, TAS3351 also demonstrated antitumor activity in an intracranially transplanted *EGFR*mt (ex19del/T790M/C797S) allograft model and improved survival time compared to the control group.

Secondary pharmacology studies for TAS3351 showed an $IC_{50}$ value of 860 nmol/L for human ether-a-go-go related gene (hERG) channel inhibition. The dog telemetry study of TAS3351 revealed a corrected QT (QTc)-prolongation at 10 mg/kg or higher at 4 hours post-dose only (up to +9% relative to the pre-dose value at the highest dose level, 40 mg/kg). There were no TAS3351-related effects on blood pressure, heart rate, or other electrocardiogram parameters at any dose level up to 40 mg/kg. In the rat functional observational battery for CNS effects, there were no relevant findings, except a 1.3% decrease in the rectal temperature was detected at 120 mg/kg TAS3351. No effect on body temperature was noted in the dog cardiovascular study in conscious dogs up to 40 mg/kg. For the respiratory system, no effects were observed in rats up to 120 mg/kg TAS3351.

#### 2.1.2.1.2. Absorption, Distribution, Metabolism, and Excretion

**<u>Absorption</u>**

Plasma concentration profiles and pharmacokinetic (PK) parameters of TAS3351 and TAS-05-14317 (active metabolite of TAS3351) were determined following a single dose of TAS3351 in mice and repeated dosing of TAS3351-10 (succinate co-crystal) in rats and dogs.

After a single oral administration of TAS3351 to male nude mice (20, 40, and 80 mg/kg), the maximum plasma concentration ($C_{max}$) and area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0-24}$) values of TAS3351 and TAS-05-14317 increased in a dose-dependent manner, and the metabolic ratios of TAS-05-14317 to TAS3351 ranged from

0.192 to 0.253. In mice, the observed total (TAS3351 and TAS-05-14317) $AUC_{0-24}$ was approximately 86 µM*hr for 20 mg/kg and approximately 473 µM*hr for 80 mg/kg.

Following 3-week repeated oral administrations of TAS3351-10 to female rats (75 and 150 mg/kg), the $C_{max}$ and $AUC_{0-24}$ values of TAS3351 and TAS-05-14317 tended to increase with repeated dosing (up to 2-fold increase for TAS-05-14317 at dose of 150 mg/kg). The metabolic ratios of TAS-05-14317 to TAS3351 ranged from 0.13 to 0.16 and showed no difference at either dose level on Day 1 and Day 21.

Following 3-week repeated oral administrations of TAS3351-10 to male and female dogs (40 and 80 mg/kg), there was no apparent change in any PK parameter by repeated dosing and no apparent sex-related differences in any PK parameter. The metabolic ratios of TAS-05-14317 to TAS3351 ranged from 0.66 to 1.32 and showed no difference at either dose level.

**Distribution**

Plasma protein binding ratios of TAS3351 and TAS-05-14317 were >99% in all animal species (mice, rats, rabbits, dogs, monkeys, and humans) and almost constant regardless of their concentrations. TAS3351 and TAS-05-14317 were bound to $\alpha_1$-acid glycoprotein (AGP) and human serum albumin (HSA).

Protein binding ratios in mouse brain homogenates (2 to 200 nmol/g) were >99.6% for both TAS3351 and TAS-05-14317.

TAS3351 and TAS-05-14317 demonstrated high brain penetrability after a single oral administration with brain to plasma concentration ratio ($K_{p, brain}$) values of 0.319 to 0.691 (20 to 80 mg/kg) for TAS3351, and 0.0558 to 0.150 (20 to 80 mg/kg) for TAS-05-14317.

**Metabolism**

Cytochrome P450 (CYP3) A4/5 were the major isoforms involved in the metabolism of TAS3351 among CYP isoforms in human liver microsomes.

The major metabolites observed in human liver microsomes were a mono-oxidized product (M18, TAS-05-14317) and a mono-oxidized and hydrated product (M11). These metabolites were also observed in rat and dog liver microsomes. M18 is a biologically active metabolite and has been evaluated in nonclinical studies. In human hepatocytes, a glutathione conjugate of hydrogenated product (M4) was observed as the major metabolite. M4 is a biologically non-active metabolite and was also observed in rat and dog hepatocytes. One metabolite (M2), a cysteinylglycine conjugate of the hydrogenated product, was observed in human hepatocytes but not observed in other animal species.

Based on these in vitro results, oxidation, hydration, and glutathione conjugations were estimated to be the main metabolic pathways.

**Elimination**

No excretion studies have been conducted with TAS3351.

**Drug-Drug Interactions**

In human liver microsomes, TAS3351 showed potential to reversibly inhibit CYP2C8, CYP2C9, and CYP2C19 with $IC_{50}$ values of 2.6, 1.2, and 2.1 µmol/L, respectively. TAS3351 inhibited CYP3A (testosterone 6β-hydroxylation) in a time-dependent manner with the maximal inactivation rate constant ($k_{inact}$) value of 0.0114 $min^{-1}$ and the concentration causing half maximal inactivation ($K_I$) of 6.97 µmol/L. For CYP3A (midazolam 1'-hydroxylation), the $k_{inact}$ and $K_I$ values were not calculable since the time-dependent inhibitory effect was weak.

In primary human hepatocytes, TAS3351 showed CYP1A2 induction potency with maximum fold induction ($E_{max}$) of 1.89-fold and 50% effective concentration ($EC_{50}$) of 1.09 µmol/L. No induction was observed for CYP2B6, CYP3A4, CYP2C8, CYP2C9, or CYP2C19 enzymes.

In vitro, TAS3351 was not a substrate for P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP). TAS3351 showed an in vitro potential to inhibit P-gp and BCRP with $IC_{50}$ values of 0.161 and 0.181 µmol/L in Caco-2 cells, respectively.

#### 2.1.2.1.3. Toxicology

The main toxicological findings for TAS3351 were overall consistent with previous reports for other EGFR TKIs.[16]

Repeated dose studies with and without a recovery period were performed in rats and dogs. Findings included abnormal stools, atrophy of epithelial tissues (eg, tongue, cornea, and skin), and regressive and atrophic changes in the gastrointestinal tract. In addition, granulomatous inflammation in various organs (eg, liver, lung) were observed, including arteritis and granulomatous vasculitis. In the 4-week repeated dose toxicity studies in rats and dogs, all toxicities showed reversibility during the 4-week recovery period.

The severely toxic dose in 10% of the animals (STD10) was determined to be 120 mg/kg/day in rats and the highest non-severely toxic dose (HNSTD) in dogs was determined to be 10 mg/kg/day in dogs.

TAS3351 demonstrated negative mutagenicity and clastogenicity in the Ames test and in vitro chromosomal aberration study, respectively.

TAS3351 was considered to have a potential for phototoxic effects based on the results of the in vitro phototoxicity study.

For further nonclinical information about TAS3351 please refer to the current version of the IB.

#### 2.1.2.2. Clinical Studies

This will be the first in human study of TAS3351; therefore, no clinical experience is available.

## 2.2. Potential Risks and Benefits

There is no human experience with TAS3351. Potential risks are based on nonclinical toxicity study results.

### 2.2.1. Possible Risks Based on Nonclinical Studies

#### 2.2.1.1. Gastrointestinal Toxicities

In nonclinical studies with TAS3351, abnormal stool (watery, mucinous, and/or bloody stool) and vomiting were observed. Histopathological findings included erosion/ulcer and atrophy of the squamous epithelium in the tongue, erosion/ulcer in the duodenum, villous atrophy, granulomatous inflammation and infiltration of foamy macrophages in in the ileum, inflammation, hemorrhage of the mucosa, and dilation of the crypts in the intestines.

Potential side effects and risks anticipated in human are mucositis, nausea, vomiting, diarrhea (and possibly dehydration and electrolyte imbalance in severe cases), bloody stool, and abdominal pain. Monitoring of patients for gastrointestinal AEs will rely mainly on careful clinical evaluation (physical examination and medical history, sign, symptoms) and on laboratory evaluation. Patients should be treated promptly for gastrointestinal AEs.

#### 2.2.1.2. Skin Disorders

In nonclinical studies, inflammatory changes, atrophy of the squamous epithelium and adnexa was observed in the skin. In addition, skin toxicities are common toxicities of EGFR TKIs.

Potential side effects and risks anticipated are dry skin, pruritus, and rash. Monitoring of patients for skin toxicities will be included during routine physical examination.

#### 2.2.1.3. Lung Disorders

In nonclinical studies, pathological findings included hemorrhage, perivascular edema, macrophage/inflammatory cell infiltration in the alveoli, and perivascular/peribronchiolar eosinophil infiltration. In addition, lung toxicities are a known class effect of EGFR TKIs.

Potential side effects and risks anticipated are hemoptysis (alveolar hemorrhage), lung infiltration, and interstitial lung disease. Monitoring of patients for lung disorders will include routine physical examination and medical history as well as adequate exploration/testing in case of respiratory symptom identification.

#### 2.2.1.4. Liver Enzyme Elevation

In nonclinical studies, elevation of liver enzymes was observed. Histopathological changes included periportal inflammation, multifocal granuloma, and single cell necrosis of hepatocytes.

Potential side effects and risks anticipated are liver function test abnormalities. Monitoring of patients for liver toxicities will include routine laboratory testing.

#### 2.2.1.5. Hematological Toxicities

In nonclinical studies, decrease in erythrocytic parameters was observed.

Potential side effects and risks anticipated are anemia and hematologic test abnormalities. Monitoring of patients for hematological toxicities will include routine laboratory testing and physical examination.

#### 2.2.1.6. QT Prolongation

Human ether-a-go-go related gene (hERG) current inhibition was detected with an $IC_{50}$ value of 860 nmol/L TAS3351, and a dog telemetry study revealed a non-dose proportional QT-prolongation at 10-40 mg/kg at a single time point. Therefore, TAS3351 has a potential to induce QT prolongation.

Patients with pre-existing increased QTc interval, cardiac comorbidity(ies), and any other risks associated with QT prolongation will be excluded per study protocol. Patients will have an ECG assessment at baseline and during treatment. Electrolytes will be monitored, and imbalance should be corrected.

#### 2.2.1.7. Eye Disorders

In nonclinical studies, atrophy of corneal epithelium was observed.

Potential side effects and risks anticipated are keratitis, corneal erosion, corneal ulcer, vision blurred, corneal opacity, and eye pain. Monitoring of patients for eye disorders will be conducted by ophthalmological examinations at baseline and any time during study treatment if clinically indicated. Patients should be advised to contact their study physician if experiencing any change in vision.

#### 2.2.1.8. Granulomatous Inflammation

In nonclinical studies, mild to moderate granulomatous inflammation in various organs (eg, liver, lung) were observed, including arteritis and granulomatous vasculitis.

Potential side effects and risks anticipated are vasculitis and thrombosis. Monitoring of patients for granulomatous inflammation will rely on clinical evaluation of signs, symptoms, and laboratory parameters indicative for vasculitis, thrombosis, or other manifestations of granulomatous inflammation.

#### 2.2.1.9. Phototoxicity

A phototoxicity risk for TAS3351 was identified based on in vitro neutral red uptake phototoxicity test using BALB/3T3 clone A31 cells.

Potential side effects and risks anticipated are photosensitivity and sunburn. Patients should be advised to use sun protection measures (eg, sunglasses, broad spectrum sunscreen) and limit direct sunlight/artificial sunlight exposure.

#### 2.2.1.10. Effects on Reproductive Organs

In nonclinical studies, pathological findings were atrophic changes in female reproductive organs and testicular germ cell degeneration.

Potential side effects and risks anticipated are possible decreases in reproductive potential.

#### 2.2.1.11. Drug Class Safety Issues

Safety findings reported for other EGFR TKIs such as erlotinib, afatinib, gefitinib, and osimertinib typically include gastrointestinal, dermatologic, and ocular toxicities. Cutaneous toxicities including rash, acne, pruritus, and dry skin were the most frequently observed toxicities. Interstitial lung disease has also been reported.

#### 2.2.1.12. Reproductive and Developmental Risks

No reproductive and developmental studies have been conducted with TAS3351. Pregnant women and breastfeeding women should not be included in studies with TAS3351. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 6 months after the last dose of study treatment for females, and 3 months after the last dose of study treatment for males, (or longer) based on local requirements.

#### 2.2.1.13. Special Patient Populations

No clinical studies of TAS3351 have been conducted to date and there is no information on use in special patient populations.

### 2.2.2. Possible Benefits

As this is a FIH study, the clinical benefit of TAS3351 is still unknown. TAS3351 is an EGFR inhibitor and may provide therapeutic benefit to patients with advanced cancer with EGFR aberrations. Patients to be enrolled in this study must have a documented *EGFR*mt status, progressed or were intolerant to available standard therapy for their disease, and have exhausted standard treatment options.

Given the disease stage, available treatment options, and potentially manageable expected toxicities, the risk/benefit assessment supports conduct of the study, with the potential for patients to benefit from TAS3351.

The planned study is designed to ensure the safety of participants. Patients will be enrolled at the Investigator's discretion, considering patient's individual benefit and risk and the availability of staff in the trial sites. The Sponsor performs a risk assessment of the study on an ongoing basis and prioritizes patient safety.

### 2.2.3. Overall Benefit/Risk Ratio Evaluation

The Sponsor considers that the overall benefit will outweigh the risks for patients with serious and life-threatening disease to be enrolled in Study 10073010.

This positive benefit/risk ratio justifies the initiation of Study 10073010 even in the context of the currently ongoing coronavirus disease 2019 (COVID-19) pandemic, as the clinical benefit/risk ratio for patients with serious and life-threatening tumor disease remain unchanged. The study procedures in this trial are designed to ensure the safety of participants during and after the COVID-19 pandemic, and appropriate measures (eg, remote visits, protocol-required laboratory safety and efficacy assessments performed at a local qualified facility) will be implemented in accordance with guidelines from regulatory authorities.[17,18]

# 3. OBJECTIVES AND ENDPOINTS

The primary, secondary and exploratory objectives and endpoints of this study are shown below.

## 3.1. Phase 1 Dose Escalation – Part A

| Objectives | Endpoints |
|---|---|
| **Phase 1 Dose Escalation** | |
| **Primary** | |
| • To investigate the safety and determine the recommended Phase 2 dose (RP2D) and dosing schedule of TAS3351 | • Safety, including (but not limited to) AEs graded by CTCAE v5.0, and incidence of dose limiting toxicities (DLTs). As supplementary data, preliminary antitumor activity and PK/PD results will be considered. |
| **Secondary** | |
| • To evaluate the antitumor activity of TAS3351 | • Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by Investigator<br>• Duration of response (DoR), disease control rate (DCR), and time on treatment<br>• Progression free survival and OS (Patients in part A2 only) |
| • To characterize the pharmacokinetics (PK) of TAS3351 and its active metabolite (TAS-05-14317) in plasma | • PK parameters including but not limited to maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($T_{max}$), area under the plasma concentration-time curve (AUC), and terminal elimination half-life ($T_{½}$) |
| **Exploratory** | |
| • To explore the relationship between exposures of TAS3351 and its active metabolite (TAS-05-14317) in plasma and QT prolongation | • Time matched plasma exposures of TAS3351 and its active metabolite (TAS-05-14317) and changes from baseline in QTcF |
| • To explore biomarkers for TAS3351 including their potential association with antitumor activity | • Biomarkers from tumor tissue and blood samples, including (but not limited to) DNA/RNA, protein, and cfDNA analysis |
| • To explore metabolites of TAS3351 in plasma | • Metabolites of TAS3351 in plasma will be characterized |

## 3.2. Phase 1 Dose Expansion – Part B

| Objectives | Endpoints |
|---|---|
| **Phase 1 Dose Expansion** | |
| **Primary** | |
| • To explore the efficacy of TAS3351 | • ORR per RECIST v1.1 by independent central review (ICR) |
| **Secondary** | |
| • To confirm the safety and tolerability of TAS3351 at the RP2D and dosing schedule | • AEs, including SAEs, clinical laboratory tests, vital signs, and 12-lead ECGs graded according to CTCAE v5.0 |
| • To further explore the anti-tumor efficacy of TAS3351 | • DoR, PFS, and DCR by ICR<br>• ORR, DoR, PFS, and DCR by Investigator assessment<br>• Intracranial ORR (icORR) and DoR (icDOR) by ICR and Investigator assessment<br>• Overall survival (OS) |
| **Exploratory** | |
| • To explore biomarkers for TAS3351 including their potential association with efficacy | • Biomarkers from tumor tissue and blood samples, including (but not limited to) DNA/RNA, protein, and cfDNA analysis |
| • To explore the potential exposure-response associations for efficacy and safety | • Exposures estimated by Population PK model and selected efficacy and safety measures |

## 3.3. Phase 2 – Part C

| Objectives | Endpoints |
|---|---|
| **Phase 2** | |
| **Primary** | |
| • To assess the efficacy of TAS3351 | • ORR per RECIST v1.1 by ICR |
| **Secondary** | |
| • To further assess the efficacy of TAS3351 | • DoR, PFS, and DCR by ICR<br>• ORR, DoR, PFS, and DCR by Investigator assessment<br>• Intracranial ORR (icORR) and DoR (icDoR) by ICR and Investigator assessment<br>• Overall survival (OS) |
| • To evaluate the safety and tolerability of TAS3351 | • AEs, including SAEs, clinical laboratory tests, vital signs, and 12-lead ECGs graded according to CTCAE v5.0 |
| • To evaluate patient reported outcomes (PROs) | • EORTC QLQ-C30 and EQ-5D-5L |
| **Exploratory** | |
| • To investigate biomarkers of response to TAS3351 and determine their potential association with efficacy | • Biomarkers from tumor tissue and blood samples, including (but not limited to) DNA/RNA, protein, and cfDNA analysis |
| • To explore the potential exposure-response associations for efficacy and safety | • Exposures estimated by Population PK model and selected efficacy and safety measures |

# 4. INVESTIGATIONAL PLAN

## 4.1. Overview of Study Design

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

The study will consist of 3 parts:

- **Part A**: Phase 1 Dose Escalation part to determine the RP2D and dosing schedule of TAS3351 in patients with advanced NSCLC
  - Part A1: Dose escalation in patients with any *EGFR*mt
  - Part A2: Backfill patients with C797S *EGFR*mt
- **Part B**: Phase 1 Dose Expansion part to explore the efficacy of TAS3351 in patients with C797S *EGFR*mt NSCLC
- **Part C**: Single-arm Phase 2 study to evaluate efficacy of TAS3351 in patients with C797S *EGFR*mt NSCLC

The study design is summarized graphically in Section 1.2.

## 4.2. Study Design

### 4.2.1. Phase 1 Dose Escalation (Part A)

The primary objective of Part A is to determine the recommended Phase 2 dose (RP2D) of TAS3351 based on observed DLTs, safety, antitumor activity, PK, and pharmacodynamics. Part A of Study 10073010 will consist of a Dose Escalation part (Part A1) and a part for "Backfill" patients (Part A2)

**Part A1**: Dose Escalation

The Phase 1 Dose Escalation is designed to evaluate 6 dose levels of TAS3351 from 50 to 700 mg/day (Table 5) using a Bayesian Optimal Interval (BOIN) design. [redacted].

TAS3351 will be administered once daily (QD) on a 21-day cycle at a starting dose of 50 mg QD and escalated based on tolerability (see Section 6.1.1) to patients who harbor any EGFR mutation, with consideration of lower increments than planned if clinically relevant toxicities are observed (intermediate dose levels). In the event of unacceptable toxicities at Dose Level 1, lower dose levels may be explored (eg, Dose Level -1). If PK, pharmacodynamic, and/or safety data indicate, twice daily (BID) dosing of TAS3351 may be explored. In order to appropriately characterize the PK profile of TAS3351, there will be a PK lead-in with a single administration of TAS3351 followed by PK sampling 3 days prior to the start of continuous daily dosing of TAS3351 for patients enrolled in the Dose Escalation Part A1 only.

**Part A2**: Backfill Patients

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 in that dose level (for a total of up to 20 backfill patients). A dose is deemed to be safe in Part A1 if there is an acceptable DLT rate in that dose level as per the BOIN design. Antitumor activity is defined as evidence of tumor shrinkage in at least one of the patients at that dose level.

If no preliminary antitumor activity is observed in Part A1, the totality of nonclinical in vitro and in vivo data as well as clinical PK data may be used to inform selection of dose level(s) for "backfill" patients. This will include $IC_{50}$ values from various in vitro assays and/or the total exposure of TAS3351 and its active metabolite associated with tumor shrinkage in preclinical xenograft mouse models to be used as thresholds for targeted efficacious $C_{min}$ and/or AUC, respectively. The exposure linked with nonclinical activity is a total TAS3351 and TAS-05-14317 $C_{min}$ of 40.3 nM. Clinical PK simulation will be applied to project dosing regimen(s) which may achieve the targeted threshold(s). The doses explored in the A2 part of the trial will be chosen in consultation between the investigators and the Sponsor based on the above safety and efficacy criteria as well as a review of the PK data. "Backfill" patients enrolled are required to have a tumor harboring a C797S *EGFR*mt. The additional information from these "backfill" patient cohorts will broaden the amount of safety and preliminary antitumor activity data for TAS3351 at potential active dose levels to inform the selection of the RP2D of TAS3351.

### 4.2.2. Phase 1 Dose Expansion (Part B)

The Phase 1 Dose Expansion part of the study will be initiated after an RP2D and a dosing scheme has been identified in Part A. NSCLC patients with C797S *EGFR*mt will be enrolled to explore the efficacy and confirm the safety of TAS3351 at the RP2D in a larger patient population. Moreover, a second dose level of TAS3351 may be evaluated in an additional cohort of patients in Part B if promising antitumor activity is observed at another lower TAS3351 dose level during Part A. In this case, patients enrolled in Part B will be randomized at a 1:1 ratio between the two treatment arms to evaluate the optimal RP2D of TAS3351 based on a comparative analysis considering the totality of efficacy and safety data observed.

The results from Part B will confirm the RP2D of TAS3351 and are expected to provide, in combination with the "Backfill" patients from Part A2, the proof of concept for the efficacy of TAS3351 in NSCLC patients with the C797S *EGFR*mt. Based on these results, the Phase 2 part of this study will be initiated.

In addition, further cohorts may be added by an amendment to explore the activity of TAS3351 in further subgroup(s) of patients based on activity observed in the Part A dose escalation and/or emerging scientific data. This may include an additional cohort for *EGFR*mt NSCLC patients with brain metastases to explore the efficacy of TAS3351 against CNS metastases or against other type of *EGFR*mt, if promising results are observed during Part A of this study.

### 4.2.3. Phase 2 (Part C)

The Phase 2 part of the study will be an open-label, single-arm, Phase 2 study to assess the safety and efficacy of TAS3351 in advanced NSCLC patients with C797S *EGFR*mt who progressed on a prior treatment with another EGFR inhibitor. Patients will receive TAS3351 at the RP2D and dosing scheme confirmed in Part B and be evaluated for ORR based on

RECIST v1.1 by Independent Central Review (ICR) as the primary endpoint. A key secondary endpoint of this part of the study will be duration of response (DoR) by ICR.

### 4.2.4. Study Stopping Criteria

The study will be stopped in the event of unacceptable toxicities. If the following toxicities are observed in at least 1 patient, dosing of new patients will be suspended until further review of safety to determine if dosing can resume. These toxicities will include, but are not limited to, the following:

- Any death other than disease progression in any patient in which the cause of death is judged to be at least possibly related to the study treatment by the investigator.
- Liver function test increase that is considered to be a Hy's Law case
- ≥Grade 4 severe cutaneous adverse reactions (Steven-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome)

In Part A1, dosing of patients in a dose level will stop if there is an unacceptable DLT rate as per the BOIN design.

For the patients participating in Part A2 ("back-fill") and Part B (dose expansion), if adverse events meeting the DLT definition surpass 30% during Cycle 1 in a particular cohort, enrollment will be stopped for that cohort. Patients in other cohorts without such safety issues may continue dosing.

After approximately 25% of patients are enrolled in Part C, the data will be reviewed to determine if there are safety concerns that justify modification to or termination of the trial. Timing of subsequent reviews will depend on the rate of recruitment in this part of the study.

The Sponsor's medical monitor, in consultation with the study investigators, will decide following review whether suspension of patient accrual may be lifted and if any adjustments of the protocol are required prior to reopening enrollment. Prior to the start of Phase 2, a Data Monitoring Committee (DMC), including members external to the Sponsor, will be established (Section 4.12). The DMC will review all safety data after dose expansion before proceeding to Part C (Phase 2). The trial may be terminated by the Sponsor, if after discussion with the investigators or DMC, the benefit risk ratio is no longer favorable for patients.

## 4.3. Scientific Rationale for Study Design

The study design of this Phase 1/2 study will allow efficient assessment of the safety and efficacy of TAS3351 in the target population of patients with advanced NSCLC with tumors harboring an acquired C797S *EGFR*mt. The Phase 1 Dose Escalation will use the BOIN design, a simple and well-performing design for Phase 1 oncology trials[15] followed by a Dose Expansion part to confirm the RP2D and explore efficacy. In order to appropriately characterize the PK profile of TAS3351, there will be a PK lead-in for patients enrolled in the Dose Escalation part with a single administration of TAS3351 3 days prior to the start of daily dosing of TAS3351 with subsequent PK sampling.

The Phase 2 part of this study will be a single-arm study of TAS3351 monotherapy in the absence of any approved or well-established standard of care treatment options for these

patients on a potential control arm, highlighting the unmet medical need in this patient population.

In trials of molecularly targeted agents, minimal toxicity may arise over all doses under consideration and higher doses may not result in a greater response.[19] The Phase 1/2 study design employed here could facilitate selection of a dose/regimen with acceptable toxicity that maximizes efficacious response. It allows for faster adaptation and refinement of subsequent parts of the study based on emerging data. It could enhance monitoring of cumulative safety data over time. If Phase 1 data show a favorable benefit/risk profile, the Phase 2 can start to enroll patients right away, which would speed up the drug development in an area of high unmet medical need.[20]

## 4.4. Justification for Primary Endpoint and Key Secondary Endpoint

The primary endpoint of the Phase 1 Dose Escalation part of this study is to identify the RP2D based on safety and preliminary antitumor activity observed as standard for Phase 1 first in human studies.

The primary endpoint of the Phase 1 Dose Expansion and the Phase 2 part is ORR assessed by ICR according to RECIST v1.1. ORR is a clinically meaningful and accepted endpoint by regulatory agencies for studies in later-line *EGFR*mt NSCLC patients.[21] ORR will be assessed by ICR to avoid any potential Investigator bias and to increase the validity of the ORR results observed.

As a key secondary objective, this study will include DoR as assessed by ICR to evaluate the durability of responses. Durability of responses are considered a key factor to determine whether an observed ORR is clinically meaningful.[22]

## 4.5. Justification for Starting Dose

The starting dose is based on toxicology studies in dogs, where the HNSTD was 5 mg/kg BID (10 mg/kg/day), and intolerable toxicities were observed at doses ≥10 mg/kg BID (20 mg/kg/day) (see Section 2.1.2.1). The starting dose was adjusted to 1.67 mg/kg/day (1/6 of HNSTD) which translates to a human equivalent dose (HED) of 33.4 mg/m$^2$ based on normalization of dose to body surface area as described in the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) S9 guideline on using animal data for FIH dose selection. Using the STD10 from rodent studies resulted in a HED of 72 mg/m$^2$ based on allometric scaling; therefore, the lower dose of 33.4 mg/m$^2$ observed for dogs was chosen for calculating the starting dose for human studies. Based on an average human body surface area of 1.62 m$^2$, the starting dose of TAS3351 was calculated to be 54.1 mg in humans.

Based on the availability of 25 mg, 100 mg, or 200 mg tablet sizes, 50 mg QD was selected as the FIH starting dose.

## 4.6. Study Period

The study periods for each patient are defined in Table 4.

**Table 4: Definition of Study Periods**

| 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 main ICF signature to the day before the first dose |
| Treatment Period | From the first day of dosing 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 |

## 4.7. Study Completion

The study will be considered completed (that is, the scientific evaluation will be finished) when it has been determined by the Sponsor that the scientific evaluation of this study is sufficient and complete.

Investigators will continue to follow the Schedule of Events (Table 1, Table 2, and Table 3) for all patients until notified by the Sponsor that study completion has occurred.

## 4.8. Study Extension

Following study completion (Section 4.7), all patients who are still receiving TAS3351 and deriving clinical benefit with no undue risk may continue to receive study treatment in a study extension phase. During study extension, patients may receive treatment until any of the study treatment discontinuation criteria (Section 5.4) are met.

During study extension, assessments are to be conducted according to the Schedule of Events shown in Table 3.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the Investigator's discretion. The Sponsor will not routinely collect the results of these assessments.

In the event that an SAE occurs, the Sponsor may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

## 4.9. End of Study

The end of the study is defined as the date of the last visit of the last patient in the study including the last scheduled procedure shown in the Schedule of Events (Table 1, Table 2, or Table 3 in case of study extension).

## 4.10. Patient Enrollment

Eligibility must be verified prior to patient enrollment. Upon eligibility verification, patient information will be entered into an Interactive Web Response System (IXRS). Patients are considered enrolled in the study when consented, screened, and determined to be eligible.

## 4.11. Randomization and Blinding

No blinding of treatment assignments is required as this study is open-label.

No randomization is planned in Part A and Part C, and is only planned in Part B if 2 dose levels of TAS3351 are evaluated in Part B (see Section 4.2.2). Should 2 dose levels be evaluated, a total of 40 patients with C797S *EGFR*mt will be enrolled in Part B and will be randomized at a 1:1 ratio between the two treatment arms (ie, TAS3351 dose levels).

## 4.12. Data Monitoring Committee

A data monitoring committee (DMC), including members external to the Sponsor, will be established prior to the transition from the Phase 1 study part to the Phase 2 part to monitor data on an ongoing basis to ensure the continuing safety of the patients enrolled in this study. The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study. The details will be provided in a separate DMC charter.

# 5. SELECTION AND WITHDRAWAL OF PATIENTS

Eligibility must be verified prior to patient enrollment. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) is not permitted.

## 5.1. Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Provide written informed consent
2. ≥18 years of age (or meets the country's regulatory definition for legal adult age, whichever is greater)
3. Histologically or cytologically confirmed, locally advanced, non-resectable or metastatic NSCLC
4. Has received the following prior treatment and no more than 2 lines of prior cytotoxic chemotherapy for locally advanced or metastatic disease setting:
    a. **Part A1** (Phase 1 Dose Escalation): Standard of care (SOC) that is available to the patient, unless contraindicated, or intolerable to the patient
    b. **Part A2**: Progression on third-generation EGFR TKI (eg, osimertinib, lazertinib)
    c. **Parts B and C**: Progression on third-generation EGFR TKI (eg, osimertinib, lazertinib)
5. Has the following *EGFR*mt status as determined by a CLIA certified (US), locally certified (outside of the US), or the study central laboratory based on tumor tissue or plasma cfDNA:
    a. **Part A1** (Phase 1 Dose Escalation): Any *EGFR*mt
    b. **Parts A2, B, and C**: Any sensitizing *EGFR*mt and a confirmed C797S *EGFR*mt (Note: no T790M *EGFR*mt required)
6. Has tumor tissue available collected after progression on the most recent systemic EGFR TKI treatment in a quantity sufficient to allow for analysis of *EGFR*mt status by the Sponsor's central laboratory (optional for **Part A1 only**). Please refer to the Laboratory Manual for details.
7. Has measurable disease per RECIST v1.1 (optional for patients in Part A1)
8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
9. Adequate organ function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    b. Platelet count $\geq 100{,}000/mm^3$ ($\geq 100 \times 10^9$/L); last transfusion of blood products must be ≥2 weeks prior to start of study treatment.
    c. Hemoglobin ≥ 9.0 g/dL
    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 × upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5.0 × ULN
    e. Total bilirubin ≤ 1.5 × ULN, or ≤ 3.0 × ULN for patients with Gilbert's syndrome
    f. Creatinine clearance (CrCl) (calculated or measured value): ≥50 mL/min. For calculated CrCl, use the Cockcroft-Gault formula

g. Potassium blood levels ≥3.0 mmol/L

10. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test prior to administration of the first dose of study treatment. Female patients are not considered to be of child-bearing potential if they are post-menopausal (no menses for 12 months without an alternative medical cause) or permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
11. Both males and females of reproductive potential must agree to use highly effective birth control throughout the study and at least for:
    - 6 months after the last dose of study treatment for females
    - 3 months after the last dose of study treatment for males

    or longer, based on local requirements.

## 5.2. Exclusion Criteria

A patient must not meet any of the following exclusion criteria to be eligible for participation in this study:

1. Currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study
2. Has received prior treatment with any of the following within the specific time frame prior to the first dose of study treatment:
    a. Major surgery/surgical therapy for any cause within 4 weeks; the patient must have recovered adequately from the toxicity and/or complications of the intervention prior to starting study treatment
    b. Chemotherapy, biologic therapy, targeted therapy, immunotherapy, or investigational agents within 5 half-lives or within 4 weeks (whichever is shorter) prior to the first dose of study treatment. Patient must have recovered from toxicities of the prior therapy based on the Investigator's judgement prior to starting study treatment
    c. No prior treatment with:

        (i). **Part A1** (Phase 1 Dose Escalation): Systemic immunotherapy (eg, PD-1/PD-L1 antibody)

        (ii). **Parts A2, B, and C:** Any EGFR C797S mutation-targeting agent (eg, BLU-945)

    d. Radiotherapy prior to the start of study treatment within:

        (i). 2 weeks for radiation therapy of non-thoracic regions (7 days for palliative radiation of single lesions)

        (ii). 3 months for radiation therapy including thoracic region.

        Patients must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
3. Have any unresolved clinically relevant toxicity of Grade ≥2 from previous anti-cancer treatment, except for alopecia, skin pigmentation, and Grade 2 prior platinum-therapy related neuropathy. Patients with chronic, but stable Grade 2 toxicities may be allowed to enroll if the Investigator and Sponsor agree.

4. Any strong and moderate inhibitors/inducers of cytochrome P450 (CYP) 3A two weeks prior to start of therapy. If a patient is receiving strong inhibitors/inducers of CYP3A (see Appendix A), these medications and substances must be discontinued ≥2 weeks prior to the first dose of study treatment.
5. Has the following CNS metastases disease status:
    a. **Part A1** (Phase 1 Dose Escalation): Known untreated central nervous system (CNS) metastases, or history of uncontrolled seizures, or leptomeningeal disease. Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT scan) during the screening period, and they are on a stable or decreasing dose of corticosteroids for at least 2 weeks prior to the first dose of study treatment.
    b. **Parts A2, B, and C**: Spinal cord compression, symptomatic and unstable CNS metastases, requiring steroids over the last 4 weeks prior to enrollment (asymptomatic and symptomatic brain metastases stable for at least 4 weeks and off steroids are allowed). Patients with leptomeningeal disease are allowed if it is determined that immediate CNS treatment is unlikely to be required.
6. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
    a. Baseline QT interval > 470 msec corrected for heart rate using Fridericia's formula (QTcF, verified on repeat measurements)
    b. History of QTc prolongation or predisposition for QTc prolongation (clinically relevant electrolyte abnormalities, cardiac disorder, bradycardia, etc.), or family history of sudden cardiac death or QT prolongation (long QT syndrome)
    c. Regular use of medications known to prolong QTc interval or to be arrhythmogenic (such as ondansetron, erythromycin, droperidol) within 2 weeks of the first dose of TAS3351. A list of these medications can be found at: http://crediblemeds.org.
    d. History or presence of clinically important abnormalities in rhythm or conduction in resting ECG (eg, sinus arrest, second- or third-degree atrioventricular block (first degree atrioventricular block not excluded), serious uncontrolled ventricular arrhythmias), or severe myocardial infarction within 6 months of screening.
7. General health condition of the patient is not suitable for the study including:
    a. Disease or condition that significantly affects gastrointestinal absorption of the study treatment
    b. Clinically relevant active infection (ie, known HBV, HCV, HIV – screening not required) or other uncontrolled medical condition
    c. History of interstitial lung disease/pneumonitis, drug-induced lung disease/pneumonitis
    d. Known additional malignancy that is progressing or requires active treatment, with the exception of patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or antitumor assessment of the investigational regimen. Exceptions must be discussed with the Sponsor prior to patient enrollment
8. Known hypersensitivity to the ingredients of TAS3351
9. Unable to swallow whole tablets

10. Pregnant female or breastfeeding female
11. Any other clinically significant acute or chronic medical or psychiatric condition that may increase the risk associated with study drug administration, or may interfere with the interpretation of study results based on Investigator discretion

## 5.3. Screen Failure

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE after completion of the ICF.

Patients who do not meet the criteria for participation in this study (ie, screen failures) may be rescreened twice or after discussion with the Medical Monitor. Previously completed study assessments remaining within the protocol-defined window will be accepted for rescreening.

If the Sponsor or the Investigator identifies a patient who did not meet the eligibility criteria and was inadvertently enrolled, a decision on whether or not the patient may remain on study will be made between the Investigator and the Sponsor. If both agree that it is medically appropriate, the patient may continue on study following written approval by the Sponsor.

## 5.4. Discontinuation of Treatment

Discontinuation of study treatment does not represent a withdrawal from the study.

A patient must be discontinued from study treatment for any of the following reasons, but will continue to be monitored in the study:

1. Documentation of radiographic disease progression assessed by Investigator per RECIST v1.1* criteria.
2. Clinical progression.
3. Unacceptable AEs or change in an underlying condition such that the patient can no longer tolerate therapy, for instance any Grade ≥3 toxicity that does not resolve to Grade 1 or baseline (or to Grade 2 for toxicities that are manageable with supportive care) within 21 days should result in permanent discontinuation.
4. Physician’s decision, including the need for other anticancer therapy not specified in the protocol or surgery or radiotherapy to the only site(s) of the disease being followed in the study.
5. Pregnancy or intent to become pregnant.
6. Termination of the study by the Sponsor.
7. At the patient’s request at any time irrespective of the reason (including withdrawal of consent from further treatment with the study drug or follow-up).
8. Noncompliance with the study protocol that, in the opinion of the Investigator or the Sponsor, warrants withdrawal from treatment with the study drug.

Patients who withdraw consent for further study treatment may choose to remain on study and should continue with all study evaluations as outlined in this protocol. If the patient

withdraws consent to all follow-up assessments, the patient is considered to have discontinued the study.

* Note: If a patient demonstrates radiographic disease progression but continues to have clinical benefit (including stable performance status and absence of symptoms and signs indicating clinically significant progression of the disease), the continuation of TAS3351 may be considered in exceptional cases following consultation with the Sponsor and in accordance with the following criteria:

- Absence of unacceptable toxicity
- Absence of clinical symptoms or signs indicating clinically significant disease progression
- No decline in ECOG performance status
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

Written informed consent will need to be obtained prior to continuation of study treatment beyond radiologic disease progression and after discussion of alternative treatment options, including any available approved therapies and participation on alternative clinical trials.

## 5.5. Post-treatment Discontinuation Considerations

The Investigator remains responsible for following the patient through an appropriate health care option for AEs that are considered related to the study or caused the patient to discontinue the study and have not been resolved at the 30-day Safety Follow-up visit. The patient should be followed up until the events are resolved or explained. Frequency of follow-up is left to the discretion of the Investigator.

Investigators are not obligated to actively seek any new AEs after the 30-day Follow-up period. However, if the Investigator learns of any SAE at any time after a participant has been discontinued from the study and the Investigator considers the event to be reasonably related to the study treatment or participation, the Investigator must promptly notify the Sponsor.

## 5.6. Withdrawal from the Study

A patient will be withdrawn from all study interventions and assessments (ie, discontinued from the study without follow-up) for any of the following reasons:

1. Death
2. Patient withdrawal of consent to further follow-up assessments, irrespective of the reason.
3. Lost to follow-up
    - A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
    - The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (when possible, 3 telephone calls, and [if necessary] a certified letter to the patient's last known mailing address, or local equivalent methods). These contact attempts should be documented in the patient's medical records.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

# 6. STUDY TREATMENT

## 6.1. Study Drug Administration

TAS3351 will be administered orally once daily (QD) on Days 1 to 21 of a 21-day cycle. Patients enrolled in Part A1 will also be administered a single dose of TAS3351 on Cycle 1 Day -3 during the PK Lead-in Period. If PK, pharmacodynamic, and/or safety data indicate, twice daily (BID) dosing of TAS3351 may also be explored.

- TAS3351 should be taken at approximately the same time every day on an empty stomach and should be taken with water. Patients should not consume food 2 hours before and ending 1 hour after taking TAS3351 but will be allowed to drink water during this period. Patients should be instructed to swallow the tablets whole and not to chew or crush them.
- In the event of a dosing delay up to 12 hours (6 hours for BID dosing) after the scheduled dosing time, the patient should still take that day's dose. If the dosing delay is >12 hours (6 hours for BID dosing) or if the patient vomits after a dose, the patient should skip that dose and continue with the planned subsequent dose (skipped or missed doses should not be made up).

On PK sampling days, TAS3351 should be administered on-site after the pre-dose PK sample collection (Table 13). Actual dosing time will be recorded.

Patients will receive TAS3351 until disease progression, unacceptable toxicity, or any other discontinuation criterion or withdrawal criterion is met (Section 5.4, Section 5.6).

### 6.1.1. Dose Escalation

The starting dose of TAS3351 will be 50 mg QD (Table 5). The study is designed to escalate TAS3351 up to a dose of 700 mg daily based on safety and tolerability observed, with lower increments considered, if clinically relevant toxicities are observed. The upper end of 700 mg TAS3351 total daily dose levels are based on more conservative assumptions for PK predictions and non-clinical efficacy data observed. In case of toxicity, other dose levels, such as intermediate or dose levels lower than Dose Level 1, may be explored following discussion and agreement between the Sponsor and the Investigators.

**Table 5: TAS3351 Dose Levels**

| Dose Level | Total Daily Dose (mg/d) | Absolute and % Change from Previous Total Daily Dose |
|---|---|---|
| -1 | 25 | -25 mg / -50% |
| 1 (Starting dose) | 50 | - |
| 2 | 100 | 50 mg / 100% |
| 3 | 200 | 100 mg / 100% |
| 4 | 350 | 150 mg / 75% |
| 5 | 500 | 150 mg / 43% |
| 6 | 700 | 200 mg / 40% |

**Note**: If no DLTs observed at 700 mg QD, any further dose escalation will not exceed 33% increments.

In addition, if PK, pharmacodynamic, and/or safety data indicate that splitting the dose of TAS3351 in two daily doses might be preferable (eg, due to short half-life, saturation of exposure), then twice daily (BID) dosing of TAS3351 may be explored following discussion and agreement between the Investigators and the Sponsor. In such case, the dose of the highest QD dose shown previously to be safe and tolerable will be divided into two equal doses to be taken in the morning and evening approximately 12 hours apart. Dose escalation for twice daily dosing will follow total daily doses shown in Table 5 (ie, total daily dose divided by 2 for BID dosing).

The planned dose escalation will follow a BOIN design, [redacted]. For further information about statistical considerations, please see Section 12.

The Dose Escalation part (Part A1) will enroll approximately 40 evaluable patients. After treatment of the first patient in the study, a waiting period of 2 weeks will be implemented to evaluate safety before treatment of subsequent patients at the first dose level. For subsequent dose levels, additional patients will not be allowed to initiate study drug until the first patient at each dose level has been evaluated for safety 48 hours after initiating treatment. Subsequent patients may be enrolled in parallel in absence of toxicities meeting DLT criteria. With the maximum sample size of 15 patients per dose level, the boundary guiding the number of patients treated at the current dose is displayed in Table 6. This table provides the dose-finding decisions given the numbers of patients treated at the current dose level, and the observed numbers of patients experiencing toxicity.

**Table 6: Dose Escalation and De-Escalation Rules**

| Actions[a] | Number of patients treated at the current dose level | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** |
| Escalate if patients with DLT ≤ | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 3 | 3 | 3 |
| De-escalate if patients with DLT ≥ | 1 | 1 | 2 | 2 | 2 | 3 | 3 | 3 | 4 | 4 | 4 | 5 | 5 | 6 | 6 |
| Eliminate if # of DLT ≥ | NA | NA | 3 | 3 | 4 | 4 | 5 | 5 | 5 | 6 | 6 | 7 | 7 | 8 | 8 |

[a] If no actions (ie, escalate, de-escalate, eliminate) are triggered, stay at the current dose for treating the next cohort of patients.
**Abbreviations:** DLT=dose-limiting toxicity; NA=not applicable
**Note:** # of DLT = number of patients with at least 1 DLT; NA = this dose cannot be eliminated before treating 3 patients.

A minimum of 3 patients at each dose level are required. The general stopping rules are as follows:

- Escalation stops if 40 evaluable patients have already been dosed
- Escalation stops if there are 15 patients already dosed on next dose level

For the purpose of overdose control, a dose level will be eliminated if at least 3 patients have been treated and the probability of overdose is greater than 95%.

For patients in Part A1 who have completed the DLT assessment period, intra-patient dose escalation (IPDE) of TAS3351 to dose levels demonstrated to be safe and tolerable (eg, only Grade ≤2 toxicities were observed during previous treatment cycles including the DLT assessment period) may be allowed to minimize patient exposure at subtherapeutic doses following discussion between the Investigator and the Sponsor's medical monitor and written

approval by the Sponsor. The decision to allow for IPDE should be made after considering the potential safety profile of the investigational drug including cumulative drug toxicity.

### 6.1.2. Dose-limiting Toxicity

Dose-limiting toxicity (DLT) will be assessed during the first cycle (including the PK lead-in period for patients in Part A1). The occurrence of any toxicity outlined in Table 7 that is clinically significant will be considered a DLT, excluding toxicities clearly related to disease progression or intercurrent illness. The investigator must report all DLTs to the Sponsor promptly during the dose escalation part and well in advance of the dose escalation call. In addition, meetings between the Sponsor and investigators will be held on a regular basis to review safety data and in the event of emerging safety issues.

**Table 7: Definition of Dose Limiting Toxicity**

| Toxicity | DLT Definition |
|---|---|
| Hematologic | • Grade 4 neutropenia lasting >7 consecutive days<br>• Grade 4 thrombocytopenia<br>• Grade 3 thrombocytopenia associated with clinically significant bleeding requiring intervention<br>• Febrile neutropenia (ANC <1000/mm$^3$ with a single body temperature of >38.3°C [101 °F] or a sustained temperature of ≥38°C [100.4°F] for more than 1 hour) |
| Hepatic | • Grade ≥3 total bilirubin elevation<br>• Grade ≥3 AST and/or ALT elevation<br>• For patients with liver metastases, AST or ALT >8 × ULN regardless of duration or AST or ALT >5 × ULN but ≤8 × ULN lasting ≥7 consecutive days |
| | • Hy's Law criteria concurrent observation of the following, with no other reason found to explain the findings (such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed liver injury):<br>– Elevated aminotransferase enzymes >3 × ULN<br>– Associated with an increase in bilirubin >2 × ULN<br>– Absence of initial findings of cholestasis (elevated ALP) |
| Renal | • Calculated CrCl <30 mL/min for >3 days despite optimal supportive care |
| Skin | • Grade ≥3 skin toxicity uncontrolled by adequate skin therapy, including topical steroid and/or systemic corticosteroid therapy that does not return to Grade ≤2 within 7 days |
| Other Nonhematologic | • Any other Grade ≥3 toxicities with the following exceptions:<br>– Grade 3 nausea, vomiting, and diarrhea lasting <72 hours despite optimal supportive care. Grade 4 vomiting or diarrhea will be considered a DLT.<br>– Fatigue lasting <7 days<br>– Asymptomatic Grade 3 electrolyte abnormality with a duration of ≤72 hours that can be substituted or treated and are clinically uncomplicated (eg, not requiring hospitalization).<br>– Grade 3 amylase or lipase elevation not associated with symptoms or clinical manifestations of pancreatitis |

| Toxicity | DLT Definition |
|---|---|
| Other | • Prolonged dose interruption (>2 weeks) in initiating Cycle 2 due to study drug-related toxicity)<br>• Any study drug related AE(s) leading to treatment discontinuation during Cycle 1 despite optimal supportive treatment<br>• Any death not clearly due to the underlying disease or extraneous causes.<br>• Any other toxicity deemed a DLT and agreed upon between Sponsor and Investigator |

**Abbreviations:** AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; DLT=dose-limiting toxicity; ULN=upper limit of normal

A patient evaluable for DLT is defined as a patient who either experienced a DLT during the first cycle (including the PK Lead-in period for patients in Part A1), or who completed the first cycle without experiencing a DLT and with at least 80% of study treatment administered. Patients who are not evaluable for DLTs may be replaced. Trends for toxicities observed after the DLT period will be considered when selecting the RP2D.

## 6.2. Dose and Schedule Modifications

The following general dose modification guidelines for patients receiving TAS3351 should be followed:

- Supportive treatment for any AE should be optimized before any modification is considered.
- If the symptoms of AE promptly resolve with supportive care, consideration should be given to continuing study drug along with appropriate continuing supportive care.

Recommended dose modifications are based on the occurrence of treatment-related AEs and are provided for hematological toxicities (Section 6.2.1.1) and non-hematological toxicities (Section 6.2.1.2). If an Investigator suspends treatment or reduces doses without one of the dose reduction, interruption and resumption criteria being met, this is acceptable and would not be considered a protocol deviation.

### 6.2.1. Dose Reduction, Interruption, and Resumption

Dose reductions for TAS3351 should be made according to Table 8. No more than 3 dose reductions are allowed. If dose reductions fail to result in achieving the minimum criteria to resume treatment or if toxicities occur that would necessitate reducing TAS3351 dosing below 25 mg QD (or BID), the patient should be discontinued from TAS3351 treatment.

**Table 8: Dose Reduction**

| TAS3351 Total Daily Dose | |
|---|---|
| **Current Dose (mg/d) [a]** | **Reduce to (mg/d)[a]** |
| 50 | 25 |
| 100 | 50 |
| 200 | 100 |
| 350 | 175 |
| 500 | 300 |
| 700 | 500 |

[a] In case of BID dosing, total daily dose to be divided in two equal doses to be administered 12 h apart. For a current dose of 50 mg, dose would be reduced to 25 mg QD.
**Abbreviations:** BID=twice daily; d=day; h=hour; mg=milligram

Patients with dose reduction of TAS3351 may be re-escalated up to the starting dose, if the toxicity leading to dose reduction has been resolved and the benefit/risk assessment favors re-escalation of TAS3351. A discussion between Investigator and the Sponsor's medical monitor is required prior to the TAS3351 dose re-escalation.

If dosing of TAS3351 needs to be interrupted, the 21-day cycle will be maintained. There will be no delay in the start of a new cycle except the start of Cycle 1 for patients with a PK Lead-in period in Part A1, if clinically indicated.

#### 6.2.1.1. Dose Modifications for Hematological Toxicities

Recommendations for dose modification due to study drug-related hematologic toxicities are presented in Table 9.

**Table 9: Recommendations for Management of Hematologic Toxicities**

| Grade by CTCAE v5.0 | Management Recommendation |
|---|---|
| Grade 1 and 2 | No dose modifications required |
| **Anemia and Thrombocytopenia** | |
| Grade 3 | Suspend TAS3351 until resolved to Grade ≤2 or baseline, then:<br>• If resolved ≤14 days, resume at the same dose level<br>• If resolved >14 days or re-occurrence, resume at next lower dose level |
| Grade 4 | Suspend until resolved to Grade ≤2 or baseline, then resume at next lower dose level |
| **Neutropenia (ANC)** | |
| Grade 3 lasting ≤3 days | No dose modifications required |
| Grade 3 lasting >3 days<br>or Grade 4 | Suspend TAS33551 until resolved to Grade ≤2 or baseline, then<br>• If resolved ≤7 days, resume at the same dose level<br>• If resolved >7 days or re-occurrence, resume at next lower dose level |
| Febrile neutropenia | Suspend TAS3351 until resolved, then resume at next lower dose level |

**Abbreviations:** ANC=absolute neutrophil count; CTCAE=Common Toxicity Criteria for Adverse Events

#### 6.2.1.2. Dose Modifications for Non-hematologic Toxicities

Recommendations for dose modification due to study drug-related diarrhea, hepatic events, skin rash, QT prolongation, interstitial lung diseases (ILD), and other non-hematologic toxicities are presented in Table 10.

**Table 10: Recommendations for Managing Non-Hematologic Toxicities**

| Grade by CTCAE v5.0 | Management Recommendation |
|---|---|
| **Diarrhea** (see also Section 6.4.4.2) | |
| Grade 1 and 2 | No dose modifications required, initiate supportive therapy (see Section 6.4.4.2)<br>If persistent / recurrent Grade 2 that does not resolve with maximal supportive measures, reduce to next lower dose level |
| Grade 3 | Suspend dose until resolved to ≤Grade 2, then:<br>• If resolved ≤14 days, resume at the same dose level and consider anti-diarrheal prophylaxis<br>• If resolved >14 days or re-occurrence, resume at next lower dose level |
| Grade 4 | Suspend dose until resolved to ≤Grade 1 or baseline, then resume at next lower dose level. |
| **Hepatic events** | |
| **Bilirubin increased** | |
| Grade 1 and 2 | No dose modifications required<br>Note: Assess AST and ALT for ≥ Grade 2 bilirubin (see Hy's law below) |
| Grade 3 | Suspend dose until resolved to ≤ Grade 1 or baseline, then:<br>• If resolved ≤14 days, resume at the same dose level<br>• If resolved >14 days or re-occurrence, resume at the next lower dose level |
| Grade 4 | Discontinue study drug |
| **AST or ALT increase** | |
| Grade 1 and 2 | No dose modifications required<br>NOTE: Assess bilirubin for ≥ Grade 2 AST/ALT (see Hy's law below) |
| Grade 3 | Suspend dose until resolved to ≤Grade 1 (≤ Grade 2 in the presence of liver metastasis) or baseline, then:<br>• If resolved ≤14 days, resume at the same dose level<br>• If resolved >14 days, resume at the next lower dose level |
| Grade 4 | Discontinue study drug |
| **Hy's law** | |
| AST or ALT >3.0 × ULN<br>with<br>bilirubin >2.0 × ULN | Discontinue study drug, except:<br>• Other reason found to explain the findings (such as viral hepatitis A, B, or C, pre-existing or acute liver disease, or another drug capable of causing the observed liver injury) **or**<br>• Initial findings of cholestasis (elevated serum ALP) |

| Grade by CTCAE v5.0 | Management Recommendation |
|---|---|
| **Skin Rash** | |
| Grade 1 and 2 | No dose modifications required<br>Topical steroid (eg, hydrocortisone 2.5%) and clindamycin cream BID, as needed, and consider oral antibiotic (eg, doxycycline 100 mg BID) for 2 to 4 weeks |
| Grade ≥ 3 | Suspend dose until resolved to ≤Grade 2 and manage as shown above for Grade 1/2 considering additional oral steroids, then:<br>• If resolved ≤14 days, resume at the same dose level and consider prophylactic management of skin rash<br>• If resolved >14 days or re-occurrence, resume at next lower dose level |
| **QT prolongation** | |
| Grade 1 | • Repeat ECG (triplicates, 2-3 minutes apart)<br>• If QTcF is still on average >450 ms, check electrolytes and replace to maintain K ≥ 4.0 mmol/L, Mg ≥1.8 mg/dL (0.9 mmol/L) and Ca >8.0 mg/dL (2.0 mmol/L) and repeat ECG<br>• No dose modifications required |
| Grade 2 | For first occurrence:<br>• Repeat ECG (triplicates, 2-3 minutes apart)<br>• Check electrolytes and replace to maintain K ≥ 4.0 mmol/L, Mg ≥1.8 mg/dL (0.9 mmol/L) and Ca >8.0 mg/dL (2.0 mmol/L) and repeat ECG<br>• If QTcF is still on average >481 ms, suspend drug until resolved to ≤ Grade 1, and then resume at the same dose level<br>If re-occurrence:<br>- Suspend drug until resolved to ≤ Grade 1 and then resume at the next lower dose level |
| Grade 3 | • Repeat ECG (triplicates, 2-3 minutes apart)<br>• Check electrolytes and replace to maintain K ≥ 4.0 mmol/L, Mg ≥1.8 mg/dL (0.9 mmol/L) and Ca >8.0 mg/dL (2.0 mmol/L) and repeat ECG<br>• If QTcF is still >500 ms and/or >60 ms change from baseline, suspend drug until resolved to ≤Grade 1 and obtain an evaluation by a cardiologist. If study drug can be resumed, it should be at the next lower dose level<br>• If re-occurrence, consider discontinuing the study drug |
| Grade 4 | Discontinue study drug |

| Grade by CTCAE v5.0 | Management Recommendation |
|---|---|
| **Interstitial Lung Disease (ILD) / Pneumonitis** (see also Section 6.4.4.3) | |
| Grade 1 | No dose modifications required, consider follow-up at regular intervals as per institutional standards |
| Grade 2 | Suspend dose until resolved to ≤Grade 1, then:<br>• If resolved ≤14 days, maintain dose level<br>• If resolved >14 days, resume at the next lower dose level<br>If clinical symptoms persist/worsen despite treatment, consider discontinuing study drug |
| Grade 3 and 4 | Discontinue study drug |
| **Corneal ulceration** | |
| Grade ≥ 3 | Discontinue study drug |
| **Other Non-hematologic Toxicities** | |
| Grade 1 and Grade 2 | No dose modifications required, administer supportive therapy as indicated |
| Grade 3 | Suspend dose until resolved to ≤Grade 1 or baseline (≤Grade 2 for toxicities that are manageable by supportive therapy, such as asymptomatic electrolyte changes, dyspepsia, hypertension), then:<br>• If resolved ≤14 days, resume at the same dose level<br>• If resolved >14 days or re-occurrence, resume at next lower dose level |
| Grade 4 | Suspend dose until resolved to ≤ Grade 1 or baseline, then resume at next lower dose level.<br>Discontinue study drug if re-occurrence or occurrence of an irreversible treatment related clinically significant event. |

**Abbreviations:** ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; QD=once daily; QTc=corrected QT interval; QTcF=Fridericia's Correction Formula for corrected QT interval; T-bil=total bilirubin; ULN=upper limit of normal.

## 6.3. Treatment Compliance

The patient will be instructed to comply with the dosage and dosing regimen of study treatment. The Investigator or designated study-site personnel will maintain a log of all study drug dispensed and returned. Compliance to all study drug administration should be documented in the patients' source documents. Additionally, noncompliance can also be considered in the event a patient intentionally takes more study drug than prescribed. In the event a patient is noncompliant with study treatment, discontinuation of the patient may be considered after discussion between the Sponsor and Investigator.

## 6.4. Concomitant Medications and Therapies

### 6.4.1. Prohibited Concomitant Medications

Patients are not permitted to receive any other investigational or anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers, or antineoplastic endocrine

therapy during the study treatment period (with the exception of permitted tumor therapies listed in Section 6.4.4).

Acid-reducing agents may have the potential to reduce TAS3351 plasma concentration and potentially the activity of TAS3351. The use of proton pump inhibitors (PPI) is prohibited for patients receiving TAS3351. For other acid reducing agents (ARAs), see Section 6.4.2.

### 6.4.2. Concomitant Medications and Therapies Requiring Precautions

Drug interaction studies have not been conducted in humans. The following information is based on results from in vitro studies. Caution is advised if these drugs (examples provided in Appendix A) are given concomitantly:

Potential effects of TAS3351 on other drugs:

- **CYP2C8, CYP2C9, and CYP2C19 substrates:** TAS3351 is a potential reversible inhibitor of CYP2C8, CYP2C9, and CYP2C19. Depending on achievable steady-state plasma TAS3351 concentrations, TAS3351 may increase the concentration and activity of CYP2C8, CYP2C9, and CYP2C19 substrates.
- **CYP3A substrates:** TAS3351 has the potential to time-dependently inhibit CYP3A. Depending on achievable steady-state plasma TAS3351 concentrations and doses, TAS3351 may increase the concentration and activity of CYP3A substrates.
- **CYP1A2 substrates:** TAS3351 is a potential inducer of CYP1A2. Depending on achievable steady-state plasma TAS3351 concentrations, TAS3351 may reduce the concentration and activity of CYP1A2 substrates.
- **P-gp and BCRP substrates:** TAS3351 is a potential inhibitor of P-gp and BCRP. Depending on achievable steady-state plasma TAS3351 concentrations and dose, TAS3351 may increase the concentration and activity of P-gp and BCRP substrates.

Potential effects of other drugs on TAS3351:

- **Strong and moderate inhibitors/inducers of CYP3A:** TAS3351 is a potential substrate of CYP3A metabolism. CYP3A inhibitors/inducers (see Appendix A) may increase/reduce the concentration and activity of TAS3351.

Strong or moderate CYP3A inhibitors inducers and medications known to prolong QTc interval or to be arrhythmogenic (such as ondansetron, erythromycin, droperidol; see also: http://crediblemeds.org) should be avoided or substituted with other concomitant therapies while receiving TAS3351, if possible. However, if concomitant use cannot be avoided, patients should be closely monitored for any potential AEs and TAS3351 dose modifications should be performed accordingly as outlined in Section 6.2. The Investigator may also consider a TAS3351 dose reduction while concomitant treatment with a strong or moderate CYP3A inhibitor is being administered (eg, ciprofloxacin for an infection).

Acid-reducing agents (ARAs) may have the potential to reduce TAS3351 plasma concentration and potentially the activity of TAS3351. As mentioned in Section 6.4.1, the use of proton pump inhibitors (PPI) is prohibited for patients receiving TAS3351. Concomitant use of other ARAs should be avoided whenever possible. If concomitant use of ARAs is unavoidable, staggered dosing of histamine H2 receptor antagonists (H2 blockers) (TAS3351

administered at least 2 hours before or at least 12 hours after administration of H2 blockers) or antacids (TAS3351 administered at least 2 hours before or at least 2 hours after antacids) is recommended. Caution is advised with concomitant administration of ARAs with TAS3351.

### 6.4.3. Permitted Concomitant Medications

Local or regional palliative cryotherapy or radiation, such as for bone pain or palliative surgery (non-antineoplastic intent), are permitted (provided the target lesion is not a site of measurable disease and is not indicative of disease progression). If extended field radiation therapy or palliative radiation to a focal site of measurable disease is deemed to be in the best interest of the patient following discussion between the Investigator and the Sponsor, the patient will be censored for the primary analysis of efficacy. Study therapy should be ceased a minimum of 2 days prior to administration of palliative treatment and may be resumed 7 days after the procedure or when the patient has recovered from the side effects of the procedure. Moreover, endocrine therapy for controlled prostate or breast cancer is permitted, if approved by the treating physician. Patients are allowed to receive COVID-19 vaccination while being on study.

### 6.4.4. Supportive Care

Supportive treatment should be provided based on available institutional or local guidelines.

#### 6.4.4.1. Hematologic Support

Hematologic support (blood transfusions, granulocyte colony-stimulating factor [G-CSF], erythropoietin-stimulating agents) may be administered as medically indicated, according to the institutional site standards or American Society of Clinical Oncology (ASCO) guidelines.[23,24,25]

#### 6.4.4.2. Gastrointestinal Toxicities

Prophylactic treatment for diarrhea (such as loperamide) is permitted during the study if clinically indicated according to the institutional or published guidelines.[26]

In the event of diarrhea, antidiarrheal therapy should be initiated as early as possible if not already receiving such therapy (eg loperamide). Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day). Dehydration and any associated electrolyte disturbances should be prevented or corrected at the onset.

For the management of nausea/vomiting, antiemetics may be administered as clinically indicated. Antiemetics which have the potential to prolong QTc, such as 5-HT3 receptor antagonists (eg, ondansetron) should be avoided when possible. Suggested antiemetics for the treatment of nausea include diphenhydramine, prochlorperazine, lorazepam, and/or steroids. If nausea is not controlled by these agents, and if antiemetics such as metoclopromide need to be used, then there should be additional ECG monitoring per Investigator discretion. In addition, dehydration and any associated electrolyte disturbances should be prevented or corrected at onset of symptoms.

#### 6.4.4.3. Interstitial Lung disease (ILD) / Pneumonitis

If new or worsening pulmonary symptoms (eg, dyspnea) occur or radiological abnormalities suggestive of interstitial lung disease is observed, a full diagnostic workup (including high-resolution CT (HRCT), blood and sputum culture, and hematological parameters) should be performed. It is strongly recommended to perform a full diagnostic workup in

order to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered. Consult lung disease specialists as indicated and consider corticosteroid administration.

#### 6.4.4.4. Amylase or Lipase Elevations

If amylase or lipase are >3×ULN, radiological imaging should be performed to evaluate the presence/absence of pancreatitis or other etiologies.

## 6.5. Lifestyle Considerations

### 6.5.1. Dietary

Patients will be prohibited from consuming herbal supplements and/or ingestion of foods and beverages known to be strong inducers or strong inhibitors of CYP3A. Furthermore, the consumption of grapefruit juice, grapefruit hybrids, pomegranates, starfruit, pomelos, Seville oranges, or juice products is prohibited during the study.

### 6.5.2. Sun Protection

A preclinical toxicity study using TAS3351 indicated a potential risk for phototoxicity. For this reason, it is recommended to advise patients to avoid prolonged exposure to natural sunlight, avoid artificial sunlight (eg, suntan bed), wear protective clothing, lip balm, and use broad-spectrum sunscreen with a high sun protection factor (SPF) ≥30 when outdoors.

## 6.6. Contraceptive Guidance

To participate in the study, patients of childbearing potential must adhere to the contraception requirements from the day of study medication initiation, throughout the study, and up to 6 months after the last dose of study treatment.

For WOCBP (for definition see Section 5.1), including female study patients and partners of male patients, highly effective contraception is required during the study, and for 6 months after the last dose of study medication.

Highly effective contraception is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation with an oral, intravaginal or transdermal form
- Progestogen-only hormonal contraception associated with inhibition of ovulation with an oral, injectable, or implantable form
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner with documentation of the success of the vasectomy
- Complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients, unless sterile (vasectomy with post-procedure semen analysis), with partners who are WOCBP should use a male condom in combination with at least one of the effective contraception methods during the study and for 3 months after the last dose of study drug.

Donation of sperm or ova is not allowed during the study and for 6 months after the last dose of TAS3351.

## 6.7. Study Drug Materials and Management

TAS3351 will be supplied by the Sponsor.

Detailed information such as the requirements for accountability and disposal of study drug can be found in the Pharmacy Manual, which will be provided separately.

### 6.7.1. Description of Study Drug

A description of the study drug and the recommended storage condition are provided in Table 11.

**Table 11: Description of TAS3351**

| | |
|---|---|
| Generic name | Not assigned |
| Dosage form | 25, 100, and 200 mg tablets |
| Appearance | Pale yellow to grey solid |
| Formulation | TAS3351 tablets (25, 100, and 200 mg) contain 25, 100, and 200 mg of TAS3351 drug substance free base, respectively. In addition, these tablets contain the following inactive ingredients:<br>Microcrystalline cellulose<br>Lactose monohydrate<br>Croscarmellose sodium<br>Hydroxypropyl methyl cellulose<br>Colloidal silicone dioxide<br>Sodium stearyl fumarate<br>Magnesium stearate<br>HPCM-based color coating |
| Storage condition | Store TAS3351 tablets according to the label. |

### 6.7.2. Packaging and Labeling

TAS3351 will be packaged and labeled according to local laws and regulations.

### 6.7.3. Accountability

The Investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. All study drugs will be stored and disposed of according to the Sponsor's instructions. The dispensing of study drug to the patient and the return of study drug from the patient must be documented. Patients must be instructed to return all original containers, whether they are empty or still containing the study drug.

Refer to the Pharmacy Manual for more details.

# 7. STUDY ASSESSMENTS

## 7.1. Study Assessments and Procedures

The Schedule of Events (Section 1.3) summarizes the frequency and timing of all study assessments applicable to this study.

Descriptions of the study assessments required are presented in Table 12.

**Table 12: Study Assessments**

| Assessment | Details |
|---|---|
| **General Study Assessments** | |
| Written informed consent/consent for study continuation | Date when written informed consent was obtained. |
| Review of inclusion/exclusion criteria | Eligibility must be assessed during the screening period and should be confirmed prior to the first dose of study drug as clinically indicated. See Sections 5.1 and 5.2. |
| Demographics/medical history | Sex, age, race/ethnicity, clinical diagnosis, date of diagnosis, method of diagnosis, prior cancer therapy, and relevant medical history (past and concurrent). |
| Baseline signs and symptoms | Signs and symptoms which occurred after signing of ICF but before administration of first dose of TAS3351. |
| Concomitant medication/concomitant therapy | Medication/therapy with period and the reason of concomitant use (including blood and blood products). Include all medications/therapies administered from the time ICF is signed through 30 days after administration of the last dose of TAS3351 or until the start of new anticancer therapy. |
| Compliance | Drug accountability of investigational drug.<br>See Section 6.3 and Section 6.7.3. |
| **Safety** | |
| Physical examination | Physical examinations at screening include assessments of general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems. Targeted symptom directed physical examinations may be utilized on the basis of clinical observations at subsequent visits. Examination of skin should be performed at each timepoint indicated in the Schedule of Events. |
| AE monitoring | See Section 10. |
| Local and central ECGs | Resting, semi-recumbent 12-lead ECGs; triplicates at baseline, Cycles 1-3, and as clinically indicated (eg, for QT prolongation, see dose modifications in Section 6.2.1.2); RR interval (heart rate), QT interval, QTcF interval and abnormal finding by 12-lead ECG. See Section 7.1.2. |

| Assessment | Details |
|---|---|
| Vital signs, height and body weight | Systolic and diastolic blood pressure, pulse rate, body temperature, height (for body mass index calculations, recorded at baseline only) and body weight. |
| Echocardiography/MUGA | Baseline echocardiography/MUGA (multi-gated acquisition scan) is required. Left ventricular ejection fraction (LVEF) monitoring is needed every 4 cycles during TAS3351 treatment, and as clinically indicated.<br>LVEF can be assessed by ECHO or MUGA; same modality should be used for a patient at screening and after dosing. See Section 7.1.3. |
| Hematology | Red blood cell (RBC) count, hemoglobin, hematocrit, platelets, white blood cell (WBC) count with differential: neutrophils (ANC), lymphocytes, monocytes, eosinophils, basophils. See Section 7.1.4. |
| Serum chemistry | AST, ALT, ALP, total bilirubin, direct bilirubin, albumin, LDH, triglyceride, total cholesterol, creatinine, BUN, Na, K, Cl, Ca (corrected value), Mg, blood glucose, C reactive protein (CRP), lipase, amylase, creatinine clearance (if there is a measured value, use the measured value) or eGFR. See Section 7.1.4.<br><br>For a calculated CrCl value, use the Cockcroft-Gault formula:<br>Male: $\mathrm{CrCl} = \frac{(140 - [\text{insert age in years}]) \times [\text{insert weight in kg}]}{72 \times [\text{insert serum creatinine in mg/dL}]}$<br>Female: $\mathrm{CrCl} = \frac{(140 - [\text{insert age in years}]) \times [\text{insert weight in kg}]}{72 \times [\text{insert serum creatinine in mg/dL}]} \times 0.85$ |
| Coagulation | PT-INR, APTT, and fibrinogen. See Section 7.1.4 . |
| Urinalysis | Urine protein (qualitative), sediment, occult blood by dipstick or laboratory. If urine protein is 2+, add urinary β2-microglobulin and quantitative measurement of proteinuria (24-hour urine collection for protein preferred). See Section 7.1.4. |
| Pregnancy test | For all female patients of childbearing potential:<br>Serum or urine human chorionic gonadotrophin (human chorionic stimulating hormone) test (see the local regulation and/or CTFG recommendations). For screening, serum test required. |
| ECOG performance status | See Oken et al. for details.[27] |
| **Efficacy and other** | |
| Efficacy assessments | Efficacy assessment by tumor imaging. See Section 7.1.1. |
| Survival follow-up | Patient or family should be contacted for survival follow-up until withdrawal of consent, death, or loss to follow-up, until study completion. This should also include further anti-cancer treatments administered. |
| PK blood sampling | See Section 8.1 and Laboratory Manual. |
| Pharmacodynamic biomarker sampling | See Section 11. |

### 7.1.1. Efficacy Assessments

Efficacy assessments (including CT scan/MRI) will be performed by Investigator/local radiologist according to RECIST v1.1 guidelines at the timepoints outlined in the Schedule of Events (Section 1.3).

Radiological assessment must include MRI/CT of the chest, abdomen (and pelvis, if clinically indicated or obtained at baseline) at each time point, as well as assessment of all other known sites of disease. MRI of the brain should be performed if signs or symptoms suggestive of CNS metastases are present. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at screening, throughout the study including the follow-up period. Contrast-enhanced CT scans or MRIs are the preferred methods for tumor assessments. If a contrast agent is contraindicated in a patient, obtain a non-contrast chest CT and enhanced MRI of the abdomen (and pelvis if clinically indicated). A CT should be performed using a ≤5 mm contiguous reconstruction algorithm.

For Part B and C of this study, all radiological imaging will be performed as indicated in the Site Imaging Manual provided by the central imaging core laboratory. Scans will be submitted to a Sponsor designated central imaging core laboratory for response assessment including RECIST v1.1, and/or exploratory analysis (eg, volumetric and viable tumor measurements). Detailed information regarding submission of images to the central imaging core laboratory is found in the Site Imaging Manual.

Note that complete response and partial response (PR) require confirmatory CT or MRI repeat assessment at least 4 weeks after the first detection of response. PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.[28]

Patients who discontinue without documented radiographic disease progression per RECIST 1.1 should continue to undergo tumor assessments/scans according to the Schedule of Events until radiographic PD per RECIST v1.1 is documented, the study is completed, or consent is withdrawn.

### 7.1.2. 12-Lead Electrocardiogram

Electrocardiograms (ECGs) will be collected using a 12-lead tracing. Patients should be in supine position in a rested and calm state for at least 10 minutes before ECG assessment is conducted. If the patient is unable to be in the supine position, the patient should be in most recumbent position as possible. ECGs should be performed on D1 of every cycle and more frequently for patients in Part A1 during the PK lead in period (for PK lead in, see Table 13). For ECGs during Extension, see Table 3.

All ECGs should be performed in triplicate on Day 1 of Cycles 1 to 3 for all patients in Parts A1, A2, B and C. Patients in Part A1 will have additional triplicate ECGs performed during selected time points of the PK Lead-in period. After C3D1, ECGs are not required to be performed in triplicate unless clinically indicated. ECGs should be run consecutively, prior to blood draws or other invasive procedures. An ECG machine with the capacity to calculate standard intervals automatically should be used. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent medical history condition. If there is a clinically significant abnormal ECG finding during the treatment period, this should be recorded on the AE eCRF, according to standard AE collection and reporting processes.

For Parts A2, B, and C, all ECGs will be performed using local ECG machines. Patients in Part A1 will have both local and central ECGs (see Table 13).

For central ECGs in Part A1 (see Schedule of Events; Table 1), the Investigator or delegate will review all ECGs for any on treatment decisions. Once signed, the original ECG tracing will be retained with the patient's source documents. All digital ECG data will be transferred electronically for central analysis of heart rate, PR, R-R, and QT intervals by an external cardiologist.

### 7.1.3. Cardiac Function Evaluation

The commonly available imaging modalities (ECHO 2D, MUGA) will be used for the evaluation of LVEF evolvement during therapy with TAS3351 to detect presence of cardiotoxicity defined by the European Society of Cardiology as a decrease in LVEF of >10% points to a value below 50%.[29] Imaging will be performed by the cardiologist or qualified delegate per the Schedule of Activities (Table 1). Additional on-study evaluation may be performed as needed based on physician judgment and/or symptoms or signs of LV dysfunction. Each evaluation will encompass:

- LVEF assessment using MUGA, conventional 2DE biplane Simpson method or 3DE, if available
- Clinical symptoms of Congestive Heart Failure (CHF) will be noted and graded according to NYHA

Signs of CHF will be detected by routine clinical examination, including auscultation to detect S3 gallop, tachycardia, or both.

### 7.1.4. Laboratory Assessments

The laboratory must provide normal reference ranges for all hematology, chemistry, coagulation tests, and urinalysis/urine parameters shown in Table 12. Laboratory results for hematology, serum chemistry, coagulation and urine assessments must be reviewed for clinically significant events. Any clinically significant events must be followed and reported as required by the protocol (see Section 10). Laboratory assessment prior to the first day of dosing may be done up to 72 hours prior to dosing.

### 7.1.5. Ophthalmological Assessments

Ophthalmological examination will be performed by an ophthalmologist or qualified person at the time points described in Section 1.3.

Ophthalmologic exam should be performed for each eye and should encompass:

- Best corrected visual acuity
- External ocular examination
- Routine slit lamp examinations, including the anterior and posterior chambers (Fluorescein or rose Bengal or other dyes used to evaluate the ocular surface can be used according to institutional guidelines and local clinical practice)

Any clinically significant findings must be reported as an AE. The type of examination used to identify any potential ocular adverse event AEs will be captured in the electronic case report form (eCRF).

### 7.1.6. PRO Measurements

For patients enrolled in Part C, patients' health-related quality of life, symptoms, functioning, and general well-being will be captured using PRO measures and collected according to the Schedule of Events (Section 1.3).

EORTC-QLQ-C30:

The EORTC-QLQ-C30 consists of 30 core items, with the 4-point Likert scales ranging from 1: "Not at all" to 4: "Very much". There are 2 items for global health status/quality of life. Functional scales include physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), and social functioning (2 items). Symptom scales/items include fatigue (3 items), nausea and vomiting (2 items), pain (2 items), dyspnea; insomnia; appetite loss; constipation; diarrhea; and financial impact (1 item each).[30,31]

EQ-5D-5L:

The EuroQol-5D (EQ-5D) is a standardized measure of the patient's health-related quality of life. The 5-level version of the EQ-5D (EQ-5D-5L) consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement. See https://euroqol.org/eq-5d-instruments/.

### 7.1.7. COVID-19 Pandemic Considerations

- During the COVID-19 pandemic, the Sponsor will perform a risk assessment of the study on an ongoing basis to ensure:
- The protection of patient safety, particularly if scheduled visits to the sites are postponed
- The uninterrupted supply of drugs to patients for whom the drugs continue to benefit, while assuring patient safety (even if they are forced to remain at home)
- The collection of key safety and efficacy data even if patients cannot keep their scheduled visits to the site due to the exceptional circumstances in relation to COVID-19

The following considerations may be applied in accordance with guidelines from regulatory authorities[17,18] and individual site policies:

- If a patient is unable to sign an informed consent for the study in person, the consent may be obtained electronically or remotely via a phone call or video conference.
- If a patient is unable to attend a scheduled on-site visit and/or complete any protocol-required study assessments, the Sponsor should be contacted. Clinical assessments should be performed remotely via a phone call or video conference, assuring safety assessment and collection of new/follow-up AEs.

- To ensure compliance with the protocol-required laboratory tests and assessments, the possibility for these tests to be performed at an external qualified laboratory or facility should be evaluated. The results of any tests or assessments performed by an external laboratory or facility must be communicated to the Investigator and documented in the patient's source files. If it is not possible to have assessments performed at an external facility, the patient may be evaluated for safety via a phone call or video call, assuring the collection and follow-up of AEs are documented in the patient's source file.
- Tumor assessments should be performed (as much as the circumstances allow) as specified in the protocol. If a patient is unable to reach the site, an external qualified imaging facility can be used. Every effort should be made to ensure that the same imaging modality and image acquisition parameters (eg, anatomic coverage, imaging sequences, etc.) are used consistently for each patient throughout the study.
- The results (including the images obtained from all radiographic procedures) should be sent to the Investigator. The imaging facility used, the time points, and the Investigator's review of the images should be documented in the patient's source files and the eCRF.
- If a patient becomes infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and/or develops any symptoms suggesting COVID-19 infection, Investigators must follow local guidelines for the management of patients with COVID-19. Symptomatic COVID-19 cases should be reported as AEs or SAEs; however, asymptomatic COVID-19 cases do not have to be reported. The Sponsor needs to be contacted to discuss the continuation of the study treatment. However, the Investigator has the right to decide the continuation of treatment in COVID-19 infected patients.
- Considering the rarity of the disease (even after the COVID-19 pandemic settlement), the remote management options described above may apply to patients who are unable to frequently visit the sites for any other reasons (eg, extremely long distance to the sites) after discussion with the Sponsor.
- All decisions and deviations due to COVID-19 must be documented in the patient's source files and the eCRF.

# 8. PHARMACOKINETICS

## 8.1. Sample Collection

Blood samples for PK analysis and ECG sampling will be collected at specific time points listed in Table 13 (Table 14 in case BID dosing will be explored) and used to evaluate PK of TAS3351 and its active metabolite (TAS-05-14317). ECGs should also be obtained prior to on-site TAS3351 administration. When a 12-lead ECG is obtained at the same timepoint as a PK blood draw, the 12-lead ECG should be obtained first.

Detailed information about collection procedures including blood sampling, collection, processing, and sample shipment will be provided in a separate Laboratory Manual.

**Table 13: Schedule for PK and ECG Sampling (QD Dosing)**

| **Phase 1 Dose Escalation (Part A1)** | | | |
|---|---|---|---|
| **Day of Study**[a] | **Collection time relative to TAS3351 administration** (time window[b]) | **PK sample** | **ECG**[c] |
| PK Lead-in, Day -3 | Pre-dose (up to -30 minutes) | | X |
| | 0.5 hours (±10 minutes) | X | |
| | 1 hour (±10 minutes) | X | X |
| | 2 hours (±15 minutes) | X | X |
| | 3 hours (±20 minutes) | X | |
| | 4 hours (±25 minutes) | X | X |
| | 6 hours (±35 minutes) | X | |
| | 8 hours (±45 minutes[d]) | X | X |
| | 24 hours (±2 hours) | X | X |
| | 48 hours (±2 hours) | X | |
| | 72 hours (± 2 hours[e]) | X | X |
| Cycle 1 Day 15 | Pre-dose (up to -30 minutes) | X | X |
| | 0.5 hours (±10 minutes) | X | |
| | 1 hour (±10 minutes) | X | X |
| | 2 hours (±15 minutes) | X | X |
| | 3 hours (±20 minutes) | X | |
| | 4 hours (±25 minutes) | X | X |
| | 6 hours (±35 minutes) | X | |
| | 8 hours (±45 minutes[d]) | X | X |
| | 24 hours (±2 hours[e]) | X | X |
| Cycle 2 Day 1 | Pre-dose (up to -30 minutes) | X | X (Local) |
| Cycle 3 Day 1 | Pre-dose (up to -30 minutes) | X | X (Local) |

| Phase 1 "Backfill" (Part A2), Dose Expansion (Part B), and Phase 2 (Part C) | | | |
|---|---|---|---|
| **Day of Study**[a] | **Collection time relative to TAS3351 administration** (time window[b]) | **PK sample** | **ECG**[c] |
| Cycle 1 Day 1 | Pre-dose (up to -30 minutes) | X | X (Local) |
| | 2 hours (±1 hour) | X | X (Local) |
| Cycle 2 Day 1 | Pre-dose (up to -30 minutes) | X | X (Local) |
| | 2 hours (±1 hour) | X | X (Local) |
| Cycle 3 Day 1 | Pre-dose (up to -30 minutes) | X | X (Local) |

[a] For patients with TAS3351 dose interruptions, PK days might be postponed or waived upon discussion and written approval by the Sponsor. Additional optional PK samples may be collected if any safety concerns are identified. If no longer needed for PK evaluation, collection time points might be skipped upon written notification by the Sponsor.
[b] Time window given for guidance; collection outside these windows will not be considered a protocol deviation as long as the exact time of dosing and sampling is documented.
[c] ECG must be collected prior to PK sampling. All ECGs through C3 should be performed in triplicate. Central ECGs will be performed for all timepoints unless otherwise specified.
[d] This PK sample is mandatory for Dose Level 1. Following PK analysis for Dose Level 1, PK sampling at this timepoint at subsequent dose levels may be waived by the Sponsor, with this decision to be communicated to sites.
[e] This PK sample must be collected prior to TAS3351 administration on this day. The ECG should be performed within 30 min prior to C1D1 dosing.

**Table 14: Schedule for PK and ECG Sampling (BID Dosing)**

| Phase 1 Dose Escalation (Part A1) | | | |
|---|---|---|---|
| **Day of Study**[a] | **Collection time relative to TAS3351 administration** (time window[b]) | **PK sample** | **ECG**[c] |
| Cycle 1 Day 1 | Pre-dose (up to -30 minutes) | | X |
| | 0.5 hours (±10 minutes) | X | |
| | 1 hour (±10 minutes) | X | X |
| | 2 hours (±15 minutes) | X | X |
| | 3 hours (±20 minutes) | X | |
| | 4 hours (±25 minutes) | X | X |
| | 6 hours (±35 minutes[d]) | X | |
| | 8 hours (±45 minutes[e]) | X | X |
| | 24 hours (±2 hours[f]) | X | |
| Cycle 1 Day 15 | Pre-dose (up to -30 minutes) | X | X |
| | 0.5 hours (±10 minutes) | X | |
| | 1 hour (±10 minutes) | X | X |
| | 2 hours (±15 minutes) | X | X |
| | 3 hours (±20 minutes) | X | |

| | | | |
|---|---|---|---|
| **Phase 1 Dose Escalation (Part A1)** | | | |
| | 4 hours (±25 minutes) | X | X |
| | 6 hours (±35 minutes[d]) | X | |
| | 8 hours (±45 minutes[e]) | X | X |
| | 24 hours (±2 hours[f]) | X | |
| Cycle 2 Day 1 | Pre-dose (up to -30 minutes) | X | X (Local) |
| Cycle 3 Day 1 | Pre-dose (up to -30 minutes) | X | X (Local) |

[a] For patients with TAS3351 dose interruptions, PK days might be postponed or waived upon discussion and written approval by the Sponsor. Additional optional PK samples may be collected if any safety concerns are identified. If no longer needed for PK evaluation, collection time points might be skipped upon written notification by the Sponsor.
[b] Time window given for guidance; collection outside these windows will not be considered a protocol deviation as long as the exact time of dosing and sampling is documented.
[c] ECG must be collected prior to PK sampling. All ECGs through C3 should be performed in triplicate. Central ECGs will be performed for all timepoints unless otherwise specified.
[d] Following PK analysis for Dose Level 1 (QD dosing), PK sampling at this timepoint may be waived by the Sponsor, with this communication to be communicated to sites.
[e] This PK sample must be collected prior to administration of the second BID dose.
[f] This PK sample must be collected prior to administration of the first BID dose on next study day.
**Note:** For patients enrolled in Phase 1 "Backfill" cohorts (Part A2), Dose Expansion (Part B), or Phase 2 (Part C), PK and ECG sample collection will follow the same schedule outlined in Table 13.

## 8.2. Drug Concentration Measurements

PK samples will be analyzed by liquid chromatography/tandem mass spectrometry (LC-MS/MS) to determine plasma concentrations of TAS3351 and its active metabolite (TAS-05-14317) using validated bioanalytical methods. The detailed analytical plans will be described in a bioanalytical study protocol.

## 8.3. Pharmacokinetics Analysis

Plasma concentration data by time and study day will be summarized descriptively.

### 8.3.1. Pharmacokinetic Parameters

PK analyses for TAS3351 and its active metabolite (TAS-05-14317) in plasma following administration of TAS3351 in Part A1 on PK Lead-in (QD dosing) or Cycle 1 Day 1 (BID dosing) and Cycle 1 Day 15 (QD dosing and BID dosing) will be included in the calculation of the parameters listed below, whenever possible, according to the noncompartmental method.

- $C_{max}$, $T_{max}$, $AUC_n$, $AUC_{last}$, and $T_{1/2}$

The following PK parameters will be calculated only for PK Lead-in:

- $AUC_{inf}$, CL/F (only TAS3351), Vz/F (only TAS3351), and MRT (only TAS3351)

The following items will be calculated using PK parameters.

- Accumulation ratio and metabolic ratio

Other PK parameters or items not listed above may be calculated if deemed appropriate.

### 8.3.2. Dose-proportionality

Dose-proportionality of PK parameters will be evaluated using statistical method in Part A1.

### 8.3.3. Population PK Modeling and Exposure-response Analysis

A population PK analysis may be conducted as appropriate. In case such analysis is conducted, the concentration data obtained from Part A1, Part A2, Part B, and Part C of the study will be used to develop a Population PK model. Effects of intrinsic and/or extrinsic factors (eg, subject demographics, clinical laboratory values, disease characteristics) on PK of TAS3351 and TAS-05-14317 will be exploratorily evaluated by the population PK analysis as appropriate. PK data of TAS3351 and TAS-05-14317 obtained in other studies may be also combined with data from this study, if available. Individual exposures such as $C_{max}$, $C_{min}$, and AUC will be estimated by the Population PK analysis and used for the exploratory exposure-response analysis of safety and efficacy. Detailed procedures of Population PK and exposure-response analyses will be described in a separate statistical analysis plan (SAP), and the analysis results will be reported in the main CSR or a separate PK study report.

## 8.4. Metabolite Profiling

Exploratory metabolite profiling will be performed using plasma samples collected in this clinical study. The concentration of major metabolites may be measured as appropriate.

# 9. EFFICACY EVALUATIONS

## 9.1. Efficacy Criteria

Efficacy parameters will be evaluated by the investigator/local radiologist based on tumor imaging (including CT/MRI) according to RECIST v1.1 guidelines.[28] Planned time points for all efficacy assessments are provided in the Schedule of Events (Table 1 and Table 2).

Primary efficacy evaluation of TAS3351 will be based on independent central review (ICR) for patients enrolled in Part B and C of this study. In addition, efficacy will be assessed by the investigator/local radiologist for all patients.

Determination of disease response for clinical management and discontinuation of study treatment of patients will be assessed at the clinical sites per RECIST v1.1. If the investigator determines that a patient has developed clinical disease progression manifested by symptomatic deterioration but not supported by radiographic evidence of progression, the patient may stop treatment. Symptoms of clinical disease progression must be documented in the patient's source documents and must be reported as AEs. Every effort should be made to document objective radiographic disease progression even after discontinuation of treatment.

For additional guidance, refer to RECIST v1.1 specification for standard anatomical radiological imaging.[28]

See Section 7.1.1 for additional efficacy assessment details.

## 9.2. Efficacy Endpoints

Efficacy endpoints based on radiographic imaging will be assessed per RECIST 1.1; endpoint definitions are summarized in Table 15.

**Table 15: Efficacy Endpoint Definitions**

| Endpoint | Definition |
|---|---|
| ORR | Proportion of patients experiencing a best overall response of PR or CR (per RECIST v1.1). Intracranial ORR be assessed based on ORR of CNS lesions only |
| DoR | Time from the first documentation of response to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. Intracranial DoR be assessed based on DoR of CNS lesions only |
| DCR | Percentage of patients who have achieved a CR, PR, or stable disease (SD) |
| PFS | Time from date of first dose to the date of documentation of disease progression, or date of death, whichever occurs first |
| OS | Measured from the date of first dose until the date of death due to any cause |

**Abbreviations:** CNS=central nerve system; CR=complete response; DCR=disease control rate; DoR=duration of response; ICR=independent central review; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease

# 10. SAFETY EVALUATIONS

## 10.1. Adverse Events

### 10.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study patient and does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Disease progression is not an acceptable AE term. In cases of nonfatal disease progression, the relevant signs, symptoms, and complications that led to the diagnosis of clinical disease progression should be reported as an AE. If the relevant signs, symptoms, and complications meet any of the serious criteria, they should be reported as SAEs. In both cases it should be indicated whether the signs, symptoms, and complications are related to clinical disease progression. Radiological progression without relevant signs, symptoms, and complications will not be reported as an AE or SAE.

### 10.1.2. Events Meeting the Adverse Event Definition

- Laboratory test results outside the normal range (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, diagnostic radiological scans, or vital signs measurements), including any that worsen in NCI CTCAE v5.0 grade from baseline, which are considered clinically significant in the medical and scientific judgment of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition resulting in an increase in NCI CTCAE grade.
- Condition detected or diagnosed that is new in onset or increased in NCI CTCAE v5.0 grade from the baseline condition, except clinically nonsignificant changes in laboratory test results in the opinion of the Investigator.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
  - Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE.

### 10.1.3. Time Period for Collection of AE and SAE Information

All AEs will be collected from the time the ICF is signed through 30 days after the last dose of study therapy (Safety Follow-up) or until the start of new antitumor therapy, whichever is earlier (see Section 10.2 regarding the assessment of AEs associated with laboratory results.)

The collection of AEs/SAEs after the 30-day follow-up period has ended has been described in Section 5.5.

### 10.1.4. Reporting of Adverse Events

#### 10.1.4.1. Terms of Reported Adverse Events

All AEs will be documented in the eCRF according to the eCRF Completion Guidelines. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study drug, and outcome of the event.

When a diagnosis for the reported signs or symptoms is known, the Investigator should report the diagnosis (not the symptoms) as the AE.

#### 10.1.4.2. Severity of Adverse Events

The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be used to grade the severity of AEs.

#### 10.1.4.3. Causal Relationship with Study Drug

The causal relationship between an AE and the study drug will be assessed using the following 2-point scale, considering the patient's condition, medical history, concomitant medications, and the temporal relationship between study drug administration and onset of the AE.

1. An AE is considered to be "**Related**" if the event follows a reasonable temporal sequence from administration of study drug and there is a reasonable possibility that at least one of the following conditions is true:
    - A positive dechallenge: This means that the event improves or resolves after the drug is stopped (temporarily or permanently).
    - A positive rechallenge: This means that the event reappears after the drug is restarted.
    - The event cannot be reasonably explained by the patient's clinical state and/or other therapies administered.
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson syndrome).
2. An AE is considered to be "**Not related**" if at least one of the following conditions is true:
    - The event occurred prior to study drug administration.
    - There is no reasonable possibility that the study drug caused the event. ("No reasonable possibility" means there is no evidence to suggest a causal relationship between the study drug and the AE.)
    - The event does not follow a reasonable temporal sequence from administration of study drug and could have been produced by a documented pre-existing condition, concomitant medication, or patient's clinical state.

#### 10.1.4.4. Outcome of Adverse Events

Record the outcome of AEs as follows:

1. Recovered/resolved
2. Recovering/resolving
3. Not recovered/not resolved
4. Recovered/resolved with sequelae
5. Fatal

#### 10.1.4.5. Follow-up of Adverse Events

Any ongoing AEs should be followed until the earliest occurrence of one of the following:

- AE has resolved
- Completion of Safety Follow-up visit
- Start of new antitumor therapy
- Patient's refusal of follow-up
- Death
- Other (eg, transfer to another hospital)

## 10.2. Laboratory Assessments

See Table 12 for the list of clinical laboratory assessments to be performed and the Schedule of Events (Table 1 and Table 2) for timing and frequency.

All laboratory assessments will be performed locally. The laboratory must provide normal reference ranges for hematology, chemistry, urine, and coagulation tests. If justified (eg, deterioration of the patient's health conditions and/or distance from the clinical site) and permitted by the country and institution, laboratory tests performed by external laboratories may be used for the study. However, laboratory reference ranges and accreditation are required.

### 10.2.1. Reporting and Evaluation of Laboratory Test Results

All laboratory test results (internal or external) except for those at screening (which are considered baseline) must be reviewed for clinical significance by the Investigator. Laboratory test results that are outside the normal range (hematology, clinical chemistry, or urinalysis) that worsen in NCI CTCAE v5.0 grade from baseline and are considered clinically significant in the medical and scientific judgment of the Investigator should be reported as AEs. A new laboratory abnormality that has a clinical impact on a patient (eg, resulting in study drug dose reduction, treatment delay, treatment discontinuation, and/or requirement of intervention) should be reported as an AE, unless it is considered part of clinical manifestations of a clinical diagnosis that is already reported as an AE.

All laboratory values that are outside the normal range are to be evaluated for their clinical impact before exposing the patient to the next dose of TAS3351.

### 10.2.2. Repeat Testing

Evaluation of any clinically significant laboratory test will be repeated, as clinically indicated, until the value returns to the baseline level or clinically stabilizes, or until another treatment is given.

## 10.3. Serious Adverse Events

### 10.3.1. Definitions of Serious Adverse Events

An adverse event that results in one of the following is a serious adverse event (SAE):

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization to treat the AE

  The following are not considered hospitalizations for the purposes of assessing seriousness (however, one of the other serious criteria may apply):

  – Emergency room visits <24 hours

  – Hospitalizations for preplanned procedures

  – Hospitalization for study-related treatment and procedures
- Results in persistent or significant disability/incapacity, where disability is defined as a substantial disruption of a person’s ability to conduct normal life functions, either reported or defined as per clinical judgment.
- Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).
- Is any other important medical event that based upon appropriate medical judgement may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above (eg, may not result in death, be life-threatening, or require hospitalization). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

### 10.3.2. Reporting of Serious Adverse Events (within 24 hours)

All SAEs occurring from the time the ICF is signed through the Safety Follow-up period (30 days after the last dose of study treatment or discontinuation of the Safety Follow-up period, whichever is earlier) must be reported to Sponsor’s Pharmacovigilance group or its designee immediately and should not exceed 24 hours from the time the Investigator first becomes aware of the SAE.

Any untoward medical event that occurs after the Safety Follow-up Period is not considered an SAE, unless the Investigator considerers that the medical condition is related to the investigational drug.

Comprehensive information available at the time of initial reporting (including narrative description, medical history, and concomitant medications) needs to be provided with careful consideration regarding causality and serious criterion. The SAE reporting process and contact information are provided in supplemental guidelines.

After the initial SAE notification to the Sponsor's Pharmacovigilance group or its designee, all follow-up SAE information will be submitted each time they become available (for example, clinical diagnosis, outcome, causality assessment, and results of specific investigations) on a follow-up SAE form. The Investigator also must submit further information if it is required by the Sponsor or the director of the study site or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Every SAE should be followed until it has resolved, stabilized, or returned to baseline.

### 10.3.3. Reporting of Deaths (within 24 hours)

All deaths from the time the ICF is signed through the Safety Follow-up period (30 days after the last dose of study treatment or discontinuation, whichever is earlier) need to be recorded on the death page of the eCRF. Deaths, including death due to disease progression, if related to study drug, occurring from the time the ICF is signed through the Safety Follow-up period (30 days after the last dose of study treatment or discontinuation, whichever is earlier) must be reported immediately as SAEs and should not exceed 24 hours from the time the Investigator first becomes aware of the death. The primary cause of the death should be reported as the SAE term, if available, and entered on the death page of the eCRF.

When reporting a death, the Investigator will be required to identify which of the following best describes the category of death:

- Toxicity caused by adverse event
- Disease progression
- Clinical disease progression
- Other causes

Death is not an acceptable SAE term; death is an outcome of an SAE. Only if cause of death is not immediately known can death be reported as the SAE term. In those instances, the cause of death must be reported once obtained upon follow-up.

### 10.3.4. Follow-up of Serious Adverse Events

Any ongoing SAEs should be followed until the earliest occurrence of one of the following:

- SAE has resolved
- SAE has stabilized. An SAE can only be considered "stabilized" if the physical or laboratory AE being followed/assessed has remained constant (is not worsening) based on the Investigator's assessment for a minimum of 30 days post study drug discontinuation.
- Start of new antitumor therapy
- Death

- Patient's refusal of follow-up

## 10.4. Other Safety Information

### 10.4.1. Pregnancy

If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information in a female patient (or, with consent, for the female partner of a male patient while on study and during contraceptive period after last administration of the study drug) should be reported within 24 hours from the time the investigator first becomes aware of a pregnancy or its outcome. This should be performed by completing a Pregnancy Form and e-mailing it to Sponsor's Pharmacovigilance department or designee.

New and/or corrected information regarding the pregnancy obtained after submitting the initial Pregnancy Form must be submitted an updated Pregnancy Form to the Sponsor's Pharmacovigilance department or designee. Pregnancies must be followed to outcome by the investigator, even after study completion.

If the outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, it should be reported as an SAE to the Sponsor's Pharmacovigilance department or designee. Live births will be followed up by the investigator up to one month or per local regulations/practice. Any information that may be associated with the study drug should be reported even after study completion.

### 10.4.2. Overdose

An overdose for this clinical study is defined as taking an intentional or unintentional dose of TAS3351 beyond the recommended dose for 1 day or beyond the recommended total dose in each cycle.

An overdose of TAS3351 must be recorded on the SAE form and/or eCRF (or other specified report form) and reported to the Sponsor's Pharmacovigilance department or designee **as soon as possible** from the time the Investigator first becomes aware of the overdose, whether or not the patient developed an AE (even if not fulfilling a seriousness criteria).

An accidental or intentional overdose of concomitant medication should only be reported if it is associated with an (S)AE.

There is no known antidote available in case of overdose. Overdose should be managed with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

## 10.5. Communication of New Information Affecting the Conduct of the Study

The Sponsor will notify investigators within 7 days of receipt of fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) and within 15 days of receipt of other SUSARs, or per local requirements. Upon knowledge of serious adverse events which could affect patient safety, communication will be sent by the Sponsor to all investigators.

When new information becomes available that may adversely affect the safety of patients or the conduct of the study, including serious adverse events judged to have an impact on patient safety, the Sponsor will inform all investigators involved in the clinical study and IRBs/IECs

of such information, and when needed, will amend the protocol, and update the investigator brochure and/or the informed consent.

The investigators should immediately inform patients whenever new information becomes available that may be relevant to the patient's consent or may influence the patient's willingness to continue participation in the study. The communication should be documented, and it should be confirmed whether the patient is willing to remain in the study.

If the informed consent form is revised, it must be re-approved by the IRB/IEC. The investigator should obtain written informed consent to continue participation with the revised written information even if patients were already informed of the relevant information.

# 11. ANALYSES OF BIOMARKERS

The objectives related to evaluation of biomarkers are presented in Section 3. Biomarkers may be explored to identify patients who will be most likely to respond positively or negatively to TAS3351. The pharmacodynamic evidence and biological impact of TAS3351 by characterization of changes in level of gene (DNA or RNA) or protein expression of downstream effectors of EGFR and related markers may be used to further investigate TAS3351.

## 11.1. Biomarker Sample Collection

Collection of biomarker samples will be performed at the time points shown in the Schedule of Events (Table 1 and Table 2). Any tumor tissue provided for pre-screening and confirmation of C797S *EGFR*mt status must have been collected after progression of the most recent systemic EGFR TKI treatment in a quantity sufficient for analysis. Formalin-fixed paraffin-embedded (FFPE) blocks or unstained slides of tumor tissue must be collected prior to enrollment and are to be sent to the Sponsor-designated central laboratory along with a copy of the corresponding pathology / molecular report. Detailed information about collection procedures for biomarkers including blood sampling, collection, processing, and sample shipment will be described in a separate Laboratory Manual. (Tumor tissue collection is optional for Part A1).

## 11.2. Biomarkers for Patient Eligibility

In order to meet the eligibility criteria of this study, patients must have documented evidence of *EGFR*mt status as determined by a CLIA certified laboratory (US), locally certified laboratory (outside of the US), or the study central laboratory based on tumor tissue or plasma cfDNA. For pre-screening, tumor tissue or cfDNA from blood samples are acceptable for *EGFR*mt status testing at the study central laboratory.

For central lab analysis of *EGFR*mt status, submission of both tumor tissue and blood for cfDNA will be mandatory for patients enrolled based on local results in Parts A2, B, and C. For patients in Parts A2, B, and C who are prescreened based on blood cfDNA results, tumor tissue must also be submitted for central lab analysis. Tumor tissue collection is optional for Part A1. If during pre-screening an already sufficient amount of tumor tissue (eg, tumor tissue block, see also Lab Manual) was provided, no additional tumor tissue submission will be required during screening. The central testing of *EGFR*mt status post dosing will be conducted with the intent to have confirmation of the patient's C797S *EGFR*mt status (either blood or tissue) by the study central laboratory in temporal proximity to the enrollment of the patient rather than at the end of the study ("early confirmation of *EGFR*mt status").

## 11.3. Exploratory Biomarkers

Tumor and blood samples will be collected and may be analyzed for exploratory biomarkers to assess potential associations with disease activity, effects of the study drug, and clinical outcomes. This may include, but is not limited to, changes in pharmacodynamic biomarkers in tumor samples (such as EGFR/pEGFR expression if optional baseline and on-treatment biopsies are available), molecular profiling to investigate and better understand the tumor's response to TAS3351, and/or development of tissue-based diagnostic tests. Also, cfDNA extracted from blood samples collected before and during study treatment may be assessed for a range of oncology biomarkers (eg, change of genomic variants following TAS3351 treatment, co-occurring genomic alterations). Patients will be also asked to consent for the

use of these samples to further investigate the relationship between drug response and/or disease progression and blood-borne biomarkers, and to develop blood-based diagnostic tests.

## 11.4. Sample Storage and Disposal

All samples and associated results will be coded prior to being shipped from the site for analysis or storage to ensure confidentiality. After sample processing, samples (including but not limited to slides or DNA/RNA extracted) may be stored for a maximum of 15 years for the associated exploratory analysis with this study and indication following the completion of the study at Sponsor-designated central laboratories after which time they will be destroyed.

## 11.5. Analytical Procedures

Analysis will be conducted using adequately validated assays at Sponsor-designated laboratory(ies). The detailed analytical procedures will be described in the SOP at the assay laboratory(ies).

# 12. STATISTICAL CONSIDERATIONS

The statistical analysis methods will be documented in detail in the statistical analysis plan (SAP). The SAP will be finalized prior to database lock.

## 12.1. Timing of Analyses

The primary analyses for Phase 1 Dose Escalation (Part A) will be performed continuously until RP2D is identified.

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

The primary analysis of the Phase 2 part (Part C) will be conducted when the majority of patients responding to TAS3351 have been observed for at least 6 months from their first onset of response.

## 12.2. Statistical Hypothesis

No formal statistical hypothesis.

## 12.3. Estimation of Sample Size

**Part A:**

**Part A1**: Phase 1 Dose Escalation

There will be up to 40 evaluable patients enrolled using the BOIN design, [redacted]. Table 4 provides the dose-finding decisions given the numbers of patients treated at the current dose level, and the observed numbers of patients experiencing toxicity. A minimum of 3 patients at each dose level is required.

**Part A2:** Backfill patients

Approximately 20 patients will be added for "backfill" cohorts as needed in the Phase 1 Dose Escalation. The additional information from these "backfill" 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%; see also Section 2.1.1)[6,7,8,9] at 2-sided significance level of 10%.

**Part C**: Phase 2

Approximately 100 patients will be enrolled. Sample size considerations were based on estimating the proportion of responders with certain precision. The 95% exact CI for ORR would exclude the current standard of care ORR of 25%[6,7,8,9] if the observed ORR is 35% or higher. If there are 35 confirmed responses, a sample size of 100 patients would allow to exclude the current standard of care ORR of 25% (95% CI: 25.7%, 45.2%) at 2-sided significance level of 5%. See Table 16.

**Table 16: ORR 95%CI for Sample Size of 100 Patients**

| Observed ORR | Exact 95% CI |
|---|---|
| 35% | (25.7%, 45.2%) |
| 40% | (30.3%, 50.3%) |
| 45% | (35.0%, 55.3%) |

## 12.4. Planned Interim Analyses

No interim analysis is planned.

Unplanned interim analyses may be performed if required for regulatory purposes or at the Sponsor's discretion.

## 12.5. Analysis Populations

The analysis populations in the study are defined in Table 17.

**Table 17: Definitions of Analysis Populations**

| Analysis Population | Definition |
|---|---|
| All Consenting Population | All patients who signed the 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. |
| 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 data point for analyses. |

**Abbreviations:** DLT=dose-limiting toxicity; ECG=electrocardiogram; PK=pharmacokinetic

## 12.6. Criteria for Handling of Patient Data

The criteria for handling patient data will be provided in the SAP.

## 12.7. Statistical Analyses

### 12.7.1. Demographic and Baseline Characteristics

The number of patients in each population and the reasons for exclusion will be summarized. In addition, patients who discontinue study treatment will also be summarized, along with the reasons for study discontinuation.

Patient demographics, baseline and disease characteristics will be summarized as appropriate.

### 12.7.2. Study Drug Administration

The following data will be summarized descriptively:

- Administration status
- The total dose, total duration of administration, and the number of administration cycles
- Status of administration completion
- The presence or absence of study discontinuation and reasons for study discontinuation
- Dose intensity. Actual dose intensity and relative dose intensity in each patient will be calculated, and descriptive statistics will be presented

### 12.7.3. Efficacy Analyses

#### 12.7.3.1. Primary Endpoint Analyses

**Part A:** Phase 1 Dose Escalation

Not applicable.

**Parts B and C:** Phase 1 Dose Expansion and Phase 2

ORR per RECIST v1.1 by ICR will be summarized descriptively. ORR will be estimated and the 2-sided 95% confidence interval (CI) will be calculated using the Clopper–Pearson method.

#### 12.7.3.2. Secondary Endpoint Analyses

**Parts A:** Phase 1 Dose Escalation

ORR, DCR, and DOR per RECIST v1.1 by Investigator will be summarized descriptively. ORR and DCR will be calculated and the 2-sided 95% CI will be estimated using the Clopper–Pearson method. For time to event endpoint, DOR, 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.

**Parts B and C:** Phase 1 Expansion and Phase 2

A key secondary endpoint is DOR per RECIST v1.1 by ICR and will be summarized descriptively. Further secondary endpoints include ORR, DCR, and PFS per RECIST v1.1 by Investigator assessment and intracranial ORR and DOR by ICR and Investigator assessment.

ORR and DCR will be calculated and the 2-sided 95% CI will be estimated using the Clopper–Pearson method.

For time to event endpoints, including DORs and PFS, 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. These endpoints will also be summarized based on Investigator assessment.

OS will be summarized descriptively as a time to event endpoint in the same way as PFS.

### 12.7.4. Safety Analyses

#### 12.7.4.1. Primary Endpoint Part A1 Dose Escalation

During the Dose Escalation part of the trial, the rates of DLT will be controlled by the BOIN algorithms. Incidence of DLT will be summarized by dose level and the analysis will be based on the DLT-evaluable Population. The RP2D will be based on the accumulated DLT data, taking the totality of data into account.

Dose escalation will follow a BOIN design 28,13 to find the MTD. The decision to escalate or de-escalate the dose of TAS3351 will be based on the cumulative DLT rate at the current dose level and the predetermined DLT rate threshold for dose escalation/de-escalation boundaries as defined by the BOIN model.

The target DLT rate for the MTD is set to $\Phi = 0.30$ with the assumptions that $\Phi 1 = 0.6\Phi$ is the highest sub-therapeutic DLT rate and $\Phi 2 = 1.4\Phi$ is the lowest DLT rate that has excessive toxicity. Under these assumptions, the thresholds that minimize the decision error at end of each cohort are $\lambda 1 = 0.236$ and $\lambda 2 = 0.359.28$

As shown below, the BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

1. If the observed DLT rate at the current dose level is $\leq 0.236$, escalate.
2. If the observed DLT rate at the current dose level is $\geq 0.359$, de-escalate.
3. Otherwise, stay at the same dose level.

#### 12.7.4.2. Safety Analysis for All Parts

Safety analysis will be performed using the All Treated Population except for DLT analysis which will be based on the DLT Evaluable Population.

All AEs will be summarized by incidence, and by grade according to the CTCAE v5.0 and listed by the MedDRA System Organ Class, preferred term, toxicity/severity grade, and causal relationship to study treatment.

AEs leading to death or to discontinuation of study treatment, and SAEs will be summarized.

On study laboratory parameters including hematology, chemistry, liver function, and renal function will be graded according to the CTCAE v5.0 where applicable. The worst severity grade, time to maximum Grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized for selected laboratory parameters. In addition, concomitant medications, physical examination, vital sign measurements, ECG results, ECOG performance status, and other safety observations at the time points indicated in the Study Schedule of Events will be analyzed.

### 12.7.5. Other Analyses

Refer to Section 8 for PK analysis.

The relationship between exposures of TAS3351 and its active metabolite (TAS-05-14317) in plasma and QT prolongation will be explored.

Biomarkers and pharmacodynamic data specified in Section 11 will be summarized descriptively by dose level and schedule. Where possible, relationship between plasma PK parameters or concentration of TAS3351 will be evaluated by correlation analysis or visual inspections. When further exploratory analyses are performed, the methods and the results may be reported in the main CSR or a Pharmacodynamic Analysis Report.

For patients enrolled in Part C, patients' health-related quality of life, symptoms, functioning, and general well-being will be captured using two PRO measures: EORTC-QLQ-C30 and EQ-5D-5L. They will be analyzed using the statistical methods which are described in the SAP.

# 13. ADMINISTRATIVE CONSIDERATIONS

## 13.1. Protocol Compliance

The Investigator will agree to comply with the protocol by signing the Declaration of Investigator. In the event that the Investigator is unable to continue the study and another suitable person is designated as the Investigator, the Sponsor must be notified in advance. The new Investigator must accept the responsibility in writing and be approved by the Sponsor and the IRB.

## 13.2. Protocol Deviations

The Investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study patients without prior IRB approval/favorable opinion. As soon as possible, the implemented deviation or change and the reasons for it should be documented and submitted to the IRB and Sponsor.

The Investigator is to record any deviation from the protocol in the source documents, describing this departure and the circumstances under which it was required.

## 13.3. Protocol Amendments

All protocol amendments must be issued by the Sponsor and signed and dated by the Investigator. Documentation of the amendment approval by the Investigator and IRB must be provided to the Sponsor.

If the changes involve only logistic or administrative aspects of the study, these changes will be notified in writing by the Sponsor.

## 13.4. Study Termination

If the Sponsor and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. The Sponsor also reserves the right to discontinue this study for administrative or discretionary reasons at any time.

## 13.5. Case Report Forms

The Investigator should complete all eCRFs in accordance with the eCRF Completion Guidelines. Data in the eCRFs shall be consistent with source documents.

An eCRF should be completed for each screened and enrolled patient.

The Investigator, or assigned personnel, should verify the data and correct as necessary prior to approval of the eCRFs.

## 13.6. Access to Source Data/Documents

The Investigator and the site must make all study-related records available for study-related monitoring, audit, IRB review, and regulatory inspection.

### 13.6.1. Source Data/Documents

Source documents are original documents, data, and records such as hospital records, clinical and office charts, laboratory notes, memoranda, patient’s evaluation checklists, pharmacy

dispensing records, recorded data from automated instruments, microfilm or magnetic media, X-ray, patient files, and records kept at the pharmacy, laboratories, and medical-technical departments involved in the study.

Specific details regarding source documents and source data to be recorded directly on the eCRFs for the study should be documented with the Investigator prior to and during the study.

### 13.6.2. Access to Source Data

The Sponsor's study monitor, or its representatives, should verify the entries in the eCRF and source documents to confirm the completeness and accuracy of the data. If there are any discrepancies between the entries in eCRFs and source documents, the monitor, data manager or Medical Monitor will query the Investigator.

## 13.7. Data Handling

All study information is confidential. The patient's and Investigator's personal data which may be included in the Sponsor's database shall be treated in compliance with all applicable laws and regulations.

When processing and archiving personal data pertaining to the Investigator and to the patients, the Sponsor or its representatives shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

## 13.8. Responsibilities of Recordkeeping

### 13.8.1. Investigator and Study Site

The Investigator and the study site are responsible for the retention of all study documents according to institutional policies, local laws, and ICH E6 Guidelines.

The Investigator and the study site agree to inform the Sponsor in writing of the intention to remove or destroy any study-related records. Prior to contacting the Sponsor, the Investigator and study site must ensure that the applicable regulatory requirements have been satisfied. The Sponsor will evaluate the requests from the Investigator and the study site and will provide authorization for destruction of such records in writing.

In the event that all retention of records requirements has been fulfilled, but the Sponsor requests that the Investigator and study site maintain the records for a longer period of time, additional arrangements will be made.

### 13.8.2. Sponsor

The Sponsor must retain all Sponsor-specific essential documents in conformance with the applicable regulatory requirements of the countries where the product is approved, and where the Sponsor intends to apply for approvals.

If the Sponsor discontinues the clinical development of the study drug, the Sponsor must maintain all Sponsor-specific essential documents in conformance with the applicable regulatory requirements.

## 13.9. Monitoring

The Sponsor and designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator and the site agree to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

## 13.10. Financial Disclosure

Financial disclosure for Investigators will be obtained and record keeping of financial records will be in accordance with local regulatory requirements. Investigators will provide the Sponsor with sufficient, accurate financial information upon the Sponsor's request.

## 13.11. Compensation for Health Injury

The clinical study is insured according to applicable regulatory requirements. The Compensation Policy Document will be provided to the study site by the Sponsor.

Sponsor should address the policies and payment procedures of compensation for the event of study-related injuries as the Compensation Policy Document.

When patients receive compensation, the policies and payment procedure of compensation should comply with the Compensation Policy Document.

## 13.12. Study Administrative Structure

The study organization details will be maintained in a supplement.

# 14. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will perform quality control and quality assurance procedures in accordance with the Sponsor's standard operating procedures (SOPs) to ensure the quality of the clinical study.

## 14.1. Quality Control

The Sponsor is responsible for controlling the quality of the clinical study according to the SOPs regarding study operation, monitoring, data collection and management, statistical analysis, and handling of safety information to verify that the study-related activities have been fulfilled.

## 14.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Authorized representatives of the Sponsor, a regulatory authority, or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator and the site will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents pertaining to the clinical study.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to ensure that these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP E6 Guidelines, and any applicable local regulatory requirements. The Investigator and the site should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

Any results arising from such inspections will be immediately communicated by the Investigator and the site to the Sponsor. The Investigator and the Sponsor will take corrective actions for all findings and observations found during audits and/or inspections. The auditors and inspectors will not disclose private information unless required by law.

# 15. ETHICS

## 15.1. Ethical Conduct of the Study

It is mandatory that all considerations regarding the protection of patients be carried out in accordance with the latest versions of the protocol, ICH GCP Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

## 15.2. Written Informed Consent

The ICF(s) must be approved by the IRB/IEC before patients sign consent for any study-related activity. It must be in a language that the patient can read and understand. The ICF process should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP Guidelines, and applicable regulatory requirements. Each patient must give written consent according to local requirements.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

There must be documentation in each patient's case history/medical record that informed consent was obtained prior to any study procedure being performed. Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

## 15.3. Institutional Review Board/Independent Ethics Committee

The study must be approved by an appropriately constituted IRB/IEC, as required in the applicable local regulation such as ICH E6 Guidelines before the study is initiated. At the end of the study, the Investigator will notify the IRB/IEC of the conclusion of the study and its outcome.

# 16. PUBLICATION POLICY

## 16.1. Publication Policy

The Sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country or region.

The results of the study may be presented during scientific symposia and/or published in a scientific journal only after review by the Sponsor in accordance with the guidelines set forth in the applicable publication.

The Investigator(s) and the Sponsor will discuss and determine the presenter(s) or author(s) and timing of any presentation or publication related to this study and/or its results. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## 16.2. Secondary Use of Data

The Sponsor maintains the right to secondary use of data in this study.

Secondary use of data describes the use of data from this study for other study/studies for purposes including, but not limited to, drug development and/or academic research. Secondary use of data also includes external offerings of study data to domestic and/or foreign organization(s), other companies and researcher(s), on a case-by-case basis.

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# APPENDIX A. EXAMPLES OF CLINICAL SUBSTRATES, INHIBITORS, AND INDUCERS OF CYP ENZYMES AND TRANSPORTERS

The classification below is based on the Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. This is not an exhaustive list. An updated list can be found at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

## Clinical Substrates of CYP Enzymes

| CYP Enzyme | Sensitive Clinical Substrates | Moderate Clinical Substrates |
|---|---|---|
| CYP1A2 | alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine | clozapine, pirfenidone, ramosetron, theophylline |
| CYP2C8 | repaglinide | montelukast, pioglitazone, rosiglitazone |
| CYP2C9 | celecoxib | glimepiride, phenytoin, tolbutamide, warfarin |
| CYP2C19 | S-mephenytoin, omeprazole | diazepam, lansoprazole, rabeprazole, voriconazole |
| CYP3A | alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil | alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil |
| | budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, isavuconazole, ivabradine, lemborexant, lurasidone, maraviroc, mobocertinib, quetiapine, sildenafil, ticagrelor, tolvaptan, venetoclax | |

Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line.

## Clinical Inhibitors of CYP3A Enzymes

| CYP Enzyme | Strong Clinical Inhibitors | Moderate Clinical Inhibitors |
|---|---|---|
| CYP3A | cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and ombitasvir (and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole | aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit juice, imatinib, isavuconazole, tofisopam, verapamil |
| | ceritinib, clarithromycin, idelalisib, nefazodone, nelfinavir | |

Note: Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively. Strong inhibitors of CYP3A causing ≥10-fold increase in AUC of sensitive index substrate(s) are shown above the dashed line.

## Clinical Inducers of CYP3A Enzymes

| CYP Enzyme | Strong Clinical Inducers | Moderate Clinical Inducers |
|---|---|---|
| CYP3A | apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenytoin, rifampin, St. John's wort | bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, sotorasib |

Note: Strong, moderate, and weak inducers are drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%, ≥50% to <80%, and ≥20% to <50%, respectively.

## Clinical Substrates of P-gp and BCRP

| Transporter | Clinical Substrates |
|---|---|
| P-gp | dabigatran etexilate, digoxin, edoxaban, fexofenadine |
| BCRP | rosuvastatin, sulfasalazine |

Note: A clinical substrate should meet the following criteria:
P-gp: (1) AUC fold-increase is ≥1.5 with itraconazole, quinidine, or verapamil co-administration; (2) not extensively metabolized in humans; and (3) in vitro transported by P-gp expression systems.
BCRP: (1) AUC fold-increase is ≥1.5 with pharmacogenetic alteration of ABCG2 (421C>A) and (2) in vitro transported by BCRP expression systems.

Taiho

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# SIGNATURE PAGE

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# SUMMARY OF CHANGES

The purpose of this amendment was to address the FDA's comments. All changes have been incorporated into the study synopsis as appropriate; the Table of Contents has also been updated.

In addition to these substantive changes, minor administrative alterations were made as necessary throughout the protocol, including formatting adjustments and correction of typographical errors. These editorial changes do not affect the rationale or planned conduct of the study or analyses, and therefore are not summarized in the table below.

| **Section #**<br>Section Name | **Description of Change** |
|---|---|
| **Section 1.3**<br>Schedule of Activities<br>Table 1: Schedule of Activities Phase1 (Parts A and Part B)<br>Table 2: Schedule of Activities Phase 2 (Part C) | Updated lab collection window.<br>Added table number specifying PK sampling and ECG collection schedule<br>Added Echocardiography to procedures<br>Updated notes in Table 2 local ECG to monitor as clinically indicated.<br>Updated notes in Table 2 for ECOG performance status appendix |
| **Section 4.2**<br>Study Design | Updated text to dosing description of Part 1. |
| **Section 4.2.4**<br>Study Stopping Criteria | Added new heading. |
| **Section 4.11**<br>Randomization and Blinding | Added text for Part B randomization. |
| **Section 5.1**<br>Inclusion Criteria | Modified inclusion criterion #3 to include cytologically confirmed<br>Modified inclusion criterion #9(e) Creatine Clearance to account for broader patient disposition.<br>Modified exclusion criterion #5 to include chemotherapy, biologic therapy, targeted therapy, immunotherapy, or investigational agents within the specified time period. |
| **Section 5.2**<br>Exclusion Criteria | Modified exclusion criterion #4 to include moderate inhibitors/inducers of cytochrome P450.<br>Modified exclusion criterion # 6 baseline QT interval.<br>Modified exclusion criterion # 7 to remove Investigator judgement language. |
| **Section 5.2**<br>Discontinuation of Treatment | Modified #3 |
| **Section 6.1.1**<br>Part 1: Dose Escalation | Updated dose levels<br>Updated text to allow for re-escalation or intrapatient dose escalation. |
| **Section 6.1.2**<br>Dose Limiting Toxicities<br>Table 9: Dose-Limiting Toxicity Definition | DLT criteria in Table 9 were modified for "Hepatic" and "Other" categories. |
| **Section 6.2.1**<br>Dose Reduction, Interruption, and Resumption | Added language for maximum dose reductions allowed.<br>Updated Table 9 Dose Reduction. |
| **Section 6.2.1.2**<br>Dose Modifications for Non-hematologic Toxicities | Modified other non-hematologic toxicities management. |

| **Section #**<br>Section Name | **Description of Change** |
|---|---|
| **Section 6.2.1.2**<br>Discontinuation of Study Treatment | Clarified discontinuation reason #3. |
| **Section 6.4.1**<br>Prohibited Concomitant Medication | Added ARAs language and prohibited use of PPI language. |
| **Section 6.4.2**<br>Concomitant Medications and Therapies Requiring Precautions | Added language for dose reduction when concomitant treatment is used.<br>Added ARAs and prohibited use of PPI language. |
| **Section 6.5.1**<br>Dietary | Added language for prohibited food consumption |
| **Section 7.1**<br>Study Assessments and Procedures | Updated Table 13 to account for Echocardiography/MUGA. |
| **Section 7.1.3**<br>Cardiac Function Evaluation | Added new section. |