Hansoh Pharmaceutical Group Co. Ltd.

CLINICAL STUDY PROTOCOL: HS-10296-12-01

A Phase 1/2, Open-label, Multicenter Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Oral Once-Daily Administration of HS-10296 in Patients with Locally Advanced or Metastatic Non-Small-Cell Lung Cancer Who Have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent

Phase 1/2

IND Number: 129609
Indication: Advanced or Metastatic Non-Small-Cell Lung Cancer
Investigators: Multicenter across the United States and Asia

Sponsor:
Hansoh Pharmaceutical Group Co. Ltd.
[redacted]

Sponsor Contact:
[redacted]

Protocol Date: 29 August 2017

Confidentiality Statement

1. ADMINISTRATIVE INFORMATION

1.1. Contacts

A separate contact information list will be provided to each site.

Hansoh-sponsored US-based and Asian Pacific-based Investigators will be provided with emergency medical contact information cards to be carried by each patient.

1.2. Approval

REPRESENTATIVES OF HANSOH

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

[redacted]
[redacted] Date
Associate Director, Clinical Science

[redacted]
[redacted] Date
Vice President & Head of Clinical Development

[redacted]
[redacted] Date
Senior Manager, Pharmacovigilance

[redacted]
[redacted] Date
Vice President & Head of DM and Statistics

[redacted]
[redacted] Date
Director, Regulatory Affairs

[redacted]
[redacted] Date
Senior Manager, Quality Assurance

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in this protocol (see Appendix A).

_____

Signature of Investigator Date

_____

Investigator's Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State)

_____

Location of Facility (Country)

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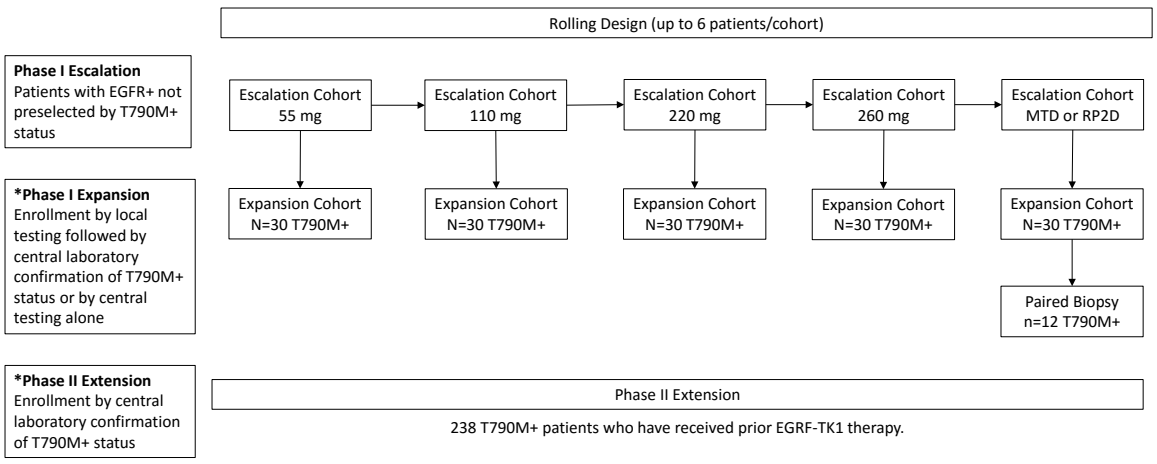
Title of Protocol: A Phase 1/2, Open-label, Multicenter Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Oral Once-Daily Administration of HS-10296 in Patients with Locally Advanced or Metastatic Non-Small-Cell Lung Cancer Who Have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent	**IND No.:** 129609	**EudraCT No.:** Not applicable
Study Number: HS-10296-12-01	**Phase:** 1/2	

Study Design:

This is a Phase 1/2, open-label, multicenter study of HS-10296 with dose escalation, dose expansion, and extension cohorts in locally advanced or metastatic non-small-cell lung cancer (NSCLC) patients who have progressed following prior therapy with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) agent. The study is designed to evaluate safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of once-daily and orally (PO) administered HS-10296. The overall study design is shown in the flow chart below, which consists of 3 phases: (1) dose escalation, (2) dose expansion, and (3) extension.

Study Flow Chart



* Expansions may include more than one dose depending upon emerging data.

Dose escalation (Phase 1 Escalation)

Approximately 30 evaluable patients with advanced NSCLC will be enrolled in the dose-escalation phase (Phase 1 Escalation) of this study. The total number of patients will depend on the number of dose escalations necessary. At least 3 and up to 6 evaluable patients will be enrolled for each dose-escalation cohort.

Dose expansion (Phase 1 Expansion)

Approximately 162 evaluable patients will be included in the dose-expansion phase (Phase 1 Expansion) of this study in order to further explore the tolerability, pharmacokinetics, efficacy, and biological activity of HS-10296 in specific patient subgroups. In each of the expansion cohorts, approximately 30 evaluable patients are planned to be enrolled, but approximately 12 will be enrolled for the paired biopsy cohort to further confirm the proof of mechanism. The total number of patients will depend on the number of dose

expansions necessary.

Extension (Phase 2 Extension)

Once the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) is reached, an additional cohort of approximately 238 evaluable patients who have confirmed T790M$^+$ status by central testing may be included in the Phase 2 extension cohort to further investigate the tolerability and efficacy of HS-10296.

Duration of Treatment: A cycle of study treatment will be defined as 21 days of continuous dosing. Patients are allowed to continue the study treatment until the disease progression or discontinuation criterion is met.	**Duration of Study:** Approximately 36 months based on the sequential design of the study
Number of Patients: Estimated total: approximately 430 The total number of patients will depend upon the number of dose escalations and dose expansions necessary • Approximately 30 evaluable patients will be required for Phase 1 dose-escalation cohorts. • Approximately 162 patients will be enrolled in Phase 1 dose expansion cohorts. • Approximately 238 evaluable patients may be included in the Phase 2 extension cohort.	**Number of Sites:** Estimated total: more than 20 sites in the US, China, and Taiwan
Investigational Product Dosage and Administration HS-10296: 5-, 10-, and 40-mg tablet, immediate-release formulation; the starting dose will be 55 mg PO once daily (QD). Patients should avoid consumption of food for at least 1 hour prior to and 2 hours post dosing.	**Route of Administration:** PO

Patient Population:

The patient population eligible for dose escalation will consist of adults 18 years of age or older with locally advanced or metastatic NSCLC with histological or cytological confirmation and refractory or resistant to previously continuous treatment with an EGFR TKI (e.g., gefitinib or erlotinib).

For Phase 1 expansion cohorts, patients will have confirmed tumor T790M$^+$ status with EGFRm$^+$ advanced NSCLC who have received and progressed on an EGFR TKI agent.

The patient population in the Phase 2 extension cohort who has T790M$^+$ status confirmed by central testing, received and progressed on an EGFR TKI agent will be enrolled to further investigate the safety, tolerability, and efficacy of HS-10296.

Primary Objectives:

- To investigate the safety, tolerability, and efficacy of HS-10296 administered orally to patients with locally advanced or metastatic NSCLC who have progressed following prior therapy with an EGFR TKI agent.

Secondary Objectives:

- To determine the dose-limiting toxicities (DLTs), MTD, and RP2D of HS-10296.
- To evaluate the PK of HS-10296 and its metabolite (HAS-719) after a single oral dose and at steady state after multiple oral doses.
- To evaluate preliminary anti-tumor outcomes in the escalation and expansion cohorts, by assessment of objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), and disease control rate (DCR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).
- To obtain further evaluation of the anti-tumor activity of HS-10296 in the extension cohort by assessment of ORR, DoR, DCR, tumor shrinkage, and PFS using RECIST 1.1.

Exploratory Objectives:

- To explore the relationship between PK and selected endpoints (which may include patient-reported outcomes [PROs] and blood-borne biomarkers), where deemed appropriate.
- To collect and store plasma for potential exploratory research of blood-borne biomarkers, which may correlate development of NSCLC and/or response to HS-10296 with respect to anti-tumor activity, tolerability, or safety.
- To collect and store diagnostic tumor sample and any fresh tumor biopsies for potential future exploratory research, which may correlate development of NSCLC and/or response to HS-10296 with respect to efficacy, tolerability, or safety.
- To collect and store deoxyribonucleic acid (DNA) for future assessment of polymorphic variations in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of HS-10296 and/or in genes that may potentially be associated with clinical response and/or study drug-related toxicity.
- To characterize the PK of HS-10296 and its metabolite (HAS-719) in cerebrospinal fluid (CSF).
- To collect and store residual CSF for potential exploratory research of factors that may impact NSCLC development and/or response to HS-10296.
- To collect PRO data to explore disease-related symptoms and health-related quality of life (HRQoL).

Criteria for Inclusion:

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of starting study treatment. Under no circumstances can there be exceptions to this rule.

1. Provision of signed and dated written informed consent prior to any study-specific procedures, sampling, and analyses. If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the patient and he or she will not be excluded from other aspects of the study.
2. Age at least 18 years.
3. Histological or cytological confirmation diagnosis of NSCLC.
4. Radiological documentation of disease progression while on a previous continuous treatment with an EGFR TKI (e.g., gefitinib or erlotinib). In addition, other lines of therapy may have been given. All patients must have documented radiological progression on the last treatment administered, prior to enrolling in the study.
5. Patients must fulfill one of the following:
    a. Confirmation that the tumor harbors an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q) OR
    b. must have experienced clinical benefit from EGFR TKI, according to the Jackman criteria (followed by systemic objective progression, RECIST or World Health Organization [WHO]) while on continuous treatment with an EGFR TKI.
6. For the dose expansion and extension cohorts, patients also must have confirmation of tumor $T790M^+$ mutation status from a biopsy sample taken after disease progression on the most recent treatment regimen with an EGFR TKI.
   Prior to entry, a result from the central analysis of the patient's $T790M^+$ mutation status must be obtained.
7. A WHO performance status equal to 0-1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.
8. At least 1 lesion that has not previously been irradiated, that has not been chosen for biopsy during the study screening period, and that can be accurately measured at Baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15mm) with computerized tomography (CT) or magnetic resonance imaging (MRI), whichever is suitable for accurately repeated measurements.
9. Females should be using adequate contraceptive measures throughout the study; should not be breastfeeding at the time of screening, during the study and until 3 months after completion of the

study; and must have a negative pregnancy test prior to start of dosing if of childbearing potential or must have evidence of non-childbearing potential by fulfilling 1 of the following criteria at Screening (refer to Section 7.3 for restrictions):

a. Postmenopausal defined as age more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
b. Women under 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more, following cessation of exogenous hormonal treatments, and with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the postmenopausal range for the laboratory.
c. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not by tubal ligation.

10. Male patients should be willing to use barrier contraception (i.e., condoms).
11. For the dose-expansion paired biopsy cohort:
    a. Presence of at least 1 non-target lesion (NTL) suitable for multiple biopsies while on treatment.
12. For inclusion in optional genetic research, patient must provide a written informed consent for genetic research.

Criteria for Exclusion:

Any patient who meets any of the following exclusion criteria will not qualify for entry into the study.

1. Treatment with any of the following:
    a. An EGFR TKI (e.g., erlotinib, gefitinib, or osimertinib) within 8 days or approximately 5 x half-life, whichever is longer, of the first dose of study drug. (If sufficient washout time has not occurred due to schedule or PK properties, an alternative appropriate washout time based on known duration and time to reversibility of drug-related adverse events (AEs) must be agreed upon by Hansoh and the Investigator).
    b. Previous or current treatment with third-generation EGFR TKIs (Expansion and Extension Cohorts only)
    c. Any cytotoxic chemotherapy, investigational agents, or anticancer drugs for the treatment of advanced NSCLC used for a previous treatment regimen or clinical study within 14 days of the first dose of study drug.
    d. Medications that are predominantly CYP3A4 strong inhibitors or inducers or sensitive substrates of CYP3A4 with a narrow therapeutic range within 7 days of the first dose of study drug.
    e. Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug.
    f. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study drug, with the exception of patients receiving radiation to > 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
2. Previously untreated NSCLC patients. To be eligible for this study, patients must have received and progressed on EGFR TKI therapy.
3. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment, with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy.
4. Spinal cord compression or brain metastases unless asymptomatic, stable, and not requiring steroids for at least 4 weeks prior to start of study treatment.
5. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension or active bleeding diatheses, which, in the Investigator's opinion, makes it undesirable for the patient to participate in the trial OR which would jeopardize compliance with the protocol such as active infection (e.g., hepatitis B, hepatitis C, or human immunodeficiency virus [HIV]). Screening for chronic conditions is not required.

6. Any of the following cardiac criteria:
    a. Mean resting corrected QT interval (QTc) > 470 ms obtained from 3 electrocardiograms (ECGs), using the screening clinic's ECG machine and Fridericia's formula for QT interval correction (QTcF).
    b. Any clinically important abnormalities in rhythm, conduction, or morphology of the resting ECG (e.g., complete left bundle branch block, third-degree heart block, second-degree heart block, PR interval > 250 ms).
    c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval.
    d. Left ventricular ejection fraction (LVEF) ≤ 40%.
7. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis that required steroid treatment, or any evidence of clinically active interstitial lung disease.
8. Inadequate bone marrow reserve or organ function, as demonstrated by any of the following laboratory values:
    - Absolute neutrophil count (ANC) < 1.5×10^9/L.
    - Platelet count < 100×10^9/L.
    - Hemoglobin < 90 g/L (< 9 g/dL).
    - Alanine aminotransferase > 2.5 × upper limit of normal (ULN) if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases.
    - Aspartate aminotransferase (AST) > 2.5 × ULN if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases.
    - Total bilirubin (TBL) > 1.5 × ULN if no liver metastases or > 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases.
    - Creatinine > 1.5 × ULN concurrent with creatinine clearance < 50 mL/min (measured or calculated by the Cockcroft-Gault equation); confirmation of creatinine clearance is only required when creatinine is > 1.5 × ULN.
9. Refractory nausea, vomiting, or chronic gastrointestinal diseases, inability to swallow the study drug, or previous significant bowel resection that would preclude adequate absorption of HS-10296.
10. History of hypersensitivity to any active or inactive ingredient of HS-10296 or to drugs with a similar chemical structure or class to HS-10296.
11. Women who are breastfeeding or have a positive urine or serum pregnancy test at the Screening Visit.
12. Involvement in study planning and conduct (i.e., Hansoh staff or staff at the study site).
13. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.
14. Any disease or condition that, in the opinion of the Investigator, would compromise the safety of the patient or interfere with study assessments.
15. The following are considered criteria for exclusion from the exploratory genetic research:
    - Previous allogenic bone marrow transplant.
    - Non-leukocyte leukocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection.
16. Any severe and uncontrolled ocular disease that may, in the ophthalmologist's opinion, present a specific risk to the patient's safety.

Evaluation and Analyses:

Definition of study endpoints

– Safety and tolerability (primary for dose escalation and expansion, secondary for extension)

- PK of HS-10296 and its metabolite HAS-719 (secondary)
- Tumor response including ORR (primary for extension, secondary for escalation and expansion), DCR, and PFS (secondary)
- Overall survival (OS) and tumor shrinkage (secondary for extension only)
- Pharmacodynamic markers in $EGFRm^+$, $T790M^+$ tumors at selected clinical doses (secondary)
- DoR (exploratory)
- Patient-reported outcomes (exploratory)
- Other biomarker data (exploratory)
- Pharmacogenetics (exploratory)
- Diagnostic tumor samples (exploratory)
- Metabolite identification (exploratory)

Safety Assessments

Safety and tolerability will be assessed by summarizing the incidence of AEs, clinical laboratory values, physical examination findings, ECGs, and vital signs.

Efficacy Assessments

The primary efficacy variable of the extension phase is ORR. For the extension cohort only, an independent central review (ICR) of RECIST assessment will be used for the primary analysis of ORR and other RECIST-based outcomes.

Pharmacokinetic Assessments

The PK parameters for HS-10296 and its metabolite HAS-719 will be determined by noncompartmental methods.

Sample Size Determination

- The primary objective of this study is to investigate the safety and tolerability, and thereby identify the MTD, of HS-10296 and to recommend the dose(s) for evaluation in future clinical studies. Hence, the number of patients in the cohorts has been based on the desire to obtain adequate safety, tolerability, PK, and pharmacodynamic data while exposing as few patients as possible to the study drug and procedures. Tumor response as measured using RECIST 1.1 will be assessed to provide preliminary anti-tumor activity in a patient population thought most likely to respond to HS-10296.
- For the dose-escalation phase of the study, cohorts of 3 to 6 evaluable patients will be required. The total number of patients will depend upon the number of dose escalations necessary.
- In the case that anti-tumor activity, in the form of responses, is observed, 30 evaluable patients in each dose-expansion cohort will provide reasonable confidence of estimating what the true response rate would be in this population as well as in the ≥ second-line $T790M^+$ population. Confidence intervals (CIs) will be constructed (using the Clopper-Pearson interval) around the response rates observed in each population to enable decisions to be made about the likely success of future studies in each of the populations.
- Approximately 238 evaluable patients with $T790M^+$ advanced NSCLC will be enrolled in the extension cohort phase, whose disease has progressed following either 1 prior therapy with an EGFR-TKI following treatment with both EGFR-TKI and another anticancer therapy.

3. STUDY REFERENCE INFORMATION

3.1. Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. For Study-Related Responsibilities, the identified vendors, if applicable, will perform these activities in full or in partnership with the Sponsor.

3.2. Coordinating Investigator

Hansoh Pharmaceutical Group, Ltd. (Hansoh) will select a Signatory Coordinating Investigator from the Investigators who participate in the study. Investigator selection criteria will include significant knowledge of the study protocol, the study drug, the therapeutic area, and the conduct of clinical research and study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that the report accurately describes the results of the study.

LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Acquired resistance
AST	Aspartate aminotransferase
AUC_{0-24}	Area under plasma concentration-time curve from zero to 24 hours [amount time/volume]
AUC_{0-t}	Area under plasma concentration-time curve from zero to time t [amount time/volume]
AUC_{ss}	Area under plasma concentration-time curve during any dosing interval at steady state [amount time/volume]
cfDNA	Cell-free DNA
CI	Confidence interval
CL/F	Total body clearance of drug from plasma after an oral dose
CL_{ss}/F	Total body clearance of drug from plasma after an oral dose at steady state
C_{max}	Maximum plasma concentration
CR	Complete response
CSF	Cerebrospinal fluid
$C_{ss\ max}$	Maximum (peak) steady state drug concentration in plasma during dosing interval [amount/volume]
$C_{ss\ min}$	Minimum steady state drug concentration in plasma during dosing interval [amount/volume]
C_{stasis}	Concentration required for tumor stasis
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid

DoR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
$EGFRm^+$	Epidermal growth factor receptor sensitizing mutation positive
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ C-30	EORTC Quality of Life Questionnaire
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FGFR	Fibroblast growth factor receptor
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
Gmean	Geometric mean
HAS-719	Major circulating metabolite of HS-10296
HED	Human equivalent dose
HER	Human epidermal growth factor receptor
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HL	Hy's Law
HNSTD	Highest non-severely toxic dose
HRCT	High-resolution computed tomography
HRQoL	Health-related quality of life
IC_{50}	Half-inhibitory concentration
ICH	International Council for Harmonisation
ICR	Independent central review
ID	Investigational drug identification
IEC	Independent ethics committee
IRB	Institutional review board
LH	Luteinizing hormone
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities

MRI	Magnetic resonance imaging
MRT	Mean residence time
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NE	Not evaluable
NF1	Neurofibromin 1
NOAEL	No-observed-adverse-effect-limit
NSCLC	Non-small-cell lung cancer
NTL	Non-target lesion
ORR	Objective response rate
OS	Overall survival
PD	Progression of disease
PFS	Progression-free survival
PHL	Potential Hy's Law
PK	Pharmacokinetics
PO	Orally
PR	Partial response
PRO	Patient reported outcome
QD	Once daily
QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Lung Cancer
QRS	Combination of 3 of the graphical deflections seen on a typical ECG
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected with Fridericia's formula
RAC	Accumulation ratio
RECIST (1.1)	Response Evaluation Criteria in Solid Tumors (version 1.1)
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SD	Stable disease
SRC	Safety review committee
STD_{10}	Severely toxic dose in 10% of animals

$t_{½}$	Half-life
$t_{½\lambda z}$	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve [time]
T790M	"Gatekeeper" amino acid 790 to methionine
$T790M^{+}$	T790M mutation-positive
TBL	Total bilirubin
TKI	Tyrosine kinase inhibitor
TL	Target lesion
t_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
V_{ss}/F or Vz/F	volume of distribution
WHO	World Health Organization
WT	Wild-type
λx	Smallest (slowest) disposition (=hybrid) rate constant [time-1]

4. INTRODUCTION

4.1. Background

As the first-generation tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib are most effective in advanced non-small-cell lung cancer (NSCLC) patients whose tumors harbor recurrent somatic activating mutations occurring in the exons encoding the kinase domain of epidermal growth factor receptor (EGFR).[1] Tumors with these activating mutations (EGFRm$^+$) account for approximately 10% to 17% in Western populations and 30% to 50% in Asian populations.[2] Patients with EGFRm$^+$ typically show good initial responses to first-generation TKIs; however, most patients develop acquired resistance (AR) and, hence, disease progression, after 9 to 14 months of treatment.[3] In addition, these first-generation TKIs are associated with side effects, including skin rash and diarrhea, resulting from the inhibition of wild-type (WT) EGFR in skin and gastrointestinal organs.[4]

Several mechanisms of AR have been reported, such as human epidermal growth factor receptor 2 (HER2) amplification,[5] MET amplification,[6] PIK3CA mutation,[7] BRAF mutation,[8] neurofibromin 1 (NF1) loss,[9] and potentially fibroblast growth factor receptor (FGFR) signaling.[10] However, it is now well established that acquisition of a second mutation in EGFR, resulting in substitution of threonine at the "gatekeeper" amino acid 790 to methionine (T790M), is the most common resistance mechanism and is detected in tumor cells from more than 50% of patients after disease progression.[11]

Second-generation irreversible EGFR TKIs, such as afatinib[12] and dacomitinib,[13,14] are effective in untreated EGFR mutation lung cancer.[15] As monotherapy, these second-generation TKIs have failed to overcome T790M-mediated resistance in patients[16] because concentrations at which these irreversible TKIs overcome T790M activity preclinically are not achievable in humans due to dose-limiting toxicity related to nonselective inhibition of WT EGFR.[17]

There is significant unmet medical need for an EGFR TKI agent that more effectively targets T790M tumors while sparing the activity of WT EGFR. This has led to the development of "third-generation" EGFR TKIs. WZ4002 was the first such agent to be published.[18] Another agent closely related to the WZ4002 series, CO-1686, has been reported,[19] and HM1713 is another "third-generation" agent that is in early development.[20] Osimertinib was recently approved and is indicated for the treatment of patients with metastatic EGFR T790M mutation-positive (T790M$^+$) NSCLC who have progressed on or after EGFR TKI therapy.[21]

4.2. Summary of Relevant Nonclinical Data

4.2.1. Pharmacology

In *in vitro* enzymatic and cell proliferation assays, HS-10296 displayed potent inhibition of the EGFR T790M-resistant mutation and exhibited notably less inhibitory activity on the WT EGFR.[22] HAS-719, a major metabolite of HS-10296, showed a similar enzymatic activity

profile to its parent compound.[22] HS-10296 showed weak or no inhibition of 38 closely related kinases, suggesting that HS-10296 was a selective EGFR mutant kinase inhibitor with limited potential for off-target effects.[23]

In the nude mouse tumor models, HS-10296 potently inhibited tumor growth of NSCLC cell lines H1975 and LU1868 with the EGFR T790M mutation, as well as NSCLC line HCC827 with EGFR-sensitizing mutations.[24] At a high dose of 20 mg/kg, HS-10296 was able to induce almost complete tumor regression in these EGFR-mutant tumor models. HS-10296 exhibited much less inhibition of the WT EGFR tumor A431, implying a more favorable safety profile compared with other EGFR inhibitors tested. HS-10296 potently and specifically inhibited the EGFR T790M-resistant mutation while sparing WT EGFR, exhibiting the characteristics of the new generation of EGFR inhibitors.

4.2.1.1. Safety Pharmacology

In the *in vitro* human *ether-à-go-go*-related gene (hERG) assay, the 50% inhibitory concentration (IC_{50}) of HS-10296 was 2.958 µM, indicating that HS-10296 mildly inhibits hERG current.[25] The C_{max} at the efficacious dose in the NCI-H1975 xenograft model (5 mg/kg HS-10296, oral [PO]) was 190 ng/mL, and provided a 12.2-fold margin to the hERG IC_{50} value.[24] In addition, plasma binding for HS-10296 was > 99.5% in rats, dogs, and human plasma and the free drug concentration in plasma would be much lower.[26] No central nervous system effects (rats) or cardiovascular or respiratory system effects (dogs) occurred following oral administration of HS-10296.[27, 28]

4.2.2. Nonclinical Pharmacokinetics and Drug Metabolism

HS-10296 was rapidly absorbed by both rats and dogs after oral administration.[29, 30] The major circulating metabolite of HS-10296, HAS-719, is formed via an *N*-demethylation pathway. Plasma AUC_{0-t} values increased dose-proportionally, and no accumulation was noted following repeated oral dosing.

Plasma protein binding was ≥ 99.5% for both HS-10296 and HAS-719 in rat, dog, and human plasma.[26] In rats, HS-10296 and HAS-719 were rapidly detected in most tissues, with peak tissue concentrations occurring at 2 hours postdose.[31] Lung and spleen, followed by adrenal gland, marrow, and liver, were the primary sites of distribution. HS-10296 tissue concentrations were higher than in plasma, and HS-10296 exhibited high distribution to the brain. Urinary excretion of HS-10296 and HAS-719 were minimal (<0.1%) in rats.[32] HS-10296 and the *N*-demethylated metabolite, HAS-719, accounted for 3.4% and 0.2% of the dose in rat feces and bile, respectively.

The projected intrinsic clearance (CL_{int}) of HS-10296 in liver microsomes would be intermediate in dogs and humans and high in mice, rats, and monkeys.[33] A cross-species metabolic profile of

HS-10296 in mouse, rat, dog, monkey, and human hepatocytes demonstrated that HS-10296 is extensively metabolized without any unique human metabolites.[34,35] HS-10296 does not appear to be an inhibitor of the major human cytochrome P450 (CYP) enzymes and has little potential to cause drug-drug interactions due to inhibition of these major CYP enzymes.[36] HS-10296 had no induction potential on CYP1A2, CYP2B6, and CYP3A4.[37] An assessment of cell permeability and efflux using human Caco-2 cells showed that HS-10296 had low permeability and the efflux transporters may be involved in the transport of HS-10296.[38]

4.2.3. Nonclinical Toxicology

Single doses of up to 900 mg/kg in rats and 200 mg/kg in dogs were not lethal.[39,40] Clinical observations seen at these high doses included hair fluffiness, piloerection, prostration, hunched back, decreased motor activity, loose/soft stools, and/or dirty anal area in rats and emesis and soft, loose, and/or bloody stool in dogs.

In 13-week toxicity studies, lethality occurred after repeated doses of 120 mg/kg per day in female rats and 25 mg/kg per day in dogs.[41,42,43,44,45] HS-10296-related effects in rats and dogs were observed in the skin, gastrointestinal system, and eyes and were either secondary to the pharmacodynamics of an EGFR inhibitor, or were a result of the notable decreases in body weight and/or food consumption seen in these animals. The observations were reversible or in the process of reversing during a 4-week recovery period.

In rats, HS-10296-related effects included soft stool, salivation, skin lesions, and ophthalmologic findings. Histopathologic findings were noted in the mammary glands and vagina of rats and in the tongue, skin, oral cavity, and thymus of dogs. The skin lesions seen in the rats and dogs correlated with folliculitis of the skin and have been reported in rodents and humans administered EGFR inhibitors.[46,47,48] Ulceration and inflammation of the tongue that was seen in dogs have been associated with administration of TKIs in humans.[46,49] In addition, changes in the oral mucosa are associated with anti-EGFR antibodies.[50]

Ocular findings that were noted in rats and dogs, such as conjunctival congestion, corneal changes, and other ocular abnormalities were reported in patients using anti-EGFR treatment.[51,52] Atrophy of the mammary glands and mucification of that vaginal epithelium were considered to be secondary to the treatment-related effects on food consumption, body weights, and/or body weight gains seen in life.[53,54] Thymic involution/atrophy was attributed to stress.[55] The severely toxic dose in 10% of the rats (STD_{10}) was 60 mg/kg/day in females and 120 mg/kg/day in male and, the highest non-severely toxic (HNSTD) dose in dogs was 10 mg/kg/day.

In vitro and *in vivo* genotoxicity assays were negative, indicating that HS-10296 is not mutagenic or clastogenic at relevant concentrations.[56,57,58]

HS-10296 had no adverse effects on fertility or early embryonic development in males at 100 mg/kg/day in males and in females at 30 mg/kg/day.[59] Statistically significant decreases in gravid uterus weight, mean numbers of corpora lutea, implantation sites, and live fetuses occurred at 100 mg/kg/day. No HS-10296-related changes were noted in sperm counts, motility, or sperm morphology examinations. HS-10296 was not teratogenic in rats; the no-observed-adverse-effect-limit (NOAEL) for embryo-fetal development toxicity was 100 mg/kg per day.[60]

4.3. Rationale for the Study

The presence of activating mutations in exons 18-24 of EGFR (including L858R and Ex19del, collectively described as EGFRm$^+$) in patients with NSCLC tumors confers sensitivity to the EGFR TKI class of drugs in a high percentage of patients. However, the subsequent on treatment emergence of the T790M gatekeeper mutation in patients treated with an EGFR TKI agent has been described as a major route of development of resistance to this class of therapy. HS-10296 is a novel irreversible, small-molecular inhibitor of receptor tyrosine kinase of EGFR. It selectively inhibits EGFR mutant kinases, including resistant mutation T790M, and sensitizing mutations (exon 19 deletion, and L858R mutants), with less inhibitory activity on the WT EGFR. HS-10296 also inhibits the activity of HER2 and human epidermal growth factor receptor 4 (HER4). Therefore, HS-10296 can be developed as second-line therapy to overcome EGFR T790M mutation, the most common resistance mechanism. It also can be developed as first-line therapy for NSCLC with EGFR-activating mutations.

Compared with osimertinib, HS-10296, a third-generation irreversible small molecular EGFR inhibitor, showed comparable antitumor potency, but less toxicity potential since the formation of a nonselective metabolite was blocked through structural optimization. In nonclinical studies, HS-10296 also showed a favorable pharmacokinetic (PK) profile. It was rapidly absorbed in both rats and dogs, and the oral bioavailability appeared to increase proportionally with the dose levels. Data obtained in the toxicity studies were either secondary to pharmacodynamics of an EGFR inhibitor or were a result of the notable decreases in body weight and/or food consumption seen in these animals. No new toxicities were identified, and the studies clearly identified an STD_{10} in rodents and an HNSTD in nonrodents.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary Objective

- To investigate the safety, tolerability, and efficacy of HS-10296 administered orally to patients with locally advanced or metastatic NSCLC who have progressed following prior therapy with an EGFR TKI agent.

5.1.2. Secondary Objectives

- To determine dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) of HS-10296.
- To evaluate the PK of HS-10296 and its metabolite (HAS-719) after a single oral dose and at steady state after multiple oral doses.
- To evaluate preliminary anti-tumor outcomes in the escalation and extension cohorts, by assessment of duration of response (DoR), objective response rate (ORR), and progression-free survival (PFS), using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).
- To obtain further evaluation of the anti-tumor activity of HS-10296 in the extension cohort by assessment of ORR, DoR, disease control rate (DCR), tumor shrinkage, and PFS, using RECIST 1.1.

5.1.3. Exploratory Objectives

- To explore the relationship between PK and selected endpoints (which may include patient reported outcomes [PRO] and blood-borne biomarkers), where deemed appropriate.
- To collect and store plasma for potential exploratory research of blood-borne biomarkers, which may correlate development of NSCLC and/or response to HS-10296 with respect to anti-tumor activity, tolerability, or safety.
- To collect and store diagnostic tumor sample and any fresh tumor biopsies for potential future exploratory research, which may correlate development of NSCLC and/or response to HS-10296 with respect to efficacy, tolerability, or safety.
- To collect and store deoxyribonucleic acid (DNA) for future assessment of polymorphic variations in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of HS-10296 and/or in genes that may potentially be associated with clinical response and/or study drug-related toxicity.
- To characterize the PK of HS-10296 and its metabolite (HAS -719) in cerebrospinal fluid (CSF).
- To collect and store residual CSF for potential exploratory research of factors that may impact on NSCLC development and/or response to HS-10296.

- To collect PRO data to explore disease-related symptoms and health-related quality of life (HRQoL).

5.2. Endpoints

To meet the study objectives, the following endpoints will be collected:

5.2.1. Definition of Study Endpoints

- Safety and tolerability (primary for dose escalation and expansion, secondary for extension)
- PK of HS-10296 and its metabolite HAS-719 (secondary)
- Tumor response including ORR (primary for extension, secondary for escalation and expansion), DCR, and PFS (secondary)
- Overall survival (OS) and tumor shrinkage (secondary for extension only)
- Pharmacodynamic markers in $EGFRm^+$, $T790M^+$ tumors at selected clinical doses (secondary)
- DoR (exploratory)
- PRO (exploratory)
- Other biomarker data (exploratory)
- Pharmacogenetics (exploratory)
- Diagnostic tumor samples (exploratory)
- Metabolite identification (exploratory)

For the extension cohort, an independent central review (ICR) of the RECIST assessments will be used for the primary analysis of ORR and other RECIST-based outcomes. Safety endpoints are defined in Section 9.7.

5.2.2. Determination of Sample Size

The primary objective for the phase of dose escalation and expansion cohorts in this study is to investigate the safety and tolerability and thereby identify the MTD of HS-10296 to recommend the dose(s) for evaluation in future clinical studies. Hence, the number of patients in the cohorts has been based on the desire to obtain adequate tolerability, safety, pharmacokinetic, and pharmacodynamic data, while exposing as few patients as possible to HS-10296 and procedures. Tumor response as measured using RECIST 1.1, will be assessed to provide preliminary anti-tumor activity in a patient population thought most likely to respond to HS-10296.

Dose-Escalation Cohorts

For the dose-escalation phase of the study, cohorts of 3 to 6 evaluable patients will be required. The total number of patients will depend upon the number of dose escalations necessary.

5.2.2.1. Dose-Expansion Cohorts

Patients are evaluable for the assessment of response in the expansion cohorts if they are dosed and have a baseline RECIST assessment. In addition, for the purposes of decision-making on the expansion cohorts, a patient's $T790M^+$ status must also have been identified via central testing and match the cohort expansion population under assessment.

The expansion cohorts will consist of patients whose NSCLC has progressed following therapy with an EGFR TKI agent and whose tumor status is $T790M^+$. Data from these cohorts will provide a preliminary assessment of anti-tumor activity based on ORR (providing an acceptable false-negative risk of concluding that there is no activity if the true response rate is at least 30%).

A conclusion of no evidence of activity will be reached if no objective RECIST responses (confirmed partial response [PR] or complete response [CR]) are observed. If the true response rate is ≥ 30%, the chance of observing no responses in 30 evaluable patients is < 1%.

If anti-tumor activity in the form of responses is observed, 30 evaluable patients in each dose-expansion cohort will provide reasonable confidence of estimating what the true response rate would be in this population as well as in the ≥ second-line $T790M^+$ population with $EGFRm^+$ advanced NSCLC. Confidence intervals (CIs) will be constructed (using the Clopper-Pearson interval) around the response rates observed in each population to enable decisions about the likely success of future studies in each of the populations, such as:

- 17% ORR (5 of 30 responses); 80% CI [8%, 29%]
- 30% ORR (9 of 30 responses); 80% CI [19%, 43%]
- 50% ORR (15 of 30 responses); 80% CI [37%, 63%]
- 70% ORR (21 of 30 responses); 80% CI [57%, 81%]

In the event that there is little evidence of anti-tumor activity observed within the cohort expansions, individual cohorts may be closed prior to 30 evaluable patients being recruited. This will avoid exposing patients to a potentially ineffective therapy, providing that the evidence of no antitumor activity is strong enough at that time. If no responses are observed in up to 8 evaluable patients recruited to the first expansion cohort at the 55-mg dose, it may be appropriate to conclude no evidence of activity, because if the true response was ≥ 30%, the chance of observing no responses in 8 evaluable patients is < 6%. If this individual cohort expansion is terminated prior to the full 30 evaluable patients being recruited, other cohorts at the next dose level within the expansion will still be able to initiate recruitment as planned. Any such decision will be at the discretion of Hansoh. The same role specified above for the first expansion cohort will be followed for subsequent expansion cohorts prior to the full 30 evaluable patients being recruited.

5.2.2.2. Paired Biopsy Cohort

Patients are evaluable for the paired biopsy cohort if they have provided at a minimum the prestudy tumor biopsy and 1 tumor biopsy on study treatment. There currently are no published data available that adequately characterize or describe the variability of the biomarkers of

interest in this patient population; thus, the sample size cannot be calculated with consideration to statistical power. Data from 12 evaluable patients are considered to be adequate to allow a preliminary investigation of the objectives of this study.[61]

5.2.2.3. Phase 2 Extension Cohort

The primary endpoint of the extension phase is ORR. A sample size of 238 evaluable patients achieves 90% power to detect a difference (P1 – P0) of 0.1 using a 2-sided binomial test with a significance level of 0.05 to test the following hypotheses:

H_0: $P \leq 0.3$ (P0 = 0.3)

H_1: $P > 0.3$ (P1 = 0.4)

In addition, with 238 evaluable patients, the precision of the estimation of ORR 0.4 in the overall study population will be ± 6.4% (e.g., ORR 40%, 95% CI 33.7%, 46.5%). Thus, the lower bound of the 95% CI for ORR 40% is 33.7%, which is greater than 30%.

In addition, the number of 238 evaluable patients is considered to be adequate to assess the safety and tolerability of HS-10296.

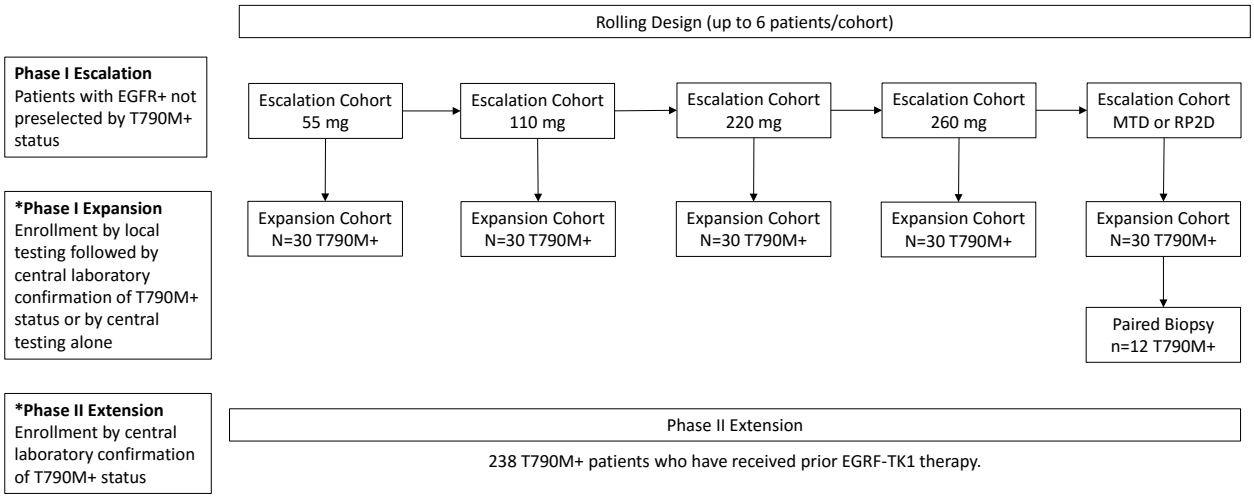
6. STUDY DESIGN AND DESCRIPTION

6.1. Overall Study Design

The purpose of the present study is to assess the safety, tolerability, PK, and anti-tumor activity of HS-10296 in patients with advanced NSCLC who have already received at least 1 course of specific anti-cancer treatment, but the tumor has started to regrow following the treatment.

In this first-in-human study, HS-10296 will initially be administrated orally (PO) once daily (QD) to patients with advanced NSCLC at a starting dose of 1/10 of the STD_{10} in rodent toxicity studies and will be escalated to reach either a MTD or maximum feasible dose in patients as defined by DLT. This study design consists of 3 phases (Figure 1) and aims to allow an escalation of dose with intensive safety monitoring to ensure safety of the patients.

Figure 1 Study Flow Chart



* Expansions may include more than one dose depending upon emerging data.

Dose Escalation (Phase 1 Expansion)

Up to 6 patients will be enrolled in each dose escalation cohort to ensure a minimum of 3 and a maximum of 6 evaluable patients using the rolling 6 approach.[62] The total number of patients will depend on the number of dose escalations necessary.

Following completion of Cycle 1 of each escalation cohort, a SRC will review the safety and PK data and make a decision regarding subsequent dose escalation or expansion. Each subsequent dose cohort represents a 100% increase from prior dose with the exception of the final dose escalation from 220 mg QD to 260 mg QD.

Patients will receive a single dose on Day 1. Following a 7 ± 2-day washout, multiple dosing, QD, will be initiated.

In the first cohort, a delay of at least 7 days will be mandatory between the administration of the first (single) dose to the first patient and administration of the first (single) dose to subsequent patients. Dosing frequency may be adjusted during the study on the basis of emerging safety and PK data.

Dose Expansion (Phase 1 Expansion)

Approximately 162 evaluable patients may be included in the dose-expansion phase of this study to further explore the tolerability, PK, efficacy, and biological activity of HS-10296 in specific patient subgroups. In each expansion cohort, approximately 30 evaluable patients are planned to be enrolled, but approximately 12 will be enrolled for the paired biopsy cohort to further confirm the proof of mechanism. The total number of patients will depend on the number of dose expansions necessary.

Extension Cohort (Phase 2)

Once the MTD or RP2D is reached, an additional cohort of approximately 238 evaluable patients who have confirmed $T790M^{+}$ status by central testing may be included in the Phase 2 extension cohort to further investigate the tolerability and efficacy of HS-10296.

6.2. Treatment and Duration of Therapy

HS-10296 will be administered orally as a single daily dose (although alternative frequencies or intermittent schedules may be initiated in response to emerging safety, tolerability, or PK data). Hansoh will supply HS-10296 as tablets for oral dosing. Additional information about the study drug may be found in the Investigator's Brochure.

A cycle of study treatment will be defined as 21 days of continuous dosing. Patients should continue on treatment with HS-10296 until RECIST 1.1-defined progression or until treatment discontinuation criteria is met. There is no maximum duration of treatment, as patients may continue to receive HS-10296 beyond RECIST 1.1-defined progression as long as they are continuing to show clinical benefit, as judged by the Investigator.

If HS-10296 is discontinued for reasons other than disease progression, the patient must continue RECIST 1.1 assessments every 6 weeks until disease progression occurs, even if further lines of anticancer therapy are administered.

6.3. Justification for Starting Dose, Dose Escalation, and Stopping Criteria

6.3.1. Starting Dose Justification

The starting dose for the Phase 1/2 study of HS-10296 at 55 mg QD in patients with locally advanced or metastatic NSCLC were calculated in accordance with the International Council for

Harmonisation (ICH) S9[63] guidance "Nonclinical Evaluation for Anticancer Pharmaceuticals." The guidance recommends the starting dose should be based on either 1/10 of the STD_{10} in rodent toxicity study or 1/6 of the HNSTD observed in non-rodent studies.

Male rats tolerated higher doses compared with female rats, which is partly explained by sex-related differences in drug exposure. Sex-related difference in drug exposure in rats is well documented and has been attributed differences in expression of CYP3A1 and CYP3A2 specific to rats.[64, 65] Based on data from the rat 13-week study, the rat STD_{10} 60 mg/kg/day in females and 120 mg/kg/day in males (see Section 4.2.3). To ensure a conservative approach in setting the starting dose, the female rat STD_{10} will be used in dose calculations. In the 13-week dog study, the HNSTD was the mid dose, 10 mg/kg/day. Using the conversion factors published on the Food and Drug Administration (FDA) website (FDA Guidance 2005[66]), the human equivalent dose (HED) derived from 1/10 of the rat STD_{10} (6 mg/kg per day) was calculated to be 58 mg/day, while the HED derived from 1/6 of the dog HNSTD (1.67 mg/kg per day) was calculated to be 56 mg/day. As a result of using the most conservative data, a starting dose of 55 mg/day is proposed for HS-10296.

Pharmacology data from the nude mouse human xenograft model derived from the NCI-H1975 cell line with EGFR T790M mutation (HS-10296 [*in vivo*]) was fit to a PK/pharmacodynamic model developed based on method of Gong et al, 2013.[67] The predicted HS-10296 concentrations (278 ng/mL) for maximal efficacy (75% tumor stasis) from the nude mouse human xenograft model are lower than the maximal HS-10296 concentrations (C_{max}) at the STD_{10} in rats (953 ng/mL in females and 749 ng/mL in males) and the HNSTD (475.59 ng/mL) in dogs, respectively. Thus, HS-10296 exposures at the planned starting clinical dose are anticipated to be in range of biologically active exposures.

Plasma HS-10296 concentration data will be monitored after each dose cohort in the clinical trial. The planned dose escalation scheme in the clinical protocol has the flexibility to be amended in light of emerging safety and PK data.

6.3.2. Dose Escalation and Stopping Criteria

A cycle of study treatment will be defined as 21 days of continuous dosing. In the first cohort, a delay of at least 7 days will be mandatory between the administration of the first (single) dose to the first patient and administration of the first (single) dose to subsequent patients.

- Providing there are no serious or unexplained safety issues, dosing of the remainder of the cohort will continue as suitable patients are identified. However, should ambiguous findings occur, the SRC may choose to stagger the start of dosing for the remainder of the cohort of patients.
- Providing there are no safety concerns after completion of the first cohort, subsequent cohorts of patients will be dosed as suitable patients are identified. If ambiguous findings occur after the first cohort, the SRC may choose to stagger dosing in the second cohort and likewise for subsequent cohorts.

Patients will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable patients per cohort. Dose escalation and de-escalation will follow the scheme below, according to the following process:

- If no DLT is observed in a cohort of 3 to 6 evaluable patients, then dose escalation may occur. Dose increases will be permitted after review of data from a minimum of 3 evaluable patients has been performed.
- If 1 patient experiences a DLT in a group of 3 or more evaluable patients, then the cohort will be expanded to include 6 evaluable patients. If only 1 DLT is observed in the complete cohort of 6 evaluable patients, then dose escalation may occur.
- If 2 or more patients experience a DLT in a group of 3 to 6 evaluable patients, irrespective of the number of patients enrolled, the dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease. A lower intermediary dose (de-escalation) may be considered to better define the MTD.
- Prior to achieving the MTD, dose escalation will stop if:
  - Delivery of the next dose level would require dosing of > 8 tablets per single administration, or
  - There is evidence in the dose-exposure relationship of saturation of absorption.

The proposed dose escalation schedule is shown in Table 1. All dose levels beyond Cohort 1 may change in light of emerging safety and PK data. The planned dose escalations will not exceed doubling of the dose in principle; however, up to a quadrupling of dosing may be permitted in the first 2 escalations only, if the drug concentrations from the first or second dose level are not measurable or are deemed to be far from predicted drug exposure (i.e., greater than 2-fold difference) and there have been no significant safety or tolerability issues.

Table 1 Planned Dose-Escalation Schedule

Cohort	Oral Daily Dose (mg)	Number of Tablets & Strength
1	55	3 tablets (1-40 mg, 1-10 mg, 1-5 mg)
2	110	5 tablets (2-40 mg, 3-10 mg)
3	220	7 tablets (5-40 mg, 2-10 mg)
4	260	8 tablets (6-40 mg, 2-10 mg)
to be determined	if required	

There will be a minimum of 2 days between conduct of the last patient assessment required for SRC review from 1 cohort and the start of dosing in the subsequent cohort. The dose for the subsequent cohort or a decision to stop recruitment into the escalation phase of the study will be agreed upon by the SRC after review of the data from each cohort.

There will be no intra-patient dose escalations, with the exception of patients who were started and have remained on treatment at a dose lower than 220 mg for at least 6 months, who have shown clinical benefit (as judged by the Investigator), and who then have developed RECIST-confirmed disease progression. The escalated dose must be agreed to in advance between the Investigator and the Hansoh Study Physician and will not exceed 220 mg. The escalated dose will also have been declared safe and tolerable by the SRC.

6.3.3. Dose Expansion, Extension, and Stopping Criteria

Cohorts may be expanded to further evaluate PK, tolerability, and safety of HS-10296. Patients will be enrolled in each cohort until approximately 30 evaluable patients have been enrolled in each dose expansion cohort, while approximately 238 evaluable patients may be included in the Phase 2 extension cohort. Patients should continue on treatment with HS-10296 until RECIST 1.1-defined progression or until treatment discontinuation criteria is met. There is no maximum duration of treatment, as patients may continue to receive HS-10296 beyond RECIST 1.1-defined progression as long as they are continuing to show clinical benefit, as judged by the Investigator. However, data from the expansion cohort will be evaluated by the SRC with the proposed toxicity management in place (see Section 6.8).

6.4. Definition of Dose-Limiting Toxicity

A DLT is defined as any toxicity not attributable to the disease or disease-related processes under investigation, which occurs from the first dose of study drug (Day 1, Cycle 0) up to the last day of Cycle 1 (21 days after the start of multiple dosing) in dose-escalation cohorts and which includes the following, despite optimal therapeutic intervention:

1. Hematological toxicity ≥ Common Terminology Criteria for Adverse Events (CTCAE) (version 4)

– Grade 4 neutropenia lasting more than 5 days

– Febrile neutropenia of any duration (absolute neutrophil count [ANC]) < 1.0×10^9/L and fever ≥ 38.5°C)

– Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion

– Grade 4 anemia, unexplained by underlying disease

2. Non-hematological toxicity ≥ CTCAE, Grade 3 including:

– Infection including febrile neutropenia

– Confirmed prolongation of QT interval corrected with Fridericia's (QTcF) (> 500 ms absolute or > 60 ms above Baseline)

– Cardiac toxicity greater than Grade 3

3. Any other toxicity that is:

- Greater than that at Baseline, clinically significant and/or unacceptable, and judged to be a DLT by the SRC
- A protocol-defined stopping criteria (i.e., confirmed corneal ulceration)
- Results in a disruption of dosing schedule of more than 7 days

A DLT excludes:

- Alopecia, Grade 2
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance

Note: The incidence and type of DLT-type toxicity from Cycle 2 and beyond will be taken into account by the SRC in determining dose-escalation steps.

6.5. Definition of Maximum Tolerated Dose

A dose will be considered non-tolerated and dose escalation will cease if 2 or more patients in a cohort of 3 to 6 evaluable patients experience a DLT at the dose level. Once the non-tolerated dose is defined, the MTD will be confirmed at the previous dose level below the non-tolerated dose, or a dose between the non-tolerated dose and the last tolerated dose may be investigated. Six evaluable patients are required to determine the MTD.

6.6. Definition of Evaluable Patient

For decisions on dose escalation, an evaluable patient is defined as a patient that has received HS-10296 and either:

- Has completed minimum safety evaluation requirements during the single dose period and over the first 21 days of continuous dosing, *or*
- Has experienced a DLT during the single dose period or the first 21 days of continuous dosing

6.7. Safety Review Committee

After each dose level during the dose-escalation phase of the study and during the dose-expansion phase of the study, a SRC will evaluate the safety, tolerability, and PK of HS-10296 to decide the next dose. The SRC will consist of:

- Senior Level Hansoh Physician
- Global safety physician
- Lead investigator(s)
- One oncologist

– Medical Monitor

The SRC for this study will define the exact membership and who should be present for decisions to be made. Further internal or external experts may be consulted by the SRC as necessary.

Others (e.g.: Study Pharmacokineticist, Study Statistician, Safety physician, Study Clinical Trial Lead, etc.) may be invited if appropriate.

The Global Safety Physician or delegate should always be present at the SRC for safety evaluations or/and issues for discussion.

Once there are at least 3 evaluable patients at a dose level, the SRC will review and assess all available safety data from the cohort together with available PK data to decide on the dose for the next cohort of patients. Dose interruptions and reductions will be taken into account.

The decision may be to:

- Proceed with dose escalation (refer to Section 6.3.2).
- Expand the cohort to a maximum of 6 evaluable patients.
- De-escalate the dose either to a previous lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level.
- Stop the dose-escalation part of the study.
- Stop the dose-expansion part of the study.
- Consider alternative dosing frequencies or intermittent dosing schedules.

When there are other patients whose participation is ongoing at the time of this review, the SRC may decide to defer its decision until these patients become evaluable.

Any patient who was started on treatment in error (i.e., the patient did not meet all of the inclusion criteria or the patient meets any of the exclusion criteria), but meets the criteria of an evaluable patient, will be reviewed on a case-by-case basis by the SRC to determine if the patient should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the Investigators prior to dosing any new patients.

6.8. Proposed Toxicity Management

Although HS-10296 has not yet been evaluated in humans, drug class-associated adverse reactions may be observed[21] (see Table 2). For these potential drug class-associated adverse reactions and toxicities, the proposed toxicity management is specified below.

Table 2 Potential Adverse Reactions Based on Drug Class Reported Data

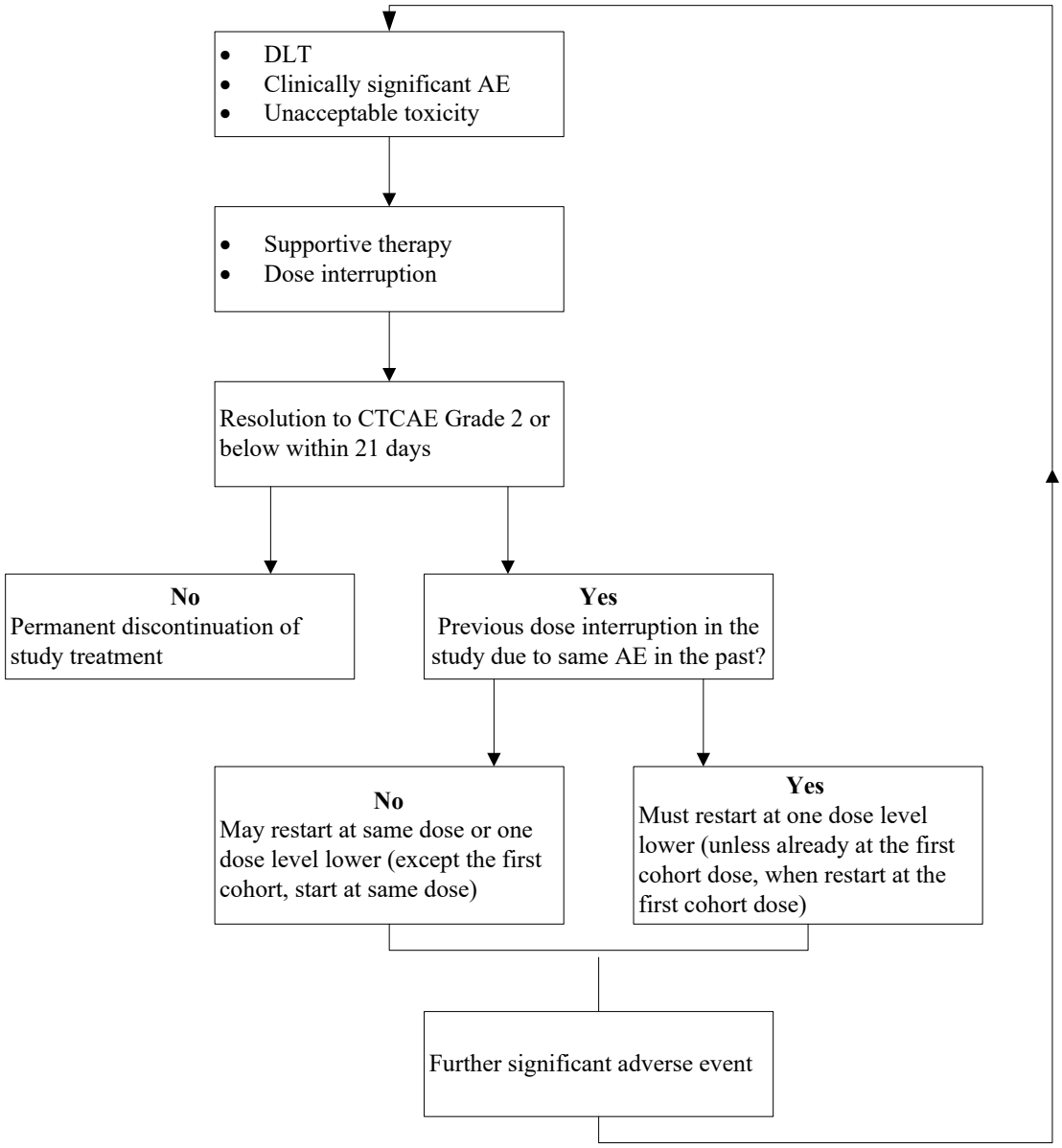
Gastrointestinal disorders Diarrhea Nausea Decreased appetite Constipation Stomatitis	Musculoskeletal Back pain
Skin disorders Rash Dry skin Nail toxicity Pruritus	Central nervous system Headache
Eye disorders Dry eye Vision blurred Keratitis Cataract Eye irritation Blepharitis Eye pain Lacrimation increased Vitreous floaters	Vascular events Venous thromboembolism
Respiratory disorders Cough Pneumonia	General Fatigue

If a patient experiences a CTCAE Grade 3 and/or unacceptable toxicity, including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. Patients with QTcF prolongation fulfilling the DLT criteria (i.e., confirmed QTcF prolongation to > 500 ms absolute or a > 60 ms increase from Baseline) should have study drug interrupted and regular electrocardiograms (ECGs) performed until resolution to Baseline. If the QTcF prolongation toxicity does not resolve to ≤ Grade 1 within 21 days, the patient will be permanently withdrawn from study treatment.

6.8.1. Dose Escalation and Expansion Cohorts

If any other toxicity resolves or reverts to ≤ CTCAE Grade 2 within 21 days of onset and the patient is showing clinical benefit, treatment with HS-10296 may be restarted at the same dose or a lower dose using the rules below for dose modifications (see Figure 2) and agreement with the Hansoh Study Team Physician as needed.

Figure 2 Dose Modification for Escalation and Expansion Cohorts



If any other toxicity does not resolve to ≤ CTCAE Grade 2 after 21 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

On resolution of toxicity within 21 days:

- If a further episode of the same adverse event (AE) subsequently requires dose interruption, HS-10296 must restart at 1 dose level lower (unless in the first cohort, when restart will be at the first cohort dose) on improvement of the AE.

- If a different AE subsequently requires dose interruption, HS-10296 may restart at the same or 1 dose level lower (unless in the first cohort, when restart will be at the first cohort dose) on improvement of the AE at the discretion of the Investigator.

Patients who are at the lowest possible dose (i.e., who have their dose previously reduced to the first cohort dose and who have demonstrated an acceptable response to the dose interruption) may be permitted to restart at the lowest dose level at the discretion of the Investigator.

6.8.2. Phase 2 Extension Cohort

If any other toxicity resolves or reverts to ≤ CTCAE Grade 2 within 21 days of onset, treatment with HS-10296 may be restarted at the same dose or a lower dose following discussion and agreement with the Hansoh Study Team Physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption. If the toxicity does not resolve to ≤ CTCAE Grade 2 after 21 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

Upon resolution of toxicity within 21 days:

- If an AE subsequently requires dose interruption, HS-10296 may be restarted at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the Investigator.

6.8.3. All Patients

Patients experiencing corneal ulceration will not be permitted to restart study treatment. If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study drug dosing is recommended, and the Hansoh Study Team should be informed.

A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, and hematological parameters) will be performed. It is strongly recommended to perform a full diagnostic workup, 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 and study treatment permanently discontinued. In the absence of a diagnosis of interstitial lung disease, study treatment may be restarted following consultation with the Hansoh Study Team Physician.

6.8.4. Assessment Timing if Dosing is Interrupted

If a patient misses any doses of HS-10296 during the 21-day evaluation period of Cycle 1 due to the dosing interruption for toxicity management, please contact the Hansoh Study Team for advice regarding the evaluability of the patient and appropriate timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST, should continue to be performed as per study plan, relative to the baseline assessments.

6.9. Premature Termination or Suspension of Study or Investigational Site

6.9.1. Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria that require temporary suspension or early termination of the study are met:

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for patients participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises patient safety.

6.9.2. Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.9.3. Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor, an institutional review board (IRB)/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor. The procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7. SELECTION AND DISCONTINUATION/WITHDRAWAL OF PATIENTS

7.1. Inclusion Criteria

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of starting study treatment. Under no circumstances can there be exceptions to this rule.

1. Provision of signed and dated, written informed consent prior to any study-specific procedures, sampling, and analyses. If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the patient and he or she will not be excluded from other aspects of the study.
2. Age at least 18 years.
3. Histological or cytological confirmation diagnosis of NSCLC.
4. Radiological documentation of disease progression while on a previous continuous treatment with an EGFR TKI (e.g., gefitinib or erlotinib). In addition, other lines of therapy may have been given. All patients must have documented radiological progression on the last treatment administered, prior to enrolling in the study.
5. Patients must fulfill 1 of the following:
   - Confirmation that the tumor harbors an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q).
   - Must have experienced clinical benefit from EGFR TKI, according to the Jackman[1] criteria (followed by systemic objective progression, RECIST or WHO) while on continuous treatment with an EGFR TKI.
6. For dose-expansion and dose-extension cohorts, patients must also have confirmation of tumor T790M$^+$ mutation status from a biopsy sample taken after disease progression on the most recent treatment regimen with an EGFR TKI.

   Prior to entry, a result from the central analysis of the patient's T790M mutation status must be obtained.
7. A WHO performance status equal to 0-1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.
8. At least 1 lesion that has not previously been irradiated, that has not been chosen for biopsy during the study screening period, and that can be accurately measured at Baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with computerized tomography (CT) or magnetic resonance imaging (MRI), whichever is suitable for accurately repeated measurements.
9. Females should be using adequate contraceptive measures throughout the study; should not be breastfeeding at the time of screening, during the study and until 3 months after

completion of the study, and must have a negative pregnancy test prior to start of dosing if of childbearing potential or must have evidence of non-childbearing potential by fulfilling 1 of the following criteria at Screening (refer to Section 7.3 for restrictions):

a. Postmenopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.

b. Women under 50 years old would be considered as postmenopausal if they have been amenorrheic for 12 months or more, following cessation of exogenous hormonal treatments, and with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the postmenopausal range for the laboratory.

c. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation.

10. Male patients should be willing to use barrier contraception (i.e., condoms; refer to Section 7.3 for restrictions).

11. For dose-expansion paired biopsy cohort:

– Presence of at least 1 non-target lesion (NTL) suitable for multiple biopsies on treatment.

12. For inclusion in optional genetic research, patient must provide a written informed consent for genetic research.

7.2. Exclusion Criteria

Any patient who meets any of the following exclusion criteria will not qualify for entry into the study.

1. Treatment with any of the following:

a. An EGFR TKI (e.g., erlotinib, gefitinib, or osimertinib) within 8 days or approximately 5 × half-life, whichever is longer, of the first dose of study drug. (If sufficient washout time has not occurred due to schedule or PK properties, an alternative appropriate washout time based on known duration and time to reversibility of drug-related AEs must be agreed upon by Hansoh and the Investigator).

b. Previous or current treatment with third-generation EGFR TKIs (Expansion and Extension Cohorts only).

c. Any cytotoxic chemotherapy, investigational agents, or anticancer drugs for the treatment of advanced NSCLC from a previous treatment regimen or clinical study within 14 days of the first dose of study drug.

d. Medications that are predominantly CYP3A4 strong inhibitors or inducers or sensitive substrates of CYP3A4 with a narrow therapeutic range within 7 days of the first dose of study drug.

e. Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug.

f. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study drug, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.

2. Previously untreated NSCLC patients. To be eligible for this study, patients must have received and progressed on EGFR TKI therapy.
3. Any unresolved toxicities from prior therapy > CTCAE Grade 1 at the time of starting study treatment, with the exception of alopecia and Grade 2 prior platinum-therapy-related neuropathy.
4. Spinal cord compression or brain metastases, unless asymptomatic, stable, and not requiring steroids for at least 4 weeks prior to start of study treatment.
5. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension or active bleeding diatheses, which, in the Investigator's opinion, makes it undesirable for the patient to participate in the trial OR which would jeopardize compliance with the protocol, such as active infection (e.g., hepatitis B, hepatitis C, and human immunodeficiency virus [HIV]). Screening for chronic conditions is not required.
6. Any of the following cardiac criteria:

   a. Mean resting QTc > 470 ms obtained from 3 ECGs, using the screening clinic's ECG machine and Fridericia's formula for QT interval correction (QTcF).

   b. Any clinically important abnormalities in rhythm, conduction, or morphology of the resting ECG (e.g., complete left bundle branch block, third-degree heart block, second-degree heart block, PR interval > 250 ms).

   c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval.

   d. Left ventricular ejection fraction (LVEF) ≤ 40%.

7. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis that required steroid treatment, or any evidence of clinically active interstitial lung disease.
8. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

   – ANC < 1.5×10^9/L

   – Platelet count < 100×10^9/L

- Hemoglobin < 90 g/L
- Alanine aminotransferase (ALT) > 2.5 × upper limit of normal (ULN) if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases
- Aspartate aminotransferase (AST) > 2.5 × ULN if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases
- Total bilirubin (TBL) > 1.5 × ULN if no liver metastases or > 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases
- Creatinine > 1.5 × ULN concurrent with creatinine clearance < 50 mL/min (measured or calculated by Cockcroft-Gault equation); confirmation of creatinine clearance is only required when creatinine is > 1.5 × ULN

9. Refractory nausea, vomiting, or chronic gastrointestinal diseases, inability to swallow the study drug or previous significant bowel resection that would preclude adequate absorption of HS-10296.
10. History of hypersensitivity to active or inactive ingredients of HS-10296 or to drugs with a similar chemical structure or class to HS-10296.
11. Women who are breastfeeding or have a positive urine or serum pregnancy test at the Screening Visit.
12. Involvement in study planning and conduct (i.e., to Hansoh staff or staff at the study site).
13. Judgment by the Investigator that the patient should not participate in the study, if the patient is unlikely to comply with study procedures, restrictions, and requirements.
14. Any disease or condition that, in the opinion of the Investigator, would compromise the safety of the patient or interfere with study assessments.
15. The following are considered criteria for exclusion from the exploratory genetic research:
    - Previous allogenic bone marrow transplant.
    - Non-leukocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection.
16. Any severe and uncontrolled ocular disease that may, in the ophthalmologist's opinion, present a specific risk to the patient's safety.

7.3. Restrictions

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after as described in the paragraphs below:

1. Females of childbearing potential should use reliable methods of contraception from the time of Screening until 3 months after discontinuing study treatment. Acceptable methods of contraception include abstinence, tubal ligation, oral or transdermal contraceptives, copper-banded intrauterine devices, and vasectomized partner. All hormonal methods of

contraception should be used in combination with the use of a condom by the patient's male sexual partner for intercourse.

2. Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all partners at the time of Screening, during the study, and until 3 months after discontinuing study treatment. Patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment. If male patients wish to father children from the start of dosing until 6 months after discontinuation of study treatment, they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.
3. Patients should avoid procreation for 6 months after completion of study treatment.
4. Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE Grade ≤ 2) while receiving treatment with HS-10296 until at least 1 week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE Grade ≥ 3) ocular events, he or she must discontinue wearing the contact lenses until at least 1 week after treatment with HS-10296 is permanently discontinued. Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed to by the Investigator, at any time during the study and until 1 week after HS-10296 has been permanently discontinued. Patients should consult the clinic promptly if they have any concerns.
5. Patients must try to avoid concomitant use of medications or herbal supplements, and/or ingestion of foods such as grapefruit with known potent substrates/inducers/inhibitors of CYP3A4 and/or CYP2D6 and/or CYP1A2 when feasible, but patients may receive any medications that are clinically indicated for treatment of AEs. Such drugs must have been discontinued for at least 1 month before patients enter Screening and for a period of 3 months after the last dose of HS-10296.

7.4. Concomitant Medications

Information on all medication taken in the 4 weeks prior to starting study treatment and all concomitant medication taken during the study, with the indications for the medication, will be recorded in the electronic case report form (eCRF). After permanent discontinuation of HS-10296 and during the 28-day follow-up period after discontinuation of HS-10296, only subsequent regimens of anti-cancer therapy will be recorded in the eCRF.

If medically feasible, patients taking regular medication should be maintained on it throughout the study period. Other anticancer agents, investigational agents, and radiotherapy should not be given while the patient is on study treatment, except that patients may also receive radiotherapy for painful bony metastases.

Premedication for management of diarrhea, nausea, and vomiting will be allowed after, but not before, the first dose of study drug. Blood transfusions are allowed at any time during the study.

Granulocyte colony-stimulating factors should not be used prophylactically during Cycle 1. Use of prophylactic colony-stimulating factors may be considered after Cycle 1 following discussion with the Hansoh Study Team Physician.

Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases.

Supportive care and other medications that are considered necessary for the patient's well-being may be given at the discretion of the Investigator.

All patients must try to avoid concomitant use of medications, herbals supplements and/or ingestion foods with known potent substrates/inducers/inhibitors of CYP3A4 and/or CYP2D6 and/or CYP1A2. Adverse events as well as concomitant medications should be closely monitored per Study Plan.

A list of prohibited medications and medicines to avoid are provided in Appendix G.

7.5. Criteria for Discontinuation or Withdrawal of a Patient

The primary reason for discontinuation or withdrawal of the patient from the study should be recorded in the eCRF, using the following categories:

- Voluntary withdrawal by patient decision
  - The patient is at any time free to withdraw his or her participation in the study, without prejudice and independent of any decision concerning participation in other aspects of this study.
- AE
  - The patient has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the patient's health or the patient is unwilling to continue because of the AE.
- Pretreatment event
  - The patient has a pretreatment event that requires early termination because continued participation imposes an unacceptable risk or the patient is unwilling to continue due to the pretreatment event.
- Pregnancy
  - If the patient is found to be pregnant, the patient must be withdrawn immediately.
- Major protocol deviation as judged by the Investigator and/or Hansoh
  - The discovery post-randomization that the patient was incorrectly initiated on investigational drug, failed to meet protocol entry criteria, or did not adhere to protocol requirements **and** continued participation poses an unacceptable risk to the patient's health.

- Confirmed disease progression
- Lost to follow-up
    - The patient did not return to the clinic and a minimum of 3 and maximum of 5 attempts to contact the patient by telephone calls, e-mail, and/or written correspondences were unsuccessful. Attempts to contact the patient must be documented.
- Compliance
    - The patient has poor compliance with study drug or study procedures.
- Additional treatment
    - The patient requires treatment with another drug that will interfere with evaluation of the study drug.

Patients that are withdrawn from the study but are evaluable will not be replaced. Any patient that is withdrawn and is not evaluable will be replaced to ensure a minimum number of evaluable patients.

7.6. Procedures for Discontinuation or Withdrawal of a Patient

The Investigator should terminate a patient's study participation at any time during the study when the patient meets the study termination criteria described in Section 7.5. In addition, a patient may discontinue his or her participation without giving a reason at any time during the study. Should a patient's participation be discontinued, the primary criterion for termination must be recorded.

7.7. Procedures for Discontinuation of a Patient from Study Drug

A patient who discontinues study treatment is not always automatically withdrawn from the study. Once study drug is permanently discontinued it cannot be restarted.

In addition, any patients who discontinue study treatment for reasons other than objective disease progression should have tumor assessment scans performed as planned in the schedule of assessments (see Appendix B) until objective disease progression is documented or death occurs, unless consent is withdrawn.

Information on serious adverse events (SAEs), AEs, and concomitant medication is provided in Section 9.1.10.1, Section 9.1.10.2, and Section 9.7.3.

8. STUDY TREATMENTS

This section contains information regarding all medication and materials (provided directly by the Sponsor, and/or sourced by other means) that are required by the study protocol, including description of management of study drug.

8.1. Investigational Product

8.1.1. Treatments Administered

HS-10296 will be orally administered once daily. Patients should avoid consumption of food for at least 1 hour prior to and 2 hours post dosing.

The administration schedule is given in Table 3.

Table 3 Dose Administration Schedule

	Single Dose/ Cycle 0 (7-day cycle)	Multiple Dose/ Cycle 1 (21-day cycle)	Cycles 2-6 (21-day cycle)	Cycle 7 and Every 6 Weeks Onwards
Phase 1 dose escalation	Day 1 dosing only	Daily dosing	Daily dosing	Daily dosing
Phase 1 dose expansion/ paired biopsy cohort	NA	Daily dosing	Daily dosing	Daily dosing
Phase 2 extension cohort	NA	Daily dosing	Daily dosing	Daily dosing

8.1.2. Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below. During the study period, the study drug will be provided according to Table 4.

Table 4 Dose Strength

Study Drug	Dosage Strength/Dosage Form	Manufacturer
HS-10296	5-mg tablets	Jiangsu Hansoh Pharmaceutical Group Co., Ltd
HS-10296	10-mg tablets	Jiangsu Hansoh Pharmaceutical Group Co., Ltd
HS-10296	40-mg tablets	Jiangsu Hansoh Pharmaceutical Group Co., Ltd

Please note that an additional strength may be developed pending results from the escalation cohorts.

The study sites will be supplied with study drug, which will be packaged in polyvinylchloride/aluminum blisters. Each blister card will have a label that will contain, but will

not be limited to: protocol number, investigational drug identification (ID) number, lot number, name and strength of the product, quantity of dosage unit, directions for use, storage conditions, country-specific regulatory caution statement, and name and address of the Sponsor.

8.1.3. Storage

All study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the Sponsor or designee for destruction. All Sponsor-supplied drugs must be stored under the conditions specified on the label and remain in the original container until dispensed. All study drug must be stored as follows:

> 20°C to 25°C (68° to 77°F); excursions allowed between 15° and 30°C (59° and 86°F). Protect from moisture and humidity.

The Investigator should ensure that study drug is used only in accordance with the approved protocol. Study drug shall be dispensed only to patients enrolled in the study.

8.2. Study Drug Assignment and Dispensing Procedures

Study drug assignment schedules will be managed through a specific electronic data capture (EDC) configuration. The decision whether to enroll the next cohort at a higher dose level will be made by the SRC, based on the safety and PK results of the previous cohort. All safety results for the study, including the SAE database, will be captured in the EDC project database. Since dosing in this study is open label, an interactive voice response system (IVRS) will not be required for this study.

8.3. Accountability and Destruction of Study Drugs

Drug supplies will be counted and reconciled at the site before being returned to the Sponsor or designee.

The Investigator or designee must ensure that the Sponsor-supplied drug is used in accordance with the approved protocol and is dispensed only to patients enrolled in the study. To document appropriate use of study drug, the Investigator must maintain records of all study drug delivery to the site, site inventory, dispensation and use by each patient, and return to the Sponsor or designee.

Upon receipt of the study drug, the Investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, that the medication is received within the labeled storage conditions, and that the package is in good condition. If quantity and conditions are acceptable, the Investigator or designee should acknowledge the receipt of the shipment. If there are any discrepancies between the packing list versus the actual product received, Hansoh must be contacted to resolve the issue. The packing list should be filed in the Investigator’s essential document file.

The Investigator must maintain 100% accountability for all study drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot (or ID or lot number) used to prepare each dose.
- Verifying that all containers used and unused are documented accurately on the log.
- Verifying that required fields are accurately completed and are legible.

If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

The Investigator must record the current study inventory on a Sponsor-approved drug accountability log. At a minimum, the following information will be recorded for each patient:

- Protocol number and title
- Name of Investigator
- Site identifier and number
- Description of Sponsor-supplied drugs
- Date and amount dispensed, including initials of the person dispensing the drug
- Date and amount returned to the site by the patient, including the initials of the person receiving the Sponsor-supplied drug

The log should include a separate entry for each patient who receives Sponsor-supplied study drug.

Prior to site closure or at appropriate intervals, a representative from the Sponsor or its designee will perform study material accountability and reconciliation before study materials are returned to the Sponsor or its designee for destruction. The Investigator will retain the original documentation regarding study material accountability and return of study materials; copies (as required) will be sent to the Sponsor or designee.

The Investigator will be notified of any expiry date or retest date extension of study material during the study conduct. On expiry date notification from the Sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired study material for return to the Sponsor or its designee for destruction.

9. STUDY PLAN AND PROCEDURE

9.1. Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, patients are to be assessed by the same Investigator or site personnel whenever possible. The Study Plan is described in Appendix B.

9.1.1. Informed Consent Procedure

The requirements of the informed consent are described in Section 13.2.

Informed consent must be obtained prior to the patient entering into the study and before any protocol-directed procedures are performed.

A unique patient ID number (patient number) will be assigned to each patient at the time that informed consent is obtained. This patient number will be used throughout the study.

9.1.2. Screening and Enrollment

At Screening, each potential patient will provide informed consent prior to starting any study-specific procedures during the 28 days prior to admission to confirm eligibility (see Study Plan, Appendix B). Tumor assessments and other clinical data obtained as standard of care prior to informed consent may be used for the study provided the assessments fall within the protocol-specified period prior to the first dose of study drug. Tumor receptor/mutation status will be recorded including EGFRm^{+}, T790M^{+}, cMET, etc.

Demographic data and other characteristics will be recorded and will include date of birth or age, gender, race and/or ethnicity, and smoking status of the patient. A standard medical, medication and surgical history will be obtained with review of the selection criteria with the patient.

Enrollment into the study will be conducted in a controlled manner. No patient will be enrolled without prior authorization from Hansoh to ensure adherence with the rolling 6 recruitment design and subsequent allocation to expansion cohorts. If a patient withdraws from the study, then the enrollment code cannot be reused.

9.1.3. Physical Examination Procedure

A baseline physical examination (defined as the pretreatment assessment immediately prior to the start of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the baseline examination, except for a neurological examination, which will be performed at each cycle physical examination.

Performance status will be assessed at Screening, prior to the first dose of study drug, at the beginning of each cycle, and at discontinuation, according to WHO criteria as follows:

0 = Fully active, able to carry out all pre-disease activities without restrictions

1 = Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)

2 = Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4 = Completely disabled; cannot carry on self-care; totally confined to bed or chair

9.1.4. Weight, Height

A patient should have weight and height measured while wearing indoor clothing and with shoes off. Weight and height will be measured as shown in the Study Plan (Appendix B).

9.1.5. Vital Sign Procedure

Vital sign measurements including body temperature (oral or otic; in centigrade), blood pressure (systolic and diastolic), and pulse (beats per minute) will be collected. Blood pressure and pulse will be measured while the patients are in a sitting position for at least 5 minutes. Assessments will be performed as shown in the Study Plan (Appendix B).

9.1.6. Laboratory Safety Assessment

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the visits as indicated in the Study Plan (Appendix B). Laboratory tests do not need to be repeated at Baseline if the baseline visit is within 7 days of obtaining the screening sample.

Following review of data from a group of patients, the timing of blood samples may be adjusted for subsequent groups of patients. Additional sampling times may be added if indicated by the emerging data. Laboratory values that meet the criteria for CTCAE (version 4) Grade 3 OR have changed significantly from Baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate. The following laboratory variables will be measured:

Clinical Chemistry	Hematology	Urinalysis
Serum (S)/Plasma (P)-Albumin	Blood (B)-Hemoglobin	U-Glucose
S/P-ALT	B-Leukocyte	U-Protein
S/P-AST	B-Hematocrit	U-Blood
S/P-Alkaline phosphatase	B-Red blood cell (RBC) count	
S/P-Bilirubin, total	B-Absolute leukocyte differential count	
S/P-Calcium, total	Neutrophils	
S/P-Creatinine	Lymphocytes	
S/P-Glucose (fasting on PK days only)	Monocytes	
S/P-HbA1C	Basophils	
S/P-Magnesium	Eosinophils	
S/P-Potassium	B-Platelet count	
S/P-Sodium	B-Reticulocytes	
S/P-Urea nitrogen		

A urine or serum pregnancy test will be performed for women of childbearing potential at Screening or within 3 days before the first dose of study drug. The results must be available and negative before the first dose of study drug is administered.

If a patient has an AST or ALT ≥ 3 × ULN or TBL ≥ 2 × ULN, please refer to Appendix C for actions required in cases of combined increase of aminotransferase and TBL – Hy's Law, for further instructions.

The Investigator or designee is responsible for transcribing laboratory results to the eCRF. The Investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

9.1.7. Electrocardiograms

A resting 12-lead ECG will be performed at the visits indicated in the Study Plan (Appendix B). The resting 12-lead ECGs will be recorded at the following times (a 5-minute window will be allowed for the ECG examination at 1 hour; a 10-minute window at 2, 4, 6 and 10 hours; and a 1-hour window at 24 hours after dosing); however, the timing and number of ECGs may be altered, depending on the emerging PK and safety profile. A summary of the ECG schedule is provided below and presented in Appendix H.

- Screening
- First dosing day (Day 1 Cycle 0 for dose escalation cohorts)
  - predose, 1, 2, 4, 6, 10, and 24 hours (Day 2) postdose

- First dosing day (Day 1 Cycle 1 for expansion and extension cohorts)
  - predose, 1, 2, 4, 6, and 10 hours postdose
- Days 1, 2, 3, 4, and 6 Cycle 1 for dose-escalation cohorts
  - Day1: predose only
  - Day 2, 3, 4 and 6: predose, 6, and 10 hours postdose
- Day 8 and Day 15 Cycle 1 (multiple dosing for all cohorts)
  - predose only
- Days 1, 8 and 15 Cycle 2
  - Escalation Cohort Day 1 Cycle 2: predose, 1, 2, 4, 6, 10 and 24 hours (Day 2) postdose
  - Expansion and Extension Cohorts Day 1 Cycle 2: predose, 1, 2, 4, 6, and 10 hours postdose
  - All Cohorts Day 8 and 15 Cycle 2: predose only
- Day 1 of each subsequent cycle
  - 1 measurement at any time during day
- On occurrence of any cardiac AE
- Discontinuation visit

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to the indicated times. All ECGs should be recorded with the patient in the same physical position. For each time point, 3 ECG recordings should be taken at about 5-minute intervals. A standardized ECG machine should be used and the patient should be tested using the same machine throughout the study, if possible.

After paper ECGs have been recorded, the Investigator or a designated physician will review each of the ECGs. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at Screening or Baseline is considered to be clinically significant by the Investigator, it should be reported as medical history as a concurrent medical condition. For all ECGs, details of rhythm, ECG intervals, and an overall assessment will be recorded.

9.1.8. Echocardiogram/MUGA Scan

An echocardiogram or multigated acquisition (MUGA) scan to assess LVEF will be conducted in escalation, expansion, and extension cohort patients at the Screening Visit, 12 weeks after the first dose of HS-10296, and every 12 weeks (± 1 week) thereafter.

The modality of the cardiac function assessments must be consistent within each patient (e.g., if an echocardiogram is performed for the screening assessment, then an echocardiogram also should be performed for subsequent scans). The patient also should be examined using the same machine and operator whenever possible.

9.1.9. Ophthalmology Examination

Full ophthalmic assessment, including slit lamp examination, should be performed at Screening, on Day 1 of Cycles 2 and 3, and then as needed per signs or symptoms of toxicity. The time window of ophthalmology assessment is ± 2 days. If a patient experiences any visual symptoms (including blurred vision) or signs and symptoms of toxicity, an ophthalmic examination should be performed within 48 hours of any ophthalmic signs and symptoms. Additional tests will be conducted if clinically indicated. Any clinically significant findings and symptoms, including those confirmed by the ophthalmologist, must be reported as an AE. Ophthalmology examination results should be collected in the eCRF.

Photographs should be taken to record any clinically significant findings. These photographs should be available for central review by Hansoh and/or Hansoh representatives, if necessary.

9.1.10. Follow-up

9.1.10.1. Safety Follow-up

A post-study assessment will be performed at the time that the study drug is permanently discontinued (see Study Plan, Appendix B). In addition, as a minimum, to follow-up any SAEs, AEs, and concomitant medications, a safety follow-up telephone contact should be made with the patient 28 ± 3 days following the discontinuation of HS-10296. Information should be obtained regarding any subsequent anticancer therapy. Any SAEs will be followed up to resolution, when possible.

9.1.10.2. Progression Follow-up

Patients who discontinue HS-10296 for reasons other than progression will continue RECIST 1.1 assessments every 6 weeks (relative to the first dose of multiple dosing). Details of concomitant medications (including any subsequent anticancer therapy) should continue to be collected as detailed in the Study Plan (Appendix B) up to the 28-day follow-up visit. Only new SAEs due to study drug should be collected. For those patients in the expansion cohorts, an additional HRQoL questionnaire should be completed on progression. Beyond the 28-day follow-up visit, only subsequent cancer therapy should be collected.

9.1.10.3. Survival Follow-up

In the Phase 2 extension, following disease progression, the patient, patient's family, or the patient's current physician must be contacted every 6 weeks for survival information. Details of subsequent treatment regimens received following withdrawal from study drug and follow-up of unresolved AEs (unless the patient withdraws consent), regardless of the date of last contact, must be collected (Appendix B).

9.2. Pharmacokinetics

9.2.1. Collection of PK Samples

Venous blood samples for determination of concentrations of HS-10296 and its metabolite (HAS-719) in plasma will be collected at the times presented in Table 5. If dose interruption occurs within 3 days of PK sampling, discussions with Hansoh will be required to determine if the PK sample schedule is affected. The date and time of collection of each sample and the date and time of the dose will be recorded.

A 3-minute window will be allowed for samples taken at 30 minutes; a 5-minute window for samples taken at 1 hour; a 10-minute window for samples taken at 1.5 to 10 hours; a 1-hour window for samples taken at 12 hours and 24 hours; and a 2-hour window for samples taken at 48 to 120 hours.

Table 5 PK Blood Sampling Schedule

Time Relative to Dose	Dose Escalation Only					All Patients			
	Single Dosing Cycle 0					Multiple Dosing Cycle 1			Multiple Dosing Cycle 2
	D1	D2	D3	D4	D6	D1	D8	D15	D1
Predose	X					X	X	X	X
30 min	X								X
1 h	X								X
1.5 h	X								X
2 h	X								X
4 h	X								X
6 h	X								X
8 h	X								X
10 h	X								X
12 h	X								X
24 h		X							X (D2, Predose)
48 h			X						
72 h				X					
120 h					X				
At time of biopsy								X[a]	

[a] Cycle 1 Day 15 predose PK sample will be collected for all patients. Collection of the Cycle 1 Day 15 "time of biopsy" PK sample is required only if a biopsy is taken and when it is feasible to do so.

9.2.2. Determination of Drug Concentration in Pharmacokinetic Samples

Samples for determination of plasma concentrations of HS-10296 and its metabolite HAS-719 will be analyzed using an appropriate bioanalytical method. Full details of the analytical method will be described in a separate bioanalytical report. All samples that are within the known stability of the analytes of interest (i.e., HS-10296 and its metabolite HAS-719) at the time of receipt by the bioanalytical laboratory will be analyzed. In addition, the PK samples may be subjected to further analyses by the Sponsor to further investigate the presence and/or identity of additional drug metabolites.

9.3. Pharmacodynamics

The pharmacodynamic effects of HS-10296 will be evaluated in tumor tissue from paired biopsies (a tumor biopsy predose and a paired tumor biopsy postdose). The biomarkers investigated may include, but are not limited to, pEGFR, pERK, pAKT, pS6, pGSK3b, p4EBP1, cleaved caspase 3, and Ki67.

9.4. Exploratory Investigation

9.4.1. Exploratory Biomarker Research

If a patient agrees to participate in the exploratory biomarker research component of the study, biological samples (e.g., plasma, serum, archived and study-obtained tumor) will be collected and may be analyzed to assess correlations of biomarkers with disease activity, effects of study drug, and clinical outcomes. The results of this exploratory biomarker research will be reported separately and will not be included within the clinical study report; the results also may be pooled with biomarker data from other studies to generate hypotheses that will be tested in future studies.

9.4.1.1. Collection of Tumor Biopsy Samples

If a sample of archival tumor block is taken at the time of diagnosis, patients will be asked to provide consent to analyze a sample of their archival tumor blocks. Any archival biopsy samples taken, following previous lines of therapy, also will be requested, if available. In each case, the patient's previous treatment must be indicated clearly for each sample provided. All patients will be asked to consent to optional biopsies as detailed in Table 6.

Table 6 Tumor Biopsy Sampling

Time Relative to Dose Escalation Expansions	Escalation	Expansion	Paired Biopsy
Archival	M*	M*	M*
Screening	O	M + O	M
Day 15	O	O	M
Discontinuation	O	O	O

M = Mandatory; O = Optional; M* = Mandatory if available

Biopsy samples will be used to support the development of the diagnostic assay and further exploratory research. The optional screening sample should be obtained at the same time and as part of the same sample procedure as the mandatory biopsy for T790M status. For patients in the paired biopsy cohort, the mandatory screening biopsy will be used as the first of the patient's paired biopsy samples, as well as for identifying T790M status. Tumor samples preferably will be in the form of a formalin-fixed paraffin-embedded block (tissue derived from the diagnostic tumor or a metastatic site). If this is not possible, 10 to 20 slides of freshly prepared unstained 5-micron sections from the archival tumor block may be provided. The biomarkers to be investigated, using tumor samples collected from the paired biopsy cohort, will not be limited to, but will include, all or some of the following:

- pEGFR
- pERK

- pAKT
- pS6
- pGSK3β
- p4EBP1
- pPRAS4
- cleaved caspase 3

9.4.1.2. Collection of Plasma for Exploratory Analysis of cfDNA

All patients will be asked to provide plasma samples which will be used for the extraction and analysis of circulating cell-free DNA (cfDNA). The sample may be used to further investigate the relationship between PK and blood-borne biomarkers. Plasma samples will be taken at the following times:

- Screening
- Predose on Day 1
- Every 6 weeks up to and including progression (corresponding with the RECIST assessments)
- Discontinuation of treatment

The samples will be analyzed for a range of oncology biomarkers, which may correlate with drug response.

9.4.2. Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study, a blood sample will be collected. The results of this pharmacogenetic research will be reported separately and will not be included within the clinical study report.

The blood-borne biomarkers (e.g., L858R, 19 exon deletion, T790M) will be specially investigated for their gene expression, mutation, or deletion to assess response to the study drug HS-10296 and development of NSCLC.

9.4.2.1 Collection of Pharmacogenetic Samples

The blood sample for genetic research will be obtained from the patients immediately prior to the first administration of HS-10296. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE. Such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn prior to dosing, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetic analysis.

9.5. Biological Sampling Procedures

9.5.1. Volume of Blood

The total volume of blood that will be drawn for each patient for mandatory samples up to the end of Cycle 2, in accordance with the PK Blood Sampling Schedule (Table 5), is as follows:

- Dose escalation approximately 145 mL
- Dose expansion approximately 75 mL
- Dose extension approximately 75 mL

The total number of samples drawn and blood volumes required might be subject to protocol-specific procedures and changes, or to the central laboratory's established methods.

Safety laboratory assessments will be performed locally at each study site's laboratory, based on its established methods. The number of samples and/or blood volumes required is, therefore, subject to site-specific change.

9.5.2. Handling, Storage, and Destruction of Biological Samples

After analysis, samples will be disposed of or retained for further use as described below. Any PK sample remaining after analysis for HS-10296 and its metabolites may be used for exploratory biomarker analyses. These analyses are for Sponsor use only and will not be included in the clinical study report.

Biological samples for future research will be retained by the Sponsor or designee for a maximum of 15 years following the finalization of the clinical study report. The results from future analysis will not be reported in the clinical study report, but separately in a bioanalytical method validation report.

9.5.3. PK Samples

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report. Samples for metabolite identification and/or analysis will be performed as an exploratory endpoint in this study. The results from the investigation(s) will not be reported in the clinical study report but will be reported separately in a drug metabolism and PK report.

9.5.4. Exploratory Research Samples

It is optional to collect once-only CSF on Day 1 in any of the treatment Cycles of 2 through 7 and every 6 weeks after that. The sample volume of CSF will be 10 to 15 mL.

Each sample for exploratory research will be identified with the study number and patient enrollment number so that exploratory biomarker and genetic data may be correlated with

clinical data. Samples may be destroyed in the case of withdrawal of consent and regulatory audit may be enabled.

Where genetic analysis will be undertaken, the processes adopted for the coding and storage of samples will be more stringent to maintain patient confidentiality. As an added precaution, the DNA sample, irrespective of the type of sample, will be assigned a unique number replacing the previous information on the sample. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will be used to identify the sample and corresponding data at the Hansoh genetics laboratories or at the designated contract laboratory.

No personal details identifying the individual will be available to any person working with the DNA. Samples and data for genetic analysis will be single coded. The link between the patient enrollment code and the DNA number will be maintained and stored in a secure environment with restricted access. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and trace samples for destruction, if consent is withdrawn when the patient has requested disposal/destruction of collected samples not yet analyzed.

9.5.5. Withdraw of Informed Consent for Donated Biological Samples

If a patient withdraws consent to the use of voluntarily donated biological samples for the exploratory research in this study, the samples will be disposed of/destroyed and the action documented. If samples have already been analyzed, the Sponsor is not required to destroy the results of this research. The patient otherwise may continue in the study. The Principal Investigator must:

- Ensure that the Sponsor is notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples.
- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensure that any laboratory housing the samples is informed immediately of the withdrawn consent and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site.
- Ensure that the patient and the Sponsor are informed of the sample disposal.

The Sponsor will ensure that any central laboratory housing the samples is immediately informed of withdrawn consent and that remaining samples are disposed of/destroyed, the action documented, and the document returned to the study site.

9.6. Anti-tumor Activity

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and NTLs, and the objective tumor response criteria are presented in Appendix D. Baseline CT or MRI assessments

of the chest and abdomen (including liver and adrenal glands) must be performed no more than 28 days before the start of study treatment and, ideally, should be performed as close as possible to the start of study treatment. Additional imaging may be performed based on individual patient signs and/or symptoms. A CT or MRI scan of the brain should be performed in patients with known or suspected brain metastases. The same method of assessment (e.g., CT, MRI) used at Baseline should be used at each subsequent follow-up assessment.

Follow-up assessments should be performed every 6 weeks (± 7 days) after the start of multiple dosing, until objective disease progression occurs, as defined by RECIST 1.1 (this also applies to patients who discontinued treatment prior to progression). Any other sites where new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits while the patient remains on study treatment.

Categorization of objective tumor response assessment will be based on the RECIST 1.1 guidelines for response:

- CR
- PR
- SD (stable disease)
- PD (progression of disease)

The TL progression will be calculated in comparison to when the tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements that were obtained before treatment start. If the Investigator is in doubt about tumor response assessment, then reassessment can be performed at the patient's next scheduled assessment or sooner, if clinically indicated. If a second scan confirms progression, the date of the initial scan should be documented as the date of progression.

To achieve "unequivocal progression" on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of HS-10296. A modest "increase" in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

All RECIST 1.1 assessment images will be reviewed at the site. Duplicates may be collected and stored by a Sponsor-appointed representative and sent for independent central RECIST 1.1 review, if deemed appropriate.

9.7. Adverse Events

9.7.1. Definition of AEs

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings, ECG).

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an AE as far as the deterioration can be anticipated.

9.7.2. Definition of SAEs

A SAE is an AE occurring during any study phase that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient's safety or may require medical intervention to prevent 1 of the outcomes listed above

9.7.3. Recording of AEs

9.7.3.1. Time Period for Collection of AEs and SAEs

All AEs will be collected throughout the study, from informed consent until the end of the follow-up period. The follow-up period is defined as 28 ± 3 days after study treatment is discontinued.

All SAEs occurring throughout the study, from informed consent until the end of the follow-up period, should be reported to the Sponsor within 24 hours of the site becoming aware of an SAE.

Following discontinuation of HS-10296, SAEs considered related to study drug and procedures should continue to be collected while patients are followed for disease progression. After the final database lock, some patients may remain on study treatment. For these patients who are continuing to receive HS-10296, the Sponsor will collect information (during the treatment period and for 28 ± 3 days after last dose) only on SAEs, deaths (including those due to disease progression), discontinuation due to AEs/SAEs, and drug accountability.

9.7.3.2. Follow-up of Unresolved AEs

Any AEs that are unresolved at the patient's last study visit will be followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary. If an Investigator learns of any new SAE, including death, at any time after a patient has completed the study and he or she considers there to be a reasonable possibility that the event is related to HS-10296, the Investigator should notify the Sponsor within 24 hours of becoming aware of the SAE.

9.7.3.3. Key Information of AEs to be Collected

Key information that will be collected for each AE will include, but not be limited to, the following:

- AE diagnosis/description
- Date when the AE started and stopped
- Maximum CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the study drug (yes or no)
- Action taken with regard to the study drug
- Outcome

For SAEs, other information will be collected, including treatment given for the event. It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 9.7.2.

An AE of severe intensity need not necessarily be considered an SAE. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

The grading scales found in the current National Cancer Institute CTCAE version 4 will be used for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used.

9.7.3.4. Causality Assessment

The Investigator will assess a causal relationship between the study drug and each AE.

For SAEs, causal relationship also will be assessed for other medication and study procedure.

Note: For SAEs that could be associated with any study procedure, the causal relationship is implied as "yes."

9.7.3.5. AEs Based on Signs and Symptoms

All AEs spontaneously reported by the patient or health care provider, reported in response to the open question from the study personnel ("Have you had any health problems since the previous visit/since you were last asked?"), or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, documentation of diagnoses is preferred (when possible) so that review of signs and symptoms can be performed; however, if a diagnosis is known and there are other signs or symptoms that generally are not part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

9.7.3.6. AEs Based on Examinations and Tests

The results from protocol-mandated laboratory tests, vital signs, ECGs, and other safety assessments will be summarized in the clinical study report. Deterioration compared to Baseline in these parameters will, therefore, only be reported as an AEs if it fulfills any of the criteria for an SAE or a DLT, or is the reason for discontinuation of treatment with the study drug (unless clearly due to progression of the disease under study).

Deterioration in a laboratory value, vital sign, ECG, or other safety assessment will be reported as an AE. Wherever possible, the reporting Investigator should use the clinical, rather than the laboratory, term (e.g., anemia versus low hemoglobin value).

Deterioration of a laboratory value that is due unequivocally to disease progression should not be reported as an AE. Any new or aggravated clinically relevant abnormal medical finding at a physical examination compared with the baseline assessment will be reported as an AE.

9.7.3.7. Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study drug is being studied. It may be an increase in the severity of the disease under study and/or an increase in the symptoms of the disease.

The development of new or progression of existing metastasis of the primary cancer under study should be considered disease progression and not an AE. Events that are due unequivocally to disease progression should not be reported as AEs during the study.

9.7.3.8. New Cancers

The development of a new cancer should be regarded as a SAE and will generally meet at least 1 of the serious criteria. New cancers are those that are not the primary reason for the administration of the study drug and have been identified after the patient's inclusion in this

study. New cancers do not include metastases of the original cancer (refer to Section 9.7.4 for SAE reporting).

9.7.3.9. Handling of Deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of study drug, should be reported as follows:

- Death that is due unequivocally to disease progression should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module but should not be reported as an SAE during the study.
- Where death is not clearly due to PD under study, the AE causing the death should be reported to the study monitor as an SAE within 24 hours (refer to Section 9.7.4 for SAE reporting). The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause always should be reported as a SAE within 24 hours of the site becoming aware of the death, but every effort should be made to establish a cause of death. A postmortem examination may be helpful in the assessment of the cause of death, and, if performed, a copy of the postmortem results (with translation of important parts into English, as applicable) should be reported within 24 hours of the postmortem examination becoming available to the Sponsor (refer to Section 9.7.4 for SAE reporting).

9.7.4. Reporting AEs

All SAEs must be reported, whether or not considered causally related to the study drug or to the study procedure(s). All SAEs will be recorded in the eCRF. If any SAE occurs throughout the study, from providing informed consent until the end of the follow-up period, the Investigator or other site personnel will inform the Sponsor immediately, but no later than 24 hours after becoming aware of the SAE. The contact information is listed in the following table:

Name	Role in the Study	Address and Phone Number
[redacted]	Hansoh study team safety physician for the AE/SAE reporting 24-hour emergency contact	[redacted]

The designated Sponsor representative works with the Investigator to ensure that all the necessary information is recorded in the appropriate Hansoh patient safety data-entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform the Sponsor of any follow-up information regarding a previously reported SAE immediately, but no later than 24 hours after becoming aware of the SAE follow-up information.

9.8. Patient-Reported Outcomes

A PRO is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. The PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered:

9.8.1. European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ C-30) EORTC Quality of Life Questionnaire–Lung Cancer (QLQ-LC13) EORTC QLQ-C30 and QLQ-LC13

The EORTC QLQ-C30 (see Appendix E) was developed by the EORTC Quality of Life Group in 1993. It consists of 30 items and measures cancer patients' functioning (HRQoL) and symptoms.[68] The QLQ-LC13 (see Appendix F) is a complementary module measuring lung cancer-associated symptoms and side effects from conventional chemotherapy and radiotherapy.[69]

9.8.2. Administration of PROs

Questionnaires will be administered using paper questionnaires. The patient should complete the questionnaires at Screening, every 6 weeks relative to the first dose of multiple dosing, at discontinuation, and at progression, as specified in the Study Plan (Appendix B).

If any scheduled PRO assessment is not completed, the reason for non-completion should be recorded. Patient reported outcomes will be filled out prior to any other site activities and encounters with a physician. The patients will be instructed to complete the PRO assessment independently.

The site will have a designated quiet space for patients to use when completing the assessments. Each center should allocate responsibility for ensuring that patients complete PRO assessments to a specified member of the study site staff (e.g., a research nurse). It is important that the value and relevance of HRQoL data are explained carefully to participating patients so that the patients are motivated to comply with data collection. The responsible study site staff member should stress to patients that the information is confidential. Therefore, if the patient has any medical problems, the patient should discuss the problems with the doctor or research staff (i.e., in addition to completing the PRO assessment).

The instructions for completion of questionnaires are as follows:

- The questionnaire must be completed before any investigations or discussions regarding the patient's disease status with the study site staff.

- The patient must complete the questionnaire himself or herself, without any input or intervention from family, friends, study site staff, or others. The only exception to this is if the patient is blind or illiterate; in such a case, the questionnaire may be read to the patient verbatim, but the reader must not aid in the interpretation of questions or in the selection of answers.
- Only 1 answer to every question should be checked.
- Study site staff should not review the responses to the questionnaire with the patient or with any other study site staff.

Following completion, the responsible study site staff member may quickly visually scan the questionnaire for completeness and should confirm verbally with the patient that the questionnaire has been fully completed.

10. EVALUATION OF ENDPOINTS AND STATISTICAL ANALYSIS

10.1. Evaluation of Pharmacokinetic Variables

The actual sampling times will be used in the parameter calculations, and PK parameters will be derived using standard non-compartmental methods. Where possible, the following PK parameters of HS-10296 will be determined:

- Following the single-dose part (or first dose) of the study:
  - Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal rate constant (λz), terminal half-life ($t_{½}\lambda z$), area under the plasma concentration-time curve from zero to 24 hours (AUC_{0-24}), from zero to the time of the last measurable concentration (AUC_{0-t}) and from zero to infinity (AUC), apparent plasma clearance (CL/F), apparent volume of distribution, mean residence time (MRT)
- Following the multiple-dose part of the study:
  - Maximum plasma concentration at steady state (C_{ss} max), time to C_{ss} max (t_{ss} max), minimum plasma concentration at steady state (C_{ss} min), area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_{ss}), apparent plasma clearance at steady state (CL_{ss}/F), extent of accumulation on multiple dosing (accumulation ratio [RAC]), time dependency of the PK

The C_{max}, the C_{ss} max, the (t_{max}, and the t_{ss} max will be determined through the concentration-time profiles. Where possible, the (λz will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and the $t_{½}\lambda z$ will be calculated as ln $2/\lambda z$. The AUC_{0-t} and the AUC_{0-24} will be calculated using the linear trapezoidal rule. Where appropriate, the AUC_{0-t} will be extrapolated to infinity using λz to obtain AUC. The AUC_{ss} will be calculated using the linear trapezoidal rule. The CL/F following the single dose and CL_{ss}/F following multiple dosing) will be determined from the ratio of dose/AUC or dose/AUC_{ss}. The volume of distribution (V_{ss}/F or Vz/F) will be determined from the MRT × CL/F and/or the RAC will be calculated as the ratio of the AUC_{0-24} on Day 1 and Day 15.

The time dependency of the PK on multiple dosing will be assessed by the calculation of the ratio of AUC_{0-24} Day 15/AUC Day 1. Where possible, the appropriate PK parameters will also be determined for the metabolite (HAS-719) of HS-10296.

A population PK analysis for HS-10296 and its metabolite HAS-719 may be conducted as deemed appropriate.

10.2. Evaluation of Pharmacodynamic Variables

The plasma concentration data for HS-10296 (and the metabolite HAS-719) will be analyzed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allow. A population pharmacodynamic approach will be used to investigate the

relationship between PK and selected primary, secondary, and/or exploratory endpoints, where deemed appropriate. Results may be reported separately from the clinical study report.

The PK, pharmacodynamic, demographic, safety, and tumor response data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK/pharmacodynamic methods. The results of any such analyses will be reported separately from the clinical study report.

10.3. Evaluation of Exploratory Research Variables

Results from the exploratory biomarker and pharmacogenetic research and from PROs may be reported separately from the clinical study report.

10.4. Evaluation of Anti-Tumor Activity Variables

For the Investigator's assessment, at each visit, patients will be programmatically assigned a RECIST visit response of CR, PR, SD, and PD, depending upon the status of their disease compared with Baseline and previous assessments. Progression of TLs will be calculated in comparison to when the tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment. If a patient has a tumor assessment that cannot be evaluated, the patient will be assigned a visit response of not evaluable (NE) unless there is evidence of progression, in which case the response will be assigned as PD.

For TL measurements, if ≤ 1/3 of the TL sizes are missing then a scaling up rule will be applied as follows:

- If ≤ 1/3 of lesions recorded at Baseline are missing, then the results will be scaled up (based on the nadir sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions that are missing, and determining at what rate the lesions are changing).
- If > 1/3 of lesions recorded at Baseline are missing, then the TL response will be NE. However, if the sum of non-missing TL diameters would result in PD (i.e., if using a value of 0 for missing lesions, the sum of diameters has still increased by 20% or more compared with the smallest sum of diameters on study, with an absolute increase of ≥ 5mm), PD takes precedence over NE.
- A visit response of CR will not be allowed if any of the TL data is missing.

10.4.1. Objective Response

Objective response rate is defined as the percentage of patients who have at least 1 confirmed response of CR or PR prior to any evidence of progression, as defined by RECIST 1.1 (Appendix D).

A visit response of CR is defined when all TLs and NTLs present at Baseline have disappeared (with the exception of lymph nodes, which must be < 10 mm to be considered non-pathological) and no new lesions have developed since Baseline.

A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared with Baseline (with no evidence of progression) and the NTLs are at least stable, with no evidence of new lesions.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging at least 4 weeks later, with no evidence of progression between confirmation visits.

In the case of SD, measurements should have met the SD criteria for a minimum interval of 5 weeks (6 weeks minus the 7-day visit window) following the start of treatment.

When the Investigator is in doubt as to whether PD has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scan(s) confirm(s) progression. For the extension cohort, the ORR is defined as the number (%) of patients with measurable disease with at least 1 visit response of CR or PR that is confirmed at least 4 weeks later. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any CR or PR that occurred after a further anti-cancer therapy was received will not be included in the numerator of the ORR calculation.

10.4.2. Progression-Free Survival

The PFS is defined as the time from date of first dosing until the date of objective disease progression as defined by RECIST 1.1 (Appendix D) or death (by any cause in the absence of progression) regardless of whether the patients withdraws from HS-10296 therapy or receives another anti-cancer therapy prior to progression.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data, the patient will be censored at 0 days unless he or she dies within 2 visits of Baseline.

If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression, then the patient will continue to be followed until there is evidence of objective

disease progression as defined by RECIST 1.1 (Appendix D), and the PFS time will be derived as defined above.

Symptomatic deterioration will not be regarded as a progression event.

10.4.3. Duration of Response

Duration of response is defined as the time from the date of first documented response until the date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint.

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a patient does not progress following a response, then DoR will be used as the PFS censoring time.

10.4.4. Disease Control Rate

The DCR is defined as the proportion of patients with a best overall response of CR, PR, or SD.

10.4.5. Change in Tumor Size

Tumor size is defined as the sum of the lengths of the longest diameters of the RECIST 1.1 TLs. Percentage change in tumor size will be determined for patients with measurable disease at Baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs compared with Baseline. For further details, see Appendix D.

10.4.6. Overall Survival

Overall survival will be assessed based on the date of first dose and survival status at the time of analysis. Overall survival is defined as the interval between the date of first dose and the date of patient death due to any cause.

Patients who have not died at the time of the statistical analysis will be censored at the time that the patient was last known to be alive.

10.5. Method of Statistical Analysis

10.5.1. Analysis Data Set

The analysis of data will be based on different subsets according to the purpose of the analysis. Analysis sets are presented in Table 7.

Table 7 Analysis Data Set

Analysis Set	Definition
Safety	All patients who received at least 1 dose of HS-10296
PK	Dosed patients who have at least 1 measurable plasma concentration collected postdose
Evaluable for response (Full Analysis Set; FAS)	Dosed patients with a baseline RECIST assessment who received at least one dose of study drug
Exploratory biomarkers	All patients that participate in the exploratory biomarker research
Paired biopsy	Dosed patients with a prestudy tumor biopsy and 1 tumor biopsy on study treatment

10.5.2. Method of Statistical Analysis

The intent of all efficacy analyses from the expansion phase is that it be focused on the population wherein tumor T790M mutation status is identified via central testing. Patient central test results must match the cohort expansion group to which the patient was assigned (i.e., $T790M^+$ in the first expansion). However, concordance between local and central testing of T790M status will be reviewed, and, if deemed appropriate, summaries incorporating local testing status may be produced. All summaries will present data by dose group.

10.5.2.1. Demographic Data

Characteristics of the patients, including medical history and disease characteristics at Baseline, will be listed for each patient and summarized by dose group. Reasons for discontinuation of study drug will be listed, including the study day of treatment discontinuation, and will be summarized by dose group.

10.5.2.2. Exposure

Exposure to the study drug (i.e., total amount of study drug received) will be listed for all patients. Total exposure and total time on study (date of last dose minus date of first dose) will be summarized by the following: mean, standard deviation, minimum, maximum, median, and number of observations. In addition, the number and percentage of patients with at least 1 dose interruption/dose delay and at least 1 dose reduction will be presented separately for the initial period, defined as 21 days of multiple dosing (Cycle 1) and for any time following this initial period of the study.

10.5.2.3. Safety

All patients who receive at least 1 dose of HS-10296 will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced. Data from all cycles of initial treatment will be combined in the presentation of safety data.

Adverse events will be listed individually by patient and dose group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The number of patients experiencing each AE will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term, and CTCAE grade. The number and percentage of patients with AEs in different categories (e.g., causally related, CTCAE grade ≥ 3) will be summarized by dose group, and events in each category will be summarized further by MedDRA system organ class and preferred term, by dose group.

Serious adverse events will be summarized separately.

Any AE occurring before the first dose of the study drug (i.e., before study Day 1) will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within the defined 28-day follow-up period after discontinuation of the study drug will be included in the AE summaries; any AEs within this period (i.e., that occur after a patient has received further therapy for cancer, following discontinuation of the study drug) will be flagged in the data listings. All AEs occurring after the 28-day follow-up period after discontinuation of the study drug will be listed separately, but not included in the summaries.

Hematology, clinical chemistry, vital signs, ECG data, ophthalmic examination data, demographic data, and concomitant medications will be listed individually by patient and suitably summarized. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum, and number of observations will be used.

Details of any deaths will be listed for all patients.

10.5.2.4. Pharmacokinetics

Plasma concentrations of HS-10296 and HAS-719 will be summarized by nominal sample time. Plasma concentrations and derived PK parameters will be summarized by dose level. Parameters following single and multiple dosing will be summarized separately. Plasma concentrations at each time point will be summarized according to dose by the following summary statistics:

- The geometric mean (Gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale
- Gmean ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum

- Maximum
- Number of observations

The following summary statistics will be presented for AUC, AUC_{0-24}, AUC_{0-t}, AUC_{ss}, C_{max}, C_{ss} max, and C_{ss} min:

- Gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for CL/F, CL_{ss}/F, volume of distribution, $t_{½}\lambda z$, RAC, and time dependency:

- Arithmetic mean
- Standard deviation
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for t_{max} and $t_{max\ ss}$:

- Median
- Minimum
- Maximum
- Number of observations

The PK data for HS-10296 and HAS-719 after a single-dose and separately at steady state will be displayed graphically. Displays will include plasma concentration patient profiles (on the linear and log-scale) versus time and mean concentration (± standard deviation) versus time, stratified by dose.

Scatter plots of PK parameters versus dose, or log-dose will also be considered following both single- and multiple-dose administration of HS-10296 to assess dose proportionality.

In a preliminary assessment of dose proportionality, log-transformed AUC and C_{max} parameter estimates will be examined using the Power Model:

$$\text{parameter} = e^{a} (\text{dose})^{b}$$

i.e., $\log(\text{parameter}) = a + (b * \log(\text{dose}))$

Where "a" is the intercept, depending on patients, and "b" is the slope, measuring the extent of dose proportionality. Dose proportionality implies that $\beta = 1$ and will be assessed by estimating β along with its CI.

If there is evidence of departures from dose proportionality, log-transformed dose-normalized AUC and C_{max}, of HS-10296 will be analyzed separately using a mixed-effects model. Dose will be fitted as a fixed effect and patient as a random effect. Point estimates and associated 90% CIs for the differences between each dose level and the reference dose (the lowest dose) will be constructed using the residual variance. The estimates will then be back-transformed to provide point estimates and corresponding 90% CIs for the ratios of each dose level to the reference dose on the original scale. No adjustments for pre-planned multiple comparisons will be made. This analysis will be performed only if there are sufficient data.

10.5.2.5. Pharmacodynamics

The pharmacodynamic effects of HS-10296 will be evaluated in tumor tissue from paired biopsies (a tumor biopsy predose and a paired tumor biopsy postdose).

The biomarkers investigated may include, but are not limited to, pEGFR, pERK, pAKT, pS6, pGSK3β, p4EBP1, cleaved caspase 3, and Ki67.

10.5.2.6. Exploratory Biomarker Research and Pharmacogenetics

The number of patients who will agree to participate in the exploratory biomarker and genetic research is unknown. Therefore, it is not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated.

10.5.2.7. PRO Analysis

The PRO analyses on the EORTC QLQ C-30 (Appendix E) and QLQ-LC13 (Appendix F) will be based on the instruments' scoring manual.

10.5.2.8. Tumor Response

The analysis population for objective tumor response rate will be the "evaluable for response" population.

For the escalation cohorts, summaries of tumor response data will be by dose.

For the expansion cohorts, the summaries will be by dose and centrally confirmed T790M status (positive, negative, unknown). A sensitivity analysis may be performed, using local T790M status, for patients whose central T790M status is not available.

For the primary objective, all RECIST outcomes will be based on the ICR, and ORR will be summarized for the patients who have measurable disease at Baseline as defined by ICR.

Tumor response data will be listed and summarized by dose group, and if appropriate using the following response categories: CR, PR, SD, PD, and NE. Objective tumor response rates will be presented together with 80% and 95% CIs (calculated using the Clopper-Pearson interval), where appropriate.

10.5.2.9. Duration of Response

For the expansion cohort, the DoR in responding patients will be summarized, and the number (%) of responding patients with a DoR > 3, > 6, > 9, and > 12 months will be presented. A Kaplan-Meier plot and median DoR with 95% CIs (calculated from the Kaplan-Meier plot) will be presented. The DCR will be summarized with 95% CIs.

10.5.2.10. Progression-Free Survival

The analysis population for PFS will be the safety population.

The PFS will be summarized for the expansion phase. The number of events, median, and proportion of patients without an event at 6, 12, and 18 months will be summarized.

Summaries of the number and percentage of patients who have died, are still in survival follow-up, lost to follow-up, or have withdrawn consent will be presented as appropriate.

10.5.2.11. Sensitivity Analysis

The same methods of analysis will be applied to analyze DoR, DCR, tumor shrinkage, and PFS based on the RECIST data assessed by the Investigator.

10.5.2.12. Change in Tumor Size

The analysis population for change in tumor size will be the “evaluable for response” population who have measurable disease at Baseline, as defined per RECIST 1.1 criteria (Appendix D). Summaries and waterfall plots (bar charts) indicating percentage change from Baseline in the sum of the diameters of TLs at Week 6 may be produced, if appropriate, depending on how much data are obtained in patients with measurable disease at Baseline. If there are limited data, percentage change in tumor size will be listed only.

11. DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in a separate Data Management Plan.

11.1. Electronic Case Report Forms

Completed eCRFs are required for each patient who signs an informed consent.

The Sponsor or its designee will supply investigative sites with access to eCRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These eCRFs are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. Data are entered directly onto eCRFs.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections also should be included.

The Principal Investigator must review the eCRFs for completeness and accuracy, and must sign and date the appropriate eCRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The Sponsor or its designee will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor. Completed eCRFs are required for each patient who signs an informed consent and assent.

11.2. Record Retention

The Investigator agrees to keep the records and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media (thermal sensitive paper should be copied and certified), source worksheets, all original signed and dated informed consent forms, patient authorization forms regarding the use of personal health information (if separate from the informed consent forms), copies of all paper eCRFs and query responses, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor, or its designees.

Furthermore, ICH E6 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least

2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The Investigator and institution guarantee access to source documents by the Sponsor or its designee and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or its designee (as long as blinding is not jeopardized), including but not limited to, the Investigator's Binder, study drug, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the Investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2. Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator should consult with the medical monitor (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

12.3. Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the US FDA and Taiwan FDA). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator and institution guarantee access for quality assurance auditors to all study documents.

13. ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each Investigator will conduct the study according to applicable local or regional regulatory requirements. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

13.1. IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, patient recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (i.e., before shipment of the Sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the Investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and Sponsor.

13.2. Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The Investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and, if applicable, the patient authorization form. The informed consent form, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The informed consent form, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the Investigator to explain the detailed elements of the informed consent form, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both verbal and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the patient is not capable of rendering adequate written informed consent, the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the patient, or the patient's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and patient authorization form (if applicable) must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and prior to the patient entering into the study. The patient, or the patient's legally acceptable representative, should be instructed to sign using his or her legal name, not nickname, using blue or black ballpoint ink. The Investigator also must sign and date the informed consent form and patient authorization form (if applicable) at the time of consent and prior to the patient entering into the study; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the Investigator's study site file. The Investigator must document the date the patient signs the informed consent in the patient's

medical record. Copies of the signed informed consent form, the signed patient authorization form (if applicable), and the patient information sheet (if applicable) shall be given to the patient.

All revised informed consent forms must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised informed consent form.

13.3. Patient Confidentiality

The Sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data only will be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority, the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process.

Copies of any patient source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., patient name, address, and other identifier fields not collected on the patient's eCRF).

13.4. Publication, Disclosure, and Clinical Trial Registration

13.4.1. Publication and Disclosure

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the Clinical Study Site Agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript

authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2. Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation, and guidance, the Sponsor will, at a minimum, register all clinical trials conducted in patients that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation. Sponsor contact information, along with each Investigator's city, state (for US Investigators), country, and recruiting status will be registered and available for public viewing.

13.4.3. Clinical Trial Results Disclosure

The Sponsor will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

13.5. Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the Sponsor or Sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the Clinical Study Site Agreement regarding the Sponsor's policy on patient compensation and treatment for injury. If the Investigator has questions regarding this policy, he or she should contact the Sponsor or Sponsor's designee.

14. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

14.1. Medical Emergencies and Sponsor Contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported (see Section 9.7.4).

In the case of a medical emergency, the Investigator may contact the Study Team Safety Physician. If the Study Team Physician is not available, contact the Sponsor's Study Leader. Sponsor contact information is noted in the table below.

Name	Role in the Study	Address and Phone Number
[redacted]	Hansoh Study Team Safety physician for AE/SAE reporting 24-hour emergency contact	[redacted]
[redacted]	Hansoh Study Team Physician responsible for the study protocol	[redacted]
[redacted]	Hansoh Study Team Leader responsible for the study management	[redacted]
[redacted]	24-hour emergency contact (alternative)	[redacted]

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Appendix A Investigator Consent to Use of Personal Information

Hansoh will collect and retain the personal information of the Investigator, including name, address, and other personally identifiable information. In addition, the Investigator's personal information may be transferred to other parties located in countries throughout the world including the following:

- Hansoh, its affiliates, and licensing partners.
- Business partners assisting Hansoh, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Hansoh and these other parties for research purposes including the following:

- Assessment of the suitability of Investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and Investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Hansoh, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting Investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites.

The Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

The Investigator acknowledges and consents to the use of his or her personal information by Hansoh and other parties for the purposes described above.

Appendix B Study Plan

Dose Escalation														
	Screening	**Single dose/Cycle 0 (7-day cycle)**					**Multiple Dose/ Cycle 1 (21-day cycle)**			**Cycles 2-6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontinuation**	**28-day follow-up**	**Progression**
Day	**-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D6**	**D1**	**D8**	**D15**	**D1**	**D1**			
Window (days)										**Cycle 3-6: ± 3**	**± 3**	**NA**	**± 3**	**± 3**
Informed consent	X													
Inclusion/exclusion criteria	X													
Demography and baseline characteristics	X													
Medical/surgical history	X													
Physical examination; neurologic examination required at each cycle physical examination	X	X					X			X	X	X		
Ophthalmologic assessment	X									X[a]				
WHO performance status	X	X					X			X	X	X		
EGFR mutation status	X													
Archival tumor tissue	X													
Vital signs	X	X	X				X	X	X	X	X	X		
Height	X													
Weight	X	X					X			X	X	X		

Dose Escalation (continued)

	Screening	Single dose/Cycle 0 (7-day cycle)					Multiple Dose/ Cycle 1 (21-day cycle)			Cycles 2-6 (21-day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day follow-up	Progression
Day	**-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D6**	**D1**	**D8**	**D15**	**D1**	**D1**			
Window (days)										**Cycle 3-6: ± 3**	**± 3**	**NA**	**± 3**	**± 3**
Clinical chemistry/ hematology/urinalysis[b]	X	X					X	X	X	X	X	X		
Pregnancy test (females of childbearing potential only)[c]	X													
ECG[d]	X	X	X				X	X	X	X	X	X		
Genetics consent and blood sample (optional)	X													
Blood sample for cfDNA (6 weekly)	X	X								X, every 6 (± 1) weeks at RECIST visit				X
PK blood samples (including metabolites)[e]		X	X	X	X	X	X	X	X	X (Cycle 2 only)				
Echocardiogram/MUGA scan	X	X, every 12 weeks (relative to first dose)												
RECIST assessments[f]	X						X, every 6 (± 1) weeks (relative to first dose of multiple dosing) until progression							
Dispense study drug		X					X			X	X			
Dose with HS-10296		X					X, daily dosing during 21-day cycle							
AEs/concomitant medications[g]	↔													
Tumor biopsy (optional)	X								X			X		
CSF (optional)										X (once only)				

cfDNA = cell-free DNA; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.

[a] For ophthalmologic assessment, Cycle 2 and 3 and then as needed per signs and symptoms.

[b] Laboratory tests do not need to be repeated at Baseline if the baseline visit is within 7 days of obtaining the screening sample.

Footnotes continued next page.

[c] A urine or serum pregnancy test will be performed for women of childbearing potential at Screening or within 3 days before the first dose of study drug. The results must be available and negative before the first dose of study drug is administered.

[d] Refer to Appendix H for further details.

[e] PK sampling times are as follows: dose escalation, single dose (Cycle 0), Day 1 (predose, 30 min, 1.0 h, 1.5 h, 2.0 h, 4.0 h, 6.0 h, 8.0 h, 10 h,12 h, 24 h (Day 2), 48 h (Day 3), 72 h (Day 4), and 120 h (Day 6); multiple dosing (Cycle 1): Days 1, 8, and 15 (predose); multiple dosing (Cycle 2), Day 1: predose, 30 min, 1.0 h, 1.5 h, 2.0 h, 4.0 h, 6.0 h, 8.0 h, 10 h, 12 h, and 24 h (Day 2 predose).

[f] Screening RECIST evaluation should be conducted as close as possible to start of treatment.

[g] For concomitant medication collection**,** after discontinuation and for 28-day follow-up, only anti-cancer medications will be recorded.

Phase 1 Expansion Cohort and Paired Biopsy									
	Screening	**Multiple Dose/ Cycle 1 (21-day cycle)**			**Cycles 2-6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontinuation**	**28-day Follow-up**	**Progression**
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**			
Window (days)					**Cycle 3-6: ± 3**	**±3**	**NA**	**±3**	± 3
Informed consent	X								
Inclusion/exclusion criteria	X								
Demography and baseline characteristics	X								
Medical/surgical history	X								
Physical examination; neurologic examination required at each cycle physical examination	X	X			X	X	X		
Ophthalmologic assessment	X				X[a]				
WHO performance status	X	X			X	X	X		
HRQoL form	X	X			X, every 6 (± 1) weeks (relative to first dose) until progression		X		X
T790M mutation status tumor sample (mandatory)	X								
Archival tumor tissue	X								
Tumor biopsy (paired biopsy cohort - mandatory)	X			X					
Tumor biopsy (optional)	X			X			X		

Phase 1 Expansion Cohort and Paired Biopsy (continued)

	Screening	Multiple Dose/ Cycle 1 (21-day cycle)			Cycles 2-6 (21-day cycle)	Cycle 7 and every 6 weeks onward	Discontinuation	28-day Follow-up	Progression
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**			
Window (days)					**Cycle 3-6: ± 3**	**±3**	**NA**	**±3**	± 3
Vital signs	X	X	X	X	X	X	X		
Height	X								
Weight	X	X			X	X	X		
Clinical chemistry/hematology/urinalysis[b]	X	X	X	X	X	X	X		
Pregnancy test (females of childbearing potential only)[c]	X								
ECG[d]	X	X	X	X	X	X	X		
Echocardiogram/MUGA scan	X	X, every 12 weeks relative to first dose							
PK blood sample (including metabolite)[e]		X	X	X	X (cycle 2 only)				
Blood sample for cfDNA (6 weekly)	X	X			X, every 6 (± 1) weeks at RECIST visit				X
RECIST assessments[f]	X	X, every 6 (± 1) weeks (relative to first dose) until progression							X
Dispense study drug		X			X	X			
Dose with HS-10296		X, daily dosing during 21-day cycle							
AEs/concomitant medications[g]	←								→
Genetic consent and blood sample (optional)	X								
CSF (optional)					X (once only)				

cfDNA = cell-free DNA; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; HRQoL = health-related quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.

[a] For ophthalmologic assessment, Cycle 2 and 3 and then as needed per signs and symptoms.

[b] Laboratory tests do not need to be repeated at Baseline if the baseline visit is within 7 days of obtaining the screening sample.

Footnotes continued next page.

Phase 1 Expansion Cohort and Paired Biopsy (continued)

	Screening	Multiple Dose/ Cycle 1 (21-day cycle)			Cycles 2-6 (21-day cycle)	Cycle 7 and every 6 weeks onward	Discontinuation	28-day Follow-up	Progression
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**			

[c] A urine or serum pregnancy test will be performed for women of childbearing potential at Screening or within 3 days before the first dose of study drug. The results must be available and negative before the first dose of study drug is administered.

[d] Refer to Appendix H for further details

[e] PK sampling times are as follows: multiple dosing (Cycle 1): Days 1, 8, and 15 (predose); multiple dosing (Cycle 2), Day 1: predose, 30 min, 1.0 h, 1.5 h, 2.0 h, 4.0 h, 6.0 h, 8.0 h, 10 h, 12 h, and 24 h (Day 2 predose).

[f] Screening RECIST evaluation should be conducted as close as possible to start of treatment.

[g] For concomitant medication collection, after discontinuation and for 28-day follow-up, only anti-cancer medications will be recorded.

Phase 2 Extension Cohort										
	Screening	**Multiple Dose/ Cycle 1 (21-day cycle)**			**Cycles 2-6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontinuation**	**28-day Follow-up**	**Progression**	**Post-progression survival F/U**
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**				
Window (days)					**Cycle 3-6: ± 3**	**±3**	**NA**	**±3**	±3	±3
Informed consent	X									
Inclusion/exclusion criteria	X									
Demography and baseline characteristics	X									
Medical/surgical history	X									
Physical examination; neurologic examination required at each cycle physical examination	X	X			X	X	X			
Ophthalmologic assessment	X				X[a]					
WHO performance status	X	X			X	X	X			
HRQoL form	X	X			X, every 6 (± 1) weeks (relative to first dose) until progression		X		X	
T790M mutation status tumor sample (mandatory)	X									
Archival tumor tissue	X									
Vital signs	X	X	X	X	X	X	X			
Height	X									
Weight	X	X			X	X	X			

Phase 2 Extension Cohort (continued)

	Screening	Multiple Dose/ Cycle 1 (21-day cycle)			Cycles 2-6 (21-day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day Follow-up	Progression	Post-progression survival F/U
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**				
Window (days)					**Cycle 3: ± 3**	**±3**	**NA**	**±3**	**±3**	**±3**
Clinical chemistry /hematology/urinalysis[b]	X	X	X	X	X	X	X			
Pregnancy test (females of childbearing potential only)[c]	X									
ECG[d]	X	X	X	X	X	X	X			
Echocardiogram/MUGA scan	X	X, every 12 weeks relative to first dose ↔								
PK blood sample (including metabolite)[e]		X	X	X	X (cycle 2 only)					
Blood sample for cfDNA (6 weekly)	X	X			X, every 6 (± 1) weeks at RECIST visit ↔				X	
RECIST assessments[f]	X	X, every 6 (± 1) weeks (relative to first dose) until progression ↔							X	
Dispense study drug		X			X	X				
Dose with HS-10296		X, daily dosing during 21-day cycle ↔								
AEs/concomitant medication[g]	↔									X
Genetic consent and blood sample (optional)	X									
CSF (optional)					X (once only)					
Survival										X

cfDNA = cell-free DNA; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; HRQoL = health-related quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.

Footnotes continued next page

Phase 2 Extension Cohort (continued)

	Screening	Multiple Dose/ Cycle 1 (21-day cycle)			Cycles 2-6 (21-day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day Follow-up	Progression	Post-progression survival F/U
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**				

[a] For ophthalmologic assessment, Cycle 2 and 3 and then as needed per signs and symptoms.

[b] Laboratory tests do not need to be repeated at Baseline if the baseline visit is within 7 days of obtaining the screening sample.

[c] A urine or serum pregnancy test will be performed for women of childbearing potential at Screening or within 3 days before the first dose of study drug. The results must be available and negative before the first dose of study drug is administered.

[d] Refer to Appendix H for further details.

[e] PK sampling times are as follows: multiple dosing (Cycle 1): Days 1, 8, and 15 (predose); multiple dosing (Cycle 2), Day 1: predose, 30 min, 1.0 h, 1.5 h, 2.0 h, 4.0 h, 6.0 h, 8.0 h, 10 h, 12 h, and 24 h (Day 2 predose).

[f] Screening RECIST evaluation should be conducted as close as possible to start of treatment.

[g] For concomitant medication collection, after discontinuation and for 28-day follow-up, only anti-cancer medications will be recorded.

Appendix C Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin – Hy's Law

1. INTRODUCTION

During the study the Investigator will remain vigilant for increases in liver biochemistry values. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study. The Investigator participates, together with Hansoh clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. Hy's Law (HL) criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the study drug.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AE) and serious adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

2.1 Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) and total bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

2.2 Hy's Law (HL)

AST or ALT ≥ 3 × ULN and TBL ≥ 2 × ULN, where no other reason, other than the study drug, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

To identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The Investigator will, without delay, review each new laboratory report, and if the identification criteria are met will:

- Notify the Hansoh representative.
- Determine whether the patient meets PHL criteria (see Section 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory CRF.

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria, the Investigator will:

- Inform the Hansoh representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria, the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (see Section 6).
- Notify the Hansoh representative who will then inform the central Study Team.

The Study Physician contacts the Investigator to provide guidance, and to discuss and agree on an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact, the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or Baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the 3 Liver CRF Modules as information becomes available.
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed for all cases where PHL criteria are met. No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Hansoh Medical Science Director and Safety Physician also will be involved in this review, together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below. If there is an agreed upon alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the Hansoh standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to Hansoh standard processes.
  - The "Medically Important" serious criterion should be used if no other serious criterion applies.
  - As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If, there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law'), applying serious criterion and causality assessment as per above.
- Continue follow-up and review according to agreed-upon plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients who meet PHL criteria on study treatment, having previously met PHL criteria at a study visit prior to starting study treatment. At the first on study treatment occurrence of PHL criteria being, even if there has been no significant change in the patient's condition compared with pre-study treatment visits, the Investigator will:

- Notify the Hansoh representative who will inform the central Study Team.
- Follow the subsequent process described in Section 4.2.

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator. This determination may be in consultation with the Study Physician if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and already has met PHL criteria at a previous on study treatment visit. The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence. The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6?
- **If No:** follow the process described in Section 4.2
- **If Yes:**
  - Determine if there has been a significant change in the patient's condition compared to when PHL criteria were previously met.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described in Section 4.2.

A "significant" change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator. This determination may be in consultation with the Study Physician if there is any uncertainty.

8. REFERENCES

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. Silver Spring, MD: July 2009.

Appendix D Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumors)

1. INTRODUCTION

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 guidelines (Eisenhauer et al 2009) for the study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Patients with at least 1 lesion measurable that can be accurately assessed at Baseline by computerized tomography (CT), magnetic resonance imaging (MRI), or plain x-ray should be included in this study.

Measurable lesions

At least 1 lesion, not previously irradiated, that can be accurately measured at Baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short access ≥ 15 mm) with CT or MRI which is suitable for accurate repeated measurements.

Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at Baseline; nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions [NTLs]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI.
- Previously irradiated lesions as localized post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been irradiated previously will not be considered measurable and should be selected as NTLs at Baseline and followed up as part of the NTL assessment.
- Skin lesions assessed by clinical examination.
- Brain metastasis.

Special cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these non-cystic lesions should be selected as the target lesions (TLs).

Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at Baseline.

Non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at Baseline.

3. METHODS OF MEASUREMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during follow-up.

The methods to be used for RECIST assessment are summarized in the below table and those excluded for tumor assessments in this study are discussed below, with the rationale provided.

Summary of Methods of Assessment

Target Lesions	Non-target lesions	New Lesions
CT (preferred) MRI	CT (preferred) MRI Clinical examination X-ray, chest x-ray	CT (preferred) MRI Clinical examination X-ray, chest x-ray Ultrasound Bone scan FDG-PET

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment, to assess NTLs, and for identification of new lesions.

In this study, it is recommended that CT examinations of the chest and abdomen be used to assess tumor burden at Baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contraindicated. For assessment of brain lesions, MRI is the preferred method.

3.2 Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they then are assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients that also have other lesions assessable by CT, MRI, or plain x-ray, and to identify the presence of new lesions.

3.3 X-rays

3.3.1 Plain x-ray

Plain x-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

3.3.2 Chest x-ray

Chest x-rays will not be used for assessment of TLs, as TLs will be assessed by CT or MRI examination. Chest x-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

3.4 Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumor size, and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed, new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor measurements.

3.6 Tumor markers

Tumor markers will not be used for tumor response assessments per RECIST 1.1.

3.7 Cytology and histology

Histology will not be used as part of the tumor response assessment per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or SD. In such circumstances, the cytology is necessary to differentiate between response/SD (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs or disease progression due to new lesions.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at Baseline and confirmed by CT, MRI, or x-ray at Baseline should be recorded as NTLs and followed by the same method as per Baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the Baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI, and x-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: new lesions will be recorded where there is positive FDG uptake (defined as an uptake greater than twice that of the surrounding tissue) not present on a Baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no Baseline FDG-PET scan

available, and no evidence of new lesions on CT/MRI scans, follow-up CT/MRI assessments should be continued, scheduled as per protocol or as clinically indicated, in order to confirm new lesions.

4. TUMOR RESPONSE EVALUATION

4.1 Schedule of evaluation

CT examinations of the chest and abdomen (including liver and adrenal glands) will be used to assess tumor burden at Baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used when CT is not feasible or it is medically contraindicated.

Baseline tumor assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. Follow-up assessments should be performed every 6 weeks (± 7 days) after the start of treatment until discontinuation of study treatment or withdrawal of consent. Any other sites at which new disease is suspected also should be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed to minimize any unintentional bias caused by some patients being assessed at different frequency than other patients.

4.2 Target lesions

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs at Baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but also should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented, as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At Baseline, the sum of the diameters for all TLs will be calculated and reported as

the Baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at Baseline should be twice the slice thickness of the Baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into 2 or more parts, record the sum of the diameters of those parts.
- If 2 or more TLs merge, the sum of the diameters of the combined lesions should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is seen faintly, but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately because it is too large, an estimate of the size of the lesion should be provided.
- When a TL has had any intervention, e.g., radiotherapy, embolization, surgery, during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

Table 1 provides the criteria used to determine objective tumor visit response for TLs.

Table 1 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all TLs since Baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the Baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the Baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.

4.3 Non-target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at Baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the Investigator. Table 2 provides the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 2 Overall Visit Response for Non-Target Lesions

Complete Response (CR)	Disappearance of all NTLs since Baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more NTLs.
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing or stopping therapy.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the Investigator's opinion an evaluable overall NTL assessment cannot be provided at this visit. *Note: For patients without TLs at Baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.*

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more NTLs usually is not sufficient to qualify for unequivocal progression status.

4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of 1 or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at Baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor).

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. Patients with "symptomatic deterioration" requiring discontinuation of study treatment without objective evidence of disease progression at that time should continue to undergo RECIST 1.1 assessments according to the clinical study protocol until objective disease progression is observed.

4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 3.

Table 3 Overall Visit Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non--PD/Non-NE	No	PR
SD	Non--PD/Non-NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NE	Non--PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease; IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no NTLs present at Baseline).

5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

5.1 CT Scan

CT scans of chest and abdomen (including liver and adrenal glands) should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic coverage

Optimal anatomic coverage for most solid tumors is the chest, abdomen, and pelvis.

Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and additionally should investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at Baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at Baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

Intravenous contrast administration

Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) at about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated as best as possible, and a consistent method should be used on subsequent examinations for any given patient. It is very important that the same technique be used at Baseline and on follow-up examinations for a given patient. For patients who develop contraindications to contrast after Baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed also should be based on the tumor type and anatomic location of the disease, and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at Baseline or at any time during the course of the study, the recommended methods are CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed, CT without intravenous contrast is an option for the thorax, abdomen, and pelvic examinations. For assessment of brain lesions, MRI is the preferred method.

Slice thickness and reconstruction material

It is recommended that CT scans be performed at 5-mm contiguous slice thickness; this guideline presumes a minimum 5-mm thickness in recommendations for the measurable lesion definition. In exceptional situations, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at Baseline should be twice the slice thickness of the Baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

5.2 MRI Scan

MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at Baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, and use of fat suppression and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the same image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

5.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging, and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 minutes prior to imaging has been determined to be the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared, thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 minutes post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

5.3.1 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and PO contrast), the CT portion of the PET/CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an Investigator if it is not routinely or serially performed.

6. REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

Appendix E EORTC QLQ-C30 (version 3)

We are interested in some things about your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |__|__|__|

Your birth date (DD MM YYYY): |__|__|__|__|__|__|__|__|

Today's date (Day, Month, Year): |__|__|__|__|__|__|__|__|

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other	1	2	3	4

		Not at All	A Little	Quite a Bit	Very Much
	leisure time activities?				
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4

		Not at All	A Little	Quite a Bit	Very Much
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix F EORTC QLQ-L13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

	During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
1.	How much did you cough?	1	2	3	4
2.	Did you cough up blood?	1	2	3	4
3.	Were you short of breath when you rested?	1	2	3	4
4.	Were you short of breath when you walked?	1	2	3	4
5.	Were you short of breath when you climbed stairs?	1	2	3	4
6.	Have you had a sore mouth or tongue?	1	2	3	4
7.	Have you had trouble swallowing?	1	2	3	4
8.	Have you had tingling hands or feet?	1	2	3	4
9.	Have you had hair loss?	1	2	3	4
10.	Have you had pain in your chest?	1	2	3	4
11.	Have you had pain in your arm or shoulder?	1	2	3	4
12.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where?				
13.	Did you take any medicine for pain?				
	Yes No				
	If yes, how much did it help?	1	2	3	4

Appendix G Prohibited Medications (including but not exclusive)

Medications Know to Prolong QT Interval

Drug	Withdrawal Period Prior to Start of HS-10296
clarithromycin, droperidol, erythromycin, procainamide	2 days
cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
levofloxacin, methadone, pimozide	4 weeks
arsenic trioxide	6 weeks
pentamidine	8 weeks
amiodarone, chloroquine	1 year

Medications, Herbals Supplements and Ingestion Foods with Known Potent Substrates or Inducers/Inhibitors of CYP3A4, CYP2D6 and CYP1A2

CYP3A4 strong inducers:

carbamazepine, phenytoin, rifampin, St. John's wort

CYP3A4 strong inhibitors:

boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonazvir, saquinavir, telaprevir, telithromycin, voriconazole

CYP3A4 sensitive substrates:

alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, ticagrelor, vardenafil

CYP1A2 strong inhibitors or sensitive substrates:

ciprofloxacin, enoxacin, fluvoxamine, alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine

CYP2D6 strong inhibitors or sensitive substrates:

atomoxetine, bupropion, desipramine, dextromethorphan fluoxetine, nebivolol, nortriptyline paroxetine, perphenazine quinidine, paroxetine, terbinafine, tolterodine, venlafaxine

Appendix H Schedule of ECG Assessments

Cohort	Screening	Single Cycle 0	Cycle 1							Cycle 2			Cycle 3
		Day 1	Day 1	Day 2	Day 3	Day 4	Day 6	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1
Escalation	X	pre-dose, 1,2,4,6,10 and 24 hours (Day 2) postdose	predose only	pre-dose, 6, and 10 hours postdose	pre-dose, 6, and 10 hours postdose	pre-dose, 6, and 10 hours postdose	pre-dose, 6, and 10 hours postdose	predose only	predose only	pre-dose, 1,2,4,6,10 and 24 hours (Day 2) postdose	pre-dose, only	pre-dose, only	X[1]
Expansion	X		pre-dose, 1,2,4,6, and 10 hours postdose					predose only	predose only	pre-dose, 1,2,4,6, and 10 hours postdose	pre-dose, only	pre-dose, only	X[1]
Extension	X		pre-dose, 1,2,4,6, and 10 hours postdose					predose only	predose only	pre-dose, 1,2,4,6, and 10 hours postdose	pre-dose, only	pre-dose, only	X[1]

[1] One measurement taken at any time during the day;

Also, 1 measurement at any time during day on Day 1 of each subsequent cycle; on occurrence of any cardiac AE; Discontinuation visit

Hansoh Pharmaceutical Group Co. Ltd.

A Phase 1/2, Open-label, Multicenter Study to Evaluate Safety, Tolerability, Pharmacokinetics and Efficacy of Oral Once-Daily Administration of HS-10296 in Patients with Locally Advanced or Metastatic Non-Small-Cell Lung Cancer Who Have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent

HS-10296-12-01

Statistical Analysis Plan

Version: 1.0

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A Phase 1/2, Open-label, Multicenter Study to Evaluate Safety, Tolerability, Pharmacokinetics and Efficacy of Oral Once-Daily Administration of HS-10296 in Patients with Locally Advanced or Metastatic Non-Small-Cell Lung Cancer Who Have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent

HS-10296-12-01

Statistical Analysis Plan

Version: 1.0

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ABBREVIATIONS

AE	Adverse event
cfDNA	Cell-free DNA
CI	Confidence interval
CR	Complete response
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLT	Dose-limiting toxicity
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EGFRm+	Epidermal growth factor receptor sensitizing mutation positive
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ C-30	EORTC Quality of Life Questionnaire
FDA	Food and Drug Administration
HRQoL	Health-related quality of life
ICR	Independent central review
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progression of disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Lung Cancer
QRS	Combination of 3 of the graphical deflections seen on a typical ECG

QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected with Fridericia's formula
RECIST (1.1)	Response Evaluation Criteria in Solid Tumors (version 1.1)
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SD	Stable disease
T790M	“Gatekeeper” amino acid 790 to methionine
T790M+	T790M mutation-positive
TKI	Tyrosine kinase inhibitor
TL	Target lesion
WHO	World Health Organization

1. INTRODUCTION

This document describes the planned data summaries, listings, and statistical analyses for protocol HS-10296-12-01 Version 7 dated 29AUG2017, "A Phase 1/2, Open-label, Multicenter Study to Evaluate Safety, Tolerability, Pharmacokinetics and Efficacy of Oral Once-Daily Administration of HS-10296 in Patients with Locally Advanced or Metastatic Non-Small-Cell Lung Cancer Who Have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent". The analysis data will be based on pre-planned cut-off date.

It is the supplemental document for the study protocol. Pharmacokinetics and pharmacodynamics analysis methods are not included in this statistical analysis plan. Supplemental analyses may also be explored in addition to the planned analyses. Any deviations from this statistical analysis plan will be described in the Clinical Study Report.

2. STUDY OBJECTIVE (S)

Primary Objective

To investigate safety, tolerability, and efficacy of HS-10296 administered orally to patients with locally advanced or metastatic NSCLC who have progressed following prior therapy with an EGFR TKI agent.

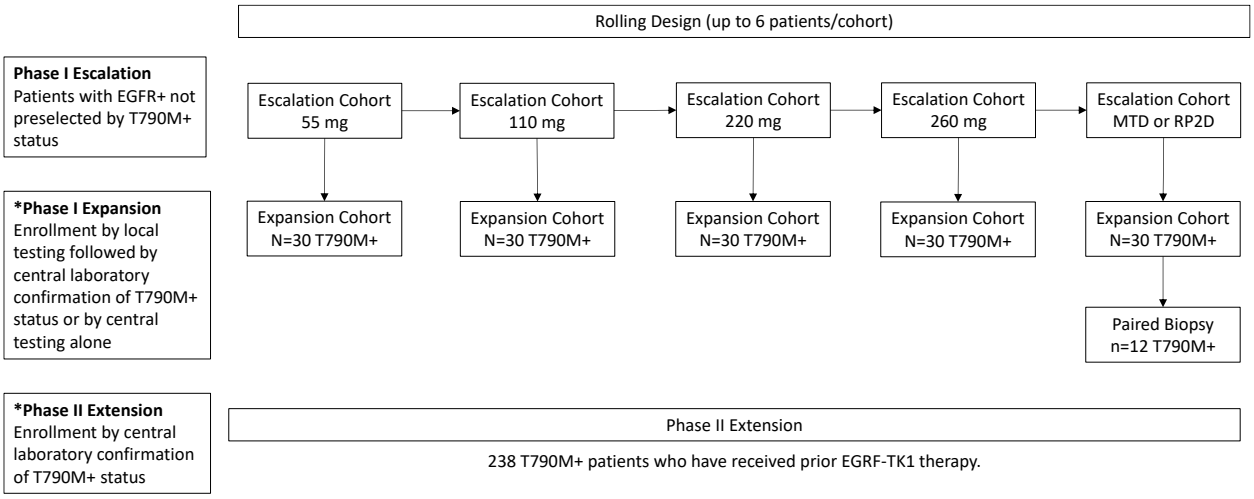
Secondary Objectives

- To determine dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) of HS-10296.
- To evaluate the PK of HS-10296 and its metabolite (HS-719) after a single oral dose and at steady state after multiple oral doses.
- To evaluate preliminary anti-tumor outcomes in the escalation and expansion cohorts, by assessment of duration of response (DoR), overall response rate (ORR), and progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
- To obtain further evaluation of the anti-tumor activity of HS-10296 in the extension cohort by assessment of ORR, DoR, DCR, tumor shrinkage, and PFS using RECIST version 1.1.

3. STUDY DESIGN

This study design consists of 3 phases (Figure 1) and aims to allow an escalation of dose with intensive safety monitoring to ensure safety of the patients.

Figure 1 Study Flow Chart



* Expansions may include more than one dose depending upon emerging data.

Dose Escalation (Phase 1 Escalation)

Up to 6 patients will be enrolled in each dose escalation cohort to ensure a minimum of 3 and a maximum of 6 evaluable patients using the rolling 6 approach. The total number of patients will depend on the number of dose escalations necessary.

Dose Expansion (Phase 1 Expansion)

Approximately 162 evaluable patients may be included in the dose-expansion phase of this study to further explore the tolerability, PK, efficacy, and biological activity of HS-10296 in specific patient subgroups. In each expansion cohort, approximately 30 evaluable patients are planned to be enrolled, but approximately 12 will be enrolled for the paired biopsy cohort to further confirm the proof of mechanism. The total number of patients will depend on the number of dose expansions necessary.

Extension Cohort (Phase 2)

Once the MTD or RP2D is reached, an additional cohort of approximately 238 evaluable patients who have confirmed $T790M^+$ status by central testing may be included in the Phase 2 extension cohort to further investigate the tolerability and efficacy of HS-10296.

4. ENDPOINTS

Besides the safety and tolerability are primary endpoints for dose escalation/expansion and secondary endpoints for extension, the following endpoints will be calculated in order to meet the study objectives.

- ORR is the primary endpoint for extension and secondary for escalation/expansion
- DoR, DCR, and PFS are secondary endpoints

- Overall survival (OS) and tumor shrinkage are secondary endpoints for extension

5. STATISTICAL HYPOTHESIS

The objective for this study is to evaluate the safety profiles and anti-tumor activity of single arm HS-10296 in treating to locally advanced or metastatic NSCLC who have progressed following prior therapy with an EGFR TKI agent, so no formal hypothesis test is planned and descriptive statistics will be adopted.

6. SAMPLE SIZE CONSIDERATION

The primary objective for the phase of dose escalation and expansion cohorts in this study is to investigate the safety and tolerability and thereby identify the MTD of HS-10296 to recommend the dose(s) for evaluation in future clinical studies. Hence, the number of patients in the cohorts has been based on the desire to obtain adequate tolerability, safety, pharmacokinetic, and pharmacodynamic data while exposing as few patients as possible to HS-10296 and procedures.

For phase 2 extension cohort, the primary endpoint is ORR. A sample size of 238 evaluable patients achieves 90% power to detect a difference (P1 – P0) of 0.1 using a two-sided binomial test with a significance level of 0.05 to test the hypotheses H0: $P \leq 0.3$ (P0 = 0.3) and H1: $P > 0.3$ (P1 = 0.4).

7. ANALYSIS SETS

The analysis sets will be based on different subsets according to the purpose of the analysis. Although only Safety and Full Analysis Set are used in this statistical analysis plan, all analysis sets listed as following have to be flagged.

Analysis Sets	**Definition**
Safety	All patients who received at least one dose of HS-10296
PK	Dosed patients who have at least one measurable plasma concentration collected post-dose
Evaluable for response (Full Analysis Set; FAS)	Patients with a baseline RECIST assessment who received at least one dose of HS-10296 (The assessment will be based on ICR for extension cohort, investigator for escalation and expansion cohorts)
Exploratory biomarkers	All patients that participate in the exploratory biomarker research
Paired biopsy	Dosed patients with a pre-study tumor biopsy and one tumor biopsy on study treatment

8. STATISTICAL METHODS

8.1. General Statistical Considerations

Data will be summarized using descriptive statistics by cohorts. Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), minimum, maximum, 95% confidence interval, median, and range as appropriate. Categorical variables will be summarized using frequencies and percentages as appropriate.

Baseline will be defined as the last non-missing measurement prior to dosing with the study drug, unless otherwise stated.

If actual assessment date is prior to first dose day then study day will be: Study day=Actual assessment date-first dose date; If actual assessment date is on or after first dose day then study day will be: Study day=Actual assessment date-first dose date+1.The baseline EGFR mutation status are based on external centralized test results. For the extension cohort only, ICR based RECIST assessments will be used for the primary analysis of ORR and other RECIST-based endpoints.

With the exception of some safety summaries that may be combined, data from escalation, expansion and extension cohorts will be presented separately.

Analyses will be performed using SAS® System Version 9.3 (SAS is a registered trademark of the SAS Institute Inc., Cary, NC, USA).

8.2. Data Handling Conventions

The minimum descriptive statistics detailed as following will be included in each summary table (Table 1).

Table 1 Specification of Number of Decimal Places for Minimum Descriptive Statistics

Label	Description	No. of decimal places (dp)
N	number of subjects in the dose group	Always present to 0 dp
n	number of subjects with non-missing values	Always present to 0 dp
Mean	Arithmetic Mean	1 dp more than raw data
SD	Standard Deviation	2 dp more than raw data
Median	Median	1 dp more than raw data
Min.	Minimum	Same as raw data
Max.	Maximum	Same as raw data
%	Percentages	Always present to 1 dp

8.2.1. Missing Data

Missing Safety data will generally not be imputed unless otherwise stated.

8.2.2. Derived and Transformed Data

Change from Baseline

The change from baseline will be calculated by subtracting the baseline values (the latest observed record before dosing) from the individual post-baseline values. If either the baseline or post-baseline value is missing, the change from baseline is set to missing as well.

Multiple Measurements at One Timepoint

When multiple measurements are recorded for a particular time point on schedule, the mean of the measurements will be calculated and used in any derivation of summary statistics. All available data will be listed.

When there are unscheduled measurements for a particular visit, all summarizations will be based on the measurements closest to the target day. All unscheduled measurements data will be listed.

8.3. Subjects Information

8.3.1. Disposition of Subjects

The number of subjects who were screened, who were enrolled, who received study drug, who completed the study, who continued the study, who discontinued from the study as well as reasons for termination of study will be summarized by dose group and overall for escalation and expansion cohort, by region and overall for extension cohort and integrated analysis of 110mg dose group. Listing of the subjects who withdrew from the study prematurely will be provided. The number of subjects included in the “evaluable for response” population (Full Analysis Set, FAS), and safety population will be summarized by dose group and overall for escalation and expansion cohort, by region and overall for extension cohort and integrated analysis of 110mg dose group.

8.3.2. Protocol Deviations

Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category. A listing of the inclusion/exclusion criteria deviation record for all subjects will be provided. A by-subject listing of protocol deviations will be provided.

8.3.3. Demographic and baseline Characteristics

Characteristics of the patients, including age, gender, height, weight, race, history of smoking, medical/surgical history, and disease characteristics at baseline will be summarized by dose

group for escalation and expansion cohort, by region and overall for extension cohort and integrated analysis of 110mg dose group and listed for each patient.

8.3.4. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary. Prior medications are defined as any therapy used before the day of first dose of study drug. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study drug, including that started before and continue on after the first dose of study drug.

Summaries of concomitant medications will be presented by ATC term. The proportion of subjects who receive each concomitant medication will be summarized by dose group for escalation and expansion cohort, by region and overall for extension cohort and integrated analysis of 110mg dose group, as well as the proportion of subjects who receive at least one concomitant medication. The standard ATC term, standard medication name, start date, end date, dose, unit, frequency, route, and indication will be listed for each patient. Prior medications will also be summarized.

8.4. Efficacy Analysis

Escalation cohort will not be included in efficacy analysis for integrated analysis of 110mg dose group.

8.4.1. Objective Response Rate

Objective response rate is defined as the percentage of patients who have at least one confirmed response of CR or PR prior to any evidence of progression, as defined by RECIST 1.1. ORR is the primary endpoint of extension cohort and the secondary endpoints of escalation and expansion cohorts. ORR will be summarized by dose group for escalation and expansion cohort, by region and overall for extension cohort and integrated analysis of 110mg dose group. The analysis set will be the Full Analysis Set.

Tumor response data will be listed and categorized into Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), and Non-Evaluable (NE). Objective response rate will be presented together with 95% confidence intervals (calculated using the Clopper-Pearson interval).

8.4.2. Disease Control Rate

The DCR is defined as the proportion of patients with a best overall response of CR, PR, or SD. It will be summarized with 95% confidence intervals and the analysis set for disease control rate will be Full Analysis Set.

8.4.3. Duration of Response

Duration of response is defined as the time from the date of first response (PR or CR) until the date of progression or death in the absence of disease progression. If a patient does not progress following a response, then DoR will use the PFS censoring time. The analysis set for DoR will be the Full Analysis Set.

Patients' duration of response will be summarized and the number (%) of responding patients with a duration of response > 3, > 6, > 9, > 12 months will be presented. A Kaplan-Meier survival curve and median duration of response with 95% CI (calculated from the Kaplan-Meier survival curve) will be presented by dose group for escalation and expansion cohort, by region and overall for extension cohort and integrated analysis of 110mg dose group.

8.4.4. Progression-Free Survival

The PFS is defined as the time from first dosing date until the date of disease progression or death by any cause regardless of whether the patient withdraws from study drug or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the date of their last evaluable RECIST assessment. If the patients have no evaluable visits or do not have baseline data, they will be censored at 0 days unless they die within 2 visits of baseline. The analysis set for PFS will be the Safety Set.

Kaplan-Meier survival curve for PFS will be presented by dose group for escalation and expansion cohort, by region and overall for extension cohort and integrated analysis of 110mg dose group. The survival time will be summarized with 25th, 50th (median), and 75th percentiles and associated 2-sided 95% confidence intervals. The number of events and proportion of patients without an event at 6, 12, and 18 months will also be summarized.

8.4.5. Overall Survival

Overall survival is defined as the interval between the first dosing and the patient death (due to any cause) date. Patients who have not died at the time of the statistical analysis will be censored at the time that the patient was last known to be alive. The analysis population for overall survival will be Safety Set.

For extension cohort, overall survival time will be summarized with 25th, 50th (median), and 75th percentiles and associated 2-sided 95% confidence intervals; Kaplan-Meier survival curve will also be presented.

8.4.6. Tumor Shrinkage（Depth of Objective Response）

Tumor size is defined as the sum of the lengths of the longest diameters of the RECIST 1.1 TLs. Percentage tumor shrinkage will be determined for patients with measurable disease at Baseline

and derived at each visit by the percentage change in the sum of the diameters of TLs compared with baseline.

For extension cohort, summaries and waterfall plot indicating percentage change from baseline in the sum of the diameters of TLs at Week 6 will be presented. Best percentage change from baseline will also be presented. The analysis set for tumor shrinkage will be Full Analysis Set.

8.4.7. Subgroup Analysis

In addition to the analysis of PFS described above, the subgroup analyses will be conducted by comparing PFS in following groups: gender (Female VS Male), race (if appropriate), region (Mainland China VS Taiwan), agegroup (>=65 VS <65), brain metastases at entry, smoking history, EGFR mutation (Ex19del VS L858R), ECOG (0 VS 1). In addition to the analysis of ORR described above, the subgroup analyses will be conducted by comparing ORR in following groups: gender (Female VS Male)， race(if appropriate), agegroup (>=65 VS <65), region (Mainland China VS Taiwan), brain metastases at entry, smoking history, EGFR mutation (Ex19del VS L858R), ECOG (0 VS 1). The forest plot will be presented.

8.4.8. Sensitivity Analysis

For extension cohort, the same methods of analysis will be applied to analyze ORR, DoR, DCR, tumor shrinkage, and PFS…etc. based on the RECIST data assessed by the Investigator.

8.5. Safety Analysis

All of the safety analyses listed as following are based on Safety Set.

8.5.1. Exposure

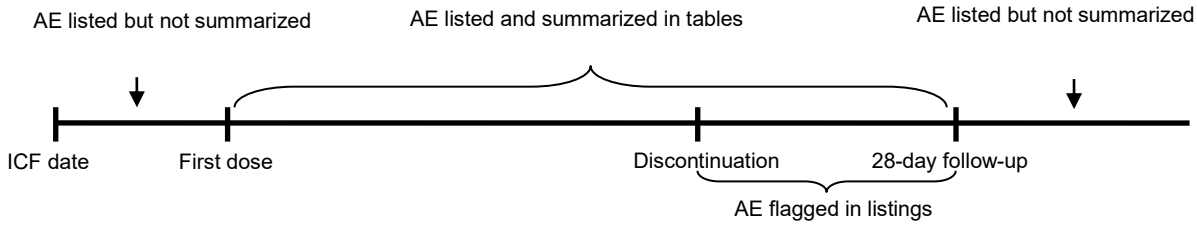
Duration of exposure (date of last dose no later than early withdrawn or completion - date of first dose + 1), dose days of exposure (duration of exposure - total duration on dose interruption), cumulative exposure (sum of daily dose), mean daily dose(sum of daily dose/duration of exposure) and actual mean daily dose (sum of daily dose/dose days of exposure) will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations. The number and percentage of patients with at least one dose interruption/dose delay and at least one dose reduction will be presented separately for the initial period, defined as 21 days of multiple dosing (cycle 1), and for any time following this initial period of the study. Exposure to the study drug will be listed for all patients.

8.5.2. Adverse Events

Adverse events will be summarized according to the system organ class (SOC) and preferred term (PT) assigned to the event using MedDRA by dose group for escalation and expansion cohort, by region and overall for extension cohort and integrated analysis of 110mg dose group

and listed individually for each patient. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group.

Any AE occurring after the first dose of study drug and within the defined 28 day follow-up period after discontinuation of the study drug will be included in the AE summaries and listings, AE in the period from discontinuation to 28 day follow-up will be flagged in the data listings. Any AE occurring before the first dose of the study drug (i.e., before study Day 1) or after the 28-day follow-up period after discontinuation of the study drug will be included in the data listings but will not be included in the summary tables of AEs.



AE will be categorized as following:

- All AEs
- All AEs with causality related to HS-10296
- All SAEs
- All SAEs with causality related to HS-10296
- AE leading to HS-10296 dose interruption
- AE leading to HS-10296 dose reduction
- AE leading to discontinuation of HS-10296
- AE leading to discontinuation of HS-10296, causality related to HS-10296
- AE with an outcome of death
- AE with an outcome of death, causality related to HS-10296
- AE with CTCAE grade 3 or higher
- AE with CTCAE grade 3 or higher, causality related to HS-10296
- Other significant AEs

An overall summary of the number and percentage of patients in each category will be presented.

The number and percentages of patients reporting adverse events will be summarized by MedDRA system organ class and preferred term. The number and percentage of patients with AEs in different categories will be summarized, and events in each category will be summarized further by MedDRA system organ class and preferred term. The adverse events that occurred ≥5% in each group will be presented by SOC and PT. For the tables classified by causally related or severity grade, if a patient has more than 1 occurrence of an AE term, the most causality or the highest severity will be chosen.

Serious adverse events will be summarized and listed separately. A summary of deaths will be provided by number and percentage of patients by dose group for escalation and expansion cohort, by region and overall for extension cohort and integrated analysis of 110mg dose group.

8.5.3. Clinical Laboratory Evaluations

Laboratory data including clinical chemistry, hematology, and urinalysis will be taken at the visits as indicated in the Study Plan (Appendix A) and will be treated as continuous or categorical variables. The absolute value and the value of change from baseline will be tabulated by dose group for continuous variables. The normality of laboratory test will be tabulated by dose group for categorical variables. In the other hand, shift tables by normality for laboratory evaluations will be presented, too. All of the laboratory evaluation results will be listed and clinically significant or not will also be included.

8.5.4. Vital signs

Weight, body temperature (in Centigrade), pulse (beats per minute), and blood pressure (systolic and diastolic) will be included in vital sign and will be treated as continuous variables. Absolute value of each assessment and the value of change from baseline will be summarized and listed. The descriptive statistics of absolute value and value of changes from baseline will be tabulated by dose group.

8.5.5. ECG

Absolute value and change from baseline for ECG measurements (HR, RR, PR, QRS, QT and QTcF) will be summarized as n, mean, standard deviation, median, min, and max by each time point and dose group. Shift table will be performed by dose group. Furthermore, QTcF will be tabulated values by <=450, >450 and <=480, >480 and <=500, >500 and change from baseline by <= 30, >30 and <=60, >60 by each time point and dose group. Listings for patients' ECG values and results will also be presented.

8.5.6. LVEF

Shift table for LVEF accessed by echocardiogram or multigated acquisition (MUGA) scan by each time point and dose group are performed. Listings for patients' LVEF results will also be presented.

8.5.7. Physical examination

Physical examination will be evaluated throughout the study and will be summarized and listed by dose group. Shift table to show the number and percentage of abnormality on physical examination by dose group will also be presented.

8.5.8. WHO performance status

WHO performance status will be listed and summarized as frequency counts by each time point and dose group.

8.5.9. Ophthalmic examination

Shift table by dose group for ophthalmic examination will be performed and details of ophthalmic examination data will also be listed.

8.6. Pharmacokinetic Analysis

Pharmacokinetic analysis is excluded from this SAP and will be described in other analysis plan if needed.

8.7. Pharmacodynamic and Biomarkers Analysis

Pharmacodynamic and biomarkers analysis is excluded from this SAP and will be described in other analysis plan if needed.

8.8. Pharmacogenetic Analysis

Pharmacogenetic analysis is excluded from this SAP and will be described in other analysis plan if needed.

8.9. Health Outcomes Analysis

Patient Report Outcomes Analyses on the EORTC QLQ C-30 and QLQ-LC13 will be based on the instruments' scoring manual. The scores for PRO are summarized and listed by dose group if needed.

8.10. Other Analysis

No other analysis in this study.

8.11. Changes for Planned Analyses in Protocol

No changes for planned analyses in protocol will be implemented.

9. TABLES, FIGURES AND LISTING SHELLS

9.1. Tables

No.	Analysis Sets	Title
1.1	All Enrolled Subjects	Subject Disposition - All Enrolled Subjects
1.2	All Enrolled Subjects	Analysis Population - All Enrolled Subjects
1.3	Safety Set	Major Protocol Deviations - Safety Set
1.4.1	Full Analysis Set	Demographics and Baseline Characteristics – Full Analysis Set
1.4.2	Safety Set	Demographics and Baseline Characteristics – Safety Set
1.5	Safety Set	Subject with Any Prior Medication - Safety Set
1.6	Safety Set	Subject with Any Concomitant Medication - Safety Set
2.1.1	Full Analysis Set	Summary of Objective Response Rate (ORR) and Disease Control Rate (DCR) – Full Analysis Set
2.1.2	Full Analysis Set	Summary of Objective Response Rate (ORR) by Gender – Full Analysis Set
2.1.3	Full Analysis Set	Summary of Objective Response Rate (ORR) by Age Group – Full Analysis Set
2.1.4	Full Analysis Set	Summary of Objective Response Rate (ORR) by Region – Full Analysis Set
2.1.5	Full Analysis Set	Summary of Objective Response Rate (ORR) by Brain Metastases at Entry – Full Analysis Set
2.1.6	Full Analysis Set	Summary of Objective Response Rate (ORR) by Smoking History – Full Analysis Set
2.1.7	Full Analysis Set	Summary of Objective Response Rate (ORR) by EGFR Mutation – Full Analysis Set
2.1.8	Full Analysis Set	Summary of Objective Response Rate (ORR) by ECOG – Full Analysis Set
2.1.9	Full Analysis Set	Summary of Objective Response Rate (ORR) and Disease Control Rate (DCR): based on the RECIST data assessed by the Investigator – Full Analysis Set

No.	Analysis Sets	Title
2.2.1	Full Analysis Set	Summary of Duration of Response (DoR) – Full Analysis Set
2.2.2	Full Analysis Set	Summary of Duration of Response (DoR) : based on the RECIST data assessed by the Investigator – Full Analysis Set
2.3.1	Safety Set	Summary of Progression-Free Survival (PFS) – Safety Set
2.3.2	Safety Set	Summary of Progression-Free Survival (PFS) by Gender –Safety Set
2.3.3	Safety Set	Summary of Progression-Free Survival (PFS) by Age Group –Safety Set
2.3.4	Safety Set	Summary of Progression-Free Survival (PFS) by Region –Safety Set
2.3.5	Safety Set	Summary of Progression-Free Survival (PFS) by Brain Metastases at Entry –Safety Set
2.3.6	Safety Set	Summary of Progression-Free Survival (PFS) by Smoking History –Safety Set
2.3.7	Safety Set	Summary of Progression-Free Survival (PFS) by EGFR Mutation –Safety Set
2.3.8	Safety Set	Summary of Progression-Free Survival (PFS) by ECOG–Safety Set
2.3.9	Safety Set	Summary of Progression-Free Survival (PFS) : based on the RECIST data assessed by the Investigator –Safety Set
2.4	Safety Set	Summary of Overall Survival (OS) –Safety Set
2.5.1	Full Analysis Set	Summary of Tumor Shrinkage (%) – Full Analysis Set
2.5.2	Full Analysis Set	Summary of Tumor Shrinkage (%) : based on the RECIST data assessed by the Investigator – Full Analysis Set
3.1	Safety Set	Overall Summary of Adverse Events [1] - Safety Set
3.2.1	Safety Set	Summary of Adverse Events [1] by System Organ Class and Preferred Term - Safety Set
3.2.2	Safety Set	Summary of Adverse Events [1] that Occurred ≥ 5% by System Organ Class and Preferred Term - Safety Set
3.2.3	Safety Set	Summary of Drug-related Adverse Events [1] that Occurred ≥ 5% by System Organ Class and Preferred Term - Safety Set
3.2.4	Safety Set	Summary of Drug-related Adverse Events [1] by System Organ Class and Preferred Term - Safety Set

No.	Analysis Sets	Title
3.2.5	Safety Set	Summary of Serious Adverse Events [1] by System Organ Class and Preferred Term - Safety Set
3.2.6	Safety Set	Summary of Adverse Events [1] Leading to Withdraw by System Organ Class and Preferred Term - Safety Set
3.2.7	Safety Set	Summary of Adverse Events [1] Leading to Death by System Organ Class and Preferred Term – Safety Set
3.2.8	Safety Set	Summary of Adverse Events [1] Leading to Dose Modification by System Organ Class and Preferred Term – Safety Set
3.2.9	Safety Set	Summary of Drug-related Serious Adverse Events [1] by System Organ Class and Preferred Term - Safety Set
3.3.1	Safety Set	Adverse Events [1] by SOC and PT and Severity - Safety Set
3.3.2	Safety Set	Drug-related Adverse Events [1] by SOC and PT and Severity - Safety Set
3.4.1	Safety Set	Summary of Physical Examination - Safety Set
3.4.2	Safety Set	Shift Table of Physical Examination - Safety Set
3.5.	Safety Set	Summary of WHO Performance Status - Safety Set
3.6.1	Safety Set	Summary of Clinical Hematology and Chemistry Laboratory Data - Safety Set
3.6.2	Safety Set	Shift Table of Clinical Hematology and Chemistry Laboratory Data - Safety Set
3.6.3	Safety Set	Summary of Change from Baseline Clinical Hematology and Chemistry Laboratory Data - Safety Set
3.6.4	Safety Set	Number and Percentage of Subjects for Urinalysis Data – Safety Set
3.6.5	Safety Set	Shift Table of Urinalysis Data - Safety Set
3.7.1	Safety Set	Summary of Vital Signs - Safety Set
3.7.2	Safety Set	Summary of Change from Baseline in Vital Signs - Safety Set
3.8.1	Safety Set	Summary of ECG - Safety Set
3.8.2	Safety Set	Summary of Change from Baseline in ECG - Safety Set

No.	Analysis Sets	Title
3.8.3	Safety Set	Summary of ECG Grouping for QTcF - Safety Set
3.8.4	Safety Set	Summary of Change from Baseline in ECG Grouping for QTcF - Safety Set
3.8.5	Safety Set	Shift Table of ECG - Safety Set
3.9	Safety Set	Summary of Study Drug Exposure - Safety Set
3.10.1	Safety Set	Shift Table of Ophthalmology Examination - Safety Set
3.11.1	Safety Set	Shift Table of LVEF - Safety Set

9.2. Listings

No.	Analysis Sets	Title
1	Safety Set	Listing of Subjects Who Discontinued from Treatment and Reason for Early Termination– Safety Set
2	Safety Set	Listing of Protocol Deviations - Safety Set
3	Safety Set	Listing of Inclusion/Exclusion Criteria Deviations - Safety Set
4	Safety Set	Listing of Demographics and Baseline Characteristics - Safety Set
5.1	Safety Set	Listing of Medical/Surgical History - Safety Set
5.2	Safety Set	Listing of Lung Cancer Disease History - Safety Set
5.3	Safety Set	Listing of Lung Cancer Disease History (Previous Chemotherapy) - Safety Set
5.4	Safety Set	Listing of Lung Cancer Disease History (Previous Radiotherapy) - Safety Set
5.5	Safety Set	Listing of Lung Cancer Disease History (Previous Surgery for Cancer) - Safety Set

No.	Analysis Sets	Title
6.1	Safety Set	Listing of Prior Medications – Safety Set
6.2	Safety Set	Listing of Concomitant Medications – Safety Set
6.3	Safety Set	Listing of Concomitant Treatment – Safety Set
7.1	Full Analysis Set	Listing of Objective Response Evaluation – Full Analysis Set
7.2	Full Analysis Set	Listing of Tumor Shrinkage – Full Analysis Set
8.1	Safety Set	Listing of Study Drug Dispensing - Safety Set
8.2	Safety Set	Listing of Study Drug Exposure - Safety Set
9.1	Safety Set	Listing of Adverse Events [1] - Safety Set
9.2	Safety Set	Listing of Adverse Events Before First Dose - Safety Set
9.3	Safety Set	Listing of Adverse Events after 28-day Follow-up - Safety Set
9.4	Safety Set	Listing of Serious Adverse Events - Safety Set
10	Safety Set	Listing of Laboratory Data - Safety Set
11	Safety Set	Listing of Vital Signs - Safety Set
12	Safety Set	Listing of Physical Examinations - Safety Set
13	Safety Set	Listing of WHO Performance Status - Safety Set
14	Safety Set	Listing of ECG - Safety Set
15	Safety Set	Listing of Ophthalmic Examination - Safety Set
16	Safety Set	Listing of Death - Safety Set
17	Safety Set	Listing of LVEF - Safety Set

9.3. Figures

No.	Analysis Sets	Title
1	Full Analysis Set	Kaplan-Meier Graph of Duration of Response by Dose Group - Full Analysis Set
2	Safety Set	Kaplan-Meier Graph of Progression Free Survival by Dose Group - Safety Set
3	Full Analysis Set	Forest Plot for Objective Response Rate by subgroups and by Dose Group - Full Analysis Set
4	Safety Set	Kaplan-Meier Graph of Overall Survival - Safety Set
5	Full Analysis Set	Waterfall Plot for Percentage Change from Baseline at Week 6 for Extension Cohort - Full Analysis Set
5.1	Full Analysis Set	Waterfall Plot for Best Percentage Change from Baseline for Extension Cohort - Full Analysis Set

Appendix A Study Plan

Dose Escalation														
	Screening	**Single dose/Cycle 0 (7-day cycle)**					**Multiple Dose/ Cycle 1 (21-day cycle)**			**Cycles 2-6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontinuation**	**28-day follow-up**	**Progression**
Day	**-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D6**	**D1**	**D8**	**D15**	**D1**	**D1**			
Window (days)										**Cycle 3-6: ± 3**	**± 3**	**NA**	**± 3**	**± 3**
Informed consent	X													
Inclusion/exclusion criteria	X													
Demography and baseline characteristics	X													
Medical/surgical history	X													
Physical examination; neurologic examination required at each cycle physical examination	X	X					X			X	X	X		
Ophthalmologic assessment	X									X[a]				
WHO performance status	X	X					X			X	X	X		
EGFR mutation status	X													
Archival tumor tissue	X													
Vital signs	X	X	X				X	X	X	X	X	X		
Height	X													
Weight	X	X					X			X	X	X		

Dose Escalation (continued)

	Screening	**Single dose/Cycle 0 (7-day cycle)**					**Multiple Dose/ Cycle 1 (21-day cycle)**			**Cycles 2-6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontinuation**	**28-day follow-up**	**Progression**
Day	**-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D6**	**D1**	**D8**	**D15**	**D1**	**D1**			
Window (days)										**Cycle 3-6: ± 3**	**± 3**	**NA**	**± 3**	**± 3**
Clinical chemistry/ hematology/urinalysis[b]	X	X					X	X	X	X	X	X		
Pregnancy test (females of childbearing potential only)[c]	X													
ECG[d]	X	X	X				X	X	X	X	X	X		
Genetics consent and blood sample (optional)	X													
Blood sample for cfDNA (6 weekly)	X	X								X, every 6 (± 1) weeks at RECIST visit ⟷				X
PK blood samples (including metabolites)[e]		X	X	X	X	X	X	X	X	(Cycle 2 only)				
Echocardiogram/MUGA scan	X	X, every 12 weeks (relative to first dose) ⟷												
RECIST assessments[f]	X						X, every 6 (± 1) weeks (relative to first dose of multiple dosing) until progression ⟷							
Dispense study drug		X					X			X	X			
Dose with HS-10296		X					X, daily dosing during 21-day cycle ⟷							
AEs/concomitant medications[g]	⟷													
Tumor biopsy (optional)	X								X			X		
CSF (optional)										X (once only)				

cfDNA = cell-free DNA; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.

[a] For ophthalmologic assessment, Cycle 2 and 3 and then as needed per signs and symptoms.

[b] Laboratory tests do not need to be repeated at Baseline if the baseline visit is within 7 days of obtaining the screening sample.

Footnotes continued next page.

[c] A urine or serum pregnancy test will be performed for women of childbearing potential at Screening or within 3 days before the first dose of study drug. The results must be available and negative before the first dose of study drug is administered.

[d] Refer to Appendix H for further details.

[e] PK sampling times are as follows: dose escalation, single dose (Cycle 0), Day 1 (predose, 30 min, 1.0 h, 1.5 h, 2.0 h, 4.0 h, 6.0 h, 8.0 h, 10 h,12 h, 24 h (Day 2), 48 h (Day 3), 72 h (Day 4), and 120 h (Day 6); multiple dosing (Cycle 1): Days 1, 8, and 15 (predose); multiple dosing (Cycle 2), Day 1: predose, 30 min, 1.0 h, 1.5 h, 2.0 h, 4.0 h, 6.0 h, 8.0 h, 10 h, 12 h, and 24 h (Day 2 predose).

[f] Screening RECIST evaluation should be conducted as close as possible to start of treatment.

[g] For concomitant medication collection**,** after discontinuation and for 28-day follow-up, only anti-cancer medications will be recorded.

Phase 1 Expansion Cohort and Paired Biopsy									
	Screening	**Multiple Dose/ Cycle 1 (21-day cycle)**			**Cycles 2-6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontinuation**	**28-day Follow-up**	**Progression**
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**			
Window (days)					**Cycle 3-6: ± 3**	**±3**	**NA**	**±3**	± 3
Informed consent	X								
Inclusion/exclusion criteria	X								
Demography and baseline characteristics	X								
Medical/surgical history	X								
Physical examination; neurologic examination required at each cycle physical examination	X	X			X	X	X		
Ophthalmologic assessment	X				X[a]				
WHO performance status	X	X			X	X	X		
HRQoL form	X	X			X, every 6 (± 1) weeks (relative to first dose) until progression		X		X
T790M mutation status tumor sample (mandatory)	X								
Archival tumor tissue	X								
Tumor biopsy (paired biopsy cohort - mandatory)	X			X					
Tumor biopsy (optional)	X			X			X		

Phase 1 Expansion Cohort and Paired Biopsy (continued)

	Screening	Multiple Dose/ Cycle 1 (21-day cycle)			Cycles 2-6 (21-day cycle)	Cycle 7 and every 6 weeks onward	Discontinuation	28-day Follow-up	Progression
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**			
Window (days)					**Cycle 3-6: ± 3**	**±3**	**NA**	**±3**	± 3
Vital signs	X	X	X	X	X	X	X		
Height	X								
Weight	X	X			X	X	X		
Clinical chemistry/hematology/urinalysis[b]	X	X	X	X	X	X	X		
Pregnancy test (females of childbearing potential only)[c]	X								
ECG[d]	X	X	X	X	X	X	X		
Echocardiogram/MUGA scan	X	X, every 12 weeks relative to first dose							
PK blood sample (including metabolite)[e]		X	X	X	X (cycle 2 only)				
Blood sample for cfDNA (6 weekly)	X	X			X, every 6 (± 1) weeks at RECIST visit				X
RECIST assessments[f]	X	X, every 6 (± 1) weeks (relative to first dose) until progression							X
Dispense study drug		X			X	X			
Dose with HS-10296		X, daily dosing during 21-day cycle							
AEs/concomitant medications[g]	←								→
Genetic consent and blood sample (optional)	X								
CSF (optional)					X (once only)				

cfDNA = cell-free DNA; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; HRQoL = health-related quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.

Phase 1 Expansion Cohort and Paired Biopsy (continued)

	Screening	Multiple Dose/ Cycle 1 (21-day cycle)			Cycles 2-6 (21-day cycle)	Cycle 7 and every 6 weeks onward	Discontinuation	28-day Follow-up	Progression
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**			

[a] For ophthalmologic assessment, Cycle 2 and 3 and then as needed per signs and symptoms.

[b] Laboratory tests do not need to be repeated at Baseline if the baseline visit is within 7 days of obtaining the screening sample.

Footnotes continued next page.

Phase 1 Expansion Cohort and Paired Biopsy (continued)

	Screening	Multiple Dose/ Cycle 1 (21-day cycle)			Cycles 2-6 (21-day cycle)	Cycle 7 and every 6 weeks onward	Discontinuation	28-day Follow-up	Progression
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**			

[c] A urine or serum pregnancy test will be performed for women of childbearing potential at Screening or within 3 days before the first dose of study drug. The results must be available and negative before the first dose of study drug is administered.

[d] Refer to Appendix H for further details

[e] PK sampling times are as follows: multiple dosing (Cycle 1): Days 1, 8, and 15 (predose); multiple dosing (Cycle 2), Day 1: predose, 30 min, 1.0 h, 1.5 h, 2.0 h, 4.0 h, 6.0 h, 8.0 h, 10 h, 12 h, and 24 h (Day 2 predose).

[f] Screening RECIST evaluation should be conducted as close as possible to start of treatment.

[g] For concomitant medication collection**,** after discontinuation and for 28-day follow-up, only anti-cancer medications will be recorded.

Phase 2 Extension Cohort										
	Screening	**Multiple Dose/ Cycle 1 (21-day cycle)**			**Cycles 2-6 (21-day cycle)**	**Cycle 7 and every 6 weeks onwards**	**Discontinuation**	**28-day Follow-up**	**Progression**	**Post-progression survival F/U**
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**				
Window (days)					**Cycle 3-6: ± 3**	**±3**	**NA**	**±3**	±3	±3
Informed consent	X									
Inclusion/exclusion criteria	X									
Demography and baseline characteristics	X									
Medical/surgical history	X									
Physical examination; neurologic examination required at each cycle physical examination	X	X			X	X	X			
Ophthalmologic assessment	X				X[a]					
WHO performance status	X	X			X	X	X			
HRQoL form	X	X			X, every 6 (± 1) weeks (relative to first dose) until progression		X		X	
T790M mutation status tumor sample (mandatory)	X									
Archival tumor tissue	X									
Vital signs	X	X	X	X	X	X	X			
Height	X									
Weight	X	X			X	X	X			

Phase 2 Extension Cohort (continued)

	Screening	Multiple Dose/ Cycle 1 (21-day cycle)			Cycles 2-6 (21-day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day Follow-up	Progression	Post-progression survival F/U
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**				
Window (days)					**Cycle 3: ± 3**	**±3**	**NA**	**±3**	**±3**	**±3**
Clinical chemistry /hematology/urinalysis[b]	X	X	X	X	X	X	X			
Pregnancy test (females of childbearing potential only)[c]	X									
ECG[d]	X	X	X	X	X	X	X			
Echocardiogram/MUGA scan	X	X, every 12 weeks relative to first dose ← →								
PK blood sample (including metabolite)[e]		X	X	X	X (cycle 2 only)					
Blood sample for cfDNA (6 weekly)	X	X			X, every 6 (± 1) weeks at RECIST visit ← →				X	
RECIST assessments[f]	X	X, every 6 (± 1) weeks (relative to first dose) until progression ← →							X	
Dispense study drug		X			X	X				
Dose with HS-10296		X, daily dosing during 21-day cycle ← →								
AEs/concomitant medication[g]	← →									X
Genetic consent and blood sample (optional)	X									
CSF (optional)					X (once only)					
Survival										X

cfDNA = cell-free DNA; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; HRQoL = health-related quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.

Footnotes continued next page

[a] For ophthalmologic assessment, Cycle 2 and 3 and then as needed per signs and symptoms.

[b] Laboratory tests do not need to be repeated at Baseline if the baseline visit is within 7 days of obtaining the screening sample.

[c] A urine or serum pregnancy test will be performed for women of childbearing potential at Screening or within 3 days before the first dose of study drug. The results must be available and negative before the first dose of study drug is administered.

[d] Refer to Appendix H for further details.

Phase 2 Extension Cohort (continued)

	Screening	Multiple Dose/ Cycle 1 (21-day cycle)			Cycles 2-6 (21-day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day Follow-up	Progression	Post-progression survival F/U
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**				

[e] PK sampling times are as follows: multiple dosing (Cycle 1): Days 1, 8, and 15 (predose); multiple dosing (Cycle 2), Day 1: predose, 30 min, 1.0 h, 1.5 h, 2.0 h, 4.0 h, 6.0 h, 8.0 h, 10 h, 12 h, and 24 h (Day 2 predose).

[f] Screening RECIST evaluation should be conducted as close as possible to start of treatment.

[g] For concomitant medication collection**,** after discontinuation and for 28-day follow-up, only anti-cancer medications will be recorded.