# Shanghai Hansoh BioMedical Co.,Ltd.

## Clinical Study Protocol No.: HS-10296-03-01

A Randomized, Controlled, Double-blind, Multicenter, Phase III Clinical Trial to Evaluate the Efficacy and Safety of HS-10296 Versus Gefitinib as First-line Therapy in Subjects with Locally Advanced or Metastatic Non-Small Cell Lung Cancer with Epidermal Growth Factor Receptor-Sensitive Mutations

**Phase III**

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| **Indications:** | Locally advanced or metastatic non-small cell lung cancer |
| **Sponsor:** | Shanghai Hansoh BioMedical Co.,Ltd. |
| **Address:** | Building 3, No. 3728, Jinke Road, Pudong New Area, Shanghai, China |
| **Version No.:** | 03 |
| **Version Date:** | December 10, 2019 |

## Confidentiality Statement

# 1.0 Administrative Information

## 1.1 Contact Information

Separate contact information will be provided to each study site.

Emergency medical contact information card will be provided to each subject.

## 1.2 Signature Page

**Shanghai Hansoh BioMedical Co.,Ltd.**

Herein, we'd like to express our highest respect to all the personnel involved in this study. The study will be conducted in accordance with the protocol and the following guidelines:

- Ethical Principles of Declaration of Helsinki
- ICH E6 GCP- Good Clinical Practice
- All applicable laws and regulations, including but not limited to: those related to data confidentiality and disclosure of clinical trials

**Signature**

[redacted] December 10, 2019
Date
[redacted]
Medical Manager

[redacted] December 11, 2019
Date
[redacted]
Senior Vice President, Clinical Department

[redacted] December 10, 2019
Date
[redacted]
Manager, Pharmacovigilance

[redacted] December 10, 2019
Date
[redacted]
Head of Quantitative Sciences

[redacted] December 10, 2019
Date
[redacted]
Head of Project Management

[redacted] December 10, 2019
Date
[redacted]
Vice President, Clinical Operations

**The Investigator**

I confirm that I have read and understood the protocol, Investigator's Brochure, and any other product-related information provided by the Sponsor. I agree to conduct the study in accordance with the requirements of the protocol and to protect the rights, safety, privacy and health of subjects in accordance with the following five regulations:

1. Ethical Principles of Declaration of Helsinki
2. ICH E6 GCP- Good Clinical Practice
3. All applicable laws and regulations, including, but not limited to, those related to data confidentiality;
4. Report serious adverse events defined in the protocol in accordance with regulatory requirements;
5. Provisions in Clinical Study Agreement;

I will further authorize my personal information to be used in this study (see Appendix A for details).

**Signature**

[redacted] December 10, 2019

Investigator's Signature Date

[redacted]

Investigator's Name (Printed or write in block letters)

[redacted]

The Investigator's Job Title

[redacted]

Study Site Address (Province and City)

[redacted]

Study Site Address (Country)

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## 2.0 Study Synopsis

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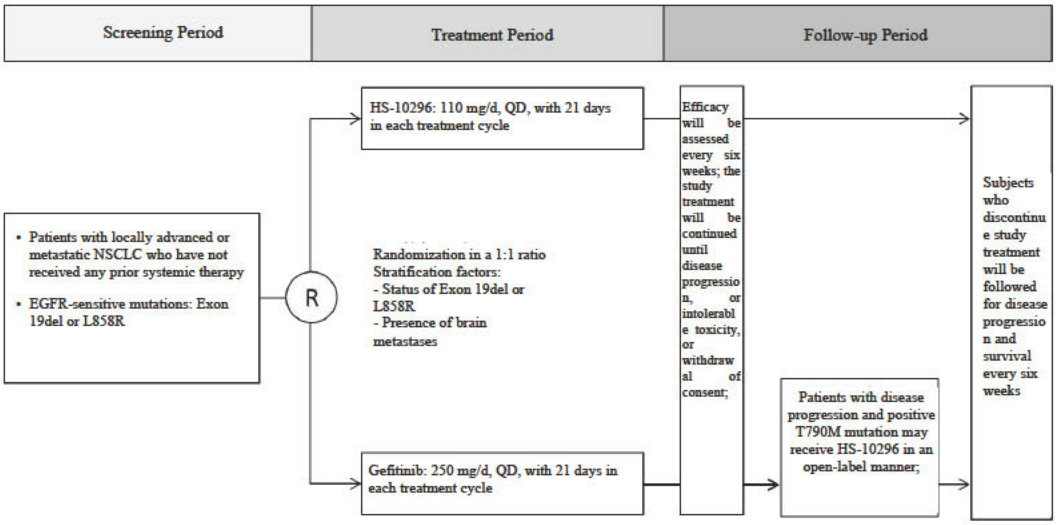
| **Sponsor:** Shanghai Hansoh BioMedical Co.,Ltd. | **Investigational Product:** HS-10296 |
| **Study Title:** A Randomized, Controlled, Double-blind, Multicenter, Phase III Clinical Trial to Evaluate the Efficacy and Safety of HS-10296 Versus Gefitinib as the First-Line Therapy in Subjects with Locally Advanced or Metastatic Non-Small Cell Lung Cancer with Epidermal Growth Factor Receptor-Sensitive Mutations | **EudraCT No.:** N/A |
| **Study No.:** HS-10296-03-01 | **Study Stage:** Phase III |

**Study Design:**

This is a randomized, controlled, double-blind, multicenter, phase III clinical trial to evaluate the efficacy and safety of HS-10296 versus gefitinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor-sensitive mutations ($EGFRm^+$) who have not received any systemic therapy. Patients will be randomized in a 1:1 ratio to HS-10296 treatment group or gefitinib treatment group to receive oral administration of HS-10296 or gefitinib once daily, in order to compare the efficacy and safety of two different treatment regimens.

**Study Procedure**

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| **Treatment Duration:**<br>A study treatment cycle is defined as repeated doses for 21 consecutive days. Patients will receive continuous administration until disease progression or the discontinuation criteria is met | **Study Duration:**<br>According to the study design, the study will last at least 36 months |
| **Number of Subjects:**<br>Estimated in total: approximately 410 | **Number of Study Sites:**<br>Estimated in total: > 20 |

**Dosage and Usage of Investigational Product:**

1. HS-10296 Tablets: strength: 55 mg/tablet; 110 mg/d (2 tablets/d), orally, once daily.
2. Gefitinib Tablets: strength: 250 mg/tablet; 250 mg/d (1 tablet/d), orally, once daily.
3. HS-10296 Placebo Tablets (placebo 55 mg): the appearance and description are consistent with those of HS-10296 tablets; 2 tablets/d, orally, once daily.

4. Gefitinib placebo tablets (placebo 250 mg): the appearance and description are consistent with those of Gefitinib tablets; 1 tablet/d, orally taken, once daily.

Note: HS-10296 tablets will be given concomitantly with gefitinib placebo tablets; gefitinib tablets will be given concomitantly with HS-10296 placebo tablets; the patients will be fasted for 1 hour before dosing and for 2 hours after dosing when taking all the drugs.

**Subject Population:**

The subjects are ≥ 18 years old, and have histologically confirmed locally advanced or metastatic NSCLC. The patients have not received any systemic therapy and harbor EGFR-sensitive mutations (exon 19 deletion or L858R mutation, either alone or in combination with other EGFR site mutations) which were confirmed prior to enrollment.

**Primary Objective:**

To compare the progression-free survival (PFS) induced by HS-10296 versus gefitinib as the first-line therapy in subjects with locally advanced or metastatic NSCLC with $EGFRm^{+}$.

**Secondary Objectives:**

1. To compare the following anti-tumor efficacy measures of HS-10296 versus gefitinib: overall survival (OS), objective response rate (ORR), duration of response (DoR), disease control rate (DCR), and depth of response (DepOR).
2. To compare the safety of HS-10296 versus gefitinib.

**Inclusion Criteria:**

Subjects must meet all of the following inclusion criteria to be eligible for the study:

1. Aged ≥ 18 years.
2. Patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC (including patients with relapsed disease after prior surgical treatment or patients with newly diagnosed disease at stage IIIB/IV. The disease stage will be determined according to 7th edition of the American Joint Committee on Cancer (AJCC) TNM staging criteria).
3. Patients who have not received any systemic therapy since they were diagnosed with locally advanced or metastatic NSCLC. Patients who have received local treatment may participate in the study if lesions within the local treatment area are non-target lesions.
4. Tumor tissue samples or blood samples collected after the diagnosis of locally advanced or metastatic NSCLC are confirmed to harbor EGFR-sensitive mutations (including exon 19 deletion or L858R mutation, either alone or in combination with other EGFR site mutations) as tested by the central laboratory. It is recommended to submit tumor tissue samples if tumor tissue is accessible; blood samples should be submitted if tumor tissue is not accessible or tissue biopsy is unacceptable to the patient.
5. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, with no worsening in the previous 2 weeks, and with a minimum expected survival of 12 weeks.
6. Patients who have at least 1 tumor lesion that has not received prior local treatment such as irradiation, or has not been performed with tissue biopsy at screening and can be accurately measured at baseline, with the longest diameter ≥ 10 mm at baseline (short axis ≥ 15 mm will be required if the lesions are lymph nodes). The selected measuring methods should be suitable for accurate and repeated measurements, such as computerized tomography (CT) or magnetic resonance scan (MRI). If there is only 1 measurable lesion that has not received prior local treatment such as irradiation, it will be acceptable as a target lesion, and a baseline evaluation of the tumor lesion will be performed at least 14 days after diagnostic biopsy.
7. Women of childbearing potential should use appropriate contraceptive measures and should not breastfeed their infants from screening to 3 months after study drug discontinuation. Female patients

with a negative pregnancy test result prior to initiation of dosing or meeting one of the following criteria are confirmed to have no risk of pregnancy:

a. Postmenopausal is defined as aged over 50 years old and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal replacement treatment.

b. Women aged less than 50 years may also be considered postmenopausal if they are amenorrhoeic for 12 months or more following cessation of all exogenous hormone therapy and have luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels within the laboratory reference range of postmenopausal status.

c. Patients who have previously received irreversible surgical sterilization, including hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, with the exception of bilateral tubal ligation.

8. Male patients should use barrier contraception (i.e., condoms) from screening to 3 months after study drug discontinuation.

9. The subjects voluntarily participate in the study and sign the informed consent form in writing.

**Exclusion Criteria:**

Subjects cannot be enrolled in the study if they meet any of the following criteria:

1. Patients who have received any of the following treatments:

   a. Prior treatment with any EGFR tyrosine kinase inhibitor;

   b. Have undergone any major surgery within 4 weeks prior to the first dose of study drug;

   c. More than 30% bone marrow have received irradiation or the patient have received extensive radiotherapy within 4 weeks prior to the first dose of study drug;

   d. Prior use of potent CYP3A4 inhibitors, inducers or drugs with a narrow therapeutic window of sensitive substrates of CYP3A4 within 7 days prior to the first dose of the investigational product.

2. Patients with other malignancies requiring standard therapy or major surgery within 2 years after the first dose of study drug.

3. Patients with unresolved > grade 1 toxicities from prior therapy at the start of study treatment, except those who have alopecia and grade 2 neurotoxicity due to prior chemotherapy.

4. Patients with spinal cord compression or brain metastases, unless asymptomatic, stable, and not requiring steroids for at least 2 weeks prior to the first dose of study treatment.

5. Patients who have any serious or poorly controlled systemic diseases, such as poorly controlled hypertension, active bleeding-prone constitution, or active infection, as judged by the investigator. Screening for chronic diseases is not required.

6. Patients who have refractory nausea, vomiting, or chronic gastrointestinal diseases, who are unable to swallow the investigational product, or who have undergone extensive enterectomy, as these conditions may affect the adequate absorption of HS-10296.

7. Patients who have any of the following cardiac examination results:

   a. QT interval is corrected (QTcF) by the Fridericia formula and the mean corrected QT interval (QTc) is > 470 msec from 3 electrocardiograms (ECGs) at rest;

   b. Results of ECGs at rest reveal clinically significant abnormalities in rhythm, conduction or ECG morphology (e.g., complete left bundle branch block, third-degree atrioventricular block, second-degree atrioventricular block, and PR interval > 250 msec);

   c. Any factors that may increase the risk of QTc prolongation or arrhythmic events, such as heart failure, hypokalemia, congenital long QT syndrome, a family history of long QT syndrome, or unexplained sudden death in an immediate family member under 40 years of age or any concomitant medications that may prolong the QT interval;

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

8. Patients who have history of interstitial lung disease, history of drug-induced interstitial lung disease, history of radiation pneumonitis requiring steroid treatment, or any evidence of clinically active interstitial lung disease.
9. Patients who have inadequate bone marrow reserve or organ function as demonstrated by the following laboratory test limits:
    a. Absolute neutrophil count < $1.5 \times 10^9$/L;
    b. Platelet count < $100 \times 10^9$/L;
    c. Hemoglobin < 90 g/L (< 9 g/dL);
    d. Alanine aminotransferase > 2.5 × the upper limit of normal (ULN) if there is no definite liver metastasis; alanine aminotransferase > 5 × ULN if liver metastases present;
    e. Aspartate aminotransferase > 2.5 × ULN if there is no definite liver metastasis; aspartate aminotransferase > 5 × ULN if liver metastases present;
    f. Total bilirubin > 1.5 × ULN if there are no definite liver metastases; total bilirubin > 3 × ULN if Gilbert's syndrome (unbound hyperbilirubinemia) or liver metastases present;
    g. Creatinine > 1.5 × ULN and creatinine clearance < 50 mL/min (calculated by Cockcroft-Gault equation); confirmation of creatinine clearance is required only if creatinine is > 1.5 × ULN.
10. Female patients who are breastfeeding or have a positive blood or urine pregnancy test result within 3 days prior to the first dose of study drug.
11. Patients who have history of hypersensitivity to any active or inactive ingredients of HS-10296, or to drugs that the chemical structures similar to HS-10296, or to drugs of the same class of HS-10296.
12. Patients who have any serious or uncontrolled ocular lesions, which may increase the safety risk to the patients as judged by the physician.
13. Patients who may have poor compliance with the study-specific procedures or requirements as judged by the investigator.
14. Patients with any condition that can jeopardize the safety of the patients or interfere with the assessment of the study in the judgment of the investigator.

**Efficacy Evaluation:**

The efficacy of HS-10296 versus gefitinib as the first-line therapy in subjects with locally advanced or metastatic NSCLC with $EGFRm^+$ will be evaluated by the investigator according to RECIST 1.1 Response Evaluation Criteria in Solid Tumors.

Efficacy Endpoints:

1. Primary endpoint: PFS
2. Secondary endpoints: OS, ORR, DoR, DCR, and DepOR

**Safety Evaluation:**

All the adverse events occurred in the subjects during the clinical trial will be observed and recorded, including abnormalities in clinical symptoms and vital signs, laboratory abnormalities, along with their severity, time and duration of onset, treatment methods and prognosis, and their relationship with the investigational product will be determined.

Safety endpoints: occurrence of adverse events; occurrence of serious adverse events; proportion of patients withdrawing due to adverse events; laboratory changes (blood chemistry, hematology, and urinalysis); changes in vital signs, physical examination, body weight, ECG, LVEF, ECOG performance status score, and ophthalmic examination.

**Sample Size Calculation:**

This is a randomized, controlled, double-blind, multicenter, superiority-designed phase III clinical study. Assuming that a PFS hazard ratio (HR) of HS-10296 to gefitinib is 0.67 (median PFS will be improved from 10 months to 15 months if the data meet the exponential distribution and statistical model meets the proportional hazard assumption), with the randomization ratio of 1:1, an enrollment duration of 8 months, a maximum observation period of 23 months after the first patient is enrolled, a two-sided alpha of 0.05, and with a power of 90% to detect the statistical differences between the two groups based on 262 events, approximately 410 patients need to be enrolled. The sample size is calculated by nQuery Advisor 8.0 software.

# 3.0 List of Abbreviations

| | |
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| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AR | Acquired resistance |
| AST | Aspartate aminotransferase |
| $AUC_{ss}$ | Area under the plasma concentration-time curve over any dose interval at steady state [amount·time/volume] |
| BIRC | Blinded Independent Review Center |
| CFDA | China Food and Drug Administration |
| C1D1 | Cycle 1 Day 1 |
| CI | Confidential interval |
| CLint | Clearance of liver microsomes |
| $C_{max}$ | Maximum plasma concentration |
| CR | Complete response |
| CT | Computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | Cytochrome P450 |
| DCR | Disease control rate |
| DepOR | Depth of response |
| DLT | Dose-limiting toxicity |
| DNA | Deoxyribonucleic acid |
| DoR | Duration of response |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| ECOG | Eastern Cooperative Oncology Group |
| EGFR | Epidermal growth factor receptor |
| $EGFRm^{+}$ | Positive epidermal growth factor receptor-sensitive mutations |
| FAS | Full analysis set |
| FDA | US Food and Drug Administration |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| HAS-719 | Major circulating metabolite of HS-10296 |

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|---|---|
| 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 |
| HR | Hazard ratio |
| HRCT | High-resolution computerized tomography |
| $IC_{50}$ | Half maximal inhibitory concentration |
| ICH | International Council for Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| LH | Luteinizing hormone |
| LPLV | Last patient's last follow up |
| IWRS | Interactive Web Response System |
| LVEF | Left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mPFS | Median progression-free survival |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| MUGA | Multi-gated acquisition scan |
| NE | Not evaluable |
| NOAEL | No-observed-adverse-effect level |
| NSCLC | Non-small cell lung cancer |
| NTL | Non-target lesion |
| ORR | Objective response rate |
| OR | Odds ratio |
| OS | Overall survival |
| PD | Disease progression |
| PFS | Progression-free survival |
| PFS2 | Time to second disease progression |
| PHL | Potential Hy's law |

| | |
|---|---|
| PK | Pharmacokinetic(s) |
| PPS | Per protocol set |
| PR | Partial response |
| PS | Performance status |
| PT | Preferred term |
| QD | Once daily |
| QRS | Combination of three contiguous waves seen on a typical ECG |
| QT | ECG intervals measured from the beginning of the QRS complex to the end of the T wave |
| QTc | Corrected QT interval |
| QTcF | QTc corrected using Fridericia method |
| RECIST 1.1 | Response Evaluation Criteria in Solid Tumors (Version 1.1) |
| SAE | Serious adverse event |
| SS | Safety set |
| SD | Stable disease |
| $STD_{10}$ | Severely toxic dose in 10% of the animals |
| SOC | System organ class |
| T790M | Amino acid at site 790 of EGFR mutated from threonine to methionine |
| $T790M^{+}$ | Positive T790M mutation |
| TBL | Total bilirubin |
| TL | Target lesion |
| TKI | Tyrosine kinase inhibitor |
| ULN | Upper limit of normal |
| WT | Wild type |

# 4.0 Study Background and Scientific Rationale

## 4.1 Study Background

Lung cancer is one of the most common malignant tumors with the highest morbidity and mortality in the world. According to the cancer statistics published in China in 2018, lung cancer has the highest morbidity and mortality in China, accounting for more than 20% of all the cancers. Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers, and approximately 70% of cases have reached a locally advanced stage or advanced stage of distant metastasis at the time of diagnosis and cannot be surgically resected. In addition, most patients who have undergone early surgical resection also develop distant metastases after recurrence, which can often result in death[1]. Patients with advanced NSCLC who are not suitable for surgical resection often have a median survival of less than one year[2].

In recent years, driver gene-based targeted drugs have been introduced one after another, and epidermal growth factor receptor (EGFR)-sensitive mutations ($EGFRm^+$) are one of the major driver genes in NSCLC. This mutation accounts for 10% to 17% of the Western populations, and for 30% to 50% of the Asian population[3]. As the first-generation EGFR tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib have shown good initial responses in patients with $EGFRm^+$ NSCLC. However, most patients develop acquired resistance (AR) after 9 to 13 months of treatment, leading to worsening of disease[4]. In addition, these first-generation TKIs can frequently cause skin and gastrointestinal organ adverse reactions such as rash and diarrhea due to their inhibition of wild-type (WT) EGFR[5].

Various mechanisms of AR have been reported, such as the second-site mutations of EGFR, bypass activation of HER2 and MET or phenotypic transformations. Of these, the T790M mutation in EGFR (the gatekeeping amino acid at site 790 mutated from threonine to methionine) is the most common mechanism of resistance. This mutation was detected in more than 50% of patients who progressed after gefitinib or erlotinib treatment[6]. In addition, some patients harbor the primary T790M mutation prior to EGFR TKIs treatment and are detectable in approximately 30% of $EGFRm^+$ patients using sensitive assays (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry and next-generation sequencing), and this proportion is higher than the previously reported proportion (2% to 3%)[7]. Regardless of whether resistant mutations are acquired mutations or primary mutations, development of new regimens and early use of third-generation EGFR TKIs that inhibit T790M-resistant mutations and EGFR-sensitive mutations help to delay the effect taking time of drug-resistant mutations, and it is expected to have better clinical benefit for patients with advanced NSCLC.

The third-generation EGFR TKI can highly selectively target the EGFR T790M mutation and reduce the toxicity and side effects caused by wild-type EGFR inhibition. Currently, osimertinib (AZD9291), a third-generation EGFR TKI has been approved for the treatment of advanced NSCLC. Its marketing authorization has been approved by the FDA in November 2015, and it is the first approved second-line therapy for the first-generation TKIs treatment, and it was approved for marketing in China in March 2017. As osimertinib inhibits both T790M-resistant mutations and $EGFRm^+$ and based on a phase III randomized controlled clinical study (FLAURA)[8] which compared osimertinib with the first-generation TKIs gefitinib/erlotinib, osimertinib was approved by FDA in April 2018 as the first-line therapy for patients with advanced NSCLC harboring positive EGFR mutation.

### 4.2 Scientific Rationale

HS-10296 is a class 1 innovative drug independently developed by Jiangsu Hansoh Pharmaceutical Group Co., Ltd. It is a third-generation small molecule EGFR TKI, which can irreversibly and selectively inhibit EGFR-sensitive mutations (e.g., exon 19 deletion and L858R mutation) and T790M resistance mutations, with very low activity against wild-type EGFR.

#### 4.2.1 Mechanism of Action and Pharmacology

In *in vitro* enzymatic and cell proliferation studies, HS-10296 exhibited potent inhibitory effect to EGFR T790M resistance mutations and weaker inhibitory effect on wild-type EGFR[9]. HAS-719 is a major metabolite of HS-10296, with similar enzymatic activity profile to that of its parent drug HS-10296[9]. HS-10296 has little-to-no inhibitory effect on 38 closely related kinases, suggesting that HS-10296 is a selective EGFR mutant kinase inhibitor with no potential off-target effect[10].

In a nude mouse tumor model, HS-10296 potently inhibited tumor growth of NSCLC H1975 and LU1868 cell lines harboring EGFR T790M mutations, and also inhibited tumor growth of NSCLC HCC827 cell lines harboring EGFR-sensitive mutations[11]. In the 20 mg/kg high-dose group, HS-10296 resulted in almost complete regression of tumors harboring EGFR mutations. HS-10296 had weak inhibitory effect on WT EGFR A431 cell lines, suggesting a superior safety profile of it over other EGFR inhibitors. HS-10296 could potently and specifically inhibit EGFR T790 resistant mutations and had weak inhibitory effects on WT EGFR. These results fully reflected the characteristics of the new generation of EGFR inhibitors.

In an *in vitro* study of the potassium channel encoded by hERG (human *ether-à-go-go* gene), the half maximal inhibitory concentration ($IC_{50}$) value of HS-10296 on hERG was 2.958 μM, indicating that HS-10296 has a slight inhibitory effect on hERG current[12]. However, in the NCI-

H1975 xenograft tumor model, the maximum plasma concentration ($C_{max}$) of HS-10296 at the effective dose of 5 mg/kg was 190 ng/mL, which was well below the hERG $IC_{50}$, and the difference was as high as 12.2-fold[11]. In addition, the plasma protein binding of HS-10296 was > 99.5% in rats, dogs, and humans, resulting in very low concentrations of unbound HS-10296[13]. No adverse effects were observed in the central nervous system of rats, cardiovascular system and respiratory system of dogs in animal studies[14,15]. All these results suggest a low likelihood of cardiotoxicity caused by HS-10296.

### 4.2.2 Nonclinical Pharmacokinetics and Drug Metabolism

In the PK studies in rats and dogs, HS-10296 was rapidly absorbed after oral administration[16,17] and its major metabolite, HAS-719, was produced by N-demethylation. The area under the plasma concentration-time curve (AUC) of HS-10296 and HAS-719 increased with the increase of dose, showing a significant linear relationship. No significant accumulation was observed after repeated doses of HS-10296.

The plasma protein binding of HS-10296 and HAS-719 was ≥ 99.5% in rats, dogs, and humans[13].The peak concentration of HS-10296 was reached within 2 hours following oral gavage administration to rats[18]. HS-10296 and its metabolite HAS-719 were widely distributed in tissues, and the concentration of HS-10296 in most tissues was higher than that in plasma. HS-10296 was mainly distributed in lung, adrenal gland, spleen, bone marrow and liver. HS-10296 could readily penetrate the blood-brain barrier with a brain-to-plasma exposure ratio > 7. A total of 36 metabolites could be detected in rat plasma following oral gavage administration of HS-10296. Cumulative urinary excretion of HS-10296 and HAS-719 was minimal, which was less than 0.1% of the administered dose[19], while the excretion was 3.4% and 0.2% in feces and bile, respectively, within 0 to 96 hours following the oral gavage administration of HS-10296 to rats.

Based on the clearance in liver microsomes ($CL_{int}$) in different species, HS-10296 is speculated to be a drug with moderate clearance in humans, dogs, and with high clearance in mice, rats and monkeys[20]. In a study of inter-species differences in hepatocyte metabolism in mice, rats, dogs, monkeys, and humans, HS-10296 was adequately metabolized and no specific metabolites were found in humans[21,22]. *In vitro* studies have shown that HS-10296 had no inhibitory effect on the major human metabolic enzymes cytochrome P450 (CYP450), and it had no inductive effect on CYP1A2, CYP2B6 and CYP3A4[23]. Therefore, its potential of causing drug-drug interactions via inhibition and induction of these CYP450 is very low[24].The results of the permeability study in the Caco-2 cell model showed that HS-10296 had low

permeability and that efflux transporters were involved in the transport of HS-10296 on Caco-2 cells[25].

### 4.2.3 Nonclinical Toxicology

In the acute toxicity study, no death was found in rats of the highest 900 mg/kg dose group and in dogs of the highest 200 mg/kg dose group[26,27]. Clinical observations revealed fluffy hair, piloerection, prone position, humped back, decreased activity, loose/soft stools, and perianal feces in rats of the high dose group. Vomiting, loose stools, or bloody feces were observed in dogs.

In the 13-week repeat-dose chronic toxicity study, death was observed in female rats of the 120 mg/kg dose group and in dogs of the 25 mg/kg dose group[28-32]. The toxicities of HS-10296 observed in rats and dogs were mainly in the skin, gastrointestinal tract and eyes, and the analysis showed that toxicities might be mainly secondary to the potent inhibition of EGFR by the drug or related to significant reductions in body weight and/or food consumption. These toxicities were reversible after a 4-week recovery period.

HS-10296-related toxicities in rats included soft stools, salivary secretion, skin damage and eye abnormalities. Histopathological findings were mainly observed in the mammary glands and vagina of rats, as well as the tongue, skin, oral cavity and thymus of dogs. The skin damage observed in rats and dogs are associated with dermal folliculitis, which is consistent with the literature report that EGFR inhibitors could cause skin damage in rodents and humans[33-35]. The ulcer and inflammatory reactions observed in the tongues of dogs were similar to the adverse reactions caused by TKIs in humans[33,36]. In addition, changes in oral mucosa have also been reported in the study with anti-EGFR antibody therapy[37].

Ocular toxicity, such as conjunctival hyperemia, corneal changes, and other eye abnormalities, was significant in rats and dogs, which have been reported in patients treated with anti-EGFR antibodies[38,39]. Mastatrophy and mucification of the vaginal epithelium were considered reactions secondary to treatment-related changes in food consumption and body weight[40,41]. Thymic involution/atrophy was considered to be due to stress response[42]. The severely toxic dose in 10% of animals ($STD_{10}$) was 60 mg/kg/d in female rats, 120 mg/kg/d in male rats, and the highest non-severely toxic dose (HNSTD) in dogs was 10 mg/kg/d.

Both *in vitro* and *in vivo* genotoxicity studies showed negative results, suggesting that HS-10296 did not induce mutations or cause chromosome breakage at relevant concentrations[43-45]. The no-observed-adverse-effect level (NOAEL) of HS-10296 on reproduction and early embryonic development was 100 mg/kg/d for male rats and 30 mg/kg/d for female rats[46].

Statistically significant decreases in mean gravid uterus weight, implantation sites, and number of live fetuses were noted in female rats dosed at 100 mg/kg/d. No drug-related changes were observed in sperm count, motility, and sperm morphology test in male rats dosed at 100 mg/kg/d. HS-10296 has no teratogenic effect on rat embryo-fetal development, with a NOAEL of 100 mg/kg/d[47].

### 4.2.4 Clinical Studies

The IND application for HS-10296 has been approved by the US FDA, TFDA in Taiwan and CFDA in mainland China, respectively, and international multicenter phase I/II clinical studies are ongoing. The phase I clinical study of HS-10296 is an open-label, multicenter study in patients with locally advanced or metastatic NSCLC who had disease progression on prior EGFR TKI therapy, including a dose escalation study and a dose expansion study.

The data of single-dose PK study of HS-10296 in patients with advanced NSCLC who had progressed on prior EGFR TKI therapy showed that a single oral dose of HS-10296 administered under fasted conditions was rapidly absorbed, and that the peak plasma concentration was reached at 4.0 h, the mean elimination half-life of the drug ranged from 30.7 to 37.5 h, and the PK parameters of $C_{max}$ and AUC of HS-10296 were generally linearly related to dose within the dose range of 55 to 220 mg. The exposure of the active metabolite HAS-719 was about 1/3 of that of the parent drug, and the PK parameters also showed a linear relationship. The time to reach peak concentration of HAS-719 was about 6 h later than that of the parent drug, and the elimination half-life of the drug ranged from 50 to 70 h. Data obtained from multiple-dose PK studies showed that following HS-10296 was administered once daily (QD) for 7 consecutive days, its plasma concentrations have reached a steady state, with little accumulation at steady state compared with single-dose administration. Within the dose range of 55 to 220 mg, when the steady state was reached following continuous dosing, the exposure of HS-10296 showed a basically linear relationship with the plasma concentration at steady state and the area under the plasma concentration-time curve.

A total of 26 subjects were included in the phase I escalation study of HS-10296. No dose-limiting toxicity (DLT) was observed in the low dose group (55/110 mg), and only 1 DLT (Grade 3 anemia) was observed in 6 subjects of the 220 mg dose group, and only 1 DLT (Grade 3 blood creatinine increased) was observed in 6 subjects of the 260 mg dose group. No maximum tolerated dose (MTD) was reached in the dose escalation study. In terms of treatment response, the overall objective response rate (ORR) was 52.4% and the disease control rate (DCR) was 85.7% in the periodic evaluable patients (n= 21). In the 55 mg (6 subjects) and 110

mg (6 subjects) dose groups, the ORR was 66.7% and the DCR was 100.0%; in the 220 mg dose group (6 subjects), the ORR was 50.0% and the DCR was 83.3%; and in the 260 mg dose group, the treatment response assessment was completed in only 3 subjects, with the DCR of 33.3%.

The enrollment of T790M mutation-positive population for the phase I extension study of HS-10296 has been completed, with a total of 91 subjects enrolled in the 55 mg (30 subjects), 110 mg (30 subjects), and 220 mg (31 subjects) dose groups. In terms of safety, common adverse events (AEs) were rash, asthenia, hazy vision, leukopenia, digestive tract symptoms (e.g., constipation, diarrhoea, nausea), blood creatine kinase increased, and blood alanine aminotransferase increased, with mild symptoms or no clinical symptoms, and most AEs could resolve spontaneously. There were no drug-related serious adverse events (SAEs) in the 55 mg and 110 mg dose groups. In the 220 mg dose group, the incidence and severity of AEs were significantly increased. In terms of treatment response, the overall ORR was 50.0% and the DCR was 92.1% in the periodic evaluable patients (n = 76). Of these, the ORR was 53.3% and the DCR was 83.3% in the 55 mg (30 subjects) dose group; the ORR was 46.7% and the DCR was 96.7% in the 110 mg (30 subjects) dose group; and the ORR was 50.0% and the DCR was 100.0% in the 220 mg (16 subjects) dose group.

The data from the 55 mg and 110 mg dose groups in the dose escalation and expansion stages were pooled and analyzed: in the phase I clinical trial of HS-10296 as the second-line therapy in the patients with advanced NSCLC, 36 T790M mutation-positive patients were enrolled in the 55 mg and 110 mg dose groups, respectively, and the last patient was followed up for up to 3 months after enrollment. At least 2 response evaluations had been performed for all the cases. Currently, there were no unexpected safety concerns in either dose group. In terms of treatment response observed in patients with T790M mutation, the overall ORR was 52.1%, of which, 55.6% were in the 55 mg dose group and 50.0% in the 110 mg dose group; the overall DCR was 92.6%, with 86.1% in the 55 mg dose group and 97.2% in the 110 mg dose group.

Taken together these preclinical and clinical data, the objective of this study was to evaluate the efficacy and safety of HS-10296 compared with gefitinib as the first-line therapy in subjects with advanced $EGFRm^+$ NSCLC who have not received any systemic therapy.

### 4.3 Potential Risks and Benefits

#### 4.3.1 Potential Risks and Control Plan

The preclinical toxicology study and phase I clinical study of HS-10296 suggested that gastrointestinal tract and skin adverse reactions and changes in laboratory test results should be

closely monitored in clinical trials.

Adverse events reported in completed clinical trials included decreased appetite, abdominal distension, vomiting, diarrhoea, constipation, rash, pruritus, pyrexia, paronychia, chest pain, back pain, chest discomfort, cough, upper respiratory tract infection, urinary tract infection, urticaria, dizziness, cataract, dry eye, anemia, electrocardiogram QT prolonged, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood creatine kinase increased, blood creatinine increased, blood bilirubin increased, blood lactate dehydrogenase increased, hematuria, hyperglycemia, hypertension, white blood cell decreased, liver injury, musculoskeletal pain, pain in extremity, rhabdomyolysis and neutrophil count decreased.

In view of the above-mentioned adverse event profiles, the following regulations are set forth in the protocol to minimize the risk: 1) The design of safety indicators has covered the common adverse reactions of similar drugs, changes that required close monitoring suggested in completed preclinical and clinical studies of HS-10296, as well as the observation of the toxicity of important organs such as heart and lungs. Discontinuation criteria for subjects and clinical trials will be specified in the protocol. 2) This study will be conducted in a medical institution with clinical study qualification, and experienced investigators will be selected to conduct the clinical studies. 3) During the conduct and implementation of the study, physicians with rich experience in clinical practice will regularly monitor and check the health status of patients, and promptly take corresponding treatment measures in the event of abnormal changes. 4) In addition to completing the safety examinations at the time points specified in the protocol, the adverse events occurring outside the hospital will be monitored via patient's diary, telephone or in-hospital follow-up. 5) Additional tests can be performed at any time if it is deemed necessary by the investigator. After the start of the study, in case of a special event, the Ethics Committee and National Medical Products Administration may immediately terminate the study when necessary.

### 4.3.2 Known Potential Benefits

Presence of sensitive mutations in EGFR exons 18 to 24 (including exon 19 deletion and L858R mutation) renders NSCLC patients sensitive to EGFR TKI therapy. However, patients treated with the first-generation EGFR TKI will inevitably develop drug resistance in subsequent therapies, and T790M mutation is the leading cause of drug resistance. HS-10296 is a novel irreversible small molecule inhibitor of EGFR. It can selectively inhibit EGFR-sensitive mutations and T790M-resistant mutations, but has only minimal inhibitory activity against WT

EGFR. Therefore, HS-10296 may provide the following clinical benefits as the first-line therapy in patients with advanced EGFRm$^+$ NSCLC:

HS-10296 is used as the first-line therapy for patients with NSCLC harboring EGFR-sensitive mutations, which can eliminate the potential EGFR T790M mutant clones at an early stage, hence, it can better control the disease progression. The results from a phase III clinical trial of osimertinib, a third-generation EGFR TKI, show that the median progression-free survival (mPFS) was 18.9 months in patients receiving the monotherapy of osimertinib and the mPFS was 10.2 months in the first-generation TKIs (gefitinib or erlotinib) group. Osimertinib reduced the risk of disease progression by 54%[8].

The incidence of brain metastases is approximately 20% to 30% in patients initially diagnosed with NSCLC[48].Approximately 50% of NSCLC patients will develop brain metastases during disease progression. The first-generation EGFR TKIs have limited therapeutic effect on brain metastases[49]. HS-10296 could readily penetrate the blood-brain barrier with a brain-to-plasma exposure ratio >7. Brain metastases are the most common cause of the first onset of disease progression following the first-generation TKI therapy. The first-line therapy with HS-10296 may potentially control, prevent, or delay the development of brain metastases.

HS-10296 can block the formation of non-selective metabolites through structural optimization. In addition, it has high selectivity, weak inhibitory effect on wild-type EGFR, with less potential toxic and side effects. The results from the current clinical studies have shown that HS-10296 was well tolerated and safe, and the main adverse reactions were gastrointestinal tract and skin adverse reactions and changes in laboratory test results. Use of HS-10296 as the first-line therapy can reduce the chance and duration of exposure to the first-generation TKIs that are associated with relatively significant side effects.

The available preclinical and clinical data suggest that HS-10296 is expected to have favorable efficacy and safety as the first-line therapy for advanced EGFRm$^+$ NSCLC.

# 5.0 Study Objective and Endpoints

## 5.1 Study Objectives

### 5.1.1 Primary Objective

To compare progression-free survival (PFS) of subjects with locally advanced or metastatic NSCLC with EGFRm+ treated with HS-10296 versus gefitinib as the first-line therapy.

### 5.1.2 Secondary Objectives

1) To compare the following anti-tumor efficacy measures of HS-10296 versus gefitinib: overall survival (OS), objective response rate (ORR), duration of response (DoR), disease

control rate (DCR), and depth of response (DepOR).

2) To compare the safety of HS-10296 versus gefitinib.

## 5.2 Study Endpoints

### 5.2.1 Efficacy Endpoints

The analysis of endpoints in this study will be based on the investigator's assessment of tumor response per RECIST 1.1.

1) Primary endpoint: PFS.

2) Secondary endpoints: OS, ORR, DoR, DCR, and DepOR.

### 5.2.2 Safety Endpoints

Occurrence of adverse events; occurrence of serious adverse events; proportion of patients withdrawn from the study due to adverse events; laboratory test result changes (blood chemistry, hematology, and urinalysis); changes in vital signs, physical examination, body weight, 12-lead electrocardiogram (ECG), left ventricular ejection fraction (LVEF), ECOG performance status (PS) score, and ophthalmic examination.

## 5.3 Sample Size

This is a randomized, controlled, double-blind, multicenter, superiority-designed phase III clinical study. Assuming that a PFS hazard ratio (HR) of HS-10296 to gefitinib is 0.67 (median PFS will be improved from 10 months to 15 months if the data meet the exponential distribution and statistical model meets the proportional hazard assumption), with the randomization ratio of 1:1, an enrollment duration of 8 months, a maximum observation period of 23 months after the first patient is enrolled, a two-sided alpha of 0.05, and with a power of 90% to detect the statistical differences between the two groups based on 262 events, approximately 410 patients need to be enrolled. The sample size is calculated by nQuery Advisor 8.0 software.

# 6.0 Study Design and Description

## 6.1 Study Design

This is a randomized, controlled, double-blind, multicenter, phase III clinical trial to evaluate the efficacy and safety of HS-10296 versus gefitinib as the first-line therapy in subjects with EGFRm$^+$ NSCLC who have not received any systemic therapy. Patients will be randomized in a 1:1 ratio to HS-10296 treatment group or gefitinib treatment group to receive oral administration of HS-10296 or gefitinib once daily. It is planned to enroll 410 subjects in the study, and the study flow chart is shown in Figure 1.

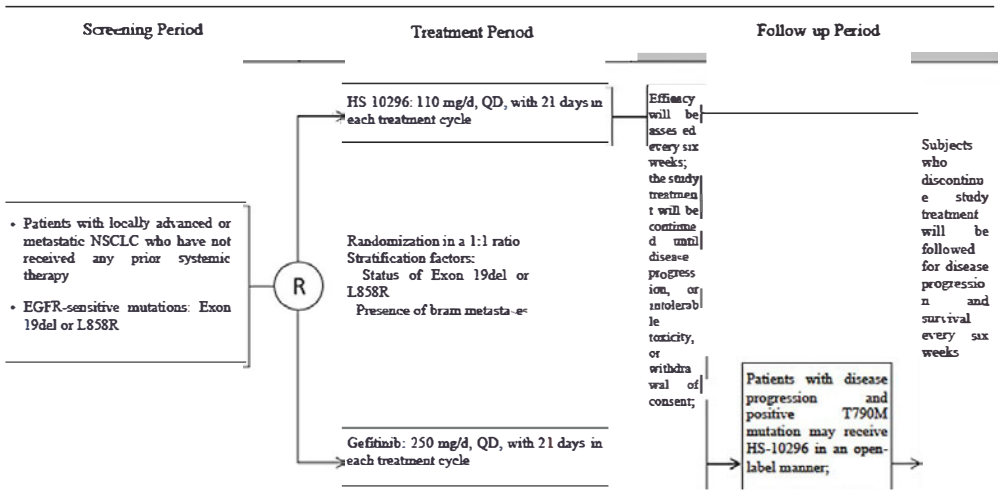


**Figure 1 Study Flow Chart**

- **Screening Period (D-28 to D-1)**

Inpatients and outpatients will be screened after signing the informed consent form, and complete relevant laboratory tests and assessments. Subjects who meet the inclusion criteria and do not meet the exclusion criteria may be enrolled.

- **Treatment Period (C1 to C7 +, D1 to D127 +)**

All eligible subjects will be randomized in a 1:1 ratio to the following two groups:

1) HS-10296 group: oral administration of 110 mg HS-10296 tablets (55 mg/tablet, 2 tablets/d) and gefitinib placebo tablets (placebo 250 mg, 1 tablet/d) once daily for 21 consecutive days (3 weeks) as one cycle.

2) Gefitinib group: oral administration of 250 mg gefitinib tablets (250 mg/tablet, 1 tablet/d) and HS-10296 placebo tablets (placebo 55 mg, 2 tablets/d) once daily for 21 consecutive days (3 weeks) as one cycle.

The drugs will be administered for 21 consecutive days, which constitute one treatment cycle. Response will be evaluated as per RECIST 1.1 every 6 weeks (every 2 cycles until C21; first 15 months) or every 12 weeks (every 4 cycles starting from C23; after Month 15) after initiation

of treatment. Patients will be given continuous administration until disease progression as assessed by the investigator as per RECIST 1.1 or withdrawal from study or discontinuation criteria are met. As long as the investigator determines that the patient can continue to benefit from treatment, the patient may continue to receive treatment even if the patient has achieved disease progression defined by RECIST 1.1, and it is recommended to make a blinded judgment based on tumor response. According to current clinical practice, it is allowed to judge after unblinding if it is difficult to judge whether continuation of treatment is beneficial in a blinded manner; the treatment cannot be resumed once it is judged that there is no clinical benefit and the treatment is terminated. If additional treatment is provided, the baseline and follow-up schedules will not be affected by the additional treatment course.

- **Follow-up Period**

Subjects who discontinue treatment due to meeting the withdrawal or discontinuation criteria will complete the discontinuation follow-up; a 28-day safety follow-up will be completed after treatment discontinuation, followed by a survival follow-up every 6 weeks as per the study plan. Subjects who have no progress at the time of treatment discontinuation will continue to be followed up every 6 weeks (C1 to C21) or every 12 weeks (C23 and thereafter) until disease progression as assessed by the investigator as per RECIST 1.1, even if the patient has received other anti-tumor therapies; and then a survival follow-up will be performed every 6 weeks as per the study plan.

- **Open-label HS-10296 Crossover Treatment**

Subjects who continue to receive the investigational product in a randomized blinded manner and have disease progression during the blinded treatment period may initiate the open-label HS-10296 crossover treatment if they are eligible for crossover treatment after being assessed with the procedures. The assessment procedures and required conditions include: 1) after the investigator evaluates disease progression in a blinded manner as per RECTST 1.1, subjects with disease progression may be unblinded if it is necessary for subsequent treatments; 2) if subjects in the gefitinib group have disease progression on gefitinib treatment, the following processes should be followed; 3) subjects should voluntarily sign the informed consent form for subsequent treatments, and the pre-crossover assessment will be started; 4) tumor tissue or blood samples after progression should be collected for T790M mutation test and the test result must be positive; 5) the pre-crossover assessment should be completed within 28 days from the date of signing the informed consent form for crossover treatment; 6) no other interventions should be received after discontinuation of the treatment with gefitinib, and gefitinib should be

washed out for at least 5 half-lives (10 days) before the first dose of crossover treatment. Refer to Section 9.2 for detailed procedures of crossover treatment.

### 6.2 Double-blind Design

This study will be conducted based on a double-blind design, i.e., from the start of randomization until disease progression as assessed by the investigator per RECIST 1.1, the information of the actual treatments will remain blinded to the subjects, the investigator, data analysts, the Sponsor, and all medical personnel involved in the treatment or clinical assessments.

### 6.3 Rationale for Study Group Design

This study includes two groups, that is, the HS-10296 group and the gefitinib group. The purpose of this grouping design is: 1) HS-10296 as the first-line therapy may inhibit potential T790M-resistant mutations in addition to the inhibition of EGFR-sensitive mutations, which may delay the time of the action of T790M-resistant mutations, and HS-10296 may have good clinical benefits for patients; 2) HS-10296 has highly selective and weak inhibitory effect on WT EGFR, with less potential toxic and side effects. The use of HS-10296 as the first-line therapy can reduce the probability that subjects are exposed to the potential toxicities caused by the first-generation EGFR TKIs with relatively significant toxic and side effects; 3) gefitinib is the standard first-line therapy in China currently, and the clinical efficacy of the investigational product can be evaluated compared with gefitinib by a superiority design. For the potential disease progression due to T790M-resistant mutations in subjects in the gefitinib treatment group during the course of the study, a standardized crossover procedure has been designed in this study.

### 6.4 Dose Selection Rationale

A Phase I dose escalation and dose expansion study of HS-10296 in patients with advanced NSCLC demonstrated that oral administration of HS-10296 once daily at doses ranging from 55 to 260 mg were safe and well tolerated and exhibited preliminary anti-tumor efficacy. HS-10296 demonstrated superior safety profile in the 110 mg group than in the 220 mg and 260 mg dose groups and a trend of better efficacy than in the 55 mg group (DCR: 97.2% VS. 86.1%). No increase in clinical efficacy was observed at the time when the dose was continuously escalated to 220 mg and 260 mg. The clinical Phase I PK study showed that the area under the plasma concentration-time curve at steady state (AUCss) was 7510 ng•h/mL of HS-10296 at 110 mg, and the AUCss of the active metabolite HAS-719 was 2820 ng•h/mL, with the total AUCss of 10330 ng•h/mL. This level was essentially comparable to the AUCss (approximately

11000 ng•h/mL) of AZD9291 at the clinically effective dose of 80 mg. Considering the periodic efficacy, safety and PK data of the clinical studies of HS-10296 comprehensively, the dose of HS-10296 in this study is selected as 110 mg (QD).

Gefitinib (Iressa, AstraZeneca Pharmaceutical Co., Ltd.) is a first-generation EGFR TKI drug formally marketed in China after having been approved by CFDA in 2005, and it is currently the standard first-line therapy for advanced $EGFRm^+$ NSCLC in China.

The recommended clinical dose of gefitinib is 250 mg/d (QD). Gefitinib 250 mg/d (QD) was also selected as one of the control drugs in the clinical studies of osimertinib as a first-line therapy. Therefore, the dose of the gefitinib control group in this study is selected as 250 mg (QD).

## 6.5 Early Termination, Suspension of Study/Study Site

### 6.5.1 Criteria for Early Termination and Suspension of Study

This study will be completed as planned unless one or more of the following criteria for suspension or early termination are met:

1) Information on the safety or efficacy of the investigational product has been updated or other evaluations are available that suggests a change in the risk/benefit ratio of the investigational product, and the risk/benefit profile of the drug is no longer accepted by the study subjects.

2) Serious violations of Good Clinical Practice (GCP), resulting in failure to achieve the main study objectives or endanger the safety of patients.

### 6.5.2 Criteria for Early Termination, Suspension of Study Site

If the study site (including the investigator) seriously violates the GCP, protocol or contractual agreements, or it is unable to ensure the sufficient conduct of the study, the study site will be prematurely terminated or suspended unless otherwise permitted in the contract.

### 6.5.3 Procedures for Early Termination, Suspension of the Study/Study Site

If the Sponsor, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or regulatory authorities choose to terminate or suspend the study/study site, the Sponsor will provide specific procedures for early termination or suspension. This procedure will be performed by the respective study site during the process of termination or suspension of study/study site.

# 7.0 Screening of Subjects

## 7.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for the study:

1. Aged ≥ 18 years.

2. Patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC (including patients with relapsed disease after prior surgical treatment or patients with newly diagnosed disease at stage IIIB/IV. The disease stage will be determined according to 7th edition of the American Joint Committee on Cancer (AJCC) TNM staging criteria).

3. Patients who have not received any systemic therapy since they were diagnosed with locally advanced or metastatic NSCLC. Patients who have received local treatment may participate in the study if lesions within the local treatment area are non-target lesions.

4. Tumor tissue samples or blood samples collected after the diagnosis of locally advanced or metastatic NSCLC are confirmed to harbor EGFR-sensitive mutations (including exon 19 deletion or L858R mutation, either alone or in combination with other EGFR site mutations) as tested by the central laboratory. It is recommended to submit tumor tissue samples if tumor tissue is accessible; blood samples should be submitted if tumor tissue is not accessible or tissue biopsy is unacceptable to the patient.

5. Patients with an ECOG PS score of 0 or 1, with no worsening in the previous 2 weeks, and with a minimum expected survival of 12 weeks.

6. Patients who have at least 1 tumor lesion that has not received prior local treatment such as irradiation, or has not been performed with tissue biopsy at screening and can be accurately measured at baseline, with the longest diameter ≥ 10 mm at baseline (short axis ≥ 15 mm will be required if the lesions are lymph nodes). The selected measuring methods should be suitable for accurate and repeated measurements, such as computerized tomography (CT) or magnetic resonance scan (MRI). If there is only 1 measurable lesion that has not received prior local treatment such as irradiation, it will be acceptable as a target lesion, and a baseline evaluation of the tumor lesion will be performed at least 14 days after diagnostic biopsy.

7. Women of childbearing potential should use appropriate contraceptive measures and should not breastfeed their infants from screening to 3 months after study drug discontinuation. Female patients with a negative pregnancy test result prior to initiation of dosing or meeting one of the following criteria are confirmed to have no risk of pregnancy:

   a. Postmenopausal is defined as aged over 50 years old and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal replacement treatment;

b. Women aged less than 50 years may also be considered postmenopausal if they are amenorrhoeic for 12 months or more following cessation of all exogenous hormone therapy and have luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels within the laboratory reference range of postmenopausal status.

c. Patients who have previously received irreversible surgical sterilization, including hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, with the exception of bilateral tubal ligation.

8. Male patients should use barrier contraception (i.e., condoms) from screening to 3 months after study drug discontinuation.

9. The subjects voluntarily participate in the study and sign the informed consent form in writing.

### 7.2 Exclusion Criteria

Subjects cannot be enrolled in the study if they meet any of the following criteria:

1. Patients who have received any of the following treatments:
   a. Prior treatment with any EGFR TKI;
   b. Have undergone any major surgery within 4 weeks prior to the first dose of study drug;
   c. More than 30% bone marrow have received irradiation or the patient have received extensive radiotherapy within 4 weeks prior to the first dose of study drug;
   d. Any use of potent CYP3A4 inhibitors, inducers or drugs with a narrow therapeutic window of sensitive substrates of CYP3A4 within 7 days prior to the first dose of the investigational product.
2. Patients with any complications or other malignancies requiring treatment or major surgery within 2 years after the first dose of study treatment.
3. Patients with unresolved > grade 1 toxicities from prior therapy (e.g., adjuvant chemotherapy) at the start of study treatment, except those who have alopecia and grade 2 neurotoxicity due to prior chemotherapy.
4. Patients with spinal cord compression or brain metastases, unless asymptomatic, stable, and not requiring steroids for at least 2 weeks prior to the first dose of study treatment.
5. Patients who have any serious or poorly controlled systemic diseases, such as poorly controlled hypertension, active bleeding-prone constitution, or active infection, as judged by the investigator. Screening for chronic diseases is not required.
6. Patients who have refractory nausea, vomiting, or chronic gastrointestinal diseases, who

are unable to swallow the investigational product, or who have undergone extensive enterectomy, as these conditions may affect the adequate absorption of HS-10296.

7. Patients who have any of the following cardiac examination results:
    a. QT interval is corrected (QTcF) by the Fridericia formula and the mean corrected QT interval (QTc) is > 470 msec from 3 ECGs at rest;
    b. Results of ECGs at rest reveal clinically significant abnormalities in rhythm, conduction or ECG morphology (e.g., complete left bundle branch block, third-degree atrioventricular block, second-degree atrioventricular block, and PR interval > 250 msec);
    c. Any factors that may increase the risk of QTc prolongation or arrhythmic events, such as heart failure, hypokalemia, congenital long QT syndrome, a family history of long QT syndrome, or unexplained sudden death in an immediate family member under 40 years of age or any concomitant medications that may prolong the QT interval;
    d. LVEF ≤ 40%。
8. Patients who have history of interstitial lung disease, history of drug-induced interstitial lung disease, history of radiation pneumonitis requiring steroid treatment, or any evidence of clinically active interstitial lung disease.
9. Patients who have inadequate bone marrow reserve or organ function as demonstrated by the following laboratory test limits:
    a. Absolute neutrophil count < $1.5 \times 10^9$/L;
    b. Platelet count < $100 \times 10^9$/L;
    c. Hemoglobin < 90 g/L (< 9 g/dL);
    d. Alanine aminotransferase > 2.5 × the upper limit of normal (ULN) if there is no definite liver metastasis; alanine aminotransferase > 5 × ULN if liver metastases present;
    e. Aspartate aminotransferase > 2.5 × ULN if there is no definite liver metastasis; aspartate aminotransferase > 5 × ULN if liver metastases present;
    f. Total bilirubin > 1.5 × ULN if there are no definite liver metastases; total bilirubin > 3 × ULN if Gilbert's syndrome (unbound hyperbilirubinemia) or liver metastases present;
    g. Creatinine > 1.5 × ULN and creatinine clearance < 50 mL/min (calculated by Cockcroft-Gault equation); confirmation of creatinine clearance is required only if creatinine is > 1.5 × ULN.

10. Female patients who are breastfeeding or have a positive blood or urine pregnancy test result within 3 days prior to the first dose of study drug.

11. With history of hypersensitivity to any active or inactive ingredients of HS-10296, or to drugs that the chemical structures similar to HS-10296, or to drugs of the same class of HS-10296.

12. With any serious or uncontrolled ocular lesions, which may increase the safety risk to the patients as judged by the physician.

13. Patients who may have poor compliance with the study-specific procedures or requirements as judged by the investigator.

14. Patients with any condition that can jeopardize the safety of the patients or interfere with the assessment of the study in the judgment of the investigator.

### 7.3 Recruitment and Screening Number

Prior to screening, each subject recruited will receive a screening number in the order in which he/she signs the informed consent form. Once a screening number has been assigned to the subject, it cannot be reused. If a subject is re-screened, a new screening number will be enabled. The investigator should document the subject's screening process on the screening diary.

### 7.4 Randomization

This is a randomized, controlled, double-blind, multicenter clinical study. In this study, patients will be randomized using an Interactive Web Response System (IWRS), and each site will compete for enrollment. Patients will be stratified by EGFR mutation status (exon 19 deletion VS. L858R mutation) and brain metastasis status (with VS. without) at enrollment, and will be randomly assigned in a 1: 1 ratio to the test group (HS-10296) and the control group (gefitinib). Subjects who are eligible for screening will be assigned with a unique randomization number on the day of the first dose of the investigational product (Cycle 1 Day 1, C1D1). The investigator will assign a randomization number and a drug number to all subjects who are eligible and suitable for the study after randomization. If more than one subject is scheduled for randomization on the same day, randomization should be performed in chronological order of subject's arrival time rather than the order of screening number. If the drug is damaged during the course of the study, the investigator will obtain a new drug number via the IWRS system and continue the clinical trial. If a subject is not randomized, the reason for not being enrolled in the study must be documented.

### 7.5 Blinding

From the start of randomization until disease progression as assessed by the investigator per

RECIST 1.1, the information of the actual treatments will remain blinded to the subjects, the investigator, data analysts, the Sponsor, and all medical personnel involved in the treatment or clinical assessments.

Randomization numbers and study drug numbers will be obtained via the IWRS. The blinded control of the drug uses a double dummy technique. The packaging, mode of administration, labeling, appearance, taste and odor of HS-10296 tablets and HS-10296 placebo tablets (and gefitinib tablets and gefitinib placebo tablets) will be exactly the same to conceal the true information of the treatment drug. HS-10296 tablets and gefitinib placebo tablets will be packaged together. Gefitinib tablets and HS-10296 placebo tablets will also be packaged together. Drugs will be numbered after the combined packaging. The blinding code will be stored in the IWRS system and at the administrator for randomization.

## 7.6 Unblinding

This study adopts a double-blind design and the study should remain as blinded as possible.

### 7.6.1 Unblinding and Procedures after Disease Progression

For the determination of subsequent treatment, the patients with disease progression may be unblinded according to the following unblinding procedures if the investigator needs to learn about the information on the randomized drug received by the patients: 1) the investigator inform the CRA of the Sponsor promptly; 2) the efficacy and safety data generated from the subject should be entered into the EDC system; 3) source data verification (SDV) and data cleaning should be performed on the data entered into the EDC system; 4) the subjects will be unblinded after data cleaning is completed.

### 7.6.2 Emergency Unblinding

Emergency unblinding in individual patients is only applicable to the situation when the investigator needs to perform urgent medical intervention and the continued blinding of the patients will affect the investigator's development of the best medical treatment measures.

If emergency unblinding is warranted, the investigator should promptly notify the Sponsor's CRA and apply for unblinding (the investigator can perform the unblinding first and then notify the Sponsor only in case that the emergency treatment of the patient is required to avoid any treatment delay). Patients will be unblinded by the investigator with the consent of the Sponsor and authorization of the IWRS system. The investigator should be aware that the occurrence of SAEs is not a prerequisite for initiate emergency unblinding. The Sponsor, the investigator at each site and the Ethics Committee must be notified of the above procedures as soon as possible, and the time, reason and results of unblinding must be recorded in the source documents.

### 7.7 Procedures for Handling Wrongly Enrolled Subjects

Subjects who do not meet the inclusion criteria but meet any of the exclusion criteria for the study are not eligible to participate in the study. If a subject who does not meet the inclusion criteria but meets any of the exclusion criteria is enrolled, the study treatment cannot be given. If study treatment has been initiated, the investigator should promptly inform and discuss sufficiently with the Sponsor to decide whether to discontinue the study treatment based on the outcome of the discussion, and the subject who is required to discontinue the study treatment should withdraw from the study. The Sponsor must fully record this process.

### 7.8 Restrictions

1) Women of childbearing potential should use reliable methods of contraception from screening to 3 months after discontinuation of study treatment. Acceptable methods of contraception include abstinence, tubal ligation, oral or transdermal contraceptives, copper-bearing intra-uterine devices, and partner receiving vasectomy. All the hormonal methods of contraception should be used in combination with the use of condoms by the patient's male partner.

2) Male patients should be required to use barrier contraception (i.e., condoms) from screening to 3 months after discontinuation of study treatment.

Male patients should refrain from donating sperm from the start of study treatment until 6 months after discontinuation of study treatment. If a male patient wishes to father a child, he should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

3) After completion of study treatment, it is recommended that female subjects of childbearing potential and male subjects may prolong contraception until 6 months after discontinuation of study treatment, if possible.

4) For patients who are wearing contact lenses during the treatment with HS-10296: if they experience a CTCAE Grade 3 or higher ocular event for the first time, they must stop wearing contact lenses until at least 1 week after permanent discontinuation of the HS-10296. If they experience a mild to moderate ocular event (CTCAE ≤ Grade 2) for the first time, they must stop wearing contact lenses until at least 1 week after the resolution of the symptoms. If they experience an ocular event of any grade again, they must stop wearing contact lenses until at least 1 week after permanent discontinuation of HS-10296. Patients are not allowed to self-administer any eye drops or ointments for the treatment of ocular symptoms throughout the study until 1 week after permanent discontinuation of HS-10296, unless approved by the investigator. The patients should consult the clinic promptly if they have any concerns.

5) It is recommended to monitor the low density lipoprotein cholesterol when statins are combined with HS-10296. If a subject experiences any potentially relevant AEs suggestive of muscular toxicity, including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, statins should be discontinued, and blood creatine kinase levels should be tested, and appropriate further examinations and management should be performed.

6) Prothrombin time or international normalized ratio (INR) should be monitored for subjects taking warfarin.

7) Patients with corneal ulcer are not allowed to resume the study treatment.

8) If new or worsening pulmonary symptoms (e.g., dyspnea) or imaging abnormalities observed suggesting interstitial lung disease, it is recommended to interrupt the study treatment and notify the Sponsor. The investigators are strongly recommended to perform a thorough diagnostic workup on the patient to exclude alternative causes such as lymphatic metastasis, infection, allergy, cardiac edema or pulmonary hemorrhage. The diagnosis of interstitial lung disease should be considered when it is confirmed by a high-resolution CT (HRCT) scan and respiratory symptoms due to other causes are excluded, and study treatment should be permanently discontinued. If the diagnosis of interstitial lung disease is excluded, the treatment may be resumed after consultation with the Sponsor's physician.

### 7.9 Concomitant Medications and Treatments

Information on all medications taken within 4 weeks prior to initiation of study treatment and all concomitant medications taken during the study, as well as the drug indications, will be recorded in the electronic case report form (eCRF). During the 28-day follow-up period after permanent discontinuation of HS-10296, all concomitant medications, including anti-tumor therapy, will be recorded in the eCRF, and only anti-tumor therapy will be recorded thereafter. Patients taking conventional medications should continue to use such medications throughout the study if medically feasible. Other anti-tumor agents, investigational products, and radiation therapy should not be administered when a patient is on study treatment and donated drugs unless the patient must receive radiation therapy to manage the pain caused by bone metastases. The pleural effusion drainage for the purpose of symptom control should be permitted in the absence of objective disease progression as assessed by radiographic assessment when a patient is on study treatment; anti-tumor agents are not allowed in the management of pleural effusion; and the investigator should re-assess the presence or absence of disease progression of this non-target lesion and overall disease progression depending on the volume and nature of the pleural

effusion after completion of pleural effusion drainage. The above information should be recorded in detail in the original medical record.

Prophylaxis for diarrhea, nausea, and vomiting should not be given prior to the first dose of study drug, but prophylaxis is allowed after the first dose. Patients are allowed to receive blood transfusions at any time during the study.

Granulocyte colony stimulating factors should not be used prophylactically during treatment for Cycle 1. Use of prophylactic colony stimulating factors may be considered after Cycle 1 following discussion with the Sponsor's physician.

Patients can receive treatment with corticosteroids and/or bisphosphonates or denosumab for bone metastases.

Drugs that may cause QTc prolongation should be avoided. Supportive care and other medications necessary for the patient's health may be used at the discretion of the investigator.

Patients should make efforts to avoid using any medications, herbal supplements, and/or food (e.g., grapefruit) known to contain substrates and potent inhibitors or inducers of CYP3A4 and/or CYP2D6 and/or CYP1A2. Adverse events as well as concomitant treatments will be closely monitored according to the study plan.

Patients may take any medication to treat an adverse event if it is clinically indicated, but non-prohibited drugs should be selected as far as possible.

Refer to Appendix E for the list of prohibited drugs.

### 7.10 Withdrawal Criteria

Withdrawal from the study means that a subject who has been enrolled is withdrawn by the investigator or the Sponsor as any condition or situation occurring during the study makes the subject no longer suitable to continue the study, or the subject voluntarily requests to withdraw from the study. The primary reasons for withdrawal from the study should be recorded in the eCRF, the reasons for withdrawal include:

1) Patient's voluntary withdrawal: a patient may withdraw from the study at any time at his/her own discretion, regardless of any decision of other parties participating in the study.

2) Adverse Events: a patient experiences AEs that require early discontinuation of the study, because continued participation will impose an unacceptable risk to the patient's health or the patient is unwilling to continue the study.

3) Pregnancy: a patient must be withdrawn from the study immediately if she becomes pregnant.

4) Major protocol deviations judged by the investigator and/or the Sponsor: after

randomization, it is found that the patient does not use the investigational product correctly, or fails to meet the protocol inclusion criteria, or does not meet the protocol requirements, and continued participation in the study will impose an unacceptable risk to the patient's health.

5) Disease progression (a patient may continue receiving the study treatment if the patient can continue to derive clinical benefit from treatment judged by the investigator, even if the patient has achieved disease progression defined by RECIST 1.1).

6) Lost to follow-up: a patient does not attend to visit on time, and the investigator should have at least 3 attempts to contact the patient by telephone, email, and/or written letter, and all fail. The attempts to contact such patients must be documented.

7) Compliance: a patient has poor compliance with the investigational product and study procedures.

8) Other treatments: a patient requires other medications that would affect the evaluation of the investigational product.

9) Patients with corneal ulcer and interstitial pneumonia should be completely discontinued from the study treatment and withdrawn from the study.

### 7.11 Withdrawal Procedure

1) Recording the reasons: in any case, the investigator should collect the information of subjects as far as possible when subjects withdraw from the trial. The investigator should ask and record the reasons for withdrawal from the study of the subject, and retrieve the investigational product at the same time.

2) Discontinuation follow-up and safety follow-up: the discontinuation follow-up will be completed at the time of treatment discontinuation; thereafter, a 28-day safety follow-up will be performed to record AEs, SAEs, and concomitant medications. If there are abnormal and clinically significant changes, the abnormal condition should be followed up until recovery (to baseline, normal laboratory values, or abnormal values judged as clinically insignificant by the investigator) or stabilization.

3) Subsequent treatment: once the study treatment is discontinued, patients will receive further treatment according to the local standard of care. A patient may continue receiving the study treatment if the patient can continue to obtain clinical benefit from treatment as judged by the investigator, even if the patient has achieved disease progression defined by RECIST 1.1. Patients in the gefitinib treatment group who have disease progression and are eligible assessed by the study procedures may receive the open-label HS-10296 crossover treatment.

4) Progression follow-up: any patient who discontinues treatment for reasons other than

objective disease progression should have a scheduled follow-up for progression until disease progression as assessed by the investigator per RECIST 1.1, unless the patient withdraws informed consent.

5) Survival follow-up: if a subject withdraws consent to participate in study treatment and assessment, they should be further asked whether to continue survival follow-up via telephone. If a subject is unwilling to have the survival follow-up, the condition should be recorded in the eCRF. In such cases, no further evaluations should be performed and no further data should be collected. The Sponsor may retain and continue to use all data prior to withdrawal of informed consent by the subject. The screening and randomization numbers for subjects who withdraw consent cannot be reused.

# 8.0 Management of Investigational Product

## 8.1 Investigational Product

### 8.1.1 Dosing Regimen

The investigational product will be administered orally once daily in both groups, and the dosing regimen is provided in the Table 1 below.

**Table 1 Dosing Regimen**

| • **Standard treatment** | | |
|---|---|---|
| | **HS-10296 group** | **Gefitinib group** |
| Dose | 110 mg/d HS-10296 | 250 mg/d gefitinib |
| Drug | HS-10296 active drug, 55 mg/tablet, 2 tablets<br>Gefitinib placebo tablets (placebo 250 mg), 1 tablet | Gefitinib active drug, 250 mg/tablet, 1 tablet<br>HS-10296 placebo tablets (placebo 55 mg), 2 tablets |
| Usage | Once daily, orally | Once daily, orally |
| • **Dose reduction treatment** | | |
| | **HS-10296 group** | **Gefitinib group** |
| Dose | 55 mg/d HS-10296 | No dose reduction, treated at the same dose |
| Drug | HS-10296 active drug, 55 mg/tablet, 1 tablet<br>HS-10296 placebo tablets (placebo 55 mg), 1 tablet<br>Gefitinib placebo tablets (placebo 250 mg), 1 tablet | No dose reduction, treated at the same dose |
| Usage | Once daily, orally | Once daily, orally |

Subjects are advised to take the investigational product as a whole tablet with 240 mL of water at room temperature and should remain fasted from 1 h before dosing to 2 h after dosing.

The administration time should be at the same time on each day, it is recommended to keep a 24-hour interval between two doses. For subjects who fail to take the drug at the scheduled time of the study: if the administration time is out of the time window for less than 12 hours, this dose can be taken to make up for the missed dose; if the administration time is out of time window for more than 12 hours, skip the missed and take the next dose at the next scheduled time.

If a subject vomit the drug after taking it, do not take the dose again, and take the next dose at the next scheduled time. Any medication-related changes should be recorded in the eCRF.

### 8.1.2 Dosage Form, Manufacturing, Packaging and Labeling

In this protocol, the investigational product will be provided to each study site after being uniformly packaged and numbered. The labeling of the drug will include, but not limited to the

following information: protocol number, investigational product number, batch number, strength, quantity of dosage units, instructions for use, storage conditions, country-specific regulatory warning statements, and name and address of the Sponsor.

HS-10296 tablets will be provided by Jiangsu Hansoh Pharmaceutical Group Co., Ltd. Gefitinib tablets are commercially packaged. The products should be stored according to package insert. All placebo tablets will be manufactured by Jiangsu Hansoh Pharmaceutical Group Co., Ltd. with the same appearance as that of the active drug of the strength used.

In this study, 3 types of drug packaging kits need to be prepared and classified as normal medication kit for the test group (HS-10296 group), normal medication kit for the control group (gefitinib group), and dose reduction kit for the test group (HS-10296 group). Each kit will contain the drugs required between two adjacent dispensing intervals, and the number of each small package in the kit will be calculated according to the dispensing cycle. There will be a single dose of active drug and placebo tablets (total of 3 tablets) in each small package, and only one small package in the kit will be required for once daily dosing. All remaining drugs and packages should be recovered after the end of the study.

During the study, the investigational product will be provided according to the Table 2.

**Table 2 Investigational Product**

| **Normal medication** | | | |
|---|---|---|---|
| **Package** | **Investigational Product** | **Small package (per dosage)** | **Manufacturer** |
| Normal medication kit for the test group | HS-10296 tablets | 55 mg/tablet (2 tablets) | Jiangsu Hansoh Pharmaceutical Group Co., Ltd. |
| | Gefitinib placebo tablets | Placebo 250 mg (1 tablet) | Jiangsu Hansoh Pharmaceutical Group Co., Ltd. |
| Normal medication kit for the control group | Gefitinib tablets | 250 mg/tablet (1 tablet) | AstraZeneca Pharmaceutical Co., Ltd. |
| | HS-10296 placebo tablets | Placebo 55 mg (2 tablets) | Jiangsu Hansoh Pharmaceutical Group Co., Ltd. |
| **Dose reduction** | | | |
| **Package** | **Investigational Product** | **Small package (per dosage)** | **Manufacturer** |
| Dose reduction kit for the test group | HS-10296 tablets | 55 mg/tablet (1 tablet) | Jiangsu Hansoh Pharmaceutical Group Co., Ltd. |
| | HS-10296 placebo tablets | Placebo 55 mg (1 tablet) | Jiangsu Hansoh Pharmaceutical Group Co., Ltd. |
| | Gefitinib placebo tablets | Placebo 250 mg (1 tablet) | Jiangsu Hansoh Pharmaceutical Group Co., Ltd. |

### 8.1.3 Storage

All the study drugs for this clinical study must be kept in an appropriate and safe place until

used or returned to the Sponsor or designated person for destruction. All drugs supplied by the Sponsor must be stored under the conditions specified on the label, and retained in the original container until dispensed to the patients. All the study drugs must be stored in tightly-closed containers and below 30°C. The study drugs should only be dispensed to the patients participating in the study.

### 8.2 Dispensing Procedures of Investigational Product

Subjects will be assigned a screening number according to the order of arrival. After relevant tests are performed, eligible subjects will be given a randomization number generated from the IWRS. They will be randomly assigned to either the HS-10296 group or the gefitinib group. The investigator will dispense the study drug according to the drug number which is generated from the IWRS randomization system. At each patient's visit, the investigator will log into the IWRS system to obtain the drug number to be dispensed at that visit. If the drug is damaged during the course of the study, the investigator will obtain a new drug number via the IWRS system and continue the clinical trial. Dispensing and returning of each portion of the study drug should be timely documented in the corresponding recording sheet. Drug management personnel should fill in the drug dispensing/return registration form accurately. All study drugs should be kept properly, and will be handed over to the Sponsor after the end of the study.

### 8.3 Medication Compliance

Subjects should take the study drug orally, once daily, as required by the study. Drugs that are not administered should be recorded in detail and the reason should be specified. The investigator will reconciliate the remaining investigational products to verify medication compliance. If there is any incompliance, appropriate explanations should be given.

### 8.4 Management of Investigational Product

The Sponsor should supply the investigational product based on the number of subjects on the contracts in each clinical study site. All the investigational products will be stored in a safe and acceptable place, and a specially designated person is responsible for managing the registration, distribution and return records of the investigational product.

1) Drug handover form: upon receipt of the investigational product, the investigator or designated personnel must check the contents of the shipment against the packing list. The verifier should ensure that the drug quantity is correct, the drug is received under labeled storage conditions, and the packaging is in good condition. If both quantities and conditions are acceptable, the investigator or designated person and the CRA should confirm the receipt of the shipments. If there is any discrepancy between the packing list and the actual product received,

the Sponsor must be contacted to resolve the problem. The packing list should be archived in the investigator's folder.

2) Drug dispensing/return registration form: the subject's initials, drug number, dispensing date, dispensed quantity, return date, returned quantity, signature of the person who dispenses and returns the drug should be registered. If any dispensing errors or discrepancies are identified, the Sponsor must be notified immediately.

3) Drug temperature record form: the unused drug should be stored according to the storage requirements after drug handover, and the storage temperature should be recorded every day.

4) Drug return record form: after the completion of the study, all the remaining drugs will be uniformly returned to the Sponsor, and signed and confirmed by the investigator and the CRA.

5) Drug destruction record form: all returned remaining investigational products will be destroyed and documented by the Sponsor. To ensure appropriate use of investigational products, the investigator must keep records of all investigational products, including delivery, inventory, distribution and use records of each subject, and return to the Sponsor (or designated person). Copies of the original data will be submitted to the Sponsor or its designated person as needed.

The investigator is responsible for receiving, storing, and dispensing of drugs during the study, including but not limited to:

- Frequently verifying that actual inventory matches the documented inventory.
- Verifying and completing the logbook of the drug batch.
- Verifying that all used and unused drugs are documented accurately.
- Verifying that the required information is completed accurately and legible.

The Sponsor or designated person will notify the investigator of the expiry or retest date of the study materials during the study. Upon receipt of a notification of the expiry date of the study materials, the study site personnel must complete all the procedures described in the notification, including collating and returning the expired study materials to the Sponsor or its designated person for destruction.

# 9.0 Study Plan and Procedures

## 9.1 Study Procedures

The following sections describe the study procedures and the data to be collected. For each procedure, each patient should be assessed by the same investigator or the study personnel of the site as far as possible. The overall follow-up schedule is presented in Appendix B.

### 9.1.1 Screening Period (D-28 to D-1)

- Subjects must be fully informed for consent and sign the informed consent form prior to any study procedures
- Submit tumor tissue samples or blood samples collected after the diagnosis of locally advanced or metastatic NSCLC for EGFR mutation test
- Demographic data (including date of birth or age, sex, race, smoking status, etc.) and comprehensive medical history (treatment history, surgical history, allergy history, etc.) will be collected.
- Full physical examination (including body weight), vital signs (blood pressure, heart rate, respiratory rate, and body temperature), and body height.
- ECOG PS score
- The non-menopausal women should undergo a blood or urine pregnancy test within 3 days prior to starting the first dose of the investigational product;
- Blood and urine samples will be collected for laboratory tests (clinical chemistry, hematology and urinalysis)
- 12-lead ECG, as well as echocardiography (the results of the echocardiography within 28 days prior to enrollment are available, regardless of the time of informed consent) will be performed;
- Full ophthalmologic examination, including best corrected visual acuity, intraocular pressure test, fundus examination, and slit lamp examination will be performed;
- Baseline tumor assessment will be performed according to RECIST 1.1 (results within 28 days prior to enrollment are available, regardless of the time of informed consent)
- Evaluate the inclusion and exclusion criteria
- Record anti-tumor and surgical treatments
- Record adverse events (from the time of signing the informed consent form)
- Record concomitant medications (from the date of 28 days prior to enrollment)

### 9.1.2 Treatment Period (C1 to C7 +, D1 to D127 +)

#### 9.1.2.1 Treatment Regimen (C1 to C7 +, D1 to D127 +)

One treatment cycle (C1 to C7 +) is defined as 21 days, and HS-10296 or gefitinib will be administered orally once daily during the treatment cycle. Subjects will be randomized on C1D1 and will continue to receive study treatment until disease progression as assessed by the investigator per RECIST 1.1. Alternatively, a subject who have disease progression may continue study treatment if the subject can continue to derive clinical benefit judged by the investigator.

#### 9.1.2.2 Treatment Visits (C1 to C7 +, D1 to D127 +)

**Treatment Visits (C1 to C7, D1 to D127)**

- Treatment visits will be performed on the first day of the first 7 treatment cycles (C1 to C7) (CnD1, n = 1 to 7), with the exception of C1D1, and two additional visits will be added on C1D8 and C1D15, respectively. The specific visit procedures are as follows:
- The investigational product will be dosed once daily
- Full physical examination, body weight examination, ECOG PS score, vital signs, laboratory tests (clinical chemistry, hematology, and urinalysis), and 12-lead ECG will be performed every 3 weeks (CnD1)
- Two additional tests will be added on C1D8 and C1D15: including vital signs, laboratory tests (clinical chemistry, hematology, and urinalysis), and 12-lead ECG
- Ophthalmic examinations will be performed as clinically indicated throughout the treatment period, and the specific items will be determined by the investigator or specialist depending on the patient's condition
- Echocardiography will be performed every 12 weeks from the first dose (and as clinically indicated)
- Response evaluations in solid tumors will be performed per RECIST 1.1 every 6 weeks
- The adverse events and concomitant medications will be recorded

**Treatment Visits (C7 +, D127 +)**

Treatment visits after Cycle 7 will be performed according to the following procedures:

- The investigational product will be dosed once daily
- Full physical examination, body weight examination, ECOG PS score, vital signs, laboratory tests (clinical chemistry, hematology, and urinalysis), and 12-lead ECG will be performed every 6 weeks (C1 to C21) or every 12 weeks (C23 and thereafter)
- Ophthalmic examinations will be performed as clinically indicated throughout the treatment period, and the specific items will be determined by the investigator or specialist depending on the patient's condition

- Echocardiography will be performed every 12 weeks (and as clinically indicated)
- Response evaluations in solid tumors will be performed per RECIST 1.1 every 6 weeks (C1 to C21) or every 12 weeks (C23 and thereafter)
- The adverse events and concomitant medications will be recorded

### 9.1.3 Follow-up Period

#### 9.1.3.1 Study Discontinuation Follow-up

Discontinuation follow-up refers to the visit procedures required to be completed when a subject completely discontinues study treatment, including the following:

- Full physical examination, body weight examination, ECOG PS score, vital signs, laboratory tests (clinical chemistry, hematology, and urinalysis), 12-lead ECG, and echocardiography
- If a subject has disease progression, tumor and/or blood samples will be collected (optional) based on the subject's willingness, for post-disease progression genetic testing so as to guide further treatments
- Response evaluations in solid tumors will be performed per RECIST 1.1
- The adverse events and concomitant medications will be recorded

During the discontinuation visit, repeated examinations will not be required if the results of the safety tests (full physical examination, body weight examination, ECOG PS score, vital signs, laboratory tests, and 12-lead ECG) within the previous 7 days are available; and repeated examinations will also not be required if the results of the RECIST response evaluations and echocardiography within the previous 4 weeks are available.

#### 9.1.3.2 Safety Follow-up (28-day follow-up)

Safety follow-up refers to the visit procedures that a subject should complete 28 days after discontinuation of study treatment (discontinuation of the investigational product). During the visit, information on newly emerged AEs or follow-up of AEs experienced at the time of discontinuation, and all concomitant medications (including anti-tumor therapy) will be collected by telephoning the patient. The follow-up should be performed until the SAE has an outcome, if possible. It includes the following items:

- Record adverse events (newly emerged AEs or follow-up of AEs experienced at the time of discontinuation)
- Record concomitant medications (all concomitant medications including anti-tumor therapy)

#### 9.1.3.3 Progression Follow-up

Progression follow-up refers to the visit procedures to be completed by subjects who discontinue treatment for reasons other than disease progression. RECIST 1.1 assessments will be performed every 6 weeks (C1 to C21) or every 12 weeks (C23 and thereafter) (relative to the date of randomization). Patients who continue treatment after progression due to possible clinical benefit will continue to undergo tumor assessments. It includes the following items:

**Progression follow-up for subjects who discontinue treatment for reasons other than disease progression:**

- Response evaluations in solid tumors will be performed every 6 weeks (C1 to C21) or every 12 weeks (C23 and thereafter) until disease progression as assessed by the investigator per RECIST 1.1
- ECOG PS score will be performed every 6 weeks (C1 to C21) or every 12 weeks (C23 and thereafter) until disease progression as assessed by the investigator per RECIST 1.1
- Record concomitant medications: only subsequent anti-tumor therapy will be recorded in detail until disease progression
- If a subject has disease progression before the completion of the 28-day safety follow-up, the safety follow-up should be continued until 28 days after discontinuation of treatment

**Progression follow-up for subjects who continue study treatment (donated drug) after disease progression:**

- It is recommended to perform tumor assessments per RECIST 1.1 every 6 weeks (C1 to C21) or every 12 weeks (C23 and thereafter) until progression after the administration of donated drug as judged by the investigator or discontinuation of treatment before progression (safety reasons or investigator's judgment or subject's decision)
- ECOG PS score will be performed every 6 weeks (C1 to C21) or every 12 weeks (C23 and thereafter) until further progression as judged by the investigator or discontinuation of treatment before progression (safety reasons or investigator's judgment or subject's decision)
- Record concomitant medications: all concomitant medications (including anti-tumor therapy) will be recorded until 28 days after discontinuation of treatment, and only anti-tumor therapy will be collected thereafter
- Record adverse events: for subjects who continue to receive study treatment after progression, AEs and SAEs will be continued collecting until 28 days after discontinuation of treatment, and only AEs with no outcome and study drug-related SAEs will be collected thereafter

#### 9.1.3.4 Survival Follow-up

After disease progression (the date of occurrence of initial disease progression will be used if the donated drug is not given; the date of occurrence of clinical progression will be used if the donated drug is given), the patient, the patient's family member, or the patient's current physician must be contacted every 6 weeks for survival information; if the progression follow-up is not completed according to the study procedures, and the date of disease progression is missing, the dates of documented refusal to progression follow-up/acceptance of survival follow-up will be used as the starting point. Details of subsequent treatment regimens (treatments received since withdrawal of the investigational product), as well as unresolved AEs (unless the patient withdraws consent) must be collected regardless of the date of the last contact. It includes the following items:

- Follow-up every 6 weeks to record details of subsequent anti-tumor therapy
- Follow-up every 6 weeks to record subsequent response/progression data
- Follow-up every 6 weeks to record survival status

Data from survival follow-up will be collected continuously until the subject dies

## 9.2 Open-label HS-10296 Crossover Treatment

Subjects in the gefitinib group who have disease progression while continuing treatment with the study drug gefitinib may initiate the open-label HS-10296 crossover treatment if they meet the required conditions for crossover treatment as assessed by the procedures.

### 9.2.1 Assessment Procedures and Required Conditions

Before determining whether a subject can receive the open-label HS-10296 crossover treatment, the following steps are required for assessment.

#### 9.2.1.1 Disease Progression and Unblinding

Subjects who have disease progression as assessed by the investigator per RECIST 1.1 may be unblinded if it is necessary for subsequent treatments. The investigator should document the process in detail and inform the Sponsor of the process.

#### 9.2.1.2 Determination of Progression Status

If a subject is found to be in the gefitinib treatment group after unblinding, it must be determined whether disease progression occurred during treatment with gefitinib, and only subjects whose disease progression occurs during gefitinib treatment will be given the crossover treatment with HS-10296.

For subjects who are planned to be given the crossover treatment with HS-10296, no other anti-tumor intervention should be administered after discontinuation of gefitinib. Crossover treatment with HS-10296 will not be given if a subject has received other interventions after

discontinuation of randomized treatment.

#### 9.2.1.3 Signing of Informed Consent Form (ICF)

Subjects who meet the above conditions should sign the ICF for all procedures of crossover treatment before proceeding to the following study procedures.

#### 9.2.1.4 Pre-crossover Assessment

Tumor tissue samples or blood samples after progression will be collected for T790M mutation testing. T790M mutation status must be determined through testing by the central laboratory. Patients with confirmed positive T790M mutation after tumor progression will be eligible for HS-10296 crossover treatment.

Pre-crossover assessments should be completed within 28 days from the date of signing the ICF for crossover treatment. Subjects will not be allowed to receive other anti-tumor interventions during this period.

#### 9.2.1.5 Treatment with HS-10296

Subjects who complete the above procedures and meet the relevant conditions will be eligible for receiving the open-label HS-10296 crossover treatment.

### 9.2.2 Crossover Visit Procedures

Eligible subjects will be treated with HS-10296, and the procedure will be similar to that of the randomized treatment with HS-10296, i.e., the subjects will receive 110 mg of HS-10296 once daily in a 21-day treatment cycle. The subjects will continue to receive study treatment (C1 to C7 +, D1 to D127 +) until disease progression as assessed by the investigator. Discontinuation follow-up and survival follow-up will be performed after progression. Refer to Appendix B for complete procedures of crossover treatment.

#### 9.2.2.1 Pre-crossover Assessment (D-28 to D-1)

The pre-crossover assessment should be completed from the date of signing the ICF for crossover treatment to the first dose of HS-10296 crossover treatment, and the duration should not exceed 28 days.

- Sign the ICF for crossover treatment
- Collect tumor tissue samples or blood samples for T790M mutation testing after disease progression during the randomized treatment period
- Tumor assessments will be performed according to RECIST 1.1 before initiation of treatment (results within 28 days prior to crossover treatment are available)
- Record anti-tumor therapy during this period
- Record concomitant medications and adverse events

**Upon completion of the above assessments, subjects who meet the following crossover treatment inclusion criteria will be eligible for the open-label HS-10296 treatment:**

1) Patients with confirmed positive T790M mutation after tumor progression

2) Have received no other interventions after discontinuation of randomized treatment with gefitinib

3) The washed-out period for gefitinib must be at least 5 half-lives prior to the first dose of crossover treatment

4) Patients with asymptomatic and stable brain metastases, and not requiring steroids for at least 2 weeks prior to the first dose of crossover treatment

5) Any unresolved toxic reaction from prior therapy should be controlled and not greater than CTCAE Grade 1 at the start of HS-10296 (except for alopecia and Grade 2 neurotoxicity due to chemotherapy)

6) Review the current medical conditions, and no violation to the relevant randomized eligibility criteria specified in Sections 7.1 (Articles 5 and 6) and 7.2 (except Article 1a, all others are applicable) of the protocol

should be found

#### 9.2.2.2 Treatment Follow-up (C1 to C7 +, D1 to D127 +)

**Treatment Visits (C1 to C7, D1 to D127)**

Treatment visits will be performed on the first day of the first 7 treatment cycles (C1 to C7) (CnD1, n = 1 to 7), with the exception of C1D1, and two additional treatment visits will be added on C1D8 and C1D15, respectively. The specific visit procedures are as follows:

- The investigational product will be dosed once daily
- Full physical examination, body weight examination, ECOG PS score, vital signs, laboratory tests (clinical chemistry, hematology, and urinalysis), and 12-lead ECG will be performed every 3 weeks (CnD1)
- Two additional tests will be added on C1D8 and C1D15: including vital signs, laboratory tests (clinical chemistry, hematology, and urinalysis), and 12-lead ECG
- Ophthalmic examinations will be performed as clinically indicated throughout the treatment period, and the specific items will be determined by the investigator or specialist depending on the patient's condition
- Echocardiography will be performed on C1D1 and every 12 weeks (and as clinically indicated)
- Tumor assessments per RECIST 1.1 will be recommended to be performed every 6 weeks

- The adverse events and concomitant medications will be recorded

**Treatment Visits (C7 +, D127 +)**

Treatment visits after Cycle 7 will be performed according to the following procedures:

- The investigational product will be dosed once daily
- Full physical examination, body weight examination, ECOG PS score, vital signs, clinical chemistry, hematology, urinalysis, and 12-lead ECG will be performed every 6 weeks
- Ophthalmic examinations will be performed as clinically indicated, and the specific items will be determined by the investigator or specialist depending on the patient's condition
- Echocardiography will be performed every 12 weeks (and as clinically indicated) from the first dose of HS-10296
- Tumor assessments per RECIST 1.1 will be recommended to be performed every 6 weeks
- The adverse events and concomitant medications will be recorded

#### 9.2.2.3 Study Discontinuation Follow-up

Subjects who receive HS-10296 crossover treatment should discontinue HS-10296 when they meet withdrawal criteria or discontinuation criteria, and discontinuation follow-up will be required at the time of discontinuation. It includes the following items:

- Full physical examination, body weight examination, ECOG PS score, vital signs, laboratory tests (clinical chemistry, hematology, and urinalysis), 12-lead ECG, and echocardiography
- Record anti-tumor therapy
- If a subject has disease progression during the crossover treatment period, tumor and/or blood samples will be collected (optional) based on the subject's willingness for post-disease progression genetic testing so as to guide further treatments
- Record adverse events

During the discontinuation visit, repeated examinations will not be required if the results of the safety tests (full physical examination, body weight examination, ECOG PS score, vital signs, laboratory tests, and 12-lead ECG) within the previous 7 days are available; and repeated examinations will also not be required if the results of the RECIST response evaluations and echocardiography within the previous 4 weeks are available.

#### 9.2.2.4 Safety Follow-up

A 28-day safety follow-up will be performed after discontinuation of HS-10296 crossover treatment (discontinuation of the investigational product) to record AEs, SAEs, and concomitant medications. If there are abnormal and clinically significant changes, the abnormal

condition should be followed up until recovery (to baseline, normal laboratory values, or abnormal values judged as clinically insignificant by the investigator) or stabilization.

- Record adverse events (newly emerged AEs or follow-up of AEs experienced at the time of discontinuation)
- Record concomitant medications (all concomitant medications including anti-tumor therapy)

#### 9.2.2.5 Progression Follow-up

In the HS-10296 crossover treatment period, any patient who discontinues the HS-10296 crossover treatment for reasons other than objective disease progression should have a scheduled progression follow-up until disease progression as assessed by the investigator per RECIST 1.1, unless the patient withdraws the informed consent.

- Response evaluations in solid tumors will be performed every 6 weeks until disease progression as assessed by the Investigator per RECIST 1.1
- ECOG PS score will be performed every 6 weeks until disease progression as assessed by the investigator per RECIST 1.1
- Record concomitant medications: only subsequent anti-tumor therapy will be recorded in detail until disease progression
- If a subject has disease progression before the completion of the 28-day safety follow-up, the safety follow-up should be continued until 28 days after discontinuation of treatment

#### 9.2.2.6 Survival Follow-up

- Perform follow-up every 6 weeks (relative to the date of disease progression at the time of crossover treatment) to record details of subsequent anti-tumor therapy
- Perform follow-up every 6 weeks (relative to the date of disease progression) to record subsequent response/progression data
- Perform follow-up every 6 weeks (relative to the date of disease progression) to record survival status

If the progression follow-up for crossover treatment is not completed according to the study procedures, and the date of disease progression is missing, the dates of documented refusal to progression follow-up for crossover treatment/acceptance of survival follow-up will be used as the starting point.

### 9.3 Unscheduled Visits/Examinations

The investigator may schedule unscheduled visits or examinations according to the subject's condition, especially if the subject experiences an AE. Unscheduled visits and unscheduled

examinations performed during that visit will be recorded in the eCRF, along with the reason for the unscheduled visit (or examination).

# 10.0 Study Assessments

## 10.1 Study Specific Steps

The following contents specify the detailed requirements and descriptions of each step in the study procedure and the indicators for examination/assessment.

### 10.1.1 Informed Consent Process

The informed consent form (ICF) must be obtained prior to subject enrollment and study procedures. The ICFs at enrollment should include the informed consent for participation in the study, for obtaining tumor tissue samples at screening, for blood sample collection, and for tumor samples collection at disease progression (optional).

After confirmation of disease progression by central review and unblinding, subjects in the gefitinib group should sign the ICF for HS-10296 crossover treatment, including the informed consent for participation in crossover treatment, for tumor samples collection after disease progression, and for blood samples collection. The ICF for crossover treatment will be signed as an independent ICF, separate from the ICF signed at enrollment.

### 10.1.2 Assignment of Screening Number

Each patient will be assigned a unique screening number at the time informed consent is obtained. Screening numbers for subjects who have failed the screening tests or have withdrawn from the study should not be reused.

### 10.1.3 Screening and Enrollment

Each enrolled subject shall provide the informed consent form prior to the initiation of any study procedures, after which screening tests will be performed to determine the subject's eligibility.

Tumor assessments and other clinical data obtained prior to the informed consent may be used for the study without re-examination if the time of assessment is within the timeframe specified in the protocol. The screening procedure is recommended to start with confirmation of EGFR mutation status by central laboratory test.

Tumor tissue samples collection for EGFR mutation status test at screening may not be limited to the 28-day timeframe, but samples must be collected after diagnosis of locally advanced or metastatic NSCLC.

Baseline CT or MRI assessment of chest, abdomen, and brain tissue (contrast CT/MRI is recommended) must be performed within 28 days prior to the start of study treatment

(regardless of the time of signing the ICF), and it should be performed as close as possible to the start of study treatment. If the only target lesion has undergone a diagnostic biopsy, a baseline assessment of tumor lesions should be performed at least 14 days later.

If laboratory tests (clinical chemistry, hematology, and urinalysis) are performed within 7 days prior to randomization, they may not need to be repeated at the first study treatment (C1D1) visit.

If a laboratory value at screening is abnormal, the test may be repeated once within 1 week, and the re-test results will be used as the basis for assessment of eligibility criteria. For subjects who are tested out of the timeframe or fail at screening, a second screening may be performed if the Investigator believes that they may be eligible for enrollment. Subjects who are re-screened need to re-sign the ICF and use a new screening number.

#### 10.1.4 Assignment of Randomization Number

Subjects who are eligible for screening will be assigned a randomization number generated from the IWRS prior to the first dose of the investigational product (C1D1).

#### 10.1.5 Data Collection

Demographic data and other characteristics, including date of birth or age, sex, race and smoking status of patients, will be collected at screening as per the study plan (Appendix B).

Complete medical history will be collected: including past and current medical history of kidney, liver, blood system, digestive tract, endocrine, immune, metabolic, cardiovascular, lung, and nervous systems, psychiatric disorders, infections and inflammatory diseases.

Treatment history: drug (chemotherapy, prescription drugs, over-the-counter drugs, other drugs) and non-drug therapies (surgery, radiotherapy, etc.) will be recorded.

Allergy history: the subject's history of allergy to drugs or other substances will be recorded.

#### 10.1.6 Physical Examination

Physical examinations will be performed at screening, every 3 weeks for C1 to C7, every 6 weeks for C7 + cycles, and at the discontinuation follow-up as per the study plan (Appendix B).

Baseline physical examination (defined as assessments performed prior to the start of the investigational product) will include the following systems: 1) eyes; 2) ears, nose, throat; 3) cardiovascular system; 4) respiratory system; 5) gastrointestinal system; 6) skin; 7) extremities; 8) musculoskeletal system; 9) nervous system; 10) lymph nodes; 11) others. All routine physical examinations in each subsequent treatment cycle, with the exception of neurological examinations, should assess whether a significant change from baseline is clinically significant.

### 10.1.7 ECOG PS Score

ECOG PS scores will be performed at screening, every 3 weeks for C1 to C7, every 6 weeks for C7 + cycles, and at discontinuation follow-up and progression follow-up as per the study plan (Appendix B).

0=Fully active, able to carry on all pre-disease performance without restriction.

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

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

3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 = Bedridden, unable to take care of oneself.

5 = Death

### 10.1.8 Body Weight and Body Height Measurements

Height will be measured at screening as per the study plan (Appendix B); body weight will be measured at the same time as the physical examination. Subjects should wear indoor clothing and take off shoes when measuring body weight and height.

### 10.1.9 Vital Signs Measurement

Vital signs will be performed at screening, every 3 weeks for C1 to C7, every 6 weeks for C7 + cycles, on C1D8 and C1D15, and at discontinuation follow-up as per the study plan (Appendix B).

Vital sign measurements will be collected, including body temperature (oral or ear or axillary temperature in degrees Celsius), blood pressure (systolic and diastolic), pulse rate (heart rate per minute), and respiratory rate. Measure blood pressure and pulse after the patient has been sitting for at least 10 minutes. Additional tests may be performed if it is deemed necessary by the investigator as appropriate.

### 10.1.10 Laboratory Tests

Laboratory tests will be performed at screening, every 3 weeks for C1 to C7, every 6 weeks for C7 + cycles, on C1D8 and C1D15, and at discontinuation follow-up as per the study plan (Appendix B).

Additional tests may be performed if it is deemed necessary by the investigator as appropriate. The values, units, and reference ranges of the test results should be recorded in the eCRF.

Laboratory results that reach CTCAE (4.0) Grade 3 or have a significant change from baseline and are considered to be of clinical interest will be reexamined/confirmed within 7 days and

followed up accordingly.

Laboratory test items are listed in Table 3.

**Table 3 Laboratory Test Items**

| Clinical Chemistry | Hematology | Urinalysis |
|---|---|---|
| Serum (S)/Plasma (P)-albumin | Blood (B) -Hemoglobin | U-Glucose |
| S/P-ALT | B-White blood cells | U-Protein |
| S/P-AST | B-Hematocrit | U-Blood |
| S/P-Alkaline phosphatase | B-Red blood cell count (RBC) | |
| S/P-Bilirubin, Total bilirubin | B-Absolute differential white blood cell count | |
| S/P-Calcium, Total blood calcium | Neutrophils | |
| S/P-Creatinine | Lymphocytes | |
| S/P-Creatine kinase | Monocytes | |
| S/P-Glucose | Basophils | |
| S/P-LDH | Eosinophils | |
| S/P-HbA1C | B-Platelet count | |
| S/P-Magnesium | B-Reticulocytes | |
| S/P-Potassium | | |
| S/P-Sodium | | |
| S/P-Urea nitrogen or urea (either) | | |

If AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN, please refer to Appendix C (Hy's law) for further guidance for actions to be taken in the event of combined increases in aminotransferases and total bilirubin.

### 10.1.11 Electrocardiogram

12-lead ECGs will be performed at screening, every 3 weeks for C1 to C7, every 6 weeks for C7 + cycles, on C1D8 and C1D15, and at discontinuation follow-up as per the study plan (Appendix B).

Subjects will undergo a 12-lead ECG after resting in a semi-supine position for at least 10 minutes prior to the scheduled test time. All ECGs should be performed in the same body position of the patient. Three ECGs will be performed at intervals of no more than 10 minutes during each ECG. Standardized ECG machines should be used and, if possible, patients should

be tested using the same machine throughout the study. ECGs may be performed in the event of any cardiac-related AE.

Each ECG result will be reviewed by the investigator or designated physician after ECG recordings are available. If an abnormal ECG is found at screening and is clinically significant judged by the investigator, it should be recorded in the medical history. For all ECGs, the rhythm, ECG intervals, and details of the overall assessment will be recorded, including heart rate, PR, R-R, QRS, and corrected QT interval (QTcF), etc.

Abnormal ECG findings that are clinically significant during treatment should be recorded as AEs in the eCRF. If the assessment is abnormal at discontinuation of treatment, reversibility of the abnormality should be assessed during the 28-day safety follow-up.

#### 10.1.12 Echocardiography

Echocardiography will be performed to assess the patient's LVEF every 12 weeks from the first dose of the investigational product as per the study plan (Appendix B).

One subject should be examined using the same machine and operator whenever possible during the course of the study.

#### 10.1.13 Ophthalmological Examination

Full ophthalmological examination will be performed at screening as per the study plan (Appendix B), including best corrected visual acuity, intraocular pressure, fundus examination, and slit lamp examination; the investigator or specialist will decide which items should be performed depending on the subject's condition, if clinically indicated during the course of the study. If a patient experiences any visual symptoms (including hazy vision) or abnormal eye symptoms and signs, an ophthalmic examination should be performed within 48 hours. Any clinically significant findings and symptoms, including those confirmed by the ophthalmologist, must be reported as adverse events. Ophthalmological examination results should be recorded in the eCRF. Patients with corneal ulcers will no longer be allowed to resume the study treatment. Any clinically significant ophthalmological findings should be photographed for documentation. If necessary, these photographs should be provided to the Sponsor for central review.

### 10.2 Efficacy Evaluation

#### 10.2.1 Response Evaluation in Solid Tumors as per RECIST 1.1

RECIST 1.1 will be used to assess each subject's response to anti-tumor therapy and to calculate PFS, ORR, DoR, DCR, and DepOR at the time of tumor assessments performed by the investigator. The standard definitions for measurable lesions, non-measurable lesions, TLs,

NTLs, complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD), etc. specified by RECIST 1.1 are provided in Appendix D. The analysis of the primary endpoint in this study will be based on the investigator's assessment of tumor response per RECIST 1.1, and the management of subjects by the investigator will only be performed based on the results of this assessment.

Baseline CT or MRI assessments of chest, abdomen, and brain tissue must be performed within 28 days prior to the start of study treatment (regardless of the time of signing the ICF), and it should be performed as close as possible to the start of study treatment. The investigator should perform additional imaging examinations based on the signs and/or symptoms of each subject. The same method as the baseline assessment (CT/MRI) should be used at each subsequent follow-up assessment. Brain metastases will be assessed as non-target lesions. If brain lesions are found at screening, a brain tumor assessment should be performed at each subsequent follow-up; for patients without brain metastases at baseline, brain metastasis assessments are not necessary at subsequent follow-up, whichever is necessary assessed by the investigator.

During the randomized treatment period, tumor response will be assessed every 6 weeks (± 1 week; C1 to C21) or every 12 weeks (± 1 week; C23 and thereafter) after randomization until disease progression as assessed by the investigator per RECIST 1.1. Tumor assessments should be performed as per the study plan whenever possible. If the assessment exceeds the scheduled timeframe (± 1 week) and the subject does not have disease progression, every effort should be made to perform subsequent assessments at the previously scheduled visit times while continuing study treatment. If a tumor is suspected at any other site, appropriate imaging examinations should also be performed at the suspected site.

When progression of non-target lesions occurs, the following criteria must be met: the overall worsening of non-target lesions has reached to the extent that treatment must be discontinued, even if the target lesion has achieved SD or PR. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Therefore, it is less likely to determine the overall progression solely on the basis of change in non-target lesion in the presence of SD or PR of target lesion.

At each visit, the assessment of objective tumor response will be categorized as CR, PR, SD, and PD as per RECIST 1.1. During the assessment of progression of target lesions, the lesions should be compared with the smallest lesion throughout the course of treatment, and the lesions will be considered as PD if the magnitude of the increase meets the criteria. In the absence of disease progression, the lesion will be assessed as tumor response (CR and PR) and stable

disease (SD) by comparing with the lesions at baseline.

### 10.2.2 Central Review

All imaging data collected during the study, including tests performed during unscheduled visits, should be assessed with an independent central review (ICR) by a qualified Independent Review Committee (IRC) in accordance with the Imaging Independent Review Charter. The results of this independent assessment by the IRC will not be returned to the investigator.

### 10.2.3 Assessment of Progression After Administration of Donated Drug

After the first objective progression, subjects who continue to receive the original study treatment (donated drug) after disease progression may undergo tumor assessments every 6 weeks to obtain data on disease progression after the dosing of donated drug. RECIST 1.1 is recommended for the assessment of secondary progression in subjects. Central reviewing is not required for imaging results obtained during this period. The date of the secondary progression and the Investigator's assessment of progression status (progressed or not) at each assessment should be recorded in the eCRF.

### 10.2.4 EGFR Mutation Test at Screening

Tumor tissue samples for the test can be derived from primary tumors or from metastatic tumors.

Tumor biopsy samples for screening should not be collected from tumor lesions after local treatment such as irradiation. Biopsy samples are not limited to the 28-day screening timeframe. If the biopsy sample is collected from tumor tissue that has disease progression to stage IIIB or IV, a repeat biopsy will not be required.

A patient who fails screening for the first tumor tissue test may be re-screened if it is considered by the Investigator to be possibly related to sample collection, and the patient needs to re-sign the ICF before re-screening. Repeated testing will not be required if the laboratory test and imaging examination are within the timeframe at the time of re-screening, and re-testing will be required if the timeframe is exceeded.

When blood samples are submitted, if the test result is negative for EGFR mutation, a tumor tissue sample will be recommended for the second test.

### 10.2.5 Genetic Testing after Disease Progression

If a subject has disease progression, tumor tissue and/or blood samples will be collected (tumor tissue samples are recommended) based on the subject's willingness. For patients treated with HS-10296, post-disease genetic testing for progression will be performed using next-generation sequencing technology to guide further treatments.

The requirements for sample collection are shown in the following table, and the collected samples are shipped to Beijing Gene Plus Clinical Laboratory Co., Ltd., as required for gene testing, including the following genes: EGFR, ALK, ROS1, RET, MET, NTRK, TP53, BRAF, KRAS, NRAS, PI3K, and HER2.

| Sample Type | Requirements for Samples | Sample Storage | Sample Shipment |
|---|---|---|---|
| Fresh tissue | 1. Surgically resected tissue: ≥ 60 mg, approximately soybean-sized<br>2. Needle aspiration of tissue: ≥ 1 needle, sample diameter of 1-2 mm, longer than 0.5 cm | Stored at normal temperature (0-37°C) in tissue preservation tubes | Shipment at 0-37°C |
| Formalin-fixed paraffin-embedded tissue | 1. Paraffin block: 1 piece<br>2. Paraffin section: 10 pieces (3-5 μm) | Stored at normal temperature (0-37°C) in slide storage boxes | Shipment at 0-37°C |
| Peripheral blood | 10 mL Strerck peripheral blood | Temporarily stored at 6-37°C, and refrigeration is prohibited | Shipment at 6-37°C |

## 10.3 Safety Evaluation

Occurrence of adverse events; occurrence of serious adverse events; proportion of patients withdrawing due to adverse events; laboratory changes (blood chemistry, hematology, and urinalysis); changes in vital signs, physical examination, body weight, ECG, LVEF, ECOG performance status score, and ophthalmic examination.

## 10.4 Management of Biological Samples

### 10.4.1 Blood Collection Volume

The sampling volume from the start of the screening period to Cycle 7 (18 weeks) will be 150 mL according to the study plan (Table 4).

**Table 4 Vol. of blood to be collected**

| Visit | Safety (mL)[a] |
|---|---|
| Screening period | 15 |
| C1 | 45 |
| C2 | 15 |
| C3 | 15 |
| C4 | 15 |
| C5 | 15 |
| C6 | 15 |
| C7 | 15 |

| | |
|---|---|
| **Total** | **150** |

Note: [a] 6 mL for blood chemistry analysis and 9 mL for hematology analysis.

The total sample size required may be adjusted according to the specific procedures and changes in the protocol and the method established by the central laboratory.

The safety laboratory assessments will be performed at each study site's laboratory according to their established methods. Therefore, the total sample size required may vary from site to site.

### 10.4.2 Destruction of Biological Samples

Biological samples will be stored for a maximum of 15 years from the date of the last visit of the last patient (LPLV), after which they will be destroyed.

### 10.4.3 Labeling and Supervision of Biological Samples

Samples collected for purposes other than clinical testing will be identified by study number and patient's screening number to ensure that the data can be associated with clinical data. Samples may be destroyed in the event that the patient withdraws his/her consent, and may be subject to regulatory review.

# 11.0 Adverse Event and Medical Management

## 11.1 Adverse Event

### 11.1.1 Definition of Adverse Events

An adverse event (AE) is an unexpected medical condition or worsening of a pre-existing medical condition after or during exposure to the investigational product, regardless of their causal relationship to the investigational product. Unexpected medical conditions may be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, liver enlargement), or abnormal findings from tests (e.g., laboratory tests, ECGs).

Aggravation of the disease under investigation and its associated symptoms or signs will not be considered as AEs, if they are expectable judged by the investigator.

### 11.1.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that occurs during the study and meets one or more of the following criteria:

- Leading to death
- Immediately life-threatening
- Requiring inpatient hospitalization or prolongation of existing hospitalization
- Results in permanent or significant disability/incapacity to work or substantial disruption of the ability to conduct normal life functions

- Results in a congenital anomaly/birth defect
- Is a significant medical event that may jeopardize patients' safety or may require medical intervention to prevent one of the outcomes listed above

### 11.1.3 Recording of Adverse Events

#### 11.1.3.1 Time Period for Collecting AEs and SAEs

AEs will be collected throughout the study from informed consent to the end of the safety follow-up period. The safety follow-up period is defined as 28 days after discontinuation of the investigational product.

SAEs occurring throughout the study (from informed consent to the end of the follow-up period) should be reported to the Sponsor by the site within 24 hours of becoming aware of the SAEs.

After discontinuation of HS-10296, SAEs considered related to the investigational product and study procedures should be continued collecting, and the patient's disease progression should be followed. Some patients may remain on medication after the last database lock. For patients who continue receiving HS-10296, the Sponsor will collect only SAEs, as well as information on discontinuation of study treatment due to AEs/SAEs, until 28 days after discontinuation of treatment.

#### 11.1.3.2 Follow-up of Unresolved Adverse Events

At the patient's last study visit, any medically indicated unresolved AE will be followed by the investigator, but the information will not need to be further recorded in the eCRF. If necessary, the investigator will reserve the right to collect information related to ongoing AEs after the end of the study. If the investigator becomes aware of any new onset of SAEs at any time after the patient has completed the study and the investigator considers the event possibly related to HS-10296, the investigator should notify the Sponsor within 24 hours after the awareness of the SAEs.

#### 11.1.3.3 Key Information of Adverse Events to be Collected

The key information collected for each AE will include, but is not limited to the following:

- Diagnosis/description of AE
- Start date and end date of AE
- Maximum CTCAE grade
- Whether the AE is serious or not
- Investigator's assessment of causality
- Treatment of the event (drug therapy and non-drug therapy)

- Outcome

For SAEs, the following information will be collected:

- Event name (diagnosis)
- Description of the event
- Severity of the event
- Start date and end date of event onset
- Any relevant medical history, concomitant medications/therapies and laboratory results
- Treatment of the event (drug therapy and non-drug therapy)
- Investigator's assessment of causality
- Cause of death (if it is a death event)

All AEs will be graded by Common Terminology Criteria for Adverse Event (CTCAE) as per the grading criteria in CTCAE Version 4. For AEs that are not graded by CTCAE, the recommendation in the CTCAE criteria should be used to convert mild, moderate, and serious events to CTCAE grades.

### 11.1.4 Causality Assessment

The investigator will assess the causality of the investigational product and each AE. Criteria for judging the relationship of AEs and the investigational product are shown in Table 5.

**Table 5 Judgment Criteria for Relationship of Adverse Events and the Investigational Product**

| Grade | Judgment criteria |
|---|---|
| Definitely unrelated | The adverse event is not related to the use of the investigational product. For example: no investigational product is used. |
| Unlikely related | There is no evidence of a causality between the event and the investigational product. The onset of an AE is more likely to be related to other factors, such as concomitant medications or concomitant diseases. However, a correlation cannot be ruled out. |
| Possibly related | The onset of an AE shows a reasonable chronological order with the use of the investigational product, and the onset of the AE may be caused by the investigational product. Whether it may be caused by other factors cannot be ruled out, such as: concomitant medications or concomitant diseases. No withdrawal or the information is unknown. |
| Definitely related | The type of AEs has been identified as a known type of reaction to the drug and cannot be explained by other reasons (e.g., concomitant medications and concomitant diseases). The time to onset of the event strongly suggests a causal relationship (e.g., reaction after withdrawal and re-administration). |
| Not evaluable | There is insufficient information to determine the causality between the event and the investigational product. The investigator may change her/his causality assessment based on subsequent follow-up information and modify the appropriate AE/SAE report. |

### 11.1.5 Adverse Events Based on Symptoms and Signs

All AEs spontaneously reported by patients or healthcare professionals (open questions from the study personnel: "Have you had any health problems since your last visit/since last inquiry"), or the AEs identified by observation will be collected and recorded in the eCRF.

### 11.1.6 Adverse Events Based on Examinations and Testing

Protocol-specified laboratory tests and test results, i.e., vital signs, ECGs, and other safety assessments, will be summarized in the clinical study report. If these parameters suggest abnormalities compared with baseline, they will be reported as AEs only if criteria for SAEs are met, or they are clinically significant judged by the investigator, or they lead to discontinuation of study treatment (except those due to disease progression).

When abnormalities in laboratory test values, vital signs, ECGs, or other safety assessments are reported as AEs, the investigator should use clinical terms rather than laboratory terms whenever possible (e.g., use anemia instead of hemoglobin decreased).

Laboratory abnormalities due to unequivocal disease progression should not be reported as AEs. Any new or worsening clinically relevant abnormality in the physical examination compared to the baseline assessment will be reported as an AE.

### 11.1.7 Hy's Law

Occurrences of AST or ALT $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Cases that comply with Hy's law require expedited reporting in accordance with regulatory guidelines. At the first time, the investigator should be responsible for determining whether the subject complies with the Hy's law. The detailed information on Hy's Law and treatment measures are provided in Appendix C.

### 11.1.8 Disease Progression

Disease progression is considered as a worsening of the patient's condition, which can be an increase in the severity of the disease under investigation and/or an increase in the symptoms of the disease.

The development of new lesions in the primary tumor under investigation or progression of existing metastases should be considered as disease progression rather than an AE. Unequivocal disease progression should not be reported as an AE during the study.

### 11.1.9 Newly Developed Cancer

A new cancer should be considered an SAE and usually meets the criteria for severe disease. Newly developed cancers refer to those cancers that are not the main reason for the study

treatment and are found after the patient has been included in the study. Newly developed cancers do not include metastases of the original cancer.

### 11.1.10 Handling of Death Cases

All deaths that occur during the study or within the follow-up period after the discontinuation of treatment should be reported as follows:

- Death unequivocally related to disease progression should be reported to the monitor at the monitoring visit and should be recorded in the eCRF, but should not be reported as an SAE during the study.
- If death is not apparently caused by the progression of the disease under investigation, the AE leading to death should be reported as an SAE to the monitor within 24 hours. The report should include an evaluation of disease progression, the main cause of death, and other possible causes of death.
- Death with an unknown cause should be reported as an SAE within 24 hours of awareness of the study site, but every effort should be made to determine the cause of death. Autopsy may help assess the cause of death. If an autopsy is performed, a copy of the autopsy results should be reported to the Sponsor within 24 hours after the results are issued.

### 11.1.11 Reporting of Adverse Events

All SAEs must be reported regardless of the causality to investigational product or study procedures. All SAEs will be recorded in the eCRF. Any SAE occurring throughout the study (from informed consent to the end of the follow-up period) should be notified the Sponsor promptly by the investigator or other site personnel no later than 24 hours after becoming aware of the SAE. Contact information is shown in Table 6.

**Table 6 Contact Information for Adverse Event Reporting**

| Name | Responsibility in the study | Address and telephone number |
|---|---|---|
| Yi Sun | Safety Physician for AE/SAE Reporting, Sponsor Study Team<br><br>24-hour Emergency Contact | Building 3, No. 3728, Jinke Road, Pudong New Area, Shanghai, China<br>Mobile: + 86 18721189370<br>Fax: + 86 2131150801<br>E-mail: sunyi@hansohpharma.com |

The designated Sponsor's representative works with the investigator to ensure that all necessary information is recorded in the Sponsor's secure data entry system: fatal and life-threatening events are recorded within 1 calendar day of initial notification; and all other SAEs are recorded within 5 calendar days of initial notification.

For fatal or life-threatening AEs with missing important or relevant information, proactive actions will be taken immediately. The investigator or other personnel at the study site should promptly notify the Sponsor of any subsequent information of a previously reported SAE, no later than 24 hours after awareness of the subsequent information.

### 11.2 Overdose

The investigator should closely monitor any subject who receives a higher dose of the study drug than expected and should provide appropriate supportive care and close follow-up. Overdose should be recorded as follows:

- AEs or symptoms associated with overdose should be recorded in both the AE and overdose sections of the eCRF.
- Overdose without relevant symptoms will be recorded only in the overdose section of the eCRF, i.e., the overdose without discomfort is not considered an AE per se and does not need to be recorded in the AE section of the eCRF.

If an overdose occurs during the study, the investigator or other personnel at the study center should notify the Sponsor promptly or within 24 hours of awareness of the event. The designated Sponsor's representative will work with the investigator to ensure that all necessary information is recorded in the Sponsor's secure data entry system.

SAEs related to overdose will be reported according to the procedure for SAE reporting. Other cases must be reported within 30 days of occurrence.

### 11.3 Pregnancy Report

All cases of pregnancy and related outcomes during the clinical study (from the first treatment until 28 days after discontinuation of treatment) should be reported to the Sponsor.

#### 11.3.1 Pregnancy of Female Subjects

If a female subject becomes pregnant, she should immediately discontinue study treatment, and the investigator must report the pregnancy to the Sponsor within 24 hours of awareness. The investigator should follow up the pregnancy outcome until 28 days after delivery, and report the outcome to the Sponsor.

Pregnancy itself is not considered as an AE unless any negative pregnancy outcome, such as stillbirth, spontaneous abortion and fetal malformation, is considered as an SAE, and should be

reported within specified time limit for SAE reporting. Selective abortion without complications is not considered as an AE.

The designated Sponsor's representative works with the investigator to ensure that all necessary information is recorded in the Sponsor's secure data entry system: SAEs are recorded within 1 calendar day or 5 calendar days of initial notification; and other cases are recorded within 30 calendar days of initial notification.

### 11.3.2 Pregnancy of Partners of Male Subjects

If the partner of a male subject becomes pregnant during the clinical study, the subject will continue the clinical study, and the investigator must report it to the Sponsor within 24 hours of awareness of the pregnancy of the subject's partner.

Pregnancy of the partner of a male subject is not considered an AE. The investigator should follow up the pregnancy outcome of his partner until 28 days after delivery, and report the outcome to the Sponsor. Any negative pregnancy outcome, such as stillbirth, spontaneous abortion and fetal malformation, is considered as an SAE, and should be reported within specified time limit for SAE reporting.

Information regarding pregnancy should not be collected from male subjects, but should be collected from their partners with the partner's informed consent.

## 11.4 Recommended Management for Toxicity

### 11.4.1 Dose Reduction

During toxicity management, the dose of the investigational product can be reduced according to the doses specified in Table 7 below. After dose reduction, it cannot be adjusted back to the higher dose level. If the dose for a patient has been reduced to the lowest level but is still intolerable, withdrawal from the study will be recommended.

**Table 7 Dose Reduction Rules for Study Drug**

| HS-10296 group | | |
|---|---|---|
| | **Initial treatment** | **Dose reduction treatment** |
| Dose | 110 mg/d HS-10296 | 55 mg/d HS-10296 |
| Drug | HS-10296 active drug, 55 mg/tablet, 2 tablets<br>Gefitinib placebo tablets (placebo 250 mg), 1 tablet | HS-10296 active drug, 55 mg/tablet, 1 tablet<br>HS-10296 placebo tablets (placebo 55 mg), 1 tablet<br>Gefitinib placebo tablets (placebo 250 mg), 1 tablet |
| Usage | Once daily, orally | Once daily, orally |
| **Gefitinib group** | | |
| | **Initial treatment** | **Dose reduction treatment** |
| Dose | 250 mg/d gefitinib | No dose reduction, treated at the same dose |
| Drug | Gefitinib active drug, 250 mg/tablet, 1 tablet<br>HS-10296 placebo tablets (placebo 55 mg), 2 tablets | No dose reduction, treated at the same dose |
| Usage | Once daily, orally | Once daily, orally |

### 11.4.2 Dose Modifications Associated with Adverse Events

If a subject experiences CTCAE Grade 3 or higher and/or other unacceptable toxicity (any grade) judged by the investigator that cannot be attributed to disease or disease-related progression, and that is related to the dose of the investigational product judged by the investigator, the dose will be interrupted and supportive care will be administered as needed according to local practice/guidelines.

If the toxicity recovers to ≤ CTCAE Grade 1 or to baseline (whichever is met first) within 2 weeks of onset, the normal dose or reduced dose of the investigational product as shown in Table 7 may be resumed. If the normal dose is resumed, the subject should be closely monitored for 3 days, and if the same toxic effect occurs within the 3 days, a dose reduction should be considered. The above decision requires agreement between the investigator and the Sponsor's physician.

If the toxicity does not recover to ≤ CTCAE Grade 1 or to baseline within 2 weeks of onset, the subject should withdraw from the study and follow-up should be continued until recovery of the toxicity. Individual-specific dose modifications other than those shown in Table 7 will not be allowed.

### 11.4.3 Skin Reactions

In order to reduce the likelihood or severity of skin reactions in subjects, protection from light should be taken from the start of study drug treatment until three to four weeks after the discontinuation of treatment.

In the event of a skin reaction in a subject, the following formulations may be used as assessed by the investigator: steroid cream, topical or systemic anti-inflammatory drugs, topical

antihistamines, or vitamin A cream. Symptomatic measures may be taken if necessary.

Skin reactions should be recorded in the AE section of the eCRF and should contain the following information:

- Altered characteristics of skin reactions.
- CTCAE grade of skin reactions.
- If necessary, images should be taken to document skin reactions and these images should be reviewed by external experts.
- A skin biopsy may be performed if necessary.

#### 11.4.4 Gastrointestinal Toxicity

Nausea and/or vomiting may be controlled by antiemetic therapy. If diarrhea is CTCAE Grade 3 or higher, or clinically significant, or intolerable, and is related to study medication in the opinion of the investigator, necessary management or dose modification may be conducted. Relevant information should be recorded in the AE section of the eCRF.

#### 11.4.5 QTc Interval Prolongation

When a subject experiences prolongation of the mean QTcF interval (absolute QTcF > 500 msec, or > 60 msec from baseline) from 3 ECGs at rest, the dose should be interrupted and ECGs should be monitored routinely until recovery to baseline. If the event recovers to ≤ CTCAE Grade 1 or to baseline (whichever is met first) within 2 weeks, the normal dose or reduced dose of the investigational product as shown in Table 7 may be resumed. If the normal dose is resumed, the subject should be closely monitored for 3 days, and if the same toxic effect occurs within the 3 days, a dose reduction should be considered. The above decision requires agreement between the investigator and the Sponsor's physician. If the event does not recover to ≤ CTCAE Grade 1 or to baseline within 2 weeks, the subject should permanently discontinue treatment and follow-up should be continued until recovery of the toxicity. When an adverse event of QTc prolongation is required to be reported, the QTc interval will only refer to the QT interval corrected using the Fridericia's formula (QTcF).

#### 11.4.6 Interstitial Lung Disease

If new or worsening pulmonary symptoms (e.g., dyspnea) or imaging abnormalities observed suggesting interstitial lung disease, it is recommended to interrupt the study treatment and notify the Sponsor.

All diagnostic results (including HRCT, blood and sputum cultures, hematology parameters) will be investigated by questionnaire. The investigators are strongly recommended to perform a thorough diagnostic workup on the patient to exclude alternative causes such as lymphatic

metastasis, infection, allergy, cardiac edema or pulmonary hemorrhage.

The diagnosis of interstitial lung disease should be considered when it is confirmed by a HRCT scan and respiratory symptoms due to other causes are excluded, and study treatment should be permanently discontinued. If the diagnosis of interstitial lung disease is excluded, the treatment may be resumed after consultation with the Sponsor's physician.

Subjects with established interstitial lung disease will permanently discontinue the study treatment.

# 12.0 Endpoint Evaluation and Statistical Analysis

## 12.1 Evaluation of Anti-Tumor Activity

### 12.1.1 Investigator's Assessment per RECIST 1.1

At each visit, the investigator will assess the patient's tumor status as CR, PR, SD, or PD per RECIST 1.1 compared to baseline and previous assessments based on the patient's status. Progression of TLs will be calculated by comparing with the nadir of tumor burden (i.e., the smallest sum of diameters previously recorded). In the absence of progression, tumor response (CR and PR) and stable disease (SD) will be calculated by comparing to baseline tumor measurements obtained prior to the initiation of treatment. Patients who cannot be assessed for tumor status will have PD if there is evidence of progression; the tumor status will be not evaluable (NE) if there is no evidence of progression. The analysis of the endpoints in this study will be based on the Investigator's assessment of tumor response per RECIST 1.1, and the management of subjects by the investigator will only be performed based on the results of this assessment.

### 12.1.2 Central Review

All imaging data collected during the study, including tests performed during unscheduled visits, should be assessed with an independent central review.

### 12.1.3 Progression-free Survival (PFS)

According to RECIST 1.1 (Appendix D), PFS is defined as the time period from the randomization to the occurrence of objective tumor progression assessed by the Investigator or death. In the absence of disease progression, radiographic tumor assessments will need to be collected until RECIST-defined disease progression, even if the patient has discontinued the treatment with HS-10296 or has received another anti-tumor therapy prior to disease progression.

A subject who does not have disease progression or is dead at the time of analysis will be censored at the last date of his/her last assessment as per the RECIST criteria. If a subject

experiences disease progression or death after 2 or more missing visits, the subject will be censored at the last date of his/her last assessment as per the RECIST criteria. The data derived from the progression-free survival are based on assessment date rather than visit date.

If a patient discontinues study treatment prior to progression and/or receives other treatments prior to progression, the patient will be continued to be followed up until evidence of objective disease progression as per RECIST 1.1. Worsening of symptoms will not be considered as an event of progression.

#### 12.1.4 Objective Response Rate (ORR)

According to RECIST 1.1, ORR is defined as the percentage of patients achieving at least 1 CR or PR prior to progression.

The last evaluable data until disease progression or in the absence of disease progression will be recorded in the ORR assessment. However, any CR or PR occurring after discontinuation of study treatment and receiving further anti-tumor therapy will not be included in the ORR calculation.

#### 12.1.5 Duration of Response (DoR)

Duration of response is defined as the time period from the date of the first response to the date of disease progression or death due to any cause. The end date of response should be consistent with the date used for PFS endpoints. The onset of the time to response is defined as the latest date of the visit on which the criteria for PR or CR is met for the first time. If a patient has no progression after response, the PFS censoring time will be used for the duration of response.

#### 12.1.6 Disease Control Rate (DCR)

Disease control rate is defined as the proportion of patients with a best overall response of CR, PR, or SD.

#### 12.1.7 Depth of Response (DepOR)

According to RECIST 1.1, depth of response (change in tumor size) is defined as the change in the sum of the longest diameters of target lesions in the absence of new lesions or progression of non-target lesions from baseline. The percentage change in tumor size for patients with measurable disease at baseline will be calculated using the percentage change in the sum of target lesion diameters from baseline at each visit. The best depth of response will be generated from all response evaluations prior to progression or prior to initiation of subsequent anti-tumor therapy.

#### 12.1.8 Overall Survival (OS)

Overall survival is defined as the time period from the date of first dose to the date of death due

to any cause. A patient who survives to the time of statistical analysis will be censored at the time point the patient is last known to be alive.

## 12.2 Safety Evaluation

At the end of the study, all safety data will be summarized. All data from the start of treatment until 28 days after the last treatment will be summarized in the safety assessment. Data obtained prior to the initiation of treatment will be summarized but not included in the summary table of AEs.

The number of subjects with each AE will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), MedDRA preferred term (PT) and CTCAE grade. The number and percentage of subjects with AEs of different categories (e.g., the relationship to the investigational product, or CTCAE Grade 3 or higher) will be summarized by group. In addition, adverse events of each category will also be further summarized by MedDRA system organ class and preferred term by group. Serious adverse events will be separately summarized. The events of death will be tabulated in detail by subject.

Any AE that occurs prior to the subject's first dose (i.e., prior to Study Day 1) will be tabulated but will not be included in the summary tables of AEs. Any AE occurring during the specified 28-day follow-up period after a subject discontinue the study treatment will be included in the AE summary report; any AE that occurs after the subject discontinues the treatment with the investigational product and has received other further anti-tumor therapy during that follow-up period will be flagged in the data tables. Adverse events that occur during the 28-day follow-up period after the discontinuation of the investigational product will be tabulated separately and will not be included in the AE summary report. For subjects that can continue to derive benefit in the opinion of the Investigator after disease progression and continue to receive study treatment, the AEs occurred in these subjects will be tabulated separately and will not be included in the summary tables of AEs.

## 12.3 Statistical Analytical Methods

### 12.3.1 Definitions of Statistical Analysis Sets

- **Full Analysis Set (FAS)**

The full analysis set is defined as all randomized patients who have received at least one dose of the study drug, and inter-group comparisons will be based on the randomization results, regardless of whether actually receiving the study treatment assigned to this group.

- **Per Protocol Set (PPS)**

The per protocol set is defined as all patients who are complied with the protocol, have good

protocol compliance, and have no major protocol violations. The PPS is a subset of the FAS.

Baseline and demographic characteristics will be analyzed using the FAS, and efficacy evaluation will be performed on both the FAS and the PPS, with results mainly based on the FAS.

- **Safety Set (SS)**

The safety set is defined as all randomized patients who have received at least one dose of the study drug, but inter-group comparisons will be summarized by the group in which they actually receive treatment, e.g., for patients who are inappropriately administered: they are randomized to receive treatment A, while they actually receive treatment B, and the safety data should be calculated and included in the group B. Safety evaluations will be analyzed based on the SS.

### 12.3.2 Efficacy Analysis

Efficacy endpoints will be analyzed using the results assessed by the Investigator per RECIST 1.1. The results of the central review will be used for sensitivity analysis.

#### 12.3.2.1 Analysis of Primary Efficacy Endpoint

PFS will be stratified by mutation type (Exon 19 del vs. L858R) and brain metastasis status (with vs. without) as assessed by the Investigator, and will be analyzed by the log-rank test to calculate the p value. In addition, HR and its 95% confidence interval (CI) will also be directly calculated. The Kaplan-Meier plot will be plotted for each treatment group and median PFS and its 95% CI will be calculated. In addition, the proportion of subjects who experience events over 6, 12, 18, and 24 months will be summarized.

A Cox proportional hazards regression model will be used to perform subgroup analysis according to the following characteristics (including, but not limited to): gender (male vs. female), age at screening phase ($< 65$ vs. $\geq 65$), brain metastasis status at enrollment (with vs. without), smoking history, mutation type (Exon 19 del vs. L858R), and ECOG PS score (0 vs.1) to compare the PFS of HS-10296 and gefitinib.

#### 12.3.2.2 Analysis of Secondary Efficacy Endpoints

- **Analysis of Overall Survival**

The analysis method and model for calculating overall survival are the same as those used for PFS, provided that the requirements for the number of events for the analysis is met. In addition, the proportion of events occurring within 12, 24 and 36 months will be summarized.

- **Analysis of Objective Response Rate**

For the analysis of objective response rate, the odds ratio (OR), its 95% CI and p-value will be calculated using logistic regression analysis with the same stratification factors presented above.

ORR values will be summarized by treatment group and stratification factors, respectively.

- **Analysis of Duration of Response**

The analysis of duration of response will be the same as the primary analysis with the same stratification factors as above. Kaplan-Meier plots will be plotted to calculate the median and 95% CI of DoR in each group and p-value.

- **Analysis of Disease Control Rate**

For the analysis of disease control rate, the OR value and its 95% CI and p-value will be calculated using logistic regression analysis with the same stratification factors as above.

- **Analysis of Depth of Response**

Descriptive statistics will be used to summarize the change from baseline and percentage change of the sum of diameters of target lesions at different visit points. The depth of response (taking the maximum change of the sum of diameters of target lesions) will be compared between the two groups using analysis of covariance, and the unrounded mean, least squares mean, difference between the two groups, and 95% CI of the difference in each group, and p-value will be calculated.

### 12.3.3 Safety Analysis

#### 12.3.3.1 Adverse Event

AEs occurring from treatment initiation until 28 days after the last dose will be summarized in the safety evaluation. AEs that occur prior to the initiation of study treatment and those occurring 28 days after the last dose will not be included in the summary table of AEs.

Adverse events occurring post-dose will be summarized by treatment group, mainly including:

1) The number and proportion of patients with at least one AE;
2) The number and proportion of patients with at least one study drug-related AE;
3) The number and proportion of patients with at least one AE of higher severity (CTCAE Grade ≥ 3);
4) The number and proportion of patients with at least one study drug-related AE of higher severity (CTCAE Grade ≥ 3);
5) The number and proportion of patients with at least one SAE;
6) The number and proportion of patients with dose modifications due to AEs;
7) The number and proportion of patients who have withdrawn from the study due to AEs;
8) The number and proportion of patients who died due to AEs.

Adverse events will be summarized by system organ classes and preferred terms. All adverse events will be tabulated.

#### 12.3.3.2 Laboratory Tests

For laboratory test items that meet the criteria for measurement data, such as body weight and vital signs, hematology, urinalysis, and blood chemistry, baseline data, post-dose data and changes from baseline will be summarized by each follow-up visit and treatment group. For qualitative data such as whether the results are within the normal range as well as whether with clinical significance will be tabulated to describe the changes from baseline to each follow-up visit post-dose.

#### 12.3.3.3 ECG Analysis

Mean ± SD, maximum, minimum, and median will be used to describe the measurements and changes in heart rate, PR interval, QT interval, QTcF interval before and after treatment. Normal and abnormal changes before and after treatment will be described according to the normal or abnormal status as judged by the investigator.

Abnormal QTcF intervals at baseline and post-treatment will be described by the proportion of post-treatment (maximum) changes of ≤ 30 ms, 30 to 60 ms, and > 60 ms, and the post-treatment changes from baseline will be described by the proportion of changes of ≤ 30 ms, 30 to 60 ms, and > 60 ms.

#### 12.3.3.4 Ophthalmological Examination

Qualitative data from ophthalmic examinations, such as normal or not and with or without clinical significance, will be tabulated to describe the changes from baseline to each post-dose follow-up visit.

#### 12.3.3.5 ECOG PS Score

The changes of ECOG PS scores from baseline to each post-dose follow-up visit will be described in a shift table.

# 13.0 Data Processing and Storage

All the details of data processing procedures will be documented in a separate Data Management Plan.

## 13.1 Electronic Case Report Form

Each patient who has signed the informed consent form will be required to complete the eCRF. The Sponsor or its designee will provide the study site personnel with access to the eCRF. The Sponsor will provide relevant trainings to the staff about how to use the eCRF. Information collected using the eCRFs in this study will be communicated to the Sponsor and the regulatory authorities. Data will be entered directly into the eCRF.

All the revisions should be recorded, including old information, new information, personnel information amended, date of amendment, and reason for the modifications. In addition, reasons for major amendments should be included.

The Principal Investigator must review the eCRFs for completeness and accuracy and must sign and date the eCRFs. In addition, the Investigator must be solely responsible for the accuracy and authenticity of all the data entered into the eCRFs.

The eCRFs will be reviewed for completeness and accuracy during regular visits by the CRA. The Sponsor or its designee are permitted to review the patient's medical and hospital records related to the study to ensure the accuracy of the eCRFs. The ownership of all eCRF data belongs to the Sponsor and may not be made available in any form to any third parties unless written permission is obtained from the Sponsor, and unless requested by an authorized representative of the competent governmental regulatory authorities.

## 13.2 Data Storage

Records retained by the investigator include (but are not limited to): study-specific documents, identification logs for all subjects, medical records, temporary media documents (thermal paper should be photocopied and certified), raw data, all original signed and dated informed consent forms, all paper copies of eCRFs, and copies of response to query forms (including audit records and detailed handling records of the drug to enable assessment or audit by the regulatory authorities, the Sponsor, or its designee).

In addition, Section 4.9.5 of International Council for Harmonization (ICH) E6 requires the investigator to retain the essential documents specified in ICH E6 for at least 2 years after the final approval of the investigational drug indication, or for at least 2 years after study termination if the application is not approved. In addition, Section 4.9.5 of ICH E6 states that study records should be retained for the time period that required by regulatory requirements or

specified in an agreement between the investigator and the Sponsor.

Refer to the clinical study agreement to understand the Sponsor's requirements for record retention. The investigator should contact and receive written approval from the Sponsor prior to any processing of such documents.

# 14.0 Quality Control and Quality Assurance

## 14.1 Monitoring Visits

The study site will be periodically visited for monitoring during the study to ensure that the study fully complies with the protocol. The raw data will be reviewed to verify the data recorded in the eCRFs. Raw data will be defined as source documents, data, and records. The Investigator and the facility should ensure that the Sponsor or its designee, as well as the IRB or IEC, have access to the raw data.

The Sponsor or its designee will review all aspects of the study, including but not limited to, the Investigator File, study drug, patient medical records, and informed consent documents, as well as the eCRFs and relevant raw data. It is important that the investigator and other study personnel are on-site during the monitoring visits and have sufficient time for the monitoring process.

## 14.2 Protocol Violation

The Investigator should not deviate from the protocol unless a direct hazard to the study patient needs to be eliminated. In the event of other unexpected circumstances requiring deviations from protocol-specified procedures, the Investigator should consult with the medical monitor (and IRB or IEC, as required) to determine an appropriate action plan. Eligibility evaluation will not be waived.

## 14.3 Quality Assurance Audit and Official Inspection

The study sites will be subjected to quality assurance audits conducted by the Sponsor or its designees. In such circumstances, the auditors designated by the Sponsor will contact the study site in advance to arrange for the audit visit. The auditor may request visits to the facilities where laboratory samples are collected, where drugs are stored and prepared, and any other facilities used during the study. In addition, the study sites are also subjected to the inspections conducted by the regulatory authorities, including the CFDA. If a regulatory authority contacts the study site to request for an inspection, the study site should notify the Sponsor in a timely manner. The investigator and the institution should ensure that all study documents are accessible to the quality assurance auditor.

# 15.0 Ethical Factors

Subjects participating in the study will be treated with the highest respect in accordance with the agreement, the ethical principles of the Declaration of Helsinki and ICH GCP guidelines. Each investigator will conduct the study in accordance with applicable local or regional regulations. The principles of the Declaration of Helsinki will be described in the protocol and Appendix, which contain requirements for informed consent and investigator responsibilities.

## 15.1 IRB and/or IEC Approval

The Sponsor or designee should submit relevant documents to the appropriate IRB or IEC for review and approval of the protocol. This protocol, Investigator's Brochure, copy of the ICF, patient recruitment materials and/or advertisements, and all other documents required by applicable laws and regulations must be submitted to the IRB or IEC for approval. Written approval of the protocol and patient informed consent must be obtained from the IRB or IEC and submitted to the Sponsor prior to the start of the study. Approval by the IRB or IEC must involve the exact protocol title, number, and version date. The version identification number of other documents (e.g., ICF) and the date of approval must be stated. All the personnel of the study sites must comply to all the requirements stipulated by their respective IRB or IEC. This may include notification of protocol amendment to the IRB or IEC, updates to the ICF, recruitment materials intended for patient review, local safety reporting requirements, reports and updates of study reviews conducted at intervals specified by the respective IRB or IEC, and final status report submitted to the IRB or IEC. All IRB and IEC approvals and relevant documentation for these projects must be provided to the Sponsor.

## 15.2 Subject Information, Informed Consent and Subject Authorization

The ICF will reflect the elements of informed consent as described in the Declaration of Helsinki and ICH GCP Guidelines and will comply with all relevant laws and regulations. Records of the patients and their personal health information that are permitted to be used, transferred, and disclosed in the study will be described in the informed consent form. The informed consent form will explain the nature, objectives, potential risks and benefits of the study, and the date on which informed consent is provided. The informed consent form will detail the subject's requirements for participation in the study and the fact that the subject is free to withdraw at any time without giving justification and without prejudice to his/her further medical care.

The ICF must be approved by the IRB or IEC and the Sponsor prior to use. The informed consent form must be written in a language that is fully comprehensible to the patients. It is the

responsibility of the investigator to explain the detailed elements of the informed consent form to the patients. Information should be provided orally and in writing as far as possible and in a manner deemed as appropriate by the IRB or IEC. If the patient is unable to provide sufficient written informed consent, a legally acceptable representative of the patient may provide such consent in accordance with applicable laws and regulations. The Investigator must sign and date the informed consent form; however, the Sponsor may allow the investigator's designee to sign the form to the extent permitted by applicable laws.

Once signed, the original informed consent form will be stored in the Investigator's File. The investigator must record the date the patient signs the informed consent form in the patient's medical records. A copy of the signed informed consent form should be provided to the patient. All amended informed consent forms must be reviewed and signed by the patient or a legally acceptable representative thereof in the same manner as for the original informed consent form. The date of obtaining the amended consent form should be recorded in the patient's medical record and the patient should receive a copy of the revised informed consent form.

### 15.3 Privacy Protection

The Sponsor and its designee acknowledge and adhere to the principle that patients' privacy rights shall be protected from infringement. Throughout the study, the patient's raw data will be associated with the Sponsor's clinical study database or documentation only by a unique identification number. As permitted by all applicable laws and regulations, limited patient information (e.g., gender, age, or date of birth) and the patient initials may be used to confirm the accuracy of patient identity and the patient's unique identification number.

In order to comply with ICH GCP guidelines and confirm compliance with this protocol, the Sponsor will require the investigator to permit his/her CRAs or designated monitors, representatives of any regulatory authorities, the Sponsor designated auditors, and appropriate IRBs and IECs to review the patient's original medical records (raw data or documents), which include, but are not limited to, laboratory test reports, ECG reports, admission and discharge records that occur during the patient's participation in the study, and autopsy reports, etc. As part of the informed consent process, obtaining the patient's original medical records requires specific authorization from the patient.

Personal information contained in the copies of the original documents of any patient provided to the Sponsor must be de-identified (i.e., patient name, address, and other identification fields not collected in the patient's eCRF).

### 15.4 Publication, Information Disclosure and Clinical Trial Registration

### 15.4.1 Publication and Information Disclosure

The investigator has the obligation to provide the Sponsor with complete test results and all data obtained from the study. During the study, no personnel other than the Sponsor can provide study information to other investigators or regulatory authorities, unless required by law or regulations. Unless otherwise specified in the Clinical Study Site Agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, including recruitment materials and/or advertisements will be solely responsible by the Sponsor. The Sponsor may release data and information (including data and information generated by the investigator) from the study without the consent of the investigator. All publications and presentations must be prepared in accordance with the provisions of this section and the agreement signed by the clinical study site. If there is any discrepancy between the protocol and the clinical study site agreement, the agreement signed by the clinical study site will prevail.

### 15.4.2 Registration for Clinical Studies

In order to ensure that clinical study information is publicized in a timely manner and ensure compliance with applicable laws, regulations and guidance, the Sponsor will register the clinical study at least on ClinicalTrials.gov or other publicly accessible websites prior to the initiation of the study.

### 15.4.3 Disclosure of Clinical Study Results

The Sponsor will publish the results of this clinical study to ClinicalTrials.gov or other publicly accessible websites as required by applicable laws and/or regulations.

## 15.5 Insurance and Indemnities

Each patient enrolled in the study must be ensured as specified by the study site where the patient participates in the study. If the coverage by a local insurance company is required, the Sponsor or its designee will purchase clinical study insurance to compensate the patient for the injuries caused by participating in the study. Please refer to the Clinical Study Site's Agreement for the Sponsor's policy regarding patient compensation and injury management. If the investigator has any question regarding this policy, the Sponsor or its designee should be contacted.

## 16.0 Medical Emergency and Sponsor Contact Information

The Principal Investigator is responsible for ensuring that procedures and expertise are available for handling medical emergencies during the study. Medical emergencies generally constitute SAEs, hence they should be reported (see Section 11.1.12).

In case of a medical emergency, the investigator may contact the safety physician of the study team. If no physician of the study team is available, please contact the Sponsor's study supervisor. Sponsor's contact information is indicated in the table below.

| Name | Role in the Study | Address and telephone number |
|---|---|---|
| [redacted] | Safety physician of the Sponsor's study team, responsible for AE/SAE reporting, 24-hour emergency contact | [redacted] |
| [redacted] | Sponsor's study team, responsible for the study protocol | [redacted] |

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## Appendix A Use of Investigator's Personal Information with His or Her Informed Consent

The Sponsor will collect and retain the investigator's personal information, including name, address, and other personal identification information. In addition, the investigator's personal information may be obtained by the following units or institutions, including:

- The Sponsor, its affiliates and licensed partners
- Assist the Sponsor's business partners, their affiliates and licensed partners
- Regulatory authorities and other health authorities
- IRBs and IECs

The investigator's personal information may be retained and processed by the Sponsor and other interested parties for study purposes, including:

- Assessment of the investigator's suitability for the study and/or other clinical studies
- Management, supervision, inspection, and audit of the study
- Analysis, review, and confirmation of the study results
- Study-related safety reports and pharmacovigilance
- Preparation and submission of study-related declaration documents to the regulatory authorities, and relevant correspondences and communications
- Preparation and submission of declaration documents associated with other drugs and the clinical studies to regulatory authorities, and relevant correspondences and communications
- Inspections and investigations of the study by regulatory authorities
- Self-inspection and internal review by the Sponsor, its affiliates, and licensing partners
- Archival and audit of study records
- Publicize study site contact information, study details, and results on publicly accessible clinical study registries, databases, and websites

The Investigator's personal information may be transferred to other countries that do not have data protection laws. Under such circumstances, data protection will be provided at a level comparable to that of the country where the investigator is located.

The investigator acknowledges and agrees that the Sponsor and other parties, individuals or units use their personal information for the purposes described above.

## Appendix B Study Plan

| • Study Plan for Randomized Treatment | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit[a]** | **Screening Period** | **Treatment Period** | | | | | | | **Study Discontinuation Follow-up** | **Follow-up Period** | | |
| | **1** | **2** | **3** | **4** | **5** | **6** | **7-9** | **10+** | | **28-day follow-up[b]** | **Progression Follow-up Every 6/12 weeks** | **Survival Follow-up Every 6 weeks** |
| **Treatment cycle[c]/day** | | **C1 D1** | **C1 D8** | **C1 D15** | **C2 D1** | **C3 D1** | **C4-C6 D1** | **D1 of C7 and Every 6/12 weeks thereafter** | **NA** | **NA** | **NA** | **NA** |
| **Day** | **-28** | **1** | **8** | **15** | **22** | **43** | **64-106** | **127+** | **NA** | **NA** | **NA** | **NA** |
| **Window period (days)** | **NA** | **0** | **±2** | **±2** | **±2** | **±7** | **±7** | **±7** | **+7** | **NA** | **±7** | **±7** |
| Informed consent | X | | | | | | | | | | | |
| Demographic and baseline characteristics | X | | | | | | | | | | | |
| Medical/surgical history | X | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | | | | |
| EGFR mutation test | X | | | | | | | | | | | |
| Physical examination (including body weight)[d] | X | X | | | X | X | X | X | X | | | |
| Body Height | X | | | | | | | | | | | |
| ECOG PS score | X | X | | | X | X | X | X | X | | X | |
| Pregnancy test | X | | | | | | | | | | | |
| Ophthalmological Examination | X | Ophthalmic examination performed within 48 hours as clinically indicated | | | | | | | | | | |
| Vital signs[d] | X | X | X | X | X | X | X | X | X | | | |
| Clinical chemistry/hematology/urinalysis[d] | X | X | X | X | X | X | X | X | X | | | |

**• Study Plan for Randomized Treatment**

| Visit[a] | Screening Period | Treatment Period | | | | | | | Study Discontinuation Follow-up | Follow-up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7-9 | 10+ | | 28-day follow-up[b] | Progression Follow-up Every 6/12 weeks | Survival Follow-up Every 6 weeks |
| **Treatment cycle[c]/day** | | **C1 D1** | **C1 D8** | **C1 D15** | **C2 D1** | **C3 D1** | **C4-C6 D1** | **D1 of C7 and Every 6/12 weeks thereafter** | **NA** | **NA** | **NA** | **NA** |
| **Day** | **-28** | **1** | **8** | **15** | **22** | **43** | **64-106** | **127+** | **NA** | **NA** | **NA** | **NA** |
| **Window period (days)** | **NA** | **0** | **±2** | **±2** | **±2** | **±7** | **±7** | **±7** | **+7** | **NA** | **±7** | **±7** |
| Electrocardiogram[e] | X | X | X | X | X | X | X | X | X | | | |
| Echocardiography (LVEF) | X | Every 12 weeks from the first dose and as clinically indicated | | | | | | | X | | | |
| Collection of tumor and/or blood samples at disease progression during the randomized treatment phase (optional) | | | | | | | | | X | | | |
| Tumor assessment (RECIST v1.1)[f] | X | Every 6 weeks ± 7 days (first 15 months; C1 to C21)/every 12 weeks (after Month 15; C23 and thereafter) after randomization | | | | | | | | | | |
| Drug dispensing | | X | | | X | X | X | X | | | | |
| Drug intake | | Dosing everyday | | | | | | | | | | |
| Concomitant medications | ← | | | | | | | | → | | X | |
| Adverse Event | ← | | | | | | | | → | | Occurring prior to completion of 28-day follow-up | |
| Anti-tumor therapy | X | | | | | | | | | | X | X |
| Subsequent response/progression data[g] | | | | | | | | | | | | X |
| Survival status[h] | | | | | | | | | | | | X |

| • **Study Plan for Randomized Treatment** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit[a]** | **Screening Period** | **Treatment Period** | | | | | | | **Study Discontinuation Follow-up** | **Follow-up Period** | | |
| | **1** | **2** | **3** | **4** | **5** | **6** | **7-9** | **10+** | | **28-day follow-up[b]** | **Progression Follow-up Every 6/12 weeks** | **Survival Follow-up Every 6 weeks** |
| **Treatment cycle[c]/day** | | **C1 D1** | **C1 D8** | **C1 D15** | **C2 D1** | **C3 D1** | **C4-C6 D1** | **D1 of C7 and Every 6/12 weeks thereafter** | **NA** | **NA** | **NA** | **NA** |
| **Day** | **-28** | **1** | **8** | **15** | **22** | **43** | **64-106** | **127+** | **NA** | **NA** | **NA** | **NA** |
| **Window period (days)** | **NA** | **0** | **±2** | **±2** | **±2** | **±7** | **±7** | **±7** | **+7** | **NA** | **±7** | **±7** |
| Comments | a. Subjects will be followed every 3 weeks (1 cycle) from Cycles 1 to 6; every 6 weeks (2 cycles) from Cycle 7 onwards; and two additional visits will be added on C1D8 and C1D15.<br>b. Subjects should be followed up by telephone 28 days (± 7 days) after discontinuation of study drug.<br>c. One cycle is defined as 21 days of continuous treatment.<br>d. These assessments at baseline should be completed prior to dosing on the visit day. If screening tests are completed within 7 days prior to the first dose of investigational product, they will not be required to perform on C1D1.<br>e. ECGs may be performed in the event of any cardiac-related AE.<br>f. Baseline tests should be performed within 28 days prior to the first dose. Assessments will be performed every 6 weeks after the start of treatment until disease progression as determined by centralized assessment per RECIST 1.1 criteria, even if the subject discontinues treatment prior to progression or has received other anti-tumor therapies. Tumor assessment data will be obtained from CT or MRI (contrast-enhanced CT or MRI is recommended to be preferred).<br>g. Tumor response results assessed by the investigator will be collected.<br>h. Subjects should be contacted to determine their survival status after the data cutoff date as determined by OS analysis. | | | | | | | | | | | |

• **Study Plan for HS-10296 Crossover Treatment**

| Visit[a] | HS-10296 Pre-crossover Visit | Treatment Period | | | | | | | Study Discontinuation Follow-up | Follow-up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 5 | 6 | 7-9 | 10+ | | 28-Day Follow-up | Progression Follow-up Every 6 weeks | Survival Follow-up Every 6 weeks |
| **Treatment cycle[b]** | **C0** | **C1** | **C1** | **C1** | **C2** | **C3** | **C4-C6** | **Every 6 weeks from C7 onwards** | **NA** | **NA** | **NA** | **NA** |
| **Day** | **-28** | **D1** | **D8** | **D15** | **D22** | **D43** | **D64-106** | **D127** | **NA** | **NA** | **NA** | **NA** |
| **Window period (days)** | **NA** | **0** | **±2** | **±2** | **±2** | **±7** | **±7** | **±7** | **+7** | **NA** | **±7** | **±7** |
| Informed consent | X | | | | | | | | | | | |
| Collection of tumor/blood samples after disease progression during the randomized treatment phase | X | | | | | | | | | | | |
| T790M mutation test | X | | | | | | | | | | | |
| Tumor assessment | X | The assessment is recommended to perform every 6 weeks ± 7 days per RECIST 1.1 | | | | | | | | | X | |
| Physical examination (including body weight)[c] | X | X | | | X | X | X | X | X | | | |
| ECOG PS score | X | X | | | X | X | X | X | X | | X | |
| Ophthalmological Examination | As clinically indicated | Ophthalmic examination performed within 48 hours as clinically indicated | | | | | | | | | | |
| Vital signs (pulse and blood pressure)[c] | X | X | X | X | X | X | X | X | X | | | |
| Clinical chemistry/hematology/urinalysis[c] | X | X | X | X | X | X | X | X | X | | | |
| Electrocardiogram | X | X | X | X | X | X | X | X | X | | | |
| Echocardiography (LVEF)[e] | X | Every 12 weeks from C1D1 and as clinically indicated | | | | | | | X | | | |
| Collection of tumor/blood samples at disease progression during the crossover phase | | | | | | | | | X | | | |

**• Study Plan for HS-10296 Crossover Treatment**

| Visit[a] | HS-10296 Pre-crossover visit | Treatment Period | | | | | | | Study Discontinuation Follow-up | Follow-up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 5 | 6 | 7-9 | 10+ | | 28-Day Follow-up | Progression Follow-up Every 6 weeks | Survival Follow-up Every 6 weeks |
| **Treatment cycle[b]** | **C0** | **C1** | **C1** | **C1** | **C2** | **C3** | **C4-C6** | **Every 6 weeks from C7 onwards** | **NA** | **NA** | **NA** | **NA** |
| **Day** | **-28** | **D1** | **D8** | **D15** | **D22** | **D43** | **D64-106** | **D127** | **NA** | **NA** | **NA** | **NA** |
| **Window period (days)** | **NA** | **0** | **±2** | **±2** | **±2** | **±7** | **±7** | **±7** | **+7** | **NA** | **±7** | **±7** |
| Drug intake | | Dosing everyday | | | | | | | | | | |
| Concomitant medications and therapies | ← | | | | | | | | → | | × Occurring prior to completion of 28-day follow-up | |
| Adverse Event | ← | | | | | | | | → | | | |
| Anti-tumor therapy | × | | | | | | | | | | × | ×[d] |
| Subsequent response/progression data | | | | | | | | | | | | ×[d] |
| Survival status | | | | | | | | | | | | ×[d] |
| Comments | a. Subjects will be followed every 3 weeks (1 cycle) from Cycles 1 to 6; every 6 weeks (2 cycles) from Cycle 7 onwards; and two additional visits will be added on C1D8 and C1D15.<br>b. One cycle is defined as 21 days of continuous treatment.<br>c. These tests at baseline should be completed prior to dosing on the day of the visit. If screening tests are completed within 7 days prior to the first dose of crossover treatment, they will not be required to perform on C1D1.<br>d. After study discontinuation or disease progression, survival status and anti-tumor therapy will be followed-up every 6 weeks from randomization.<br>e. Results within 28 days prior to crossover treatment are available. | | | | | | | | | | | |

## Appendix C Actions to be Taken in the Event of Combined Increases in Aminotransferases and Total Bilirubin - Hy's Law

### 1. Introduction

During the course of the study, the Investigator should remain vigilant for increases in liver biochemistry test 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 will review and assess whether the potential case meets Hy's Law (HL) criteria together with the Sponsor's clinical program representative. HL criteria will be met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational medicinal product (IMP).

The Investigator is responsible for recording data related to PHL/HL cases and for reporting adverse events (AEs) and serious adverse events (SAEs) according to standard safety reporting processes.

### 2. Definition

#### 2.1 PHL

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

#### 2.2 HL

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

### 3. Identification of PHL Cases

In order to identify PHL cases, it is important to perform a comprehensive review of laboratory data for patients who meet any of the following individual or combined identification criteria:

a. ALT ≥ 3×ULN

b. AST ≥ 3×ULN

c. TBL ≥ 2×ULN

The Investigator will immediately review each new laboratory report, and if the criteria are met, the investigator will:

a. Notify the Sponsor's representative;

b. Determine whether the patient meets the PHL criteria by reviewing laboratory reports from all previous visits (see Section 2 Definition);
c. Immediately enter the laboratory data into the laboratory CRF.

**4. Follow-up**

**4.1 PHL Criteria not Met**

If a patient does not meet the PHL criteria, the investigator will:

a. Notify the Sponsor's representative that the patient does not meet the PHL criteria.
b. Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol.

**4.2 PHL Criteria Met**

If a patient meets the PHL criteria, the investigator will:

a. Determine whether the patient meets the PHL criteria before starting study treatment in the presence of liver metastases at any visit (see Section 6).
b. Notify the Sponsor's representative, who will notify the central study team.

The study doctor will contact the investigator to provide guidance and will discuss with the investigator to agree on an approach for the follow-up of study patients and continuous review of the data. Subsequent to this contact, the investigator will:

a. 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.
b. Investigate the etiology of the event and discuss with the study doctor to perform the diagnostic investigation.
c. Complete the three hepatic CRF modules when information is available.
d. Report the PHL case as an SAE according to the standard procedures if the case meets the criteria for seriousness at any time (consult the study doctor).

**5. Review and Assessment of HL Cases**

The instructions in this Section should be followed for all cases where PHL criteria are met. Within 3 weeks after the initial detection of biochemical abnormalities, the study doctor should contact the investigator to review the available data and to agree on the presence of an alternative explanation other than DILI caused by the IMP. The Sponsor's Medical Science Director and the safety physician, as well as other subject matter experts, will also participate in this review as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below. Where there is an agreed 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 an SAE:

a. If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF.
b. If the alternative explanation is an AE/SAE, the AE/SAE will be recorded on the CRF accordingly and the Sponsor's standard procedures should be followed.

If there is no alternative explanation for ALT or AST and TBL elevations other than the IMP, SAEs should be reported according to the Sponsor's standard procedures (reporting term of "Hy's Law"):

a. If no other serious criteria apply, the serious criterion of "medically important event" should be used.
b. 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 more than 3 weeks in obtaining the information necessary to assess whether the case meets the HL criteria, then it will be assumed that there is no alternative explanation until an informed decision is made:

a. The case will be reported as an SAE (reporting term of "Potential Hy's Law") using stringent criteria and causality assessment.
b. Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. The SAE report will be updated based on the review results.

**6. Actions to be Taken When the PHL Criteria are Met Before and After Start of Study Treatment**

This section is applicable to patients who meet the PHL criteria at the time of study treatment or who have met the PHL criteria at a study visit prior to starting study treatment. If a PHL occurs for the first time at the time of study treatment, even if there is no significant change in the patient's condition compared to the pre-treatment visit, the investigator will:

a. Notify the Sponsor's representative, who will notify the central study team.
b. Follow the subsequent process described in Section 4.2.

A "significant" change in a patient's condition refers to a clinically relevant change in any of liver biochemistry parameters (ALT, AST or total bilirubin), alone or in combination with, or a clinically relevant change in associated symptoms. The presence of a significant change will be judged by the investigator. If you have any uncertainty, the study doctor can be consulted.

## 7. Actions to be Taken in Case of Repeated Occurrence of PHL

This section is applicable to patients who meet the PHL criteria at the time of study treatment and have met the PHL criteria at previous study treatment visits. Repeated PHLs will be followed up, reviewed, and assessed based on other causes for PHL occurring previously. The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

a. Do other causes for the previous occurrence of PHL meet chronic or progressive malignant disease, or does the patient meet the PHL criteria prior to starting study treatment and does a PHL occur for the first time at the time of study treatment visit as described in Section 6?

b. **If no:** follow the process described in Section 4.2.

c. **If yes:**

- Determine if there is any significant change in the patient's condition compared with the time the PHL criteria are previously met.
- If there is no significant change, no action is required.
- If there is any significant change, follow the process described in Section 4.2.

A "significant" change in a patient's condition refers to a clinically relevant change in any of individual liver biochemistry parameters (ALT, AST or total bilirubin), alone or in combination with, or a clinically relevant change in associated symptoms. Significant changes will be determined at the discretion of the investigator. If you have any uncertainty, the study doctor can be consulted.

## 8. References

U.S. Food and Drug Administration (FDA): Guidance for industry. Drug-induced liver injury: premarketing clinical evaluation. Silver Spring, MD: July 2009.

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

## 1. Introduction

This appendix explains in details how to use RECIST 1.1 guidelines (Response Evaluation Criteria in Solid Tumors) (Eisenhauer et al. 2009) to assess tumor burden (including specific assessments in this protocol) in the study.

## 2. Definition of Measurable, Non-measurable, Target and Non-Target Lesions

Patients with at least 1 measurable lesion will be accurately assessed at baseline by computerized tomography (CT), magnetic resonance imaging (MRI), or plain X-ray scan.

### 2.1 Measurable Lesion

Patients must have at least 1 unirradiated lesion, which can be accurately measured at baseline, with the longest diameter of ≥ 10 mm (except lymph nodes, which must have a short axis of ≥ 15 mm), and CT or MRI scan is suitable for accurate and repeated measurements.

### 2.2 Non-measurable Lesions

a. All other lesions, including small lesions (pathological lymph nodes with a longest diameter < 10 mm or a short axis of ≥ 10 mm to < 15 mm at baseline; nodes with a short axis < 10 mm are considered non-pathological and should not be recorded as non-target lesions [NTLs]).
b. Lesions considered truly non-measurable include: bone lesions, submeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that cannot be measured by CT or MRI scan.
c. Changes in previously irradiated lesions caused by local irradiation may affect the measurement of the lesion size. Therefore, previously irradiated lesions will not be considered measurable and should be selected as NTL at baseline and followed up as part of the NTL assessment.
d. Skin lesions examined clinically.
e. Brain metastases.

### 2.3 Exceptional Cases

a. Lytic bone lesions or mixed lytic foam lesions with identifiable soft tissue components may be considered measurable if the soft tissue components are measurable. Vitreous injury is considered non-measurable.
b. Cystic metastases may be considered measurable if they can be measured radiologically,

but non-cystic lesions should be selected as target lesions (TLs) if they are identified in the same patient.

### 2.4 Target Lesions (TLs)

Up to 5 **measurable** lesions (up to 2 lesions per organ), representing all lesions involved that are suitable for accurate and repeated measurements, should be identified as baseline TLs.

### 2.5 Non-target Lesions (NTLs)

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

## 3. Measurement Method

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

The methods used for RECIST assessment are summarized in the table below, and the methods for tumor assessment that cannot be used in this study are discussed below and justified.

**Table 1 Summary of Assessment Methods**

| Target lesion | Non-target lesions | New lesions |
|---|---|---|
| CT (preferred)<br>MRI | CT (preferred)<br>MRI<br>Clinical examinations<br>X-ray, chest x-ray | CT (preferred)<br>MRI<br>Clinical examinations<br>X-ray, chest x-ray<br>Ultrasound<br>Bone scan<br>FDG-PET |

### 3.1 CT and MRI

CT and MRI are generally considered the best currently available and repeatable methods for the measurement of response of TLs, assessment of NTLs, and identification of new lesions.

In this study, CT examination of chest and abdomen is recommended to assess tumor burden at baseline and during follow-up visits. CT examination with contrast administered intravenously is the preferred method. MRI should be used when CT is not feasible or is medically contraindicated. MRI is the preferred method for the assessment of brain injury.

### 3.2 Clinical examinations

Clinical examination will not be used for the assessment of TLs. Clinically detected lesions may be selected as TLs if the lesions are subsequently assessed by CT or MRI scan. Clinical examination can be used to assess NTLs or to identify new lesions. However, these patients also need to have additional lesions that can be assessed by CT, MRI, or plain X-ray scan.

### 3.3 X-ray

#### 3.3.1 Plain X-ray

Plain X-ray can be used as a method to assess bone NTLs and to identify new bone lesions.

### 3.3.2 Chest X-ray

Chest X-ray is not used to assess TLs, and TLs will be assessed by CT or MRI scan. However, chest X-ray can be used to assess NTLs and identify new lesions.

## 3.4 Ultrasound

Ultrasonography is not used to assess TLs and NTLs because it is not a method with reproducibility; it cannot provide an accurate assessment of tumor size, and it is subjective and operator- dependent. However, ultrasonography can be used to identify new lesions. If new clinical signs develop and ultrasonography is performed, new lesions should be confirmed by CT or MRI scan.

## 3.5 Endoscopy and Laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessment as they have not been validated in the context of tumor measurement.

## 3.6 Tumor Markers

Tumor markers will not be used for tumor response assessment per RECIST v1.1.

## 3.7 Cytology and Histology

Histology will not be used for tumor response assessment per RECIST v1.1.

When measurable tumors meet the criteria for response or stable disease, cytological confirmation is required to determine the tumor origin of any effusion that newly develops or worsens during treatment. In this case, cytology is necessary to distinguish between response/stable disease (exudate may be a side effect of treatment) from progressive disease (if the tumor origin of an effusion has been proven). In the absence of cytology results, significant worsening (from trace to substantial) or clinically significant effusion (requiring a change in treatment medication) during study treatment will be considered to be progression or disease progression of NTLs caused by new lesions.

## 3.8 Isotope Bone Scan

Bone lesions identified by isotope bone scan at baseline and confirmed by CT, MRI, or X-ray scan should be recorded as NTLs and followed up using the same method as that for baseline assessment.

Isotope bone scans can be used as an assessment method to identify new bone lesions during follow-up. Positive hot spots identified by bone scans performed at any time during the study (not present at the baseline bone scan assessment) will be recorded as new lesions. The investigator should consider that a positive hotspot is a significant new site of malignant disease

and that it represents true disease progression in order to record new lesions. In cases where bone scan findings are equivocal, confirmation by CT, MRI, and X-ray is recommended.

### 3.9 FDG-PET Scan

FDG-PET scan (fluorodeoxyglucose positron emission tomography) may be used as a method of identifying new lesions according to the following procedures: if FDG uptake is positive (defined as uptake greater than twice that of surrounding tissue), but not present at baseline FDG-PET scan; or if there is a new lesion on the location confirmed by CT/MRI during the same follow-up, it will be recorded as a new lesion. If no baseline FDG-PET scan is available and there is no evidence of a new lesion on the CT/MRI scan, subsequent CT/MRI assessments should be continued to confirm new lesions as per protocol or as clinically indicated.

## 4. Tumor Response Evaluation

### 4.1 Assessment Schedule

CT examination of chest and abdomen (including liver and adrenal glands) will be used to assess tumor burden at baseline and during follow-up visits. CT examination with contrast administered intravenously is the preferred method. MRI should be used when CT is not feasible or is medically contraindicated.

Baseline tumor assessments should include all regions where the disease under evaluation is known to metastasize, should include additional assessments of areas that may be involved based on the signs and symptoms of individual patients, and should be performed no more than 28 days prior to the start of study treatment. Follow-up assessments should be performed every 6 weeks (± 7 days) from the start of treatment until discontinuation of study treatment or withdrawal of consent. If new lesions are suspected elsewhere, imaging should be performed during follow-up.

If an unscheduled assessment has been performed and there is no disease progression, every effort should be made to perform subsequent assessments on the patient at his/her scheduled visits. The schedule will be followed in order to minimize any unintentional deviations caused by the frequency of follow-up assessments of some patients differing from those of others.

### 4.2 Target lesion

#### 4.2.1 Recording of Target Lesions

Up to 5 measurable lesions, and up to 2 lesions per organ (including lymph nodes), representing all lesions involved, should be identified as baseline TLs. Target lesions will be selected based on tumor size (longest diameter for non-lymph node disease or short axis for lymph node disease), but those reproducible and repeated measurements should be used. It is possible that

sometimes the largest lesion does not lend itself to repeated measurements, in which case the next largest lesion that can be measured reproducibly should be selected.

The location of each TL, as well as the longest diameter (or the short axis of the lymph node) of the non-lymph node lesion, should be recorded. All measurements should be recorded in millimeters. At baseline, the sum of diameters of all TLs will be calculated and reported as the baseline sum of diameters. During follow-up, the sum of diameters of all TLs will be calculated and reported as the follow-up sum of diameters.

**Exceptional Cases**

a. For TLs that can be measured in 2 or 3 dimensions, the longest diameter is always reported. For pathological lymph nodes that can be measured in 2 or 3 dimensions, the short axis is always reported.
b. If the CT/MRI scan has slice thickness > 5 mm, the minimum size for a measurable lesion at baseline should be twice the slice thickness of the baseline scan.
c. If the lesion completely disappears, the longest diameter should be recorded as 0 mm.
d. If the TL splits into 2 or more portions, the sum of the diameters of these portions will be recorded.
e. If 2 or more TLs are combined, the sum of diameters of the combined lesions should be recorded and the diameter should be recorded as 0 mm for other lesions.
f. If the TL is considered to be present and looks tiny, but too small to measure, a default value of 5 mm should be assigned. If an accurate measurement can be given, it should be recorded even if it is < 5 mm.
g. If a TL is too large to be accurately measured, an estimate value of lesion size should be given.
h. The size of TL should be given whenever possible in the event of any intervention to the TL during the study, e.g., radiation therapy, embolization and surgery.

### 4.2.2 Assessment of Target Lesions

The criteria used to determine objective tumor response of TLs are presented in Table 2.

**Table 2 Overall Response of Target Lesions**

| | |
|---|---|
| **Complete Response (CR)** | All TLs disappear since baseline. The short axis of any pathological lymph node selected as TLs must be < 10 mm. |
| **Partial Response (PR)** | The sum of diameters of TLs is reduced by at least 30% from baseline. |
| **Stable Disease (SD)** | There is not enough reduction to meet PR or sufficient increase to meet PD. |
| **Progressive Disease (PD)** | The sum of diameters of TLs increases at least 20% (this includes the baseline sum if this is the minimum diameter in the study) compared with the minimum diameter in the study. In addition to a relative increase of 20%, the sum must also |

| | |
|---|---|
| | demonstrate an absolute increase of at least 5 mm. |
| **Not Evaluable (NE)** | Only relevant TLs are not assessed or not evaluable or have lesions with intervention.<br>Note: if the sum of diameters meets the criteria for disease progression, it is not unevaluable, but should be classified as progressive disease. |

### 4.3 Non-target lesions

#### 4.3.1 Assessment of Non-target Lesions

All other lesions (or sites of disease) that are not recorded as TLs should be identified as NTLs at baseline. These lesions are not required to be measured, but their status should be followed up during subsequent follow-up visits. At each visit, the investigator should record the overall assessment of the response of NTLs. The criteria used to determine and record the overall response of NTLs at each visit are presented in Table 3.

**Table 3 Overall Response of Non-target Lesions**

| | |
|---|---|
| **Complete Response (CR)** | All NTLs disappear since baseline. All lymph nodes must be non-pathological in size (< 10 mm in short axis). |
| **Without CR/PD** | With one or more residual NTLs. |
| **Progressive Disease (PD)** | With unequivocal progression of existing NTLs. Unequivocal progression may be a significant progression in one lesion or in several lesions. In all cases, the progression must be clinically significant to the physician to be considered as a change or discontinuation of study treatment. |
| **Not Evaluable (NE)** | Only one or some of the relevant NTLs are not assessed and, in the opinion of the investigator, cannot provide an overall NTL assessment at this visit. |

To achieve "unequivocal progression" on the basis of NTLs, there must be substantial worsening in non-target diseases at an overall level, even in the presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to warrant treatment discontinuation. A general increase in the size of 1 or more NTLs is usually insufficient to meet the criteria for progression.

### 4.4 New lesions

Details of any new lesions and date of assessment will be recorded. If 1 or more new lesions are present, the assessment result will be progression.

Lesions that are not identified at baseline scans but identified at follow-up assessments will be considered as new lesions, indicating disease progression.

The new lesions should be unequivocally identified, i.e., progression cannot be attributed to differences in imaging techniques, changes in imaging modes, or lesions other than tumors.

If the presence of new lesion is equivocal, e.g., due to its small size, treatment and tumor assessment should be continued until it is confirmed to be a new lesion. If a new lesion has been confirmed by repeated testings, the date of progression should be the date of initial detection of progression.

### 4.5 Worsening of Symptoms

Symptomatic deterioration is not a descriptor of an objective response, rather, it is a reason for discontinuation of study treatment. Patients with "symptomatic deterioration" who require discontinuation of study treatment but show no objective evidence of disease progression should continue to be assessed as per RECIST 1.1 according to the clinical study protocol until objective disease progression is observed.

### 4.6 Assessment of Overall Response

The overall response will be exported using the algorithm shown in Table 4.

**Table 4 Overall Response**

| Target lesion | 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 | No | PR |
| SD | Non-PD | No | SD |
| NE | Non-PD | No | NE |
| NA | CR | No | CR |
| NA | Non-CR/Non-PD | No | SD(Non-CR/Non-PD) |
| NA | NE | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

NA = not available (only if there is no such item in the baseline); "/" in the above table indicates "and".

## 5. Radiological Imaging Criteria

The following are for clinical studies only. Assessments using standardized protocols for CT and MRI scans can be compared within and across studies, regardless of where the examinations are performed.

### 5.1 CT Scan

CT scans of chest and abdomen (including liver and adrenal glands) should be continuous in all anatomical regions of interest.

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

- **Anatomic Coverage**

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

Coverage should include all areas where the disease under evaluation is known to metastasize, and areas that may be involved should be investigated based on the signs and symptoms of individual patients. Lesions subsequently identified in the body (not scanned at baseline) will

be considered as new lesions representing disease progression, and the extent of imaging coverage at baseline and during subsequent follow-up should be carefully considered. This will not only enable better consistency in tumor measurements but also in the identification of new lesions.

- **Intravenous Administration of Contrast**

Optimal visualization and measurement of metastases in solid tumors requires consistent intravenous administration (dose and rate) of contrast and sufficient scanning time. Typically, most abdominal imagings are performed during the portal venous phase and (optimally) approximately the same time frame after injection during each examination. Adequate volumes of suitable contrast should be administered to demonstrate metastases as best as possible, and a consistent approach should be used for the same patient undergoing subsequent examinations. It is very important that the same technique be used at baseline and during follow-up examinations. For patients who develop contraindications to contrast after baseline contrast CT scan is performed, the decision as to whether a non-contrast CT or MRI scan (enhanced or non-enhanced) should be performed should also be based on the tumor type and anatomical location of the disease, and should be optimized to allow for comparison with previous studies (if possible). Each case should be discussed with the radiologist to determine whether alternative approaches are feasible and, if not, the patient should be considered not evaluable from this point onwards. Care must be taken to measure TLs and to interpret non-target diseases or new lesions using different modes, as the same lesions scanned using the new mode may appear to have different sizes. Oral administration of contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodinated contrast is medically contraindicated at baseline or at any time during the course of the study, the recommended approach is plain CT scan of chest and contrast-enhanced MRI scan of abdomen and pelvis. If MRI scan cannot be performed, non-enhances CT scan of chest, abdomen, or pelvis will be performed. MRI is the preferred method for the assessment of brain lesions.

- **Slide Thickness and Reconstruction Interval**

It is recommended to perform CT scan on 5 mm serial slides. It is assumed in this guidance that at least 5 mm thickness is recommended to use to identify measurable lesions. In exceptional cases, specific institutions may perform medically acceptable scans on slices with thickness > 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scan.

All window settings should be included in the assessment, particularly the lung and soft tissue windows in the chest. When lesions are measured, repeated measurements of TLs should be performed using the same window settings throughout the study. The assessment should include all images collected from each examination, not only the "selected" images of the unequivocal lesions.

### 5.2 MRI Scan

MRI has excellent contrast, spatial, and temporal resolution. However, as many image acquisition variables are involved in the MRI, this will greatly impact the image quality, lesion significance, and measurement. In addition, the availability of MRI varies globally. The mode used during follow-up should be the same as that used at baseline, and lesions should be measured/assessed on the same pulse sequence. Generally, axial MR imaging of the abdomen and pelvis with T1- and T2-weighted imaging and 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 used. It is beyond the scope of this appendix to prescribe the specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the scanning image acquisition scheme should be as close as possible with the previous one. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the selected imaging modality.

### 5.3 FDG-PET Scan

FDG-PET has been accepted as a valuable tool for the detection, staging, and re-staging of several malignancies. If FDG-PET scans are included in the protocol, the 60 minutes of the FDG uptake period prior to imaging is determined to be the most appropriate imaging for patients with malignancy. Systemic acquisition is important as this allows sampling of all regions of interest as well as assessment of the development of new lesions to determine the likelihood of disease progression at intervals. Images from the base of the skull to the mid-thigh level should be obtained 60 minutes after medium injection. The PET camera specifications are variable and manufacturer specific, so continuous scanning using the same scanner or the same model of scanner should be attempted at each time for the same patient. Whole-body acquisition may be performed in a 2- or 3-dimensional mode with attenuation correction methods, but the method selected should be consistent in all patients and serial scans should be performed in clinical studies.

### 5.3.1 PET/CT Scan

Currently, the use of CT portion of the low-dose or attenuation-corrected PET/CT combination is limited in anatomy-based efficacy assessments, therefore, it is not recommended to replace dedicated diagnostic contrast-enhanced CT scans for tumor measurements as per the RECIST 1.1. In exceptional cases, the CT portion of the PET/CT may be used for RECIST measurements if the study site can record a CT scan that is part of the PET/CT with the same diagnostic quality as the diagnostic CT with IV and PO contrast. However, this is not recommended because the PET part of the CT may introduce additional data that will cause the investigator's bias if it is not routinely or continuously 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 List of Prohibited Drugs (including, but not limited to)

Note: patients should discontinue taking prohibited drugs before taking the investigational product and the required time window below must be satisfied. Prohibited drugs, except for topical use (e.g., skin cream, inhalation sprays, and eye drops), are prohibited throughout the study and within 28 days after discontinuation of the investigational product. Patients may take any medication to treat an adverse event if it is clinically indicated.

### ■ Drugs known to prolong QT interval

| Drug name | Discontinuation time period before HS-10296 administration |
|---|---|
| Clarithromycin, droperidol, erythromycin, procainamide | 2 days |
| Levofloxacin, cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine | 7 days |
| Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine | 14 days |
| Levomethadyl, methadone, pimozide | 4 weeks |
| Arsenic trioxide | 6 weeks |
| Pentamidine | 8 weeks |
| Amiodarone, chloroquine | 1 year |

### ■ Known sensitive substrates, potent inhibitors and inducers of CYP3A4, CYP2D6 and CYP1A2

**Potent CYP3A4 inducers**

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

**Potent CYP3A4 inhibitors**

Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, 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

**Potent inhibitors or sensitive substrates of CYP1A2**

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

**Potent inhibitors or sensitive substrates of CYP2D6**

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