Clinical Study Protocol	
Study Drug	Glumetinib (SCC244)
Study Number	SCC244 -108
Version Number	3.3
Date	Apr 05, 2024

A Phase Ib/II, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Glumetinib (SCC244), a Selective MET Inhibitor in Patients with Advanced Non-Small Cell Lung Cancer Harboring MET-alterations

The study will be conducted in compliance with the protocol, ICH-GCP, Good Clinical Practice, and requirements of applicable local laws and regulations.

Sponsor:
Haihe Biopharma Co., Ltd.

865 Zu Chongzhi Road, Zhangjiang Hi-Tech Park, Pudong Shanghai

The English version of the protocol is considered the original and the versions in other languages are the translation.

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Abbreviations

Abbreviations or terminology	Explanation
AE	Adverse event
AIDS	Acquired Immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
BOR	Best overall response
Ccr	Creatinine clearance
CFDA	China Food and Drug Administration
CL	Clearance
CL/F	Total body clearance of drug from plasma after an oral dose
C_{max}	Maximum plasma concentration
c-MET/MET	Cellular-mesenchymal to epithelial transition factor
C_{min}	Minimum plasma concentration
CNS	Central nervous system
CPK	Creatine phosphate kinase
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle (x) Day (x)
CYP	Cytochrome P450 isozyme
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture system
EOT	End of treatment
GCP	Good Clinical Practice

Abbreviations or terminology	Explanation
GVP	Good Vigilance Practice
GPSP	Good Post-Marketing Study Practice
h	Hour
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRCT	High-resolution computed tomography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
ILD	Interstitial Lung Disease
INR	International Normalized Ratio
IO	Immuno-oncology
IRB	Institutional Review Board
IRC	Independent Review Committee
IU	International unit
kg	Kilogram
KL-6	A mucin-like high-molecular-weight glycoprotein
LDH	Lactic dehydrogenase
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
ml/mL	Milliliter
mmHg	Millimeter of mercury
MRI	Magnetic resonance imaging
ms	Millisecond
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable

Abbreviations or terminology	Explanation
nM	Nanomole
NMPA	National Medical Products Administration (China)
NTL	Non-target lesion
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death-1
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
QD/Qd/qd	Once daily
QT	The time measured from the start of QRS complex to the end of the T wave on the ECG
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Stable Disease
SFUV	Safety Follow-Up Visit
SIMM	Shanghai Institute of Materia Medica, Chinese Academy of Sciences
SMC	Safety Monitoring Committee
SpO_2	Blood oxygen saturation level
$T_{1/2}$	Half-life
TBIL	Total Bilirubin
TEAE	Treatment-emergent adverse event
TL	Target lesion
ULN	Upper limit of normal
Vss	Volume of distribution at steady state
WHO	World Health Organization

Signature Page of the Sponsor

Protocol Title:	A Phase Ib/II, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Glumetinib (SCC244), a Selective MET Inhibitor in Patients with Advanced Non-Small Cell Lung Cancer Harboring MET-alterations
Protocol Number:	SCC244-108
Version Date and Number:	Apr 05, 2024; V3.3

I have read the study protocol including all appendices and current Investigator's Brochure (IB) and agree with all the details of completing the study and relevant confidentiality provisions contained in the protocol. I have fully understood the study protocol, will comply with the Declaration of Helsinki, Good Clinical Practice (GCP), International Council for Harmonization (ICH) E6 GCP (including filing of essential documents), relevant regulations of local health and regulatory authorities, and agree to conscientiously perform my duties. After the completion of this study, the remaining Japanese patients will be treated in accordance to Good Vigilance Practice (GVP) and Good Post-Marketing Study Practice (GPSP) in Japan.

Sponsor's name: Haihe Biopharma Co., Ltd.

Sponsor address: 865 Zu Chongzhi Road, Zhangjiang Hi-Tech Park, Pudong Shanghai,

Approved by:

Signature:_____ Date:_____

Fugen Li

VP of Clinical Development

Signature Page of the Investigator

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I have read the study protocol including all appendices and current Investigator's Brochure (IB) and agree to carry out the study in compliance with it. I will provide data of the study protocol and corresponding guidance and assistance to all personnel taking part in the study under my management to ensure they are fully informed of matters associated with the drug and the study.

I will comply with the Declaration of Helsinki, Good Clinical Practice (GCP), International Council for Harmonization (ICH) E6 GCP (including filing of essential documents), and applicable requirements of health and regulatory authorities and Ethics Committee (EC) to carry out the trial. After the completion of this study, the remaining Japanese patients will be treated in accordance to GVP and GPSP in Japan.

By accepting this document, I agree that I shall not publish or disclose any unpublished information contained in this document without the prior written permission of the sponsor.

Principal Investigator's Name:_____

Clinical Study Site:_____

Signature:_____ Date:_____

1. Synopsis

1.1 Protocol Synopsis

Investigational product	Glumetinib (SCC244)
Study title:	A Phase Ib/II, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Glumetinib (SCC244), a Selective MET Inhibitor in Patients with Advanced Non-Small Cell Lung Cancer Harboring MET-alterations
Protocol number:	SCC244-108
Study phase:	Phase Ib/ Phase II
Country/Region	Global
Principle Investigator	Prof. Shun LU
Planned number of subjects:	Phase Ib (China only): approximately 90 patients
	Phase II (globally): approximately 78 evaluable patients; addition of at least 6 patients in Safety Run-in (US only)
Study populations:	**Phase Ib study population (China only):** Approximately 90 patients with locally advanced or metastatic NSCLC (Stage IIIb, IIIc or IV) including pulmonary sarcomatoid carcinoma (PSC). All patients should carry at least one of the following MET alterations (confirmed by local or central laboratory): ● Patients with *MET*ex14 skipping mutation who had previously treated by other MET inhibitor(s) ● Patients with *MET*ex14 skipping mutation who had received 3 or more lines prior systemic therapies without MET inhibitor for the advanced NSCLC ● Patients with *MET* amplification (GCN ≥ 4 or *MET*/CEP7 ratio ≥ 2) ● Patients with MET over-expression (IHC2+) **Phase II - Safety Run-in Population (US only):** A minimum of 6 patients who meeting the eligibility for either Phase Ib or Phase II. **Phase II study population (globally):** Approximately 78 evaluable patients with locally advanced or metastatic

	NSCLC (Stage IIIb, IIIc or IV, including PSC) harboring *MET*ex14 skipping mutation that have been pre-screened by local or Sponsor-designated central laboratory, who are not eligible for chemotherapy or refuse of chemotherapy after well-informed or have failed one or two prior lines of systemic therapies and have not had prior MET inhibitor for the advanced NSCLC.
Study objectives	**Study endpoints**
Phase Ib	
Primary objective: 1. To evaluate the tolerability and safety of Glumetinib in patients with locally advanced or metastatic NSCLC.	Primary endpoint: 1. Tolerability and safety: incidence, duration and severity of adverse events (AEs), physical examination, laboratory data, vital signs and electrocardiogram (ECG) changes.
Secondary objectives: 1. Preliminary efficacy of Glumetinib in patients with local advanced or metastatic NSCLC harboring MET-aberrations. 2. To evaluate the pharmacokinetic (PK) characteristics of Glumetinib with Population PK analysis.	Secondary endpoints: 1. Object Response Rate (ORR), Duration of Response (DOR), Disease Control Rate (DCR), Time to Response (TTR), Progression-Free Survival (PFS), 6-month PFS rate assessed by investigator and Overall Survival (OS).
Phase II	
Primary objective: 1. To evaluate the antitumor efficacy of Glumetinib (confirm ORR by BIRC) in locally advanced or metastatic NSCLC harboring *MET*ex14 skipping mutation.	Primary endpoint: 1. ORR will be based on the blinded independent review committee (BIRC). Tumor response assessments will be made based on RECIST 1.1.
Secondary objectives: 1. To evaluate ORR (by investigator); DOR, DCR, TTR, PFS, 6-month PFS rate by BIRC and by investigator; and OS. 2. To investigate the safety and tolerability of Glumetinib. 3. To evaluate the PK characteristics of Glumetinib with Population PK analysis.	Secondary endpoints: 1. ORR assessed by investigator. 2. DOR, DCR, TTR, PFS, 6-month PFS rate by BIRC and by investigator and OS. 3. Safety: incidence, duration and severity of AEs, physical examination, laboratory data, vital signs and ECG changes.
Study design:	

This is an open-label, multicenter phase Ib/II study including two parts: Phase Ib in NSCLC patients with MET-aberrations and Phase II in patients with locally advanced or metastatic NSCLC (stage IIIb, IIIc or IV) harboring *MET*ex14 skipping mutation.

Glumetinib will be administered orally continuous once daily (QD) in 21-day treatment cycles until disease progression, unacceptable AE, withdrawal of consent or other criteria for termination of study treatment. There are no breaks in dosing between cycles. Patients should follow the instructions of the treating physician on study drug administration during treatment. Patients are required to fast for at least 2 hours before and 1 hour after administration of Glumetinib. Patients will be permitted to drink water during this period. On non-PK sampling days, Glumetinib can be administered in the morning or evening at the same time (if possible) each day. If a patient misses a dose (i.e., did not take Glumetinib for > 12 hours of the scheduled time of the day), the patient should take the dose the next day.

Phase Ib (China only)

Patients with locally advanced or metastatic NSCLC including PSC (stage IIIb, IIIc or IV) who have the MET alteration that has been pre-screened by local or Sponsor-designated central laboratory as listed below and meet the inclusion/exclusion criteria in the protocol will be enrolled.

- Patients with *MET*ex14 skipping mutation who had previously treated by other MET inhibitor(s)
- Patients with *MET*ex14 skipping mutation who had received 3 or more lines prior systemic therapies without MET inhibitor for the advanced NSCLC
- Patients with *MET* amplification (GCN $\geqslant$ 4 or *MET*/CEP7 ratio $\geqslant$ 2)
- Patients with MET over-expression (IHC2+)

During the phase Ib study, MTD or recommended phase II dose (RP2D) will be confirmed based on the latest clinical study data of Glumetinib. The phase II study will be started once the MTD or RP2D is confirmed. Phase Ib study will be continued to further evaluate the tolerability, safety, preliminary efficacy and pharmacokinetics of Glumetinib in the specified subgroup of NSCLC patients. Approximately 90 patients will be enrolled. The purpose of the Phase Ib study is to assess the tolerability, safety, preliminary efficacy and pharmacokinetics of Glumetinib in the specified subgroup of NSCLC patients.

Safety Run-in (US only)

In order to evaluate potential Glumetinib drug exposure in different ethnic groups, there will be a safety run-in of Glumetinib at the dose of 300 mg in patients from the US while China and other countries continue enrolling patients at 300 mg. A minimum of 6 patients from the US meeting the eligibility for either Phase Ib or Phase II will be enrolled. Once the first 6 patients at 300 mg are evaluated for DLT and no more than one of 6 DLT-evaluable patients experience a DLT, additional patients could be enrolled in Phase II. If > 1/6 patients experience DLT at 300 mg, 200 mg will be evaluated. In addition, based on the evaluation of safety, PK and efficacy, 400 mg may be evaluated according to the same evaluation criteria for DLT set forth for 300 mg. If > 1/6 patients experience DLT at 400 mg, 400 mg will be deemed not tolerated and no additional patients will be treated at 400 mg for the study. If no more than 1 of the 6 patients who have been treated at 400 mg and evaluated for DLT experiences a DLT, a comprehensive review of all available safety, PK, and efficacy data from ongoing SCC244

studies will be performed. Based on this review, a final RP2D will be selected to continue further enrollment until meeting the prespecified sample size for Phase II at all sites globally.

A DLT-evaluable patient is defined as a patient that either experienced a DLT during the first 21-day of the treatment or has received at least 80% of the assigned doses (i.e.17 of the 21 days of Glumetinib doses). DLT is defined as below:

A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that meets any of the following criteria assessed using the NCI-CTCAE Version 5.0 and reported to be at least possibly related to the study drug by the Principal Investigator and/or the Sponsor during the DLT evaluation period. The DLT observation period starts on Day 1 up to Day 21 of Cycle 1 (21 days).

- Hematological toxicity
    - CTCAE Grade 4 neutropenia (absolute neutrophil count < 0.5 x 10^9/L)
    - CTCAE Grade 4 thrombocytopenia (platelet count < 25 x 10^9/L)
    - CTCAE Grade 3 thrombocytopenia accompanied by clinically significant bleeding tendency (platelet count < 50 x 10^9/L)
    - ≥ CTCAE Grade 3 febrile neutropenia (absolute neutrophil count <1.0 x 10^9/L with a single temperature of > 38.3°C or a sustained temperature of ≥ 38 °C for more than one hour)
- Non-hematological toxicity, ≥ CTCAE Grade 3*. Additionally, the following will be judged to be a DLT:
    - Liver transaminase elevation (AST or ALT) > 3 x the upper limit of normal (ULN) with concurrent increase in total bilirubin > 2 x ULN without evidence of cholestasis or alternative explanations (e.g., viral hepatitis, disease progression in the liver)
    - Liver transaminase (ALT or AST) elevation > 8 x ULN or total bilirubin > 5 x ULN
    - CTCAE Grade 4 vomiting, diarrhea, and constipation, regardless of duration
    - CTCAE Grade 4 electrolyte disturbance, regardless of duration
    - CTCAE Grade 3 electrolyte disturbances that require hospitalization
    - CTCAE grade 2 pneumonitis lasting > 7 days or recurring in the same cycle
- Other adverse events:
    - Any death not clearly due to the underlying disease or extraneous causes
    - Any adverse events that is unrelated to disease progression, intercurrent illness, or concomitant medications requiring permanent discontinuation of the study drug

- Any grade toxicity that is clinically significant and/or unacceptable and is judged to be a DLT by the Investigator and/or Sponsor

*The following CTCAE Grade 3 adverse event or laboratory abnormalities will not be considered as DLT:

- Nausea/vomiting, diarrhea, and constipation return to grade 2 by appropriate supportive treatment within 3 days
- Fatigue for less than 7 days after proper supportive treatment
- Headache for less than 7 days after proper supportive treatment
- Laboratory abnormalities without clinical significance that are not already specified in the DLT criteria above will not be considered as DLT (e.g., Grade 3 elevations in serum amylase or lipase that are not associated with symptoms or clinical manifestations of pancreatitis)

In the absence of a clinical abnormality, repeat laboratory testing should be performed to confirm significant laboratory findings prior to designation as a DLT. However, isolated laboratory changes of any grade without clinical sequelae or clinical significance are not considered DLTs.

Phase II (globally)

The phase II study is a single-arm study. Patients with locally advanced or metastatic NSCLC including PSC (stage IIIb, IIIc or IV) harboring *MET*ex14 skipping mutation that have been pre-screened by local or Sponsor-designated central laboratory, who are not eligible for chemotherapy or refuse chemotherapy after well-informed or have failed one or two prior lines of systemic therapies and have not had prior MET inhibitor for the advanced NSCLC, and meet the inclusion/exclusion criteria in the protocol will be enrolled.

Approximately 78 evaluable patients will be enrolled to evaluate the antitumor efficacy of Glumetinib [to confirm ORR by Blinded Independent Review Committee (BIRC)] in NSCLC patients with *MET*ex14 skipping. Secondary objectives are to evaluate ORR (by investigator), DOR, DCR, TTR, PFS, 6-month PFS rate, OS, safety and PK.

Enrollment in other countries may be increased per country specific health authority request.

Phase Ib and Phase II will enroll patients concurrently; after the completion of enrollment of Phase II, Phase Ib will continue enrolling patients till archiving the planned subject number.

Rationale for the Dose and Frequency of Administration in Patients

Based on safety, PK and preliminary efficacy data, Glumetinib 300 mg once daily dosing was selected as recommended dose for phase 2 study (RP2D).

In study SCC244-101, the FIH study in NSCLC, a total of 19 patients have been treated at 4 dose levels (100, 200, 300, and 400 mg), the treatment of Glumetinib has been well tolerated with manageable toxicities, mainly grade 1 or 2 headache, vomiting, nausea, oedema peripheral, dizziness, decreased appetite, bilirubin elevation and ALT elevation, no MDT was identified, one patient experienced a DLT

(grade 3 vomiting) at 400 mg, no DLT was identified at other dose levels. 200 mg QD and 300 mg QD dose were selected as RD for further clinical evaluation.

In addition, as of the cut-off date August 21, 2020, 36 advanced NSCLC patients with *MET*ex14 skipping were treated with Glumetinib in SCC244-108 study:

- Treatments of 22 of the 28 patents treated at 300 mg dose level are on-going, and 7 patients out of the 15 efficacy evaluable patients were reported with the tumor assessment as PR (4 confirmed PR, treatment of other 3 is on-going and waiting confirmation), the preliminary ORR = 46.7%.
- Two of the 8 patents treated at 200 mg dose level were reported with the tumor assessment as PR, another patient was reported as SD and changed to PR at 6 weeks after the dose was titrated to 300 mg, the preliminary ORR = 37.5%.

The human PK data shows that after oral administration of Glumetinib in cancer patients, the absorption of Glumetinib was rapidly post single and multiple dose administration, the median value of T_{max} was 2 to 3 h. Within the dose range of 25 mg to 400 mg, the systemic exposure of Glumetinib (C_{max}, AUC_{0-24h}) increased with the increase of dose after single and multiple dose administration; the systemic exposure of Glumetinib showed less than proportional to dose due to individual variability and possible absorption saturation with the increase of dose. The mean value of $t_{1/2}$ was 28.7 h, Glumetinib is suitable for daily dosing; steady state was reached approximately by Day 8 following daily dosing, after reaching steady state, no further accumulation was observed.

Overall, 300 mg QD dose were well tolerated and with desirable efficacy profile; compared to 200 mg QD dose, 300 mg QD dose has relative higher systemic exposure and better efficacy profile, therefore 300 mg QD dose was selected as RP2D in this study.

Inclusion criteria and exclusion criteria

Inclusion criteria:

Patients who fulfill all the following requirements may enter the study:

a. Provide informed consent to participate in this study voluntarily.

b. Male and female patients ⩾ 18 years of age (or having reached the age of majority according to local laws and regulations, if the age is > 18 years).

c. Histologically or cytologically confirmed diagnosis of NSCLC including PSC.

d. Patients with stage IIIb or IIIc NSCLC who are not candidates for definitive surgical resection or concurrent chemoradiation or patients with stage IV NSCLC (AJCC version 8).

e. **For Phase Ib study,** patients should carry at least one of the following MET alterations (by local or Sponsor-designated central laboratory screening)**:**

- *MET*ex14 skipping mutation who had previously treated by other MET inhibitor(s) or
- *MET*ex14 skipping mutation who had received 3 or more lines prior systemic therapies

without MET inhibitor for the advanced NSCLC or

- *MET* amplification GCN ≥ 4 or *MET*/CEP7 ratio ≥ 2) or
- MET over-expression (IHC2+).

f. **For Phase II study,** patients with *MET*ex14 skipping mutation in tumor or ctDNA samples (local testing is acceptable for eligibility, however if the results of the central laboratory is available, the report of the central laboratory shall prevail); all patients in Phase II study will have confirmation of *MET*ex14 skipping mutation by Sponsor-designated central laboratory but this result is not necessary for eligibility.

g. Availability of tumor tissue sample (either fresh tumor biopsy or archival tumor tissue sample); for patients of phase II study (not mandatory for safety run-in), if screened and enrolled based on local test results of *MET*ex14 skipping, the tumor tissue sample must be available for central laboratory testing before C2D1; if local testing results meet the requirements, patients of phase Ib are exempt from the central laboratory confirm.

h. **For Phase II study,** patients are not eligible for chemotherapy or refuse chemotherapy after well-informed or have failed one or two prior lines of systemic therapies for the advanced NSCLC.

- Treatment failure is defined as documented disease progression or intolerance to treatment.
- Maintenance therapy given after first line chemotherapy will be considered as part of the first line if given to patients with documented response or stable disease before starting the maintenance therapy.
- Prior neoadjuvant/adjuvant systematic therapies will count as one prior line of treatment, provided that disease recurred within 12 months of completion of neoadjuvant/adjuvant therapy.

i. **For Phase II study,** at least one measurable lesion as per RECIST 1.1. (A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.)

j. ECOG Performance Status (PS): 0-1.

k. Adequate bone marrow reserve, renal and liver function:

- Absolute neutrophil count ≥ 1.5×10^9/L;
- Hemoglobin ≥ 9 g/dL;
- Platelet count ≥ 75×10^9/L;
- Serum total bilirubin ≤ ULN (≤ 3 × ULN for patients with Gilbert's syndrome);
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN (≤ 5.0 × ULN for patients with hepatic metastasis);
- Creatinine clearance (calculated* or measured value**) ≥ 50 mL/min

*For calculated creatinine clearance (Ccr) value, the eligibility should be determined using

the Cockcroft-Gault formula:

- Male Ccr (mL/min) = body weight (kg) x (140-age)/[72 x creatinine (mg/dL)]
- Female Ccr (mL/min) = male Ccr x 0.85

** A measured value

- International normalized ratio (INR) < 1.3 (or < 3.0 if on anticoagulation)

Exclusion Criteria:

Patients who meet any of the following criteria shall be excluded from the study:

1. Patients with targetable activating EGFR mutation, ALK rearrangement, ROS1 rearrangement, BRAF mutation or NTRK fusion that have available standard of care therapies.
2. Patients who have symptomatic CNS metastasis which is neurologically unstable or those who have CNS disease requiring increase in the dose of steroid. (Note: Patients with controlled CNS metastasis can participate in the trial. Before entering the study, patients should have finished radiotherapy, or have received operation for CNS tumor metastasis at least two weeks before. Patients' neurological function must be in a stable state; no new neurological deficit is found during clinical examination and no new problem is found during CNS imaging examinations. If patients need to use steroids to treat CNS metastasis, the therapeutic dose of steroid should be stable for ⩾ 3 months at least two weeks prior to entering the study with treatment dose no more than dexamethasone 4 mg daily or an equivalent dose of steroids.)
3. Prior exposure to MET-directed therapy (except patients in Phase Ib study).
4. Evidence of past or current primary malignancies other than NSCLC (except for non-melanoma skin cancer, in situ breast cancer or in situ cervical carcinoma and superficial bladder cancer, or other cancer curatively treated and with no evidence of disease for at least 5 years).
5. Patients with clinically significant cardiovascular disease, including:
   - NYHA Class III or higher congestive heart failure;
   - History or current evidence of serious uncontrolled arrhythmias;
   - Acute myocardial infarction, severe or unstable angina pectoris, coronary artery or peripheral artery bypass graft received within 6 months prior to the first dose;
   - Left ventricular ejection fraction (LVEF) < 50%;
   - Fridericia's corrected QT interval (QTcF) > 460 ms on ECG conducted during screening;
   - Congenital long QT syndrome, or any known history of torsade de pointes (TdP), or family history of unexplained sudden death;
   - Clinically uncontrolled hypertension (after standard antihypertensive treatment, systolic blood pressure ⩾ 140 mmHg and/or diastolic blood pressure ⩾ 90 mmHg);
6. Any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting

study treatment with the exception of alopecia and grade 2 prior neuropathy.

7. Known HIV infection with a history of acquired immunodeficiency syndrome (AIDS)-defining opportunity infection within the past 12 months; active hepatitis B and hepatitis C. Patients whose test results meet one of the following will not be enrolled:
   - for patients in China and Japan, confirmed HIV antibody positive. For patients in the US, patients with a history of HIV but no history of AIDS or an AIDS-defining opportunistic infection are allowed to be enrolled;
   - serum HBsAg positive and HBV DNA > 200 IU/ml or 1000 copies/mL;
     - For patients in Japan, whose results are HBsAg (antigen) negative; however, when HBsAb or HBcAb positive, the patients whose HBV DNA < 200 IU/ml or 1000 copies/mL could be enrolled.
   - serum HCV antibody and HCV RNA positive.
8. Anticancer therapy (including chemotherapy, targeted therapy, biotherapy, hormone therapy, traditional Chinese medication with lung cancer indication or other investigational agents) within 4 weeks or 5 times of half-lives (whichever is shorter) prior to the first dose of the study drug or who have not recovered from the side effect of such therapy.
9. Radical radiation therapy (including radiation therapy for over 25% bone marrow) within 4 weeks prior to the first dose of the investigational product or received local palliative radiation therapy for bone metastases within 2 weeks.
10. Major surgery or had significant traumatic injury within 28 days prior to the first dose of the investigational product.
11. Patients who have to receive treatment (definite strong CYP3A4 inhibitor or inducer [appendix 6]; in addition, herbals/supplements containing St. John's wart [*Hypericum perforatum* L.] and Sevillia orange etc. should also be avoided.) that is prohibited during the study and those who cannot discontinue drugs (e.g. antiarrhythmic agent) that may lead to QTc interval prolongation and with known risk of torsade de pointes. Additionally, patients who have to receive treatment of strong inhibitor for CYP2C8 and/or CYP2C9 [appendix 6] and substrates or inhibitor for transporter [appendix 7] will be excluded in safety run-in part of the study.
12. Any diseases or medical conditions, at the investigator's discretion, that may be unstable or influence their safety or study compliance, including organ transplantation, abuse of psychotropic medication, alcohol abuse or history of drug abuse.
13. Other serious illness or medical conditions at the investigator's discretion, that may influence study results, including but not limited to serious infection, diabetes, cardiovascular and cerebrovascular diseases or lung disease.
14. Patients with a history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment or any evidence of clinically active ILD.
15. Pregnant or breast-feeding patients. Pregnancy refers to the state of a woman between fertilization and the end of pregnancy confirmed by positive laboratory hCG test (> 5 mIU/mL). Breast-feeding

woman can become eligible for this study if she stops breast-feeding, however, cannot restart the breast-feeding on/after the completion of the study treatment. 16. Man and woman of childbearing potential (WOCBP refer to appendix 3) not using effective contraception (refer to appendix 3) during the trial and within 6 months after the end of treatment.	
Investigational product, dosage, administration mode, administration routes and duration of therapy:	Investigational product: Glumetinib (SCC244) is supplied as 50 mg tablet Dose and dosage regimen: Phase Ib & Phase II: Starting dose of 300 mg continuous QD will be administered in 21-day treatment cycles. Administration route: Glumetinib is administered orally. Patients are required to fast at least 2 hours before and 1 hour after administration of Glumetinib. Patients will be permitted to drink water during this period.

Statistical considerations and methods:

Safety Criteria for Evaluation

Standard safety monitoring and grading using NCI-CTCAE Version 5.0.

Efficacy Analysis

For Phase Ib, efficacy data of ORR, DOR, DCR, TTR, PFS, 6-month PFS rate and OS will be descriptive and summarized.

For Phase II, efficacy data for the primary endpoint of ORR (based on BIRC) and secondary endpoint of ORR (based on investigator), DOR, DCR, TTR, PFS, 6-month PFS rate and OS will be summarized.

Analysis Set

The *safety analysis set (SAS)* will include all patients who received at least one dose of Glumetinib. This analysis set will be the primary analysis set for safety evaluation.

The *PK analysis Set* will consist of patients who have received at least one dose of Glumetinib and have at least one Glumetinib evaluable plasma concentration data. All such patients will be evaluated for PK unless major protocol deviations have impacted the data or key dosing information is missing. Changes to the procedures, which may impact the quality of PK data, will be considered “PK relevant protocol deviations”. Examples include sample process errors that lead to inaccurate bioanalytical results and/or inaccurate dosing on the day of PK sampling.

Analysis sets which will be used for efficacy analysis are defined as follows:

Phase Ib:

F*ull analysis Set (FAS)* will include all treated patients (same as the safety analysis set)

Phase II: *Full analysis set (FAS)* will include all treated patients (same as the safety analysis set).

Efficacy analysis set will include all NSCLC patients with sponsor-designated central laboratory confirmed *MET*ex14 skipping mutation treated at RP2D (including patients in Safety Run-in part of phase II) and have valid baseline tumor assessment.

Determination of Sample Size

Phase Ib (China only):

Approximately 90 patients will be enrolled in Phase I (China only). Sample size considerations are exploratory and not based on hypothesis test.

Phase II (globally):

Approximately 78 evaluable NSCLC with *MET*ex14 skipping mutation will be treated at RP2D. Sample size considerations are based on differentiating a historic control ORR of 30% or less with a target ORR of 45% based on patient data in the current study and clinical activity of other MET inhibitors. Assuming the true ORR is 45%, the study has approximately 80% power to reject the null hypothesis that the true ORR is $\leqslant$ 30%, considering a 2-sided alpha of 5%.

At observed ORR = 41%, the lower bound of the 95% CI excludes 30%, which is the null hypothesis ORR. This translates in observing at least 32 responders of the 78 efficacy evaluable patients,ORR of 41% with 95% CI (30.0% – 52.7%).

Interim Ananlysis

Interim analysis of safety will be performed for the Phase II part of the study when approximately 25%, 50% and 75% of patients are enrolled and treated for at least for one cycle (21 days). These interim analysis will be reviewed by an Independent Data Monitoring Committee (IDMC). A complete description of the composition of the IDMC and details on the interim analysis process will be provided in a separate IDMC charter. In addition, the Sponsor will share safety data from the study with all primary investigators throughout the conduct of the study.

1.2 Study Flowchart

Table 1-1 Study Flowchart of Phase Ib/II Study

Visit	Screening period		Treatment period[c]				Follow Up period		PMS In Japan	Notes
	pre-screening	Screening -28 to -1	Cycle 1			Cycle 2 and Subsequent cycles	EOT[b]	28-day safety FU		Exact time of C2D1 and CxD1 is calculated from Day 1 of Cycle 1 (that is, administration time of Glumetinib on C1D1). The cycle of treatment is defined as 21 days (3 weeks).
			C_1D_1	C_1D_8	C_1D_{15}	C_XD_1	Within 14 days of the last dose	28 days after last dose		
Visit Window (days)			N/A	±2	±2	±3	N/A	+7	±3	
Molecular pre-screening Informed Consent	X									For patients, according to protocol, do not need to provide the tumor sample to central laboratory, the molecular pre-screening Informed Consent could be exempt.
Informed Consent for main study		X							X	
Archival or newly obtained tumor sample (if applicable)	X									Tumor tissue sample may be tested by central laboratory during pre-screening. In case where local laboratory testing results of MET alterations are used to determine eligibility, patient in Phase II must have available tumor sample from archival samples or fresh tumor biopsy sample submitted to the Sponsor Designated Central Laboratory for confirmation of MET alterations before C2D1. See section 7.1.1
Demography		X								Including date of birth, gender, and race/ethnicity
Inclusion/exclusion criteria confirmation		X	X							
Medical history		X								

Visit	Screening period		Treatment period[c]				Follow Up period		PMS In Japan	Notes
	pre-screening	Screening -28 to -1	Cycle 1			Cycle 2 and Subsequent cycles	EOT[b]	28-day safety FU		**Exact time of C2D1 and CxD1 is calculated from Day 1 of Cycle 1 (that is, administration time of Glumetinib on C1D1). The cycle of treatment is defined as 21 days (3 weeks).**
			C_1D_1	C_1D_8	C_1D_{15}	C_XD_1	Within 14 days of the last dose	28 days after last dose		
Visit Window (days)			N/A	±2	±2	±3	N/A	+7	±3	
Prior antineoplastic therapy		X								Past tumor history and antitumor treatment history, including: tumor diagnosis date, pathological type, TNM (including initial diagnosis and evaluation at enrollment in the study), diagnosis time of the first metastatic lesion, number and position of metastatic lesions, previous antitumor treatment (including start time, end time, duration and regimen), best response of each treatment, date of failure/disease progression, and grade 3 and above toxicities that occurred.
Physical examination		X	X			X	X			Physical examination: including head, eyes, ears, nose, throat, neck, heart, chest (including lungs), abdomen, extremities, skin, lymph nodes, nervous system, and general condition of patients
Vital signs		X	X	X	X	X	X			Vital signs: including blood pressure, pulse, respiratory rate, and temperature. Blood pressure should be measured after patients rest for 5 minutes.
Height		X								
Weight		X	X	X	X	X	X		X[d]	
ECOG Performance status (PS)		X	X			X	X		X[d]	ECOG evaluation is recommended to be conducted by the same investigator throughout the study
Chest X ray		X	Every 4 cycles (12 weeks) during follow-up or when it is clinical indicated						X[d]	Chest X ray: for patients suspecting ILD or early detection after the study drug treatment initiation, chest X ray is conducted at baseline, every 4 cycles (12 weeks) during follow-up or when it is clinical indicated. If the patient has taken the high resolution CT (HRCT) scan, the X-ray can be waived. If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of ILD is observed, HRCT, lung function/arterial oxygen saturation (SpO_2), and auscultation to be conducted. For Japanese patients, KL-6 to be conducted.

Visit	Screening period		Treatment period[c]				Follow Up period		PMS In Japan	Notes
	pre-screening	Screening -28 to -1	Cycle 1			Cycle 2 and Subsequent cycles	EOT[b]	28-day safety FU		Exact time of C2D1 and CxD1 is calculated from Day 1 of Cycle 1 (that is, administration time of Glumetinib on C1D1). The cycle of treatment is defined as 21 days (3 weeks).
			C_1D_1	C_1D_8	C_1D_{15}	C_XD_1	Within 14 days of the last dose	28 days after last dose		
Visit Window (days)			N/A	±2	±2	±3	N/A	+7	±3	
Hematology[a]		X	X	X	X	X	X		X[d]	
Blood biochemistry (including cardiac enzymes)[a]		X	X	X	X	X	X		X[d]	Blood biochemistry: Total protein, albumin, blood glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, alkaline phosphatase, total bilirubin, direct bilirubin or indirect bilirubin, aspartate aminotransferase, alanine aminotransferase, glutamyl transpeptidase; creatinine, urea or urea nitrogen, creatinine clearance, uric acid; electrolytes (potassium, sodium, calcium, phosphorus); LDH; cardiac enzymes (troponin T/I, and CPK); lipase and amylase.
Urinalysis[a]		X	X	X	X	X	X		X[d]	While screening, if qualitative test of urinary protein shows positive result (⩾ 1+), a 24-hour urinary protein quantitative test should be conducted. During the study, once qualitative test of urinary protein ⩾ 2+, 24-hour urinary protein quantitative test should be conducted.
Coagulation[a]		X	X	X			X		X[d]	
Pregnancy test (if applicable)		X					X		X[d]	All women of childbearing potential should receive pregnancy test (serum pregnancy test) at the following time points: within 7 days prior to the first dose of the study drug and at EOT. Women without childbearing potential do not need to receive a pregnancy test. Once pregnant, the patient must immediately and permanently discontinue the study drug and withdraw from the study; the event must be recorded in pregnancy form of clinical study.
HBV, HCV, HIV test		X								HBV, HCV and HIV tests: HBsAg, HCV antibody and HIV antibody testing should be performed at the screening period (HIV antibody will be only tested in China and Japan). HBsAg antigen positive patients should be tested for HBV DNA level and HBV DNA level should be tested once every three months after that. HCV antibody test should be conducted during screening period. If

Visit	Screening period		Treatment period[c]				Follow Up period		PMS In Japan	Notes
	pre-screening	Screening -28 to -1	Cycle 1			Cycle 2 and Subsequent cycles	EOT[b]	28-day safety FU		Exact time of C2D1 and CxD1 is calculated from Day 1 of Cycle 1 (that is, administration time of Glumetinib on C1D1). The cycle of treatment is defined as 21 days (3 weeks).
			C_1D_1	C_1D_8	C_1D_{15}	C_xD_1	Within 14 days of the last dose	28 days after last dose		
Visit Window (days)			N/A	±2	±2	±3	N/A	+7	±3	
										HCV antibody test result is positive, HCV RNA test should be conducted. (For Japanese patients HBsAg, HBsAb, HBcAb, and HCV antibody testing should be performed at the screening period.) If test reports of HBsAg, HBV DNA, HCV antibody, HCV RNA and HIV containing normal ranges issued by formal medical institutions within 28 days prior to C1D1 (and prior to informed consent) are available, these tests are exempt while screening.

Visit	Screening period		Treatment period[c]				Follow Up period		PMS In Japan	Notes
	pre-screening	Screening -28 to -1	Cycle 1			Cycle 2 and Subsequent cycles	EOT[b]	28-day safety FU		**Exact time of C2D1 and CxD1 is calculated from Day 1 of Cycle 1 (that is, administration time of Glumetinib on C1D1). The cycle of treatment is defined as 21 days (3 weeks).**
			C_1D_1	C_1D_8	C_1D_{15}	C_XD_1	Within 14 days of the last dose	28 days after last dose		
Visit Window (days)			N/A	±2	±2	±3	N/A	+7	±3	
RECIST assessments (CT/MRI)		X	Every 6 weeks ± 7days for the first 8 cycles (C3/5/7/9D1), then every 9 weeks ± 7days, or clinical indicated until progressive disease				X [if not conducted within 28 days prior to EOT]			Tumors are evaluated in accordance with RECIST 1.1. In the screening period, tumor evaluation by chest and abdominal imaging examinations (CT or MRI) is finished within 28 days prior to administration. Appropriate examination (CT or MRI) of other known or suspected disease sites (e.g. neck, pelvic cavity, brain) may be conducted if clinically necessary. If tumor evaluation has been conducted with the same method and instrument in the same hospital within 28 days prior to the first dose, it can be regarded as tumor evaluation in the screening period. Bone scanning (except for patients who have received bone scanning 60 days prior to the first dose) should be conducted in patients with or suspected of bone metastasis in the screening period. The cycle of tumor evaluation visit is calculated from Day 1 of Cycle 1 and not influenced by drug withdrawal. Tumor evaluation should be conducted when the patient discontinues treatment/withdraws from visit if tumor evaluation is not conducted within 28 days prior to discontinuation of treatment or at withdrawal. An unscheduled tumor evaluation should be conducted in patients suspected of progressive disease prior to the next scheduled evaluation. When the best response was PR or CR, it should be confirmed at Week 4 or later after the first record. For details please refer to section 7.2.1.
(12 lead) ECG		X	X		X	X	X		X[d]	The ECG should be tested at the screening period. ECG should be conducted once every 3 weeks (one treatment cycle). For C1D1 & D15 & C2D1, ECG should be conducted at pre-dose (C1D1/15&C2/3D1), 1-hour post dose PK timepoint and 3-hour post dose PK timepoint (C1D1/15&C2D1) and the ECG should be

Visit	Screening period		Treatment period[c]				Follow Up period		PMS In Japan	Notes
	pre-screening	Screening -28 to -1	Cycle 1			Cycle 2 and Subsequent cycles	EOT[b]	28-day safety FU		Exact time of C2D1 and CxD1 is calculated from Day 1 of Cycle 1 (that is, administration time of Glumetinib on C1D1). The cycle of treatment is defined as 21 days (3 weeks).
			C_1D_1	C_1D_8	C_1D_{15}	C_xD_1	Within 14 days of the last dose	28 days after last dose		
Visit Window (days)			N/A	±2	±2	±3	N/A	+7	±3	
										conducted within 15 min before PK sampling, Triplicate ECGs (about 2-3 minutes apart, all within15 mins before corresponding PK) need to be taken; then calculate QTc interval (corrected with Fridericia's formula) and the average; C4D1 and subsequent visits could select a single ECG. See section 7.2.2 for details regarding safety assessments of ECG.
Cardiac imaging (Echocardiogram or MUGA)		X	Every 4 cycles (12 weeks)				X [if not conducted within 28 days prior to EOT]		X[d]	Left ventricular ejection fraction (LVEF) is examined with echocardiography or MUGA, once every 4 cycles (12 weeks) since C1D1. The examination may be exempt if echocardiography or MUGA conducted in the screening period is within 28 days prior to C1D1 (including prior to signing an ICF). The examination at end-of-treatment visit may be exempt if echocardiography or MUGA conducted is within 28 days prior to end-of-treatment. Echocardiogram is preferred.
Adverse events	X	X	Continuous monitoring during treatment				X	X	X	The severity of adverse events will be judged in accordance with NCI CTCAE 5.0. It is recorded as an adverse event only when laboratory test value is considered to be clinically significant. Severity and correlation of all adverse events will be evaluated. Only SAEs occurring between day 28 after the last dose and the end of study, at the investigator's discretion, related to the study drug, are recorded and reported. Any AEs or SAEs directly associated with a pre-screening procedure (i.e. fresh tumor biopsy) should be reported as described in Section 8.3. During Post Marketing Study (PMS) Part in Japan, only SAE information will be collected for Japanese patients..
Concomitant medication/ procedure		X	Continuous monitoring during treatment				X	X	X[d]	All drug therapies and significant non-drug therapies within 4 weeks prior to enrollment must be recorded in eCRF, including generic name and administration of drugs, name of non-drug

Visit	Screening period		Treatment period[c]				Follow Up period		PMS In Japan	Notes
	pre-screening	Screening -28 to -1	Cycle 1			Cycle 2 and Subsequent cycles	EOT[b]	28-day safety FU		Exact time of C2D1 and CxD1 is calculated from Day 1 of Cycle 1 (that is, administration time of Glumetinib on C1D1). The cycle of treatment is defined as 21 days (3 weeks).
			C_1D_1	C_1D_8	C_1D_{15}	C_xD_1	Within 14 days of the last dose	28 days after last dose		
Visit Window (days)			N/A	±2	±2	±3	N/A	+7	±3	
										therapies, reasons for treatment, beginning and ending date of treatment, and whether to continue the drug at present.
PK sampling			X		X	X				Pharmacokinetic blood samples are collected as the timepoints in Table 7-1. , the investigators must record the time points for blood sampling and the time of dose administration before blood sampling in eCRFs. Patients who prematurely withdraw from the study may have a PK sample taken at the time of withdrawal. In addition, a PK sample may be taken at the occurrence of a toxicity or possible drug-related AE, at the discretion of the investigator.
Investigational product dispenses and return			X			X			X	
Antineoplastic therapies since discontinuation of study treatment							X	X		
Radiologic progression Follow-up										Patients who discontinue Glumetinib for reasons other than radiologic progressive disease will continue RECIST 1.1 assessments every 9 weeks (± 7days) until radiologic progression or starting new anticancer treatment, whichever occurs first. See section 7.1.6
Survival Follow-up										Telephone follow-up will be conducted every 3 months (±14 days) after progression disease or the starting of new antitumor treatment. To collect patients' information on subsequent antitumor treatment and survival condition. See section 7.1.7

a. Laboratory tests include hematology, blood biochemistry, urinalysis and coagulation. Hematology, blood biochemistry, urinalysis and coagulation on C1D1 may be exempt if results obtained within 7 days prior to C1D1 are not clinically significant at the investigator's discretion.

b. End of treatment includes premature termination of treatment and treatment discontinuation. If results of hematology, blood biochemistry, urinalysis, coagulation function, 12-lead ECG, pregnancy test (if applicable) performed within 7 days prior to end of treatment are normal at the investigator's discretion, these examinations are exempt at the end-of-treatment visit.

c. After the approval of new drug application in Japan, the remaining Japanese patients will be transferred into the post marketing part and will continue receiving treatment until the study product is commersially available in Japan and accesible to the remianing patient.

d. To be perfomed only if deemed necessary by the investigator.

2. Introduction

2.1 Study background

Lung cancer has become the disease with the highest mortality in the world, ranking first among malignancies in morbidity and mortality. Lung cancer occurs in 2.09 million people and results in 1.76 million deaths worldwide every year [Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.]. NSCLC accounts for approximately 85% of all lung cancer and has a 5-year survival rate of only 15.6% [Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.].

At present, the treatment of NSCLC is based on the tumor stage. For advanced patients with multiple distant metastases (mostly stage IIIB to IV), chemotherapy, targeted therapy and newly-emergent immunotherapy have become the primary treatment. The standard treatment for advanced NSCLC is platinum-based two-drug combination chemotherapy, but chemotherapeutic drugs can only result in a very small improvement in the survival of patients with advanced NSCLC, whose PFS is only 3.1-3.5 months and OS is only 7.4-11.3 months [Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8.]. Immuno-oncology (IO) represented by programmed cell death 1 (PD-1) has also become one of the new standard first-line treatments for patients with unresectable locally advanced or metastatic NSCLC which has no driver gene but high expression of PD-1 (≥50%), but most NSCLC patients with driver gene do not respond to PD-1/PD-L1 inhibitors, either. Currently, the treatment pattern of patients with advanced NSCLC has been changed by the development of driver gene-based targeted therapy. Following *EGFR* gene mutation and *ALK* gene fusion, *MET* is considered another important driver gene of NSCLC. Abnormally activated MET pathways mainly consist of 3 types, i.e. *MET*ex14 skipping mutation, *MET* amplification and MET protein overexpression. Total incidence of *MET*ex14 skipping mutation is 3% in NSCLC, and approximately ranging 10%-30% in pulmonary sarcomatoid carcinoma (PSC) [Vuong HG, Ho ATN, Altibi AMA, et al. Clinicopathological implications of MET exon 14 mutations in non-small cell lung cancer - A systematic review and meta-analysis. Lung Cancer 2018;123:76-82.]. *MET*ex14 skipping does not coexist with other mutations of lung cancer such as EGFR, KRAS and ALK, indicating *MET*ex14 skipping is primary oncogenic driver [Frampton et al. 2015]. Molecular mechanism of *MET*ex14 skipping is shown in Figure 2-1 [Yin & Lu 2018].
The mOS of MET-TKI treatment naive NSCLC patients including PSC with *MET*ex14 skipping mutation is only 8.1 months [Awad MM, Leonardi GC, Kravets S, et al. Impact of MET inhibitors on survival among patients with non-small cell lung cancer harboring MET exon 14 mutations: a retrospective analysis. Lung Cancer. 2019;133: 96–102.

; Pasquini G, Giaccone G. C-MET inhibitors for advanced non-small cell lung cancer[J]. Expert Opinion on Investigational Drugs, 2018:13543784.2018.1462336.]. It is characterized by rapid growth, invasion, recurrence and metastasis [Maneenil K, Xue Z, Liu M, et al. Sarcomatoid Carcinoma of the Lung: The Mayo Clinic Experience in 127 Patients. Clin Lung Cancer 2018;19:e323-e333.]. The *MET*ex14 mutation is most commonly found in PSC and the prognosis of PSC is very poor regardless of diagnosis time or metastasis; two thirds of patients are not sensitive to conventional chemotherapy [Fishback NF, Travis WD, Moran CA, et al. Pleomorphic (spindle/giant cell) carcinoma of the lung. A

clinicopathologic correlation of 78 cases. Cancer 1994;73:2936-45.; Martin LW, Correa AM, Ordonez NG, et al. Sarcomatoid carcinoma of the lung: a predictor of poor prognosis. Ann Thorac Surg 2007;84:973-80. Yendamuri et al. 2012]. According to NCCN guidelines (2020 V2), for NSCLC patients without other gene drive mutations except for *MET*ex14 skipping mutation, first-line therapy is chemotherapy and/or immunotherapy. It has been found that in NSCLC patients with *MET*ex14 skipping mutation, in response-evaluable patients (n=24), the ORR was 17% and the median PFS was 1.9 months, and the responses were not enriched in tumors with PD-L1 high expression, indicating that NSCLC patients with *MET*ex14 skipping mutation are insensitive to anti-PD-1 therapy [Sabari et al. 2018]. However, in NCCN (2021 V1), *MET*ex14 skipping testing and treatment for NSCLC harboring *MET*ex14 skipping was added, and Capmatinib, a selective MET-TKI, and Crizotinib, a multi-targeted TKI, are one of the first line choices for *MET*ex14 skipping in NCCN guideline, and are also for the treatment of high-level *MET* amplification which are considered as emerging biomarkers. And the emerging data of highly selective MET inhibitor Capmatinib, Tepotinib and Savolitinib have shown promising efficacy. ORR in phase II GEOMETRY mono-1 study of Capmatinib and VISION study of Tepotinib was achieved ranging 41 - 68% in 1st or up to 3rd line of treatment in patients with NSCLC harboring *MET*ex14 skipping mutation [Wolf et al. 2020; Paik et al. 2020]; in Savolitinib monotherapy in Chinese NSCLC patients harboring *MET*ex14 skipping, ORR was 47.5% in sixty-one efficacy evaluable patients, and the tumor histology of 35.7% of the patients enrolled were PSC [Lu et al. ASCO 2020]. Therefore, it is necessary to further improve the knowledge and develop new therapeutic methods, including Glumetinib (SCC244), a highly specific MET kinase inhibitor, for patients with *MET*ex14 skipping.

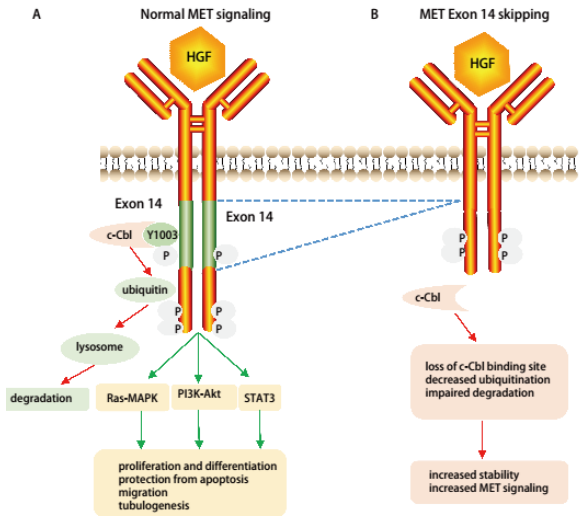


Figure 2-1 The Molecular Mechanism of *MET*ex14 Skipping

Upon binding with its ligand HGF, MET dimerization results in phosphorylation of multiple intracellular tyrosine residues, thus activating several downstream signaling cascades (Ras-MAPK, PI3K-Akt, etc.) and promoting cellular proliferation, migration and tubulogenesis. MET was degraded by E3 ubiquitin ligase c-Cbl. Exon 14 encodes the MET juxtamembrane domain containing c-Cbl tyrosine binding site (Y1003), which plays a significant part in the ubiquitination and degradation of the MET protein;

B: *MET*ex14 skipping leads to the loss of E3 ubiquitin ligase c-Cbl, thereby abrogating the ubiquitination and increasing the stability of MET.

2.2 Nonclinical Development of Glumetinib

2.2.1 Pharmacology

Glumetinib is an oral ATP competitive, reversible inhibitor with low nM IC_{50} for the MET receptor

tyrosine kinase. It is a highly specific MET kinase inhibitor having greater than 2400-fold selectivity for MET over other 312 kinase that were tested [Ai et al. 2017]. It is a Type I MET-inhibitor that binds to MET unique autoinhibitory conformation with characteristic interaction (π-stacking) with Y1230 in the MET ATP binding site. It has significant *in vitro* and *in vivo* anti-tumor activity with high sensitivity for MET-dependent non-small-cell lung cancer (NSCLC) and gastric cancer. Moreover, in all the tested models, the efficacy of Glumetinib at 10 mg/kg is comparable with that of Capmatinib at 15 mg/kg and crizotinib at 50 mg/kg. It has distinct competitive advantages including its high selectivity for MET kinase therefore potentially minimize off-target toxicities compared to multi-targeted MET inhibitors, its evident ability to identify select sensitive patients, and its capability to be integrated in combined medication regimens due to its highly selective specificity.

2.2.2 Pharmacokinetics

Within the dosage range of 2 to 18 mg/kg (rats) and 25 to 150 mg (dogs), the increase in area under the plasma drug concentration-time curve (AUC) of Glumetinib was in direct proportion of the dose. The plasma elimination half-life of Glumetinib in rats and dogs was 4.43 and 5.21 h, respectively. After intragastric administration, the absolute bioavailability of Glumetinib in rats (fasting) and dogs (feeding) was approximately 82% and 48%, respectively. After the rats were given intragastric administration of Glumetinib, it was mainly distributed in the liver, adrenal gland, digestive tract and kidneys. The volume of distribution at steady state (Vss) was 0.484 L/kg in rats and 3.63 L/kg in dogs. CYP3A4 was the main enzyme participating in the Glumetinib metabolism, and aldehyde oxidase did not participate in the metabolism of Glumetinib. After the rats were given intragastric administration of Glumetinib, the main *in vivo* metabolism route was N- or N'-demethylation (to M1-1 and M1-2) and N, N'-didemethylation (to M2). Glumetinib was mainly discharged through feces in the form of parent drug and metabolites. Glumetinib demonstrated low elimination (clearance [CL] was 2.33 mL/min/kg) in rats and moderate elimination (CL was 12.4 mL/min/kg) in dogs. The circulating metabolites of Glumetinib were preliminarily determined in patient plasma from study SCC244-101, the results showed that 9 metabolites were identified tentatively, and the chromatographic peak area of each metabolite was less than 5% of the parent drug. In view of the limited contribution of CYP3A4 to Glumetinib metabolism (< 5%), it is unlikely that the co-administration of Glumetinib with CYP3A4 inhibitors or inducers will cause problems in clinical use. Glumetinib had no inhibiting effect and no inducing effect on various CYP enzymes. Glumetinib had high permeability, and the efflux transporters is unlikely involved in the transport of Glumetinib range from 2.00 to 50.0 μM on Caco-2 cells.

2.2.3 Toxicology

In the safety pharmacological test, Glumetinib had no obvious influence on the central nervous system (CNS) in Sprague Dawley (SD) rats.

In an *in vitro* study using human HEK293 cells that stably expressing hERG (Human ether-a-go-go related gene) channels, the IC_{50} value of Glumetinib mediated hERG current inhibition was 3.30 μM.

Single oral dosing of Glumetinib in Beagle dogs with the Williams Latin-square dosing design (each dose received once with a washout period over 5 days) at three doses, 2, 8 and 32 mg/kg, did not affect cardiovascular and respiratory function. During the continuous administration experiment, when compared with the control group, no drug-related changes were seen in blood pressure,

electrocardiogram (ECG) parameters, respiratory parameters, and body surface temperature at 24 hours after administration in each administration period. No arrhythmia was observed in all animals. Therefore, Glumetinib had no obvious influence on the cardiovascular and respiratory systems in Beagle dogs.

The acute toxicity (single dose) test indicated that the maximal tolerated dose (MTD) of Glumetinib in both Sprague Dawley rats and Beagle dogs was 100 mg/kg.

The long-term toxicity (4 weeks) test indicated that the highest dose 100mg/kg in Sprague Dawley rats was tolerated, and the no observed effect level (NOEL) was 10 mg/kg. In Beagle dogs, the NOAEL was considered to be 5 mg/kg and the highest dose 60 mg/kg was tolerated. The main toxicity effects in Beagle dogs were changes in ECG parameters, gastrointestinal effects, lymphoid atrophy in thymus as well as increased myeloid cells and megakaryocytes in the bone marrow. At 5 mg/kg and 20 mg/kg, no QTcV changes were observed while at 60 mg/kg, increased heart rate in males, decreased PR interval in both males and females and prolonged QTcV in females were noted on Day 27. The ECG changes were recovered in the recovery phase.

Glumetinib did not show genotoxicity in the standard battery tests.

Please refer to IB for further information of Glumetinib (SCC244).

2.3 Clinical Development of Glumetinib

The clinical study data reported in this part are derived from three studies: two phase I clinical studies (SCC244-101 and SCC244-104) and one phase Ib/II clinical study (SCC244-108) which are ongoing in China. The clinical data presented is based on data cutoff date of November 4, 2019 (November 28, 2019 for PK).

In addition, a phase 1 study (SCC244-102) is being conducted in Japan to evaluate the safety, tolerability and pharmacokinetics of Glumetinib (SCC244) in patients with solid tumors in Japan. The clinical data from study SCC244-102 will be used along with data from other studies to determine RP2D for the global phase II study. As of April 16, 2020, 2 patients were enrolled at 200mg QD and are ongoing.

2.3.1 Human pharmacokinetics

Blood sample from patients (n=26) treated at 25, 50, 100, 200, 250, 300 and 400 mg in SCC244-101 and SCC244-104 studies for analysis as of the data cut-off date of November 28, 2019. PK analysis of Glumetinib has not been performed in SCC244-108 study as data cut-off date of November 28, 2019.

The human PK data shows that after oral administration of Glumetinib in cancer patients, the absorption of Glumetinib was rapidly post single and multiple dose, the median value of T_{max} was 2 to 3 h. Within the dose range of 25 mg to 400 mg, the systemic exposure of Glumetinib (C_{max}, $AUC_{0\text{-}24h}$) increased with the increase of dose after single and multiple dose administration; the systemic exposure of Glumetinib showed less than proportional to dose due to individual variability and possible absorption saturation with the increase of dose, The mean value of $t_{1/2}$ was 28.7 h, SCC244 is suitable for daily dosing; steady state was reached approximately by Day 8 following daily dosing, after reach steady state, no further accumulation was observed.

2.3.2 Clinical data from the ongoing study

As of November 4, 2019, there are 3 ongoing studies of Glumetinib in patients with advanced solid tumors (SCC244-101, SCC244-104 and SCC244-108) conducted in China. A total of 32 patients treated at 7 dose levels (25, 50, 100, 200, 250, 300, and 400 mg). Two patients experienced DLTs (grade 3 headache was reported in one patient, grade 3 rash and grade 3 pruritus were reported in another patient) at 300 mg (SCC244-104). One patient experienced DLT (grade 3 vomiting) at 400 mg (SCC244-101). The most common TEAEs (≥ 25%) were vomiting (14/32, 43.8%), headache (11/32, 34.4%), nausea (10/32, 31.3%), aspartate aminotransferase increased (10/32, 31.3%), bilirubin conjugated increased (10/32, 31.3%), blood alkaline phosphatase increased (10/32, 31.3%), hypoproteinemia (9/32, 28.1%) and alanine aminotransferase increased (8/32, 25%). The treatment of Glumetinib has been well tolerated with manageable toxicities, mainly grade 1 or 2. In the SCC244-108 study, among 7 patients treated at 200 mg, one patient experienced grade 3 cough due to progressive disease.

Twenty patients with advanced NSCLC in SCC244-101 and SCC244-108 studies were treated with Glumetinib with the Best Overall Response (BOR) of tumor assessment as follows: 1/20 (5%) Partial Response (PR) (200 mg), 4/20 (20%) Stable Disease (SD) (two in 200 mg and two in 400 mg), 9/20 (45%) Progressive Disease (PD) (two in 100 mg, three in 200 mg, four in 400 mg); 5 patients have not reached the time of 1st tumor assessment and 1 patients withdrew before 1st tumor assessment. One NSCLC patient with MET overexpression (IHC3+) treated at 200 mg achieved a confirmed PR at first tumor assessment (week 8th) and confirmed at week 16th with a duration of treatment of 11 months (SCC244-101 study).

In addition, after the data cut-off date, as of August 21, 2020, 36 advanced NSCLC patients with *MET*ex14 skipping were treated with Glumetinib in SCC244-108 study:

- Treatments of 22 of the 28 patents treated at 300 mg dose level are on-going, and 7 patients out of the 15 efficacy evaluable patients were reported with the tumor assessment as PR (4 confirmed PR, treatment of other 3 is on-going and waiting confirmation), the preliminary ORR = 46.7%.
- Two of the 8 patents treated at 200 mg dose level were reported with the tumor assessment as PR, another patient was reported as SD and changed to PR at 6 weeks after the dose was titrated to 300 mg, the preliminary ORR = 37.5%.

Please refer to IB for further information of clinical safety and tolerance of Glumetinib (SCC244).

2.4 Purpose and Rationale

The mesenchymal-epithelial transition factor (MET) aberrations including gene amplification, protein overexpression and mutation have been described as oncogenic drivers in several solid tumors. MET mutations that disrupt the branch point and/or 3' splice site of intron 13, and the 5' splice site of intron 14 result in aberrant splicing and exon 14 skipping, which results in oncogenesis driven by increased levels of MET [Drilon 2016; Frampton et al. 2015]. *MET* exon 14 (*MET*ex14) skipping mutation occurs in approximately 3% of non-small cell lung cancer (NSCLCs) and approximately ranging 10%-30% of pulmonary sarcomatoid carcinomas (PSC) and are often associated with poor prognosis. *MET*ex14 skipping mutations are almost mutually exclusive with the known driver genes such as EGFR, KRAS, HER2 mutations and ALK, ROS1 and RET rearrangements suggesting that they are one of the primary oncogenic drivers in NSCLC [Frampton et al. 2015]. Patients with NSCLC harboring *MET*ex14

skipping are often significantly older (median 72-year old in a recently analysis reported by Awad et al.) compared to patients with EGFR, KRAS mutation or ALK rearrangement; however, it is controversial in terms of gender and smoking status in NSCLC patients harboring *MET*ex14 skipping [Awad MM, Leonardi GC, Kravets S, et al. Impact of MET inhibitors on survival among patients with non-small cell lung cancer harboring MET exon 14 mutations: a retrospective analysis. Lung Cancer. 2019;133: 96–102.

Vuong HG, Ho ATN, Altibi AMA, et al. Clinicopathological implications of MET exon 14 mutations in non-small cell lung cancer - A systematic review and meta-analysis. Lung Cancer 2018;123:76-82.].

Emergent clinical data of MET inhibitors have demonstrated strong efficacy in patients with advanced NSCLC harboring *MET*ex14 skipping mutation, indicating that *MET*ex14 skipping may become a new target in the treatment of NSCLC (i.e., phase II GEOMETRY mono-1 study of Capmatinib, and VISION study of Tepotinib). ORR in these studies was achieved ranging 41 - 68% in 1st or up to 3rd line of treatment in patients with NSCLC harboring *MET*ex14 skipping mutation [Wolf J, Seto T, Han JY, et al. Capmatinib in MET Exon 14-Mutated or MET-Amplified Non-Small-Cell Lung Cancer[J]. New England Journal of Medicine, 2020, 383(10):944-957.; Paik PK, Felip E, Veillon R, et al. Tepotinib in Non–Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations[J]. New England Journal of Medicine, 2020, 383(10)..]. A phase II study of Savolitinib monotherapy in Chinese NSCLC patients harboring *MET*ex14 skipping mutation also showed promising results. ORR was 47.5% in sixty-one efficacy evaluable patients [Lu et al. ASCO 2020].

Glumetinib (SCC244) is an oral ATP competitive, reversible inhibitor with low nM IC_{50} for the MET receptor tyrosine kinase. It is a highly specific MET kinase inhibitor having greater than 2400-fold selectivity for MET over other 312 kinase that were tested [Ai J, Chen Y, Peng X, et al. Preclinical evaluation of SCC244 (Glumetinib), a novel, potent and highly selective inhibitor of c-Met in MET-dependent cancer models[J]. Molecular Cancer Therapeutics, 2017:molcanther.0368.2017.]. It is a Type I MET-inhibitor that binds to MET unique autoinhibitory conformation with characteristic interaction (π-stacking) with Y1230 in the MET ATP binding site.

As of November 4, 2019, there were3 ongoing studies of Glumetinib in patients with advanced solid tumors (SCC244-101, SCC244-104 and SCC244-108) conducted in China. There werea total of 32 patients treated at 7 dose levels (25, 50, 100, 200, 250, 300, and 400 mg). The treatment of Glumetinib waswell tolerated with manageable toxicities, mainly grade 1 or 2 vomiting, headache, nausea, AST elevation and bilirubin elevation. Two patients experienced DLTs (grade 3 headache was reported in one patient, grade 3 rash and grade 3 pruritus were reported in another patient) at 300 mg (Study SCC244-104). One patient experienced a DLT (grade 3 vomiting) at 400 mg (Study SCC244-101). One NSCLC patient with MET overexpression (IHC3+) treated at 200 mg achieved a confirmed PR at first tumor assessment (week 8^{th}) and confirmed at week 16^{th} with a duration of treatment of 11 months (SCC244-101 study). In Study SCC244-108, among 7 patients treated at 200 mg, one patient experienced grade 3 cough due to progressive disease.

The purpose of the Phase Ib part (China only) of this study is to further assess the safety, tolerability, PK and preliminary efficacy of Glumetinib in NSCLC patients with MET-alterations.

For the Phase II part of the study (globally), the main objectives are to evaluate the efficacy of Glumetinib as monotherapy in patients with advanced NSCLC harboring *MET*ex14 skipping mutation,

as well as the safety, tolerability and pharmacokinetics.

2.5 Rationale for the Dose and Frequency of Administration in Patients

Based on safety, PK and preliminary efficacy data, Glumetinib 300 mg once daily dosing was selected as recommended dose for phase 2 study (RP2D).

In study SCC244-101, the FIH study in NSCLC, a total of 19 patients have been treated at 4 dose levels (100, 200, 300, and 400 mg), the treatment of Glumetinib has been well tolerated with manageable toxicities, mainly grade 1 or 2 headache, vomiting, nausea, oedema peripheral, dizziness, decreased appetite, bilirubin elevation and ALT elevation, no MDT was identified, one patient experienced a DLT (grade 3 vomiting) at 400 mg, no DLT was identified at other dose levels. 200 mg QD and 300 mg QD dose were selected as RD for further clinical evaluation.

In addition, as of the cut-off date August 21, 2020, 36 advanced NSCLC patients with *MET*ex14 skipping were treated with Glumetinib in SCC244-108 study:

- Treatments of 22 of the 28 patents treated at 300 mg dose level are on-going, and 7 patients out of the 15 efficacy evaluable patients were reported with the tumor assessment as PR (4 confirmed PR, treatment of other 3 is on-going and waiting confirmation), the preliminary ORR = 46.7%.
- Two of the 8 patents treated at 200 mg dose level were reported with the tumor assessment as PR, another patient was reported as SD and changed to PR at 6 weeks after the dose was titrated to 300 mg, the preliminary ORR = 37.5%.

The human PK data shows that after oral administration of Glumetinib in cancer patients, the absorption of Glumetinib was rapidly post single and multiple dose administration, the median value of T_{max} was 2 to 3 h. Within the dose range of 25 mg to 400 mg, the systemic exposure of Glumetinib (C_{max}, AUC_{0-24h}) increased with the increase of dose after single and multiple dose administration; the systemic exposure of Glumetinib showed less than proportional to dose due to individual variability and possible absorption saturation with the increase of dose. The mean value of $t_{1/2}$ was 28.7 h, Glumetinib is suitable for daily dosing; steady state was reached approximately by Day 8 following daily dosing, after reaching steady state, no further accumulation was observed.

Overall, 300 mg QD dose were well tolerated and with desirable efficacy profile; compared to 200 mg QD dose, 300 mg QD dose has relative higher systemic exposure and better efficacy profile, therefore 300 mg QD dose was selected as RP2D in this study.

3. Study Objectives and Endpoints

Table 3-1 Study Objectives and Endpoints

Study objectives	Study endpoints
Phase Ib	
Primary objective: 1. To evaluate the tolerability and safety of Glumetinib in patients with locally advanced or metastatic NSCLC including PSC.	Primary endpoint: 1. Tolerability and safety: incidence, duration and severity of adverse events (AEs), physical examination, laboratory data, vital signs and electrocardiogram (ECG) changes.

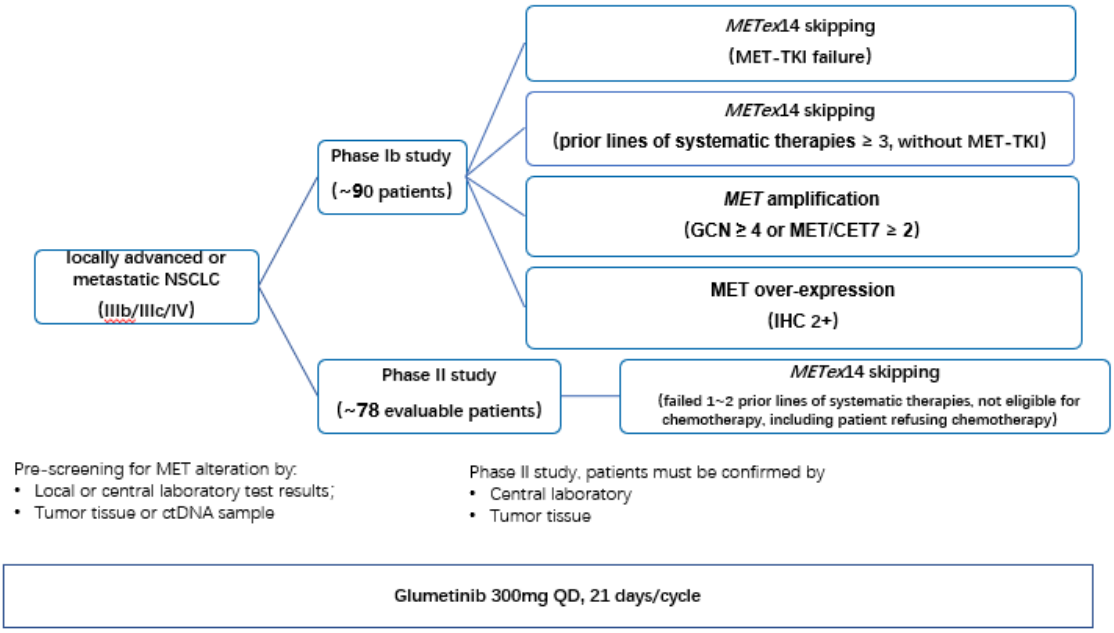
Secondary objectives: 1. Preliminary efficacy of Glumetinib in patients with local advanced or metastatic NSCLC harboring MET-aberrations. 2. To evaluate the PK characteristics of Glumetinib with Population PK analysis.	Secondary endpoints: 1. Object Response Rate (ORR), Duration of Response (DOR), Disease Control Rate (DCR), Time to Response (TTR), Progression-Free Survival (PFS), 6-month PFS rate assessed by investigator and Overall Survival (OS).
Phase II	
Primary objective: 1. To evaluate the antitumor efficacy of Glumetinib (confirm ORR by BIRC) in locally advanced or metastatic NSCLC harboring *MET*ex14 skipping mutation.	Primary endpoint: 1. ORR will be based on the blinded independent review committee (BIRC). Tumor response assessments will be made based on RECIST 1.1.
Secondary objectives: 1. To evaluate ORR (by investigator); DOR, DCR, TTR, PFS, 6-month PFS rate by BIRC and by investigator; and OS. 2. To investigate the safety and tolerability of Glumetinib. 3. To evaluate the PK characteristics of Glumetinib with Population PK analysis.	Secondary endpoints: 1. ORR assessed by investigator. 2. DOR, DCR, TTR, PFS, 6-month PFS rate by BIRC and by investigator and OS. 3. Safety: incidence, duration and severity of AEs, physical examination, laboratory data, vital signs and ECG changes.

4. Study Design

4.1 Overall Study Design

This is an open-label, multi-countries, multicenter phase Ib/II study including two parts: Phase Ib in NSCLC patients with MET alterations and Phase II study in patients with locally advanced or metastatic NSCLC (stage IIIb, IIIc or IV) harboring *MET*ex14 skipping mutation.

Figure 4-1 Study Design



Glumetinib will be administered orally in continuous once daily (QD) 21-day treatment cycles until disease progression, unacceptable AE, withdrawal of consent or other criteria for termination of study treatment. There are no breaks in dosing between cycles. Patients should follow the instructions of the treating physician on study drug administration during treatment. Patients are required to fast for at least 2 hours before and 1 hour after administration of Glumetinib.

In order to evaluate potential variations in Glumetinib drug exposure in different ethnic groups, there will be a safety run-in of Glumetinib at the dose of 300 mg in patients from the US while China and other countries continue enrolling patients at 300 mg.

Phase Ib (China only)

Patients with locally advanced or metastatic NSCLC including PSC (stage IIIb, IIIc or IV) who have the MET alteration that has been pre-screened by local or Sponsor-designated central laboratory as listed below and meet the inclusion/exclusion criteria in the protocol will be enrolled.

- Patients with *MET*ex14 skipping mutation who had previously treated by other MET inhibitor(s)
- Patients with *MET*ex14 skipping mutation who had received 3 or more lines prior systemic therapies without MET inhibitor for the advanced NSCLC or
- Patients with *MET* amplification (GCN $\geqslant$ 4 or *MET*/CEP7 ratio $\geqslant$ 2)
- Patients with MET over-expression (IHC 2+)

During the phase Ib study, MTD or RP2D will be confirmed based on the latest clinical study data of Glumetinib. The phase II study will be started once the MTD or RP2D is confirmed. Phase Ib study will be continued to further evaluate the tolerability, safety, preliminary efficacy and pharmacokinetics of Glumetinib in the specified subgroup of NSCLC patients. Approximately 90 patients will be enrolled. The purpose of the Phase Ib study is to assess the tolerability, safety, preliminary efficacy and pharmacokinetics of Glumetinib in the specified subgroup of NSCLC patients.

Safety Run-in (US only)

A minimum of 6 patients with MET-alterations (meeting the eligibility for either Phase Ib or Phase II) from the US will be enrolled. Once the first 6 patients at 300 mg are evaluated for DLT and no more than one of 6 DLT-evaluable patients experiencing DLT, additional patients could be enrolled in Phase 2. If > 1/6 patients experience DLT at 300 mg, 200 mg will be evaluated. In addition, based on the evaluation of safety, PK and efficacy, 400 mg may be evaluated according to the same evaluation criteria for DLT set forth for 300 mg. If > 1/6 patients experience DLT at 400 mg, 400 mg will be deemed not tolerated and no additional patients will be treated at 400 mg for the study. If no more than 1 of the 6 patients who have been treated at 400 mg and evaluated for DLT experiences a DLT, a comprehensive review of all available safety, PK, and efficacy data from ongoing SCC244 studies will be performed. Based on this review, a final RP2D will be selected to continue further enrollment until meeting the prespecified sample size for Phase II at all sites globally.

A DLT-evaluable patient is defined as either experienced a DLT during the first 21-day of the treatment or has received at least 80% of the assigned doses (i.e.17 of the 21 days of Glumetinib doses). DLT is defined as below:

A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that meets any of the following criteria assessed using the NCI-CTCAE Version 5.0 and reported to be at least possibly related to the study drug by the Principal Investigator and/or the Sponsor during the DLT evaluation period. The DLT observation period starts on Day 1 up to Day 21 of Cycle 1 (21 days).

- Hematological toxicity:
    - CTCAE Grade 4 neutropenia (absolute neutrophil count < $0.5x10^9$/L)
    - CTCAE Grade 4 thrombocytopenia (platelet count< 25 $x10^9$/L)
    - CTCAE Grade 3 thrombocytopenia accompanied by clinically significant bleeding tendency (platelet count < 50 $x10^9$/L)
    - ≥ CTCAE Grade 3 febrile neutropenia (absolute neutrophil count <$1.0x10^9$/L with a single temperature of > 38.3°C or a sustained temperature of ≥ 38 °C for more than one hour)
- Non-hematological toxicity, ≥ CTCAE Grade 3*. Additionally, the following will be judged to be a DLT:
    - Liver transaminase elevation (AST or ALT) >3 x the upper limit of normal (ULN) with concurrent increase in total bilirubin >2 x ULN without evidence of cholestasis or alternative explanations (e.g., viral hepatitis, disease progression in the liver)
    - Liver transaminase elevation >8 x ULN or total bilirubin > 5 x ULN
    - CTCAE Grade 4 vomiting, diarrhea, and constipation, regardless of duration
    - CTCAE Grade 4 electrolyte disturbance, regardless of duration
    - CTCAE Grade 3 electrolyte disturbances that require hospitalization

- CTCAE Grade 2 pneumonitis lasting > 7 days or recurring in the same cycle

• Other adverse events:

- Any death not clearly due to the underlying disease or extraneous causes
- Any adverse events that is unrelated to disease progression, intercurrent illness, or concomitant medications requiring permanent discontinuation of the study drug
- Any grade toxicity is clinically significant and/or unacceptable and is judged to be a DLT by the Investigator and/or Sponsor

*The following CTCAE Grade 3 adverse event or laboratory abnormalities will not be considered as DLT:

- Nausea/vomiting, diarrhea, and constipation return to grade 2 by appropriate supportive treatment within 3 days
- Fatigue for less than 7 days after proper supportive treatment
- Headache for less than 7 days after proper supportive treatment
- Laboratory abnormalities without clinical significance that are not already specified in the DLT criteria above will not be considered as DLT (e.g., Grade 3 elevations in serum amylase or lipase that are not associated with symptoms or clinical manifestations of pancreatitis)

In the absence of clinical abnormality, repeat laboratory testing should be performed to confirm significant laboratory findings prior to designation as a DLT. However isolated laboratory changes of any grade without clinical sequelae or clinical significance are not considered DLTs.

Phase II (globally)

The phase II study is a single-arm study. Patients with locally advanced or metastatic NSCLC (stage IIIb, IIIc or IV) harboring *MET*ex14 skipping mutation that have been pre-screened by local or Sponsor-designated central laboratory, who are not eligible for chemotherapy or refuse chemotherapy after well-informed or have failed one or two prior lines of systemic therapies and have not had prior MET inhibitor for the advanced NSCLC, and meet the inclusion/exclusion criteria in the protocol, will be enrolled.

Approximately 78 evaluable local advanced or metastatic NSCLC patients with *MET*ex14 skipping will be enrolled to evaluate the antitumor efficacy of Glumetinib [to confirm ORR by a Blinded Independent Review Committee (BIRC)]. Secondary objectives are to evaluate DOR, DCR, TTR, PFS, 6-month PFS rate, OS, safety and PK. An evaluable patient must meet the following criteria: 1. *MET*ex14 skipping mutation confirmed by analysis at sponsor designated central lab; 2. treated at RP2D dose; 3. at least have valid baseline tumor assessment.

Enrollment in other countries may be increased per country specific health authority request.

Phase Ib and Phase II will enroll patients concurrently; after the completion of enrollment of Phase II, Phase Ib will continue enrolling patients till archiving the planned subject number.

Post Marketing Clinical Study (Japan only)

After the approval of new drug application in Japan, the remaining Japanese patients will be rolled over to a post marketing clinical part of this study in accordanc with GVP and GPSP in Japan . This part will continue until the product is commersially available in Japan and accessible to the enrolled patients.

4.2 Interim analysis

Interim analysis of safety will be performed for the Phase II part of the study when approximately 25%, 50% and 75% of patients are enrolled and treated for at least for one cycle (21 days). This interim analysis will be reviewed by an Independent Data Monitoring Committee (IDMC). A complete description of the composition of the IDMC and details on the interim analysis process will be provided in a separate safety review charter. In addition, the Sponsor will share safety data from the study with all primary investigators throughout the conduct of the study.

4.3 End of Study

The study is considered complete when all patients treated have been followed up for at least 12 months or withdraw consent or die, whichever occurs first. After the completion of the study, if a patient still not reaches disease progression, the patients requires administration of Glumetinib and which has been assessed as beneficial per the investigator, the Sponsor will continue to provide Glumetinib in the form of a complimentary medication. At that time, patients will follow and complete the procedures described in the Study Schedules for the EOT Visit and Safety Follow-up procedures before entering the drug donation process. Subsequently all the data will not be collected and recorded in the EDC, but if any SAE happened during the medication, it's still required to report to Sponsor as per section 8.3.2.

4.4 Study Stopping Criteria

To augment safety of patients enrolled to the study, interim analysis of safety will be performed for the Phase II part of the study when approximately 25%, 50% and 75% of patients are enrolled and treated for at least for one cycle (21 days). These interim analyses will be reviewed by an Independent Data Monitoring Committee (IDMC).

If any of the following toxicity criteria are met at any time during the study that the Sponsor becomes aware of, further patient enrollment will be suspended until after additional thorough evaluation of all safety data:

- > 1 death (other than disease progression) that is at least possibly* related to the study drug (*the relationship between the study drug and AE should be evaluated by both the investigator and the sponsor)
- Occurrence of two or more Grade 4 adverse events that are at least possibly related to the study drug

Following the review of safety data, the status of the study will be one of the following:

- Resumed unchanged
- Resumed with modifications to the protocol
- Terminated

Patient safety will be monitored on a continuous basis during this study until the last patient completes his/her last scheduled study visit/assessment.

4.5 Premature Termination of Study

Haihe Biopharma Co., Ltd. may terminate the study at any time for any reason. In such case, it is necessary to arrange patients to receive end-of-treatment visit (EOT) as soon as possible, conduct EOT evaluation in patients in whom the study is prematurely terminated or who withdraw informed consent form. See Section 12 and Table 1-1 for further information. The company will notify the investigator of other regulations to be followed to ensure adequate measures are taken to protect patients' interests. The investigator will be responsible for notifying the IRB and/or EC that the study has been terminated prematurely.

5. Study Populations

Phase Ib study population (China only):

Approximately 90 patients with locally advanced or metastatic NSCLC (Stage IIIb, IIIc or IV). All patients should carry at least one of the following MET alterations (confirmed by local or central laboratory):

- Patients with *MET*ex14 skipping mutation who had previously treated by other MET inhibitor(s)
- Patients with *MET*ex14 skipping mutation who had received 3 or more lines prior systemic therapies without MET inhibitor for the advanced NSCLC
- Patients with *MET* amplification (GCN $\geqslant$ 4 or *MET*/CEP7 ratio $\geqslant$ 2)
- Patients with MET over-expression (IHC2+)

Phase II - Safety Run-in Population (US only):

A minimum of 6 patients who meeting the eligibility for either Phase Ib or Phase II.

Phase II study population (globally)

Approximately 78 evaluable patients with locally advanced or metastatic NSCLC (Stage IIIb, IIIc or IV) harboring *MET*ex14 skipping mutation that has been pre-screened by local or Sponsor-designated central laboratory, who are not eligible for chemotherapy or refuse of chemotherapy after well-informed) or have failed one or two prior lines of systemic therapies and have not had prior MET inhibitor for the advanced NSCLC.

5.1 Inclusion Criteria of Phase Ib and II study

Patients who fulfill all of the following requirements may enter the study:

1. Provide informed consent to participate in this study voluntarily.
2. Male and female patients $\geqslant$ 18 years of age (or having reached the age of majority according to local laws and regulations, if the age is > 18 years).
3. Histologically or cytologically confirmed diagnosis of NSCLC including PSC.
4. Patients with stage IIIb or IIIc NSCLC who are not candidates for definitive surgical resection or

concurrent chemoradiation or patients with stage IV NSCLC (AJCC version 8).

5. **For phase Ib study,** patients should carry at least one of the following MET alterations (by local or Sponsor-designated central laboratory screening):
   - *MET*ex14 skipping mutation who had previously treated by other MET inhibitor(s) or
   - *MET*ex14 skipping mutation who had received 3 or more lines prior systemic therapies without MET inhibitor for the advanced NSCLC or
   - *MET* amplification (GCN ⩾ 4 or *MET*/CEP7 ratio ⩾ 2) or
   - MET over-expression (IHC2+).
6. **For Phase II study,** patients with *MET*ex14 skipping mutation in tumor or ctDNA samples (local testing is acceptable for eligibility; all patients in Phase II study will have confirmation of *MET*ex14 skipping mutation by Sponsor-designated central laboratory but this result is not necessary for eligibility).
7. Availability of tumor tissue sample (either fresh tumor biopsy or archival tumor tissue sample); for patients of phase II study (not mandatory for safety run-in), if screened and enrolled based on local test results of *MET*ex14 skipping, the tumor tissue sample must be available for testing before C2D1; if local testing results meet the requirements, patients of phase Ib are exempt from the central laboratory confirm.
8. **For Phase II study,** patients are not eligible for chemotherapy or refuse chemotherapy after well-informed or have failed one or two prior lines of systemic therapies for the advanced NSCLC.
   - Treatment failure is defined as documented disease progression or intolerance to treatment.
   - Maintenance therapy given after first line chemotherapy will be considered as part of the first line if given to patients with documented response or stable disease before starting the maintenance therapy.
   - Prior neoadjuvant/adjuvant systematic therapies will count as one prior line of treatment, provided that disease recurred within 12 months of completion of neoadjuvant/adjuvant therapy.
9. **For Phase II study,** at least one measurable lesion as per RECIST 1.1. (A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.)
10. ECOG Performance Status (PS): 0-1.
11. Adequate bone marrow reserve, renal and liver function:
    - Absolute neutrophil count ⩾ 1.5×10^9/L;
    - Hemoglobin ⩾ 9 g/dL;
    - Platelet count ⩾ 75×10^9/L;
    - Serum total bilirubin⩽ ULN (⩽ 3 × ULN for patients with Gilbert’s syndrome);
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ⩽ 2.5 × ULN (⩽ 5.0 × ULN for patients with hepatic metastasis);

- Creatinine clearance (calculated* or measured value**) ⩾ 50 mL/min

  *For calculated creatinine clearance (Ccr) value, the eligibility should be determined using the Cockcroft-Gault formula:

  - Male Ccr (mL/mim) = body weight (kg) x (140-age)/[72 x creatinine (mg/dL)]
  - Female Ccr (mL/min) = male Ccr x 0.85

  ** A measured value

- International normalized ratio (INR) < 1.3 (or < 3.0 if on anticoagulation)

5.2 Exclusion Criteria of Phase Ib and II study

Patients who meet any of the following criteria shall be excluded from the study:

1. Patients with targetable activating EGFR mutation, ALK rearrangement, ROS1 rearrangement, BRAF mutation or NTRK fusion that have available standard of care therapies.
2. Patients who have symptomatic CNS metastasis which is neurologically unstable or those who have CNS disease requiring increase in the dose of steroid. (Note: Patients with controlled CNS metastasis can participate in the trial. Before entering the study, patients should have finished radiotherapy, or have received operation for CNS tumor metastasis at least two weeks before. Patients' neurological function must be in a stable state; no new neurological deficit is found during clinical examination and no new problem is found during CNS imaging examinations. If patients need to use steroids to treat CNS metastasis, the therapeutic dose of steroid should be stable for ⩾ 3 months at least two weeks prior to entering the study with treatment dose no more than dexamethasone 4 mg daily or an equivalent dose of steroids.)
3. Prior exposure to MET-directed therapy (except patients in Phase Ib study).
4. Evidence of past or current primary malignancies other than NSCLC (except for non-melanoma skin cancer, in situ breast cancer or in situ cervical carcinoma and superficial bladder cancer, or other cancer curatively treated and with no evidence of disease for at least 5 years).
5. Patients with clinically significant cardiovascular disease, including:
   - NYHA Class III or higher congestive heart failure;
   - History or current evidence of serious uncontrolled arrhythmias;
   - Acute myocardial infarction, severe or unstable angina pectoris, coronary artery or peripheral artery bypass graft received within 6 months prior to the first dose;
   - Left ventricular ejection fraction (LVEF) < 50%;
   - Fridericia’s corrected QT interval (QTcF) > 460 ms on ECG conducted during screening
   - Congenital long QT syndrome, or any known history of torsade de pointes (TdP), or family history of unexplained sudden death;
   - Clinically uncontrolled hypertension (after standard antihypertensive treatment, systolic blood pressure ⩾ 140 mmHg and/or diastolic blood pressure ⩾ 90 mmHg);
6. Any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting

study treatment with the exception of alopecia and grade 2 prior neuropathy.

7. Known HIV infection with a history of acquired immunodeficiency syndrome (AIDS)-defining opportunity infection within the past 12 months; active hepatitis B and hepatitis C. Patients whose test results meet one of the following will not be enrolled:
    - For patients in China and Japan, confirmed HIV antibody positive. For patients in the US, patients with a history of HIV but no history of AIDS or an AIDS-defining opportunistic infection are allowed to be enrolled;
    - serum HBsAg positive and HBV DNA>200 IU/ml or 1000 copies/mL;
        - For patients in Japan, whose results are HBsAg antigen negative; however, when HBsAb or HBcAb positive, the patients whose HBV DNA < 200 IU/ml or 1000 copies/mL could be enrolled.
    - serum HCV antibody and HCV RNA positive.
8. Anticancer therapy (including chemotherapy, targeted therapy, biotherapy, hormone therapy, traditional Chinese medication with lung cancer indication or other investigational agents) within 4 weeks or 5 times of half-lives (whichever is shorter) prior to the first dose of the study drug or who have not recovered from the side effect of such therapy.
9. Radical radiation therapy (including radiation therapy for over 25% bone marrow) within 4 weeks prior to the first dose of the investigational product or received local palliative radiation therapy for bone metastases within 2 weeks.
10. Major surgery or had significant traumatic injury within 28 days prior to the first dose of the investigational product.
11. Patients who have to receive treatment (definite strong CYP3A4 inhibitor or inducer [appendix 6]; in addition, herbals/supplements containing St. John's wart [*Hypericum perforatum* L.] and Sevillia orange etc. should also be avoided.) that is prohibited during the study and those who cannot discontinue drugs (e.g. antiarrhythmic agent) that may lead to QTc interval prolongation and with known risk of torsade de pointes. Additionally, patients who have to receive treatment of strong inhibitor for CYP2C8 and/or CYP2C9 [appendix 6] and substrates or inhibitor for transporter [appendix 7] will be excluded in safety run-in part of the study.
12. Any diseases or medical conditions, at the investigator's discretion, that may be unstable or influence their safety or study compliance, including organ transplantation, abuse of psychotropic medication, alcohol abuse or history of drug abuse.
13. Other serious illness or medical conditions at the investigator's discretion, that may influence study results, including but not limited to serious infection, diabetes, cardiovascular and cerebrovascular diseases or lung disease.
14. Patients with a history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment or any evidence of clinically active ILD.
15. Pregnant or breast-feeding patients. Pregnancy refers to the state of a woman between fertilization and the end of pregnancy confirmed by positive laboratory hCG test (> 5 mIU/mL). Breast-feeding woman can become eligible for this study if she stops breast-feeding, however cannot restart the

breast-feeding on/after the completion of the study treatment.

16. Man and woman with childbearing potential (WOCBP refer to appendix 3) not using effective contraception (refer to appendix 3) during the trial and within 6 months after the end of treatment.

5.3 Pre-screening Failure

Pre-screening failure refers to the patients who signed ICF for pre-screening, but archived tumor tissue or fresh biopsy samples are not qualified for testing or have negative test results for MET alterations, including *MET*ex14 skipping mutations, *MET* amplification or MET overexpression.

5.4 Screening Failure & Rescreening

"Screening failure" refers to withdrawal from the study prior to enrollment after signing an informed consent form. Any patient confirmed as a "screening failure" should not be rescreened unless one of the following conditions has been met. The patient must sign a new informed consent form while rescreening and be assigned a new identity code. In addition, patients can only be rescreened once.

- Patients meet the inclusion criteria of the clinical study as a result of revision of the study protocol.
- The inclusion criteria leading to screening failure will not result in rescreening failure again because patients' condition has changed.
- Patients have finished screening and meet all inclusion criteria but are not enrolled into the study for some extenuating circumstance (e.g. severe weather, children getting sick).

The investigator should contact and consult with the sponsor's medical monitor before rescreening patients. Examinations of hepatitis B, hepatitis C, HIV, height, tumor evaluation (RECIST 1.1) finished within 28 days prior to C1D1 do not need to be re-conducted.

Repeated laboratory test (only once) during screening is not considered as rescreening.

5.5 Criteria for Termination of Treatment with the Study Drug

Patients may withdraw the consent for taking part in the study at any time for any reason to stop the treatment and will not be punished and further treatment will not be influenced. There will be no substitutes for patients who withdraw from the treatment. In all cases, reasons for patients' termination of treatment should be recorded in the original medical record and eCRF. In case there are several reasons of termination of study drug, the investigator should point out the primary reason. In the event of termination of treatment with the study drug for an adverse event, the investigator should collect outcome information of the adverse event as far as possible. Patients' treatment will be terminated in any of the following conditions:

- Progressive disease defined by RECIST 1.1
- Clinical progression
- Unacceptable adverse events (AEs), or change in underlying condition such that the patient can no longer tolerate therapy, i.e., a dose delay of > 21 days from the scheduled start day of the next cycle
- The investigator determines to terminate the patient's treatment, including the need for other anticancer therapy not specified in the protocol, or surgery or radiotherapy to the only site(s) of disease being evaluated in the protocol

- Death
- Loss to follow-up
- End of the whole clinical study
- Pregnancy
- Major protocol deviation (The sponsor will assess whether the study treatment should be terminated.)
- Patients or their statutory guardians request to withdraw from the study treatment or withdraw from the study and withdraw the informed consent form. If a patient requests to stop treatment, it is necessary to inquiry whether or not the patient is willing to continue taking part in study evaluation and survival follow-up (e.g. by telephone). If the patient asks to withdraw from the whole study (including study evaluation and survival follow-up), it should be clearly recorded in the original record and eCRF.)

Upon discontinuation of Glumetinib treatment the investigator is to ensure the following:

- The Clinical Research Associate (CRA) must be notified immediately; and
- The Study treatment Discontinuation Form, which is a electronic case report form (eCRF), must be completed, specifying the primary reason for the patient's withdrawal from the study.

If there is strong evidence of clinical benefit and reasons to justify continuation of Glumetinib dosing, even though treatment discontinuation criteria have been met, this decision must be reviewed with the Sponsor on a case-by-case basis, and continuation of therapy may be allowed assuming all other treatment resumption criteria have been met. The following criteria must be met to continue treatment beyond RECIST-defined radiological progression of disease:

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

5.6 Criteria for Early Withdraw from Study

Patients may withdraw the consent for taking part in the study at any time for any reason to withdraw from the study and will not be punished and further treatment will not be influenced. The investigator can determine the patient withdraw from the study at any time depending on the patient's clinical needs.

Patients will early withdraw from the study in any of the following conditions:

- Patients or their statutory guardians request to withdraw from the study and withdraw the informed consent form. If a patient requests to stop study treatment and study procedure, it is necessary to inquiry whether or not the patient is willing to continue taking part in survival follow-up (e.g. by telephone). If the patient asks to withdraw from the whole study (including

survival follow-up), it should be clearly recorded in the original record and eCRF.)

- The investigator, sponsor, EC/IRB requests the patient early withdraw from the study due to safety, regulation or other reasons, such as the significant non-compliance with the study procedure and/or study treatment
- Death
- Loss to follow-up

In all cases, reasons for patient early withdraw from the study should be recorded in the original medical record and eCRF. The unused study drug should be count and return. In case there are several reasons of early withdraw from study, the investigator should point out the primary reason. In the event of withdraw from the study due to an adverse event, the investigator should collect outcome information of the adverse event as far as possible. When the patient loss to follow-up, the investigator should try his/her best to contact the patients or their statutory guardians (via telephone, email etc. according to the registration information), in order to obtain the reason of drug interruption, and recommend the patients back for EOT visit. If the investigators have tried all the available methods and cannot contact the patient, the patient is “loss to follow-up”. The investigator should document all these attempts of contacts. There will be no substitutes for patients who early withdraw from the study.

6. Treatment

6.1 Investigational Product

6.1.1 Information of the investigational product

Investigational product generic name: Glumetinib

Dosage form: tablet

Strength: 50 mg/tablet

Administration route: oral administration

6.1.2 Packaging and Labeling

Glumetinib is manufactured as pink, capsule-shaped tablet and will be provided in a sealed packaging with an open label (marking the patient's identification number in the label). The label will also include content and quantity of Glumetinib, protocol number, batch number, administration instructions, storage instruction and expiry date.

The drug will be labeled using the local language and per the regulatory requirements of different countries. The label will contain the storage condition of the drug.

6.1.3 Storage

Glumetinib tablets should be stored in accordance with the storage conditions described on the label. All study medication must be kept in a locked area with access restricted to specific personnel.

6.1.4 Randomization

Not applicable.

6.1.5 Drug Accountability

In accordance with the International Council for Harmonization (ICH) and local regulatory requirements, the investigator and/or the person responsible for dispending investigational drug must be able at all times to account for all investigational product provided to this site. The appropriate site personnel must acknowledge receipt of all Glumetinib, either by signing forms included in each shipment or via other means (i.e. IXRS).

Dose reduction, interruption and reason for these actions must be recorded in the patient's source document.

At the conclusion of the study, all unused Glumetinib shipped to the investigator must be returned to the Sponsor or designated Contract Research Organization (CRO). If on-site destruction is required by site policy, such requirements much be documented in the institution's Standard Operating Procedures (SOPs) and provided to the Sponsor or its representative for review.

No Glumetinib is to be used outside of this study.

6.2 Treatment

6.2.1 Administration dose and cycle

Phase Ib & II: Starting dose of 300 mg continuous QD will be administered in 21-day treatment cycles.

For the patients enrolled before RP2D adjusted to 300mg, whose starting dose are 200mg, if after 2 cycles' treatment (6 weeks), the tumor assessment results are SD and have not experience any treatment related AE of CTC AE grade≥2, the treatment dose should escalate to 300mg QD. (Note: 200 mg continuous QD administered in 21-day treatment cycles was selected as the initial starting dose of this study; as of 06 Dec 2019, the RP2D was determined as 300 mg QD, after then the starting dose has been adjusted to 300 mg continuous QD in 21-day treatment cycles.)

For the patients who cannot tolerant the does defined in the protocol, the dose reduction is allowed in order to enable the continuation of the study treatment. The dose interruption and dose modification should follow the protocol.

Glumetinib will be administered orally continuous once daily in 21-day treatment cycles until disease progression, unacceptable AE, withdrawal of consent or other criteria for termination of study treatment, whichever is earlier. There are no breaks in dosing between cycles. Patients should follow the instructions of the treating physician on study drug administration during treatment. Patients are required to fast for at least 2 hours before and 1 hour after administration of Glumetinib. Patients will be permitted to drink water during this period. On non-PK sampling days, Glumetinib can be administered in the morning or evening at the same time (if possible) each day. If a patient misses a dose (i.e., did not take Glumetinib for > 12 hours of the scheduled time of the day), the patient should take the dose on the next day.

6.2.2 Guidelines for Drug Administration

During the study, every effort should be made to ensure that patients take the medicine according to the study protocol. Patients do not need to take additional drug if the dose is insufficient because of vomiting after taking the investigational product. Patients can take the prescribed dose the next day.

Potential phototoxicity of Glumetinib is unknown. As a protective measure against light exposure it is highly recommended that while on study, patients should be wearing long-sleeved clothing, hats, parasols and sunscreen, when the patients are going out. Patient should contact the treating physician and/or investigator if experiencing any skin toxicity, i.e., rash or itching.

All missed doses and doses not completely taken should be reported to the investigator, recorded in patients' dairy card and entered in CRF. Unused drugs and packages must be returned to study sites at each visit.

6.3 Dose Modifications

6.3.1 Dose Modification and Dose Delay

Dose interruption or modification is permitted if AEs are observed. The following guideline need to be followed.

Dose modification should be made according to the most severe toxicity (CTCAE 5.0) that occurred; if multiple toxicities occur in the same patient, the dose should be adjusted based on the toxicity at the highest grade. Dose adjustments must be recorded in the eCRF. Dose reduction must be made according to Table 6-1.

Table 6-1 Dose reduction levels

Starting dose	1st dose reduction	2nd dose reduction	3rd Dose reduction
Glumetinib 200 mg	150 mg		
Glumetinib 300 mg	250 mg	200 mg	150 mg

If dose modification fails to result in achieving minimal criteria to resume treatment (Table 6-2 **Criteria for Interruption and Re-Initiation of Glumetinib**), the investigator should consider discontinuation of the patient from study treatment.

6.3.2 Criteria for Treatment Discontinuation and Restarting

For patients who do not tolerate the protocol-specified dosage, dose adjustments are permitted in order to allow the patients continue the study treatment. All dose adjustment plans should be made according to the most severe toxicity (CTCAE 5.0) that occurred. Both discontinuation of investigational product and dose adjustment should be recorded under investigational product administration in CRF.

If the administration needs to be delayed for more than 21 days, study treatment with Glumetinib must be terminated. If Glumetinib is discontinued, the patient should terminate the study treatment and enter the follow-up period. Patients who withdraw from the study because of study-related AEs or laboratory abnormities must be followed up according to the criteria for treatment discontinuation and restarting of Glumetinib in Table 6-2 **Criteria for Interruption and Re-Initiation of Glumetinib**. All patients should be followed up until AE resolved or in stable condition.

Patients with a past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD will be excluded from participation in this study. If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of ILD is observed, an interruption in study treatment dosing is recommended, and the investigator should complete a specific questionnaire and report it to the sponsor

within 24 hours after awareness as specified in section 8.4.3. In order to restart study treatment after the interruption in the study treatment, the consultation with the medical monitor of the sponsor is needed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered, and study treatment permanently discontinued.

During the study, recommendations for dose adjustment and discontinuation because of toxic and side effects related to the investigational product are shown in Table 6-2 **Criteria for Interruption and Re-Initiation of Glumetinib**.

Table 6-2 Criteria for Interruption and Re-Initiation of Glumetinib

Dose Modification for Nonhematologic Toxicities

Grade	Dose Interruption/Resumption [c]	Dose Adjustment
Grade 1 or 2 [a,b]	Maintain treatment at the same dose level, which should be managed as described in Table 6-3.	None
Grade 3 [a,b]	Suspend treatment until return to Baseline or Grade ≤ 1	Reduce by 1 dose level[b] from the previous level
Grade 4 [d]	NA	Permanent Discontinuation

[a] For Grade 2 or 3 pain, nausea and/or vomiting or diarrhea, if controlled by best supportive and symptomatic treatment, maintain dose level is recommended; if not controlled by best supportive and symptomatic treatment or not return to Grade 1 after 3-5 days dose interruption, dose may reduce by one dose level at the discretion of the investigator; then, when the patients recovered from the toxicities, it is allowed to resume the previous dose level.
For Grade 2 peripheral edema not reduced after the symptomatic comprehensive treatment, and not return to Grade 1 after 3-5 days dose interruption, reduce by one dose level; if return to Grade 1 after 3-5 days dose interruption, maintain dose level, if the edema increased to Grade 2 again, reduce by one dose level at the discretion of the investigator after comprehensive assessment of the patient's condition.
For Grade 2 total bilirubin elevation, withhold dose until resolved to ⩽ Grade 1 or baseline (if resolved ⩽ 7 days, maintain dose level, if resolved > 7 days, reduce 1 dose level).

[b] See table 6-1 for recommended dose level reductions.

[c] The renal, hepatic, and cardiac toxicities and other toxicities with specified follow-up may refer to table 6-3.

[d] Grade 4 non-hematologic laboratory abnormality: study drug will not be permanently discontinued if it is assessed by the investigator as the reason/condition leading to the abnormality has resolved (except the toxicity defined in table 6-3).

Dose Modification for Hematologic Toxicities

Recommended Dose Modifications for Glumetinib	
Worst toxicity CTCAE Grade (value)	**Recommended dose modification any time during a cycle of Glumetinib**
Dose modification for hematologic toxicities	
Anemia (Hgb)	
Grade 1 (Hgb < LLN - 10.0 g/dL)	Maintain dose level
Grade 2 (Hgb < 10 – 8.0 g/dL)	Maintain dose level
Grade 3 (Hgb < 8.0 - 6.5 g/dL)	Withhold dose until resolved to ≤ Grade 1 or baseline, - If resolved ≤ 7 days, then maintain dose level

Recommended Dose Modifications for Glumetinib	
Worst toxicity CTCAE Grade (value)	**Recommended dose modification any time during a cycle of Glumetinib**
	- If resolved > 7 days, then reduce 1 dose level
Grade 4 (life threatening consequences; urgent intervention indicated)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, - If resolved ≤ 7 days, then maintain dose level - If resolved > 7 days, then reduce 1 dose level
Grade 4 (ANC < 500/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a single temperature of >38.3°C or a sustained temperature of >=38 °C for more than one hour)	Withhold dose until resolved, then reduce 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, - If resolved ≤ 7 days, then maintain dose level - If resolved > 7 days, then reduce 1 dose level
Grade 4 (PLT < 25,000/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level
Abbreviations: ANC = absolute neutrophil count; Hgb = hemoglobin; LLN = lower limit of normal; PLT = platelets	

6.3.3 Follow-up for Toxicity

Treatment-emergent toxicities should be followed until stabilization according Table 6-3.

Table 6-3 Required Follow-up for Toxicities

Toxicity	Follow-up Evaluation
Hematology	If ≥ CTCAE grade 3 neutropenia or ≥ CTCAE grade 3 thrombocytopenia have been demonstrated, these parameters must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 or baseline to allow for initiation of re-treatment, and then at least weekly until either initiation of retreatment or until stabilization.
Renal	If creatinine clearance (calculated* or measured value**) < 30 mL/min has been demonstrated, withhold dose and this parameter must be repeated at least twice a week until resolution to ≥ 50 mL/min or baseline to allow for initiation of re-treatment, and then at least weekly until either initiation of re-treatment or until stabilization.
Hepatic	If ≥ CTCAE grade 2 bilirubin or ≥ CTCAE grade 3 ALT or AST, withhold dose and these parameters must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 or baseline to allow for initiation of re-treatment, and then at least weekly until either initiation of re-treatment or until stabilization. Patients with total bilirubin > 1.5 × ULN, or > 3.0 mg/dL for patients with Gilbert's syndrome (any duration) should have fractionation of bilirubin into total/direct or

Toxicity	Follow-up Evaluation
	indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinemia should proceed as per the guidelines above, irrespective of the results of fractionation.
Cardiac	If at any time a QTcF > 480 ms and ≤ 500 ms is observed, a cardiology consultation must be sought to re-evaluate the abnormal ECG finding. If at any time a QTcF > 500 ms is observed, 1) Triplicate ECGs (2-3 minutes apart) need to be taken approximately 1 hour after the initial ECG. 2) If the mean QTcF is > 500 ms, the patient must postpone study treatment until a cardiologist has re-evaluated the ECG; if QTcF > 500 ms, withhold dose and repeat ECG (as clinically indicated but at least once daily) until QTcF ≤ 500 ms (if resolved ≤ 7 days, maintain dose level, if resolved > 7 days, reduce 1 dose level). 3) Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. 4) Review concomitant medication usage for the potential to prolong the QT-interval. 5) Check compliance with correct dose and administration of Glumetinib. 6) Repeat ECGs (1 week and 2 weeks and then every 3 weeks) after dose resumption for all patients who had therapy interrupted due to QTcF > 500 ms. If QTcF of > 500 ms recurs, repeat ECGs as described above. If the cardiologist confirms a Grade 4 QTc interval prolonged, the patient must be discontinued permanently from study. If LVEF < 40% or ≥ 20% drop from baseline, LVEF must be evaluated at least once a week following demonstration of the resolution to baseline to allow for re-treatment, until stabilization of the toxicity, or until study completion.
Pancreas	If lipase/amylase elevation of Grade ≥ 3 is observed, the subject must withhold dose and undergo clinical evaluation for the presence of signs and symptoms typical of acute pancreatitis and for other risk factors for pancreatitis. And a computed tomography (CT) scan and/or magnetic resonance imaging (MRI) of the abdomen should be performed to assess the pancreas. The continuation of study treatment for the subject will be individually discussed with the sponsor on a subject by subject basis.
Non-laboratory	Patients who experience non-laboratory Grade 3 or 4 AEs must be evaluated at least once a week until the event resolution or stabilization of the AE. .
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ms = milliseconds; QTcF = Fridericia's corrected QT interval; ULN = upper limit of normal	

6.3.4 Overdosage

An overdose with Glumetinib is defined as taking a dose beyond the protocol-defined dose (taking into account any dose modifications) in one day.

An overdose of Glumetinib must be reported to the Sponsor's Pharmacovigilance(PV) team or designee within 24 hours from the time the investigator first becomes are of the overdose, whether accidental or intentional, and whether or not the patient developed an AE (even if not fulfilling seriousness criterion). This should be performed by completing a Haihe Overdose Reporting Form and email it to Sponsor PV Team or designee.

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

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

6.4 Blinding

Not applicable.

6.5 Concomitant treatment

All drugs or concomitant treatments during the study treatment should be recorded in the concomitant medication form. Antitumor treatments before enrollment, including drug therapy, radiation therapy and surgery, should be recorded separately in CRF respectively.

During the study, investigators should follow the following guidelines and cautiously use the combined drugs to ensure the safety of patients.

6.5.1 Prohibited Concomitant Therapy (during treatment and within 28 days after drug discontinuation)

Patients should not receive other anti-tumor therapy while on treatment in this study, i.e. surgery, radiotherapy therapy, cytotoxic, biological, traditional Chinese medication with lung cancer indication, or hormonal other than replacement. Exception can be made for localized palliative radiotherapy for symptom control provided that the localized palliative radiotherapy does not compromise tumor assessments of target lesions. Other anti-tumor treatments should not be administered until disease progression (as per clinical practice standards at the study center), unmanageable toxicity or no further clinical benefit occurs which requires permanent discontinuation of Glumetinib.

Patients are not allowed to take the following medications, except for management of AEs as advised by the Principal Investigator. Patients must stop taking these drugs for at least 14 days before dosing, except coumarin anticoagulants that can be stopped one week before inclusion (heparin of low molecular weight is acceptable):

- Any strong inhibitor and inducer of CYP3A4 used 2 weeks before inclusion and during the trial treatment phases (e.g. ketoconazole, clarithromycin, indinavir, itraconazole, etc. refer Appendix 6; however, this list may be not comprehensive, additional information may be obtained from the IFU of these drugs). In addition, herbals/supplements containing St. John's wart (*Hypericum perforatum* L.) and Sevillia orange etc. should also be avoided.
- Any strong inhibitor for CYP2C8 and/or CYP2C9 (e.g. Gemfibrozil, please refer to Appendix 6) in safety run-in part of the study.
- Any substrate or inhibitor for transporter (e.g. dabigatran etexilate, digoxinrefer, please refer to Appendix 7) in safety run-in part of the study.
- Any medications which can prolong QT interval and cause torsade de pointe (Refer to Appendix 8).

Inhibitors for CYP2C8 and/or CYP2C9 and substrates or inhibitors for transporters will not be prohibited in phase 2 part of the study. However, any adverse event in patients co-administer these drugs should be closely monitored.

In the interest of patients' safety and acceptable standards of medical care, the Investigator will be permitted to prescribe the treatment(s) at his/her discretion.

6.5.2 Permitted Concomitant Therapy during the study

The following therapies are permitted:

- Bisphosphonate
- Denosumab
- Steroid use of more than oral prednisone 10 mg/per day or its equivalent should be discussed between the investigator and the Sponsor
- Local or regional palliative cryotherapy or radiation, e.g., for bone pain or palliative surgery (non-antineoplastic intent)

If, after assessment by the Investigator, therapeutic intent radiation for brain metastasis, therapy for bone metastasis or locoregional therapy e.g. local ablation, TACE, SIRT or arterial infusion chemotherapy could be initiated for the best benefit of the patient The patient can start such therapy a minimum of 2 days after discontinuation of Glumetinib. Consequently, the patient will be censored for the primary endpoint analysis. Glumetinib may be restarted 2 weeks after the completion of such treatment or when the patient has recovered from the side effects of such treatment.

The following medications/therapies may be given concomitantly under the following guidelines:

Hematologic Support

For Phase Ib and Phase II (except patients in run-in), hematologic support may be administered as medically indicated (e.g., blood transfusions, granulocyte-stimulating factor (G-CSF), erythropoietin stimulating agents) according to the institutional site standard. If there are no standard procedures for the use of growth factors, the American Society of Clinical Oncology [ASCO] Guidelines for Use of Hematopoietic Colony-Stimulating Factors, available at www.asco.org, will be followed.

Management of Diarrhea

For Phase 1b and Phase 2 (except patients in run-in), prophylactic treatment for diarrhea is permitted during the study if clinically indicated according the institutional guidelines. If there are no institutional standards, refer to the guidelines published by Benson, et al. [Benson, A. B. Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea[J]. Journal of Clinical Oncology, 2004, 22(14):2918-2926.] in Journal of Clinical Oncology.

Management of Nausea/Vomiting

Antiemetics may be administered as clinical indicated. If there are no institutional standards, refer to the ASCO guidelines for Antiemetics in Oncology [Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetic Use in Oncology: Updated Guideline Recommendations from ASCO[J]. Am Soc Clin Oncol Educ Book, 2012, 32:532-540.].

Effective Contraception

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

- Oral
- Intravaginal
- Transdermal

Progestogen-only hormonal contraception associated with inhibition of ovulation:

- Oral
- Injection
- Implantable

Intrauterine device (IUD)

Intrauterine hormonal-releasing system (IUS)

Bilateral tubal occlusion

Vasectomized partner with documentation of the success of the vasectomy

Complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients with partners who are WOCBP should use a combination of male **condom** with cap, diaphragm, or sponge with spermicide during the trial and for 6 months after the last dose of Glumetinib.

7. Study procedures and assessments

7.1 Study Procedures

Table 1-1 lists all the assessments with an "X" indicating when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

The study assessments are described by procedures in the following sections.

The study schedule must be followed; however, a window of ± 3 days is allowed for study tests and procedures as long as the proper order of procedures and assessments is maintained. The ± 3-day window does not apply to assessment Cycle 1 and the visits after EOT.

For tumor assessments (i.e., CT or MRI), a window of ± 7 days is allowed. These windows are not applicable during screening.

Laboratory tests (including hematology, blood biochemistry, urinalysis and coagulation) performed during screening period within 7 days prior to dosing on C1D1 do not need to be repeated on C1D1.

PK sampling with multiple post-dose time points and pre-dose on Day 1 and Day 15 of cycle 1 and Day 1 of cycle 2 and pre-dose on Day 1 of cycle 3 should be performed on the specified days. (Please refer to PK sampling in Table 7-1 in Section 7.3.1).

For the assessment type please see Section 7.2.

Unscheduled visit: additional visits can be performed as appropriate and at the discretion of the investigator.

7.1.1 Molecular Pre-screening for MET Alterations

Archived or fresh tumor tissue biopsy samples will be tested for MET alterations, including *MET*ex14

skip mutations, *MET* amplification or MET overexpression if not already tested. Patients can be enrolled and treated based on the following:

1. Testing by the Sponsor Designated Central Laboratory:
    - Samples sent to the Sponsor Designated Central Laboratory as part of the study pre-screening; or
    - Already tested by the Sponsor Designated Central Laboratory; in this case, tumor tissue should be sent to the Sponsor Designated Central Laboratory if available
2. Local laboratory testing using NGS, FISH, IHC, RT-PCR or other assays that can determine MET alterations on tumor tissue or from ctDNA; patient enrolled on this basis in Phase II must have available tumor tissue from archival samples or fresh tumor biopsy submitted to the Sponsor Designated Central Laboratory for confirmation of MET alterations.

Testing may be performed at any time prior to enrollment into the study. Results from the testing if not done as part of the protocol, must be maintained in the source files at the site.

Any AEs or SAEs directly associated with a pre-screening procedure (i.e. fresh tumor biopsy) should be reported as described in Section 8.3. There is no need to record AEs or SAEs that occur between signing the pre-screening consent and full protocol consent if they are unrelated to the pre-screening tumor biopsy procedure unless it is mandatory by local regulations.

The requirements for tissue specimen, refer to the latest version of the central laboratory manual.

7.1.2 Screening (day -28 to day -1)

NSCLC patients with a specific molecular abnormity required by the protocol can enter clinical screening after signing the master informed consent form. Once patients submit the written informed consent form for taking part in the study, the clinical screening will be started. Except for pregnancy test that should be finished within 7 days prior to the first dose, other examinations must be completed within 28 days prior to the first dose. Clinical and imaging tumor evaluation according to RECIST 1.1 (Appendix 1 RECIST 1.1) within 4 weeks (28 days) prior to the first dose is acceptable, but it's better to conduct tumor evaluation 1 week (7 days) prior to the first dose. The disease must be staged in the screening period. Tumor assessment conducted in the screening period may be taken as baseline tumor assessment results to confirm disease response and/or progression in patients after treatment.

The complete screening evaluation list is shown in Table 1-1.

After completion of evaluation at screening visit, the investigator will evaluate the inclusion and exclusion criteria for patients' enrolment, then Eligibility Verification Form (EVF) should be completed and sent to the sponsor or designee. The sponsor or designee and the investigator will jointly audit patients' eligibility; however, it remains the investigator's responsibility to ensure that the patients meet all the entry criteria.

Complete medical history should be recorded during screening.

7.1.3 Treatment period

To schedule visits, the cycle of treatment is defined as 21 days (3 weeks). Specific schedule of study evaluation and examinations and visit window are shown in Table 1-1.

7.1.4 End-of-treatment Visit (EOT)

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible and within 14 days of the last dose of study treatment or within 14 days of the decision to permanently discontinue study treatment. At that time all of the assessments listed for the End of Treatment (EOT) visit will be performed. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit. An End of Treatment Phase Disposition Page should be completed, giving the date and reason for stopping the study treatment.

If a withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the EOT CRF page.
End of treatment/Premature withdrawal visit is not considered as the end of the study.

7.1.5 Twenty-eight-day Safety follow-up

Outpatient on-site follow-up, at least telephone follow-up, is recommended.

7.1.6 Radiologic Progression follow-up

Patients who discontinue Glumetinib for reasons other than radiologic progressive disease (PD) will continue RECIST 1.1 assessments every 9 weeks (± 7days) until radiologic progression or starting new anticancer treatment, whichever occurs first.

7.1.7 Survival follow-up

Telephone follow-up will be conducted every 3 months following the occurrence of progressive disease or the starting of new antitumor treatment in order to collect patients' information on subsequent antitumor treatment and survival condition.

If patients have started new antitumor treatment after the final dose prior to end-of-treatment visit, they will directly enter the survival visit without receiving the end-of-treatment visit.

If patients terminate treatment prior to the occurrence of progressive disease, they should take part in survival follow-up to collect patients' information on subsequent antitumor treatment and survival condition.

7.2 Efficacy and safety assessments

7.2.1 Response Evaluation

Tumors responses and progression will be evaluated by the investigator and BIRC according to RECIST 1.1. For details regarding the response criteria, please refer to Appendix 1. Tumor assessment will be conducted once every 6 weeks ± 7 days for the first 8 cycles, then every 9 weeks ± 7days (or according to clinical need). Imaging evaluation method of tumors, at the investigator's discretion, may adopt CT or MRI, but evaluation method, instrument and technical parameters should be consistent throughout the study. Contrast medium should be used if there is no contraindication. Imaging results will be read by the investigator or radiologist of each study site. During the study, it is recommended that all imaging results of each patient are read by the same reader as far as possible to ensure consistency of film reading. If tumor evaluation has been conducted with the same method and instrument in the same

hospital within 28 days prior to the first dose, it can be regarded as tumor evaluation at baseline.

Tumor assessment in the screening period includes chest and abdominal imaging (CT or MRI) examinations. Evaluation of any other sites (e.g. neck, pelvic cavity, brain) with known or suspected tumors may be conducted if clinically necessary. Bone scanning (except for patients who have received bone scanning 60 days prior to the first dose) should be conducted in the screening period in patients with or suspected of bone metastasis. If positive, the sites should be confirmed with CT or MRI, and bone metastatic lesions should be evaluated and followed up with the same examination method as required. Systemic bone scan will not be repeated after baseline, unless clinically indicated. Tumor assessment should be conducted when the patient discontinues treatment/withdraws from visit if tumor assessment is not conducted within 28 days prior to discontinuation of treatment or at withdrawal. If a patient withdraws from the study because of disease progression, imaging evaluation does not need to be repeated at the end-of-treatment visit. An unscheduled tumor assessment should be conducted in patients suspected of disease progression prior to the next scheduled evaluation. The investigator may arrange additional imaging examinations according to patients' clinical conditions.

Partial response (PR) and complete response (CR) should be confirmed by a repeat imaging assessment. The imaging for confirmation of response may be performed at least 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. Patients will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Patients who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Record of target lesions: number, position, description of lesions, maximum diameter of each lesion (except for lymph nodes) and minimum diameter of lymph node, including the sum of diameters of all target lesions.

All imaging examination data (CT/MRI) for response evaluation of phase II study including data of the patients met inclusion criteria will be collected for further efficacy validation and evaluation by the IRC. Details of the independent review will be documented in the Independent Review Committee Charter.

Tumor scans from patients previously treated in Phase II part of the study prior to protocol amendment 1 may also be retrospectively collected and forward to the core imaging laboratory if these patients sign the consent.

When progressive disease (RECIST 1.1) assessed by investigator, all radiologic data since baseline should be submitted to the central imaging laboratory for real-time BIRC review, details refer to the Independent Review Committee Charter. Patients should continue study treatment until the BIRC has completed the review, unless prohibited by the investigators. For progressive disease (RECIST 1.1), if the results of BIRC assessment are not consistent with the results of the investigator, the investigators and the sponsor will discuss whether to allow the treatment to continue.

7.2.2 Safety Assessments

Drug safety will be monitored with the following evaluation methods during the study: hematology, biochemistry, coagulation function, urinalysis, 12-lead ECG, physical examination, vital signs, height, weight, ECOG Performance Status (PS), and heart function evaluation. In addition, information on

adverse events and concomitant medications/procedures should be collected at each visit. Please see Section 8 for more information of AE collection and reporting.

Safety variables include adverse events, clinical laboratory parameters (hematology and urinalysis, blood biochemistry, coagulation function, etc.), vital signs, physical examination, 12-lead ECG and physical examination findings (including weight and ECOG Performance Status (PS)). Safety will be comprehensively evaluated according to type, frequency and severity of adverse events.

Clinical safety of the study treatment will be evaluated according to NCI CTCAE 5.0 during the study.

AEs occurring in patients should be evaluated at each visit. Start and end time, severity grade, correlation with study drug, influence on treatment with study drug of AE, whether there is concomitant treatment, and outcomes should be recorded in eCRF.

12-lead ECG: Including heart rate, P-R interval, QRS interval, QT interval, QTc interval and diagnosis; ECG will be performed at the examination time specified in the protocol and may be additionally performed during the course of the study by the investigator based on the patient's clinical indications. 12-lead ECG examination will be conducted after patients rest for at least 5 minutes in a supine position. Triplicate ECGs (2-3 minutes apart) need to be taken, then calculate QTc interval (corrected with Fridericia's formula) and the average.

Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Sponsor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page. **Echocardiography or MUGA**: LVEF evaluation of a specific patient is recommended to be performed by the same technician with the same instrument as much as possible throughout the study.

Laboratory Evaluations

Hematology, blood biochemistry and urinalysis will be conducted in the screening period, treatment period and follow-up period according to study procedures, and examination frequency will be increased according to clinical indications.

- **Hematological test:** red blood cell count, hemoglobin, hematocrit, reticulocyte count or percentage, platelet count and absolute leukocyte differential count (neutrophil, lymphocyte, eosinophils, monocyte, basophils);
- **Blood biochemical test (including cardiac enzymes):** Total protein, albumin, blood glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, alkaline phosphatase, total bilirubin, direct bilirubin or indirect bilirubin, aspartate aminotransferase, alanine aminotransferase, glutamyl transpeptidase; creatinine, urea or urea nitrogen, creatinine clearance, uric acid; electrolytes (potassium, sodium, calcium, phosphorus); LDH; cardiac enzymes (troponin T/I and CPK), lipase and amylase;
- **Urinalysis:** specific gravity, pH, urine glucose, protein, urinary cast, ketone bodies, white blood cell (quantitative) and red blood cell (quantitative). 24-hour urinary protein quantitative test should be conducted in case of urinary protein positive;

- **Coagulation function test:** prothrombin time, activated partial thromboplastin time and international normalized ratio;
- **Pregnancy test** (applicable to women of child-bearing potential);
- **HBV, HCV and HIV tests:** HBsAg, HBsAb, HBcAb, HBV DNA (tested in patients with HBsAg positive), HCV-Ab, HCV RNA (tested in patients with HCV antibody positive), and HIV antibody (in Chinese and Japanese patients only).

7.3 Pharmacokinetics Evaluation

7.3.1 PK Blood Sample Collection

Blood samples will be collected for all patients enrolled on C1D1, C1D15, C2D1, and C3D1 visit according to the collection time points in Table 7-1. A minimum of 2 mL of whole blood will be collected at each time point for the PK analysis.

Blood samples for PK evaluation will be collected and processed according to instructions provided in the Laboratory Manual.

Table 7-1 Timepoints of Blood Collection for Glumetinib PK Assessment

Scheduled time points relative to the previous dose (hours)				
Cycle	**Day**	**Scheduled time (hours)**	**Description**	**Blood Volume (mL)**
1	1	0 hr [a]	Pre-dose	2
		1 hr ± 15 min post-dose		2
		3 hr ± 15 min post-dose		2
	15	0 hr	Pre-dose	2
2	1	0 hr [a]	Pre-dose	2
		1 hr ± 15 min post-dose		2
		3 hr ± 15 min post-dose		2
3	1	0 hr [a]	Pre-dose	2

a. Pharmacokinetic blood samples should be collected within 30 min pre-dose

7.4 Storage and Destruction of Biological Samples

Tumor samples may be stored at the Sponsor's designated central laboratory for up to 5 years following completion of the study, to enable companion diagnostic bridging study.

8. Safety Monitoring and Reporting

8.1 Safety Parameters and Definitions

8.1.1 Definition of adverse events

Adverse Event (AE) refers to any untoward medical occurrence in a patient after providing written informed consent for participation in the study. AE can be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease. Therefore, an AE need not be temporally or causally associated with the use of the investigational products.

Adverse events include serious adverse events and non-serious adverse events.

Events which meet the definition of an AE include:

- Exacerbation of underlying chronic diseases or intermittent diseases, including increased frequency and/or worsening in severity.
- Newly discovered or diagnosed diseases after providing written informed consent, even though the disease might have existed before the start of the study
- Signs, symptoms or clinical sequelae which are suspected to be associated with drug-drug interactions
- Signs, symptoms or clinical sequelae which are suspected to be associated with the overdose of the investigational products or concomitant medications (overdose itself will not be reported as an AE/SAE).

"Lack of efficacy" or "expected pharmacological effect has not been reached" will not be reported as an AE or SAE. However, any signs, symptoms and/or clinical sequelae caused by "lack of efficacy", will be reported as an AE or SAE if they meet the definition of AE or SAE.

Events which do not meet the definition of AE include:

- Medical or surgical procedures (e.g. endoscopy, appendicectomy) pre-planned prior to the participation in the study.
- Situations where untoward medical events did not occur (admission due to social reasons).
- The fluctuation within predictable range of the existing diseases or conditions which have already existed at the time of study initiation and have not aggravated during the study period.
- Tumor progression or deterioration during the study (including new metastatic lesions) shall be considered as part of efficacy evaluation and will not be reported as an AE or SAE, unless the progression speed exceeds expectation.

8.1.2 Serious adverse event

Serious adverse event refers to any adverse event occurred during the study leading to any of the followings:

- Results in death;
- Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization (emergency outpatient visit, medical monitoring in hospital within 24 hours, inpatient hospitalization due to social reasons);
- Results in persistent or significant disability or incapacity: AE results in substantial harm to the patient's capacity of conducting daily life (incapacity does not include events with slight clinical significance, such as headache, nausea, vomiting, diarrhea, influenza, accidental trauma (e.g. ankle strain), etc.

- Congenital anomaly/birth defect.
- Other important medical event (refers to important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require drug or surgical intervention to prevent any of the outcomes listed in the definition above. It shall be considered an SAE based on reasonably medical judgments. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

8.1.3 Abnormal vital signs defined as AEs

Not all abnormal vital signs are considered as AEs. Vital signs meeting any of the followings should be reported as AEs:

- Induce clinical symptoms;
- Result in changes in the study treatment (e.g. dose adjustment, treatment interruption or suspension);
- Require medical intervention or result in changes in concomitant treatment;
- Consider as clinically significant by investigators.

Investigators have the responsibility to review all vital signs. Medical or scientific evaluation should be conducted in confirming whether to classify an independent abnormal vital sign as an AE.

8.1.4 Abnormal laboratory findings defined as AE

Not all abnormal laboratory findings are AEs. Laboratory test results meeting any of the followings should be reported as AEs:

- Induce clinical symptoms;
- Result in changes in the study treatment (e.g. dose adjustment, treatment interruption or discontinuation);
- Require medical intervention (e.g. potassium supplementation due to hypokalemia) or result in changes in concomitant treatment;
- Consider as clinically significant by investigators.

Investigators have the responsibility to review all laboratory test results. Medical or scientific evaluation should be conducted while confirming whether to classify an independent abnormal laboratory finding as an AE.

8.2 Collection and evaluation of safety parameters

8.2.1 Reporting timeframe for adverse events

All AEs occurring after the patient provides written informed consent and until 28 days following the last administration of study treatment should be recorded in AE page of the eCRF.

8.2.2 Severity assessment of adverse events

Investigators should evaluate the severity of all AEs on a scale of 5 grades (grades 1 - 5) in accordance with NCI CTCAE 5.0. Severity of AEs not defined in NCI CTCAE can be evaluated according to the following rules:

- Grade 1 Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences; urgent medical intervention indicated.
- Grade 5 Death related to AE.

Please distinguish seriousness from severity of adverse events. “Severe” is not necessarily equivalent to “serious”. For example, nausea which persists for several hours may be considered as severe nausea, but it is not a SAE. On the other hand, stroke that results in only mild disability may be considered as mild stroke but is nevertheless an SAE. Therefore, severity and seriousness should be evaluated separately during AE/SAE reporting.

8.2.3 Assessment of causal relationship between adverse events and investigational drug

Causal relationship between an AE and the study drug will be evaluated with binary classification (related /not related). Investigators must evaluate the relationship between the study drug and an AE (reasonable possibility that AE is related: No (not related), Yes (related)).

Related:

It refers to adverse events that are considered related or possibly related to the investigational product. An adverse event is considered "related" if two or more of the following criteria are met:

- The occurrence of an adverse event has a reasonable temporal relationship to the use of the drug.
- The adverse event cannot be reasonably explained by known patient disease state, environmental or toxic factors, or other therapies used by the patient.
- When the dose is stopped or reduced, the adverse reaction disappears or abates. There are important exceptions, however, in which certain drug-related adverse effects do not disappear even after discontinuation of the drug; such as: (1) myelosuppression, (2) tardive dyskinesia.)
- The adverse event is consistent with the suspected drug reaction pattern.
- The adverse event reappeared when reused.

Unrelated:

It refers to adverse events that are not considered related to the investigational product. An adverse

event is considered "not related" if two or more of the following criteria are met:

- The occurrence of an adverse event does not have a reasonable temporal relationship to the use of the drug.
- The AE is clearly caused by the patient's disease state, environmental or toxic factors, or other concomitant therapy used by the patient.
- The adverse event does not follow a suspected drug reaction pattern.
- The AE does not recur or worsen with re-challenge.
- The event is only caused by external factors (disease, environment, etc.).

8.3 Recording and reporting of safety parameters

8.3.1 AE recording

During the AE reporting period defined in the protocol, the investigators are responsible for collecting all AEs and recording them in the eCRF. In terms of AE recording, investigators should use correct and normative medical terminology. Investigators shall trace the occurrence of AEs by non-directive questions to patients at each visit after signing an informed consent form, during screening and the study period. AEs may also be found by patients' self-reporting during screening or between visits, or by physical examination, laboratory tests or other evaluations. For each AE, the following items should be evaluated and recorded as far as possible:

- AE terminology (verbatim)
- Severity grade (NCI CTCAE 5.0);
- Duration (start and stop date);
- Causal relationship with the study drug (whether an AE is related to the study treatment: yes or no);
- Action taken for the study or the study treatment (study drug continues, study drug interrupted, dose reduction, withdrawn, unknown, not applicable);
- Whether drugs or treatments are given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy);
- Outcomes (not recovered/not resolved, recovered/resolved, recovering/in remission, recovered/remission with sequelae, death, unknown);
- Whether it is an SAE, see Section 8.1.2 for the definition of SAE.

All AEs, regardless of causal relationship with the study drug, shall be proactively handled. Clinical treatment measures required by the protocol can be adopted if necessary. If treatment measures that are not permitted by the study protocol must be taken, a decision should be made after consulting with the sponsor.

In addition, the following items of an SAE should also be collected:

- Date when an AE met the SAE definition

- SAE awareness date by the investigator
- Serious criteria of an SAE
- Admission date
- Discharge date
- Cause of death
- Date of death
- Autopsy report.
- Assessment on causal relationship with the study process
- Evaluation of causal relationship with other drugs
- Description of SAE

Diagnosis versus signs and symptoms

During recording AEs, if a diagnosis is available it is the diagnosis rather than a single symptom and sign that should be recorded in the eCRF. For example, hepatic failure shall be recorded, rather than jaundice, aminotransferase increased and asterixis. However, if the symptoms and signs cannot be attributed to a single diagnosis during reporting AEs, each single event should be recorded as an AE. For conditions where the diagnosis is confirmed afterwards, eCRF should be updated with the diagnosis.

AEs secondary to other events

The primary event shall be recorded for AEs secondary to it, unless there's a longer secondary duration, a higher grade of severity, or it is an SAE. However, events considered to be clinically significant shall be recorded separately if the start date is different from that of the primary event, or the relationship is not clear.

Death

While recording death events, if the cause of death is available, it shall be recorded in eCRF using single medical concept and the event should be reported as an SAE. If the cause of death remains unknown, "unknown cause of death" should be recorded in AE form of eCRF and reported as an SAE. The exact cause of death shall be investigated after then. The record and SAE report shall be updated when the cause of death is confirmed.

Pre-existing medical conditions

Symptoms or signs already existed in screening period shall be recorded as an AE only when the severity grade, frequency and nature worsened (except for deterioration of the investigated disease) after enrollment. Changes compared to previous status shall be recorded (e.g. "hypertension deterioration", "headache deterioration", etc.).

Hospitalization or prolonged hospitalization

Any AE that results in inpatient hospitalization or prolongation of existing inpatient hospitalization shall be recorded and reported as an SAE except for the following circumstances:

- Scheduled inpatient hospitalization or prolongation of the existing inpatient hospitalization as defined in the protocol, such as hospitalization for drug administration, efficacy evaluation, etc.
- Hospitalization for social reasons: such as medical reimbursement, unattended, etc.
- Inpatient hospitalization due to pre-existing and unchanged medical conditions prior to participation in the study: if patients are duly hospitalized for selective surgery or treatment that has been arranged prior to participation in the study will not be considered as AE, but shall be recorded in the eCRF and screening section of the original record. In addition, if pre-existing disease deteriorates and requires surgery or treatment earlier than planned, the disease deterioration requiring inpatient hospitalization for surgery or treatment will be considered as an SAE.

Disease progression

If the event is definitely consistent with the anticipated progression of primary tumor, the event should not be considered as an AE. Hospitalization induced simply by the disease progression should also not be considered as an SAE. If symptoms cannot be confirmed to be completely induced by disease progression or does not consist with the anticipated disease progression of the tumor, the relevant clinical symptoms can be recorded as AEs, and reported as SAEs if the definition is met.

8.3.2 Reporting of serious adverse events (SAEs)

All SAEs (whether or not related to the study drug) which occur after providing written informed consent and until 28 days following the last dose administration of study medication should be reported to Haihe pharmacovigilance Team/its representative drug safety department within 24 hours upon investigator awareness by filling out the Haihe SAE reporting form. SAEs that occur after 28 days following the last dose administration of study medication and until study completion shall only be reported if they are considered to be related to the study medication by the investigator.

Any additional information on SAEs, such as SAE recurrence, complications or progression should be reported as follow-up information to the initial SAE and reported within 24 hours upon investigator awareness. Report requirements on SAE follow-up information are the same with that of the initial SAE report. If an SAE occurred at different intervals or is considered to be completely irrelevant to previously reported events, it shall be separately reported as a new event.

8.3.3 Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative is required to report certain study events in an expedited manner to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations. The following describes the safety reporting timeline requirements for SUSARs and other reportable events:

Immediately and within 7 calendar days

Any suspected adverse reaction that is associated with the use of the study drug, unexpected, and fatal or life threatening, and its follow-up information should be reported within 7 days upon sponsor awareness.

Immediately and within 15 calendar days

Any suspected adverse reaction that is associated with the use of the study drug, unexpected, and

serious, but not fatal or life threatening, and its follow-up information should by reported within 15 days upon sponsor awareness. Any finding from tests in laboratory animals that suggest a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity, any event in connection with the conduct of the study or the development of the study drug that may affect the safety of the trial patients should also be reported.

In addition, periodic safety reporting to regulatory authorities will be performed by the Sponsor or its representative according to national and local regulations.

All investigators involved in any study with SCC244 as investigational product, would be informed about the SUSARs cases, newly identified important safety issues or other safety documents by the sponsor, and relevant ethics committees/IRB would also be informed by the investigators or the sponsor according to relevant requirements.

After the approval of new drug application in Japan, the Sponsor becomes obliged to safety reporting to the regulatory authority in accordance with GVP and GPSP in Japan.

8.4 Special event reporting

8.4.1 Pregnancy report

Female patients shall immediately discontinue the study drug therapy if they become pregnant while receiving the study drug. Investigators must fill in the Pregnancy Reporting Form of Haihe Biopharma Co., Ltd. within 24 hours upon investigator awareness and report it to Haihe PV Team. Investigators must follow up each pregnancy until the end of pregnancy to confirm its outcome (e.g. spontaneous abortion, selective termination of pregnancy, ectopic gestation, normal birth or congenital malformation, details of delivery, maternal or neonatal complications, etc.) and whether there is any AE occurred. If an SAE occurs during pregnancy, it shall be reported according to the procedures addressed in section 8.3.2.

The pregnancy itself is not an AE. However, the investigator shall report the event to the sponsor with a specific form and follow up the pregnancy until the end of pregnancy even if the patient discontinues the study treatment. Investigators shall fill the pregnancy outcome in the Pregnancy Reporting Form and send the form to the sponsor within 24 hours upon investigator awareness on the pregnancy result.

Pregnancy that involves of sexual partner of a male patient is not an AE. However, if possible, the pregnancy outcome shall be followed up and recorded as described above. Informed consent from his sexual partner on collection of conditions and results related to pregnancy shall be obtained (the approval of the Ethics Committee shall also be obtained to handle one by one).

8.4.2 Drug overdose

The definition of drug overdose is defined in Section 6.3.4.

- If relevant AEs occurred with drug overdose, they shall be recorded as diagnoses/symptoms in the AE page of the CRF by investigators. In addition, investigators shall fill it in the Overdose Reporting Form of Haihe Biopharma Co., Ltd. and report it to Haihe PV Team within 24 hours upon investigator awareness.
- For asymptomatic drug overdose, investigators shall fill in the Overdose Reporting Form of Haihe

Biopharma Co., Ltd. and report it to Haihe PV Team within 24 hours upon investigator awareness.

8.4.3 Special safety monitoring

Hepatotoxicity

If any of the three criteria listed below are met, the patient's serologic monitoring should be strengthened (for example, the 4 types of common serum measurements [ALT, AST, ALP and TBIL] should be re-tested within 48 to 72 hours). Patient who meets (1) + (3) or (2) + (3) below will be considered a PHL (Potential Hy's Law) case and a questionnaire should be completed to confirm if it is a HL (Hy's Law) case or not. If other reasons of ALT or AST or TBIL increased (e.g. viral hepatitis, other drugs, alcoholism, etc.) are ruled out by collection of further information via the questionnaire, the case will be handled as a HL case, i.e. be handled as SAE (serious adverse event), and the study drug will be permanently discontinued.

• (1) For patients with normal aminotransferase levels at baseline, AST or ALT increased to >3 × ULN

• (2) For patients with hepatic metastasis and abnormal aminotransferase levels at baseline AST or ALT increased to ≥ 2 × baseline level

• (3) Total bilirubin increased to ≥ 2×ULN

* PHL: At any time of the study, AST or ALT ≥3 × ULN and TBIL ≥2 × ULN.

** HL: ALT or AST ≥3 × ULN, TBIL ≥2 × ULN in the absence of cholestasis (serum alkaline phosphatase [ALP] >2 × ULN), and there are no other reasons*** to explain the combined elevation of aminotransferase and TBL.

*** Other reasons include acute viral hepatitis A, B or C, autoimmune or alcoholic hepatitis, fatty liver, non-alcoholic steatohepatitis, biliary tract diseases, and hypotension which may resulted in ischemic or hypoxic liver disease, or circulatory disorders caused by right congestive heart failure, or concomitant use of hepatotoxic drugs, etc.

Interstitial Lung Disease (ILD)

If new or worsening pulmonary symptoms or radiological abnormality suggestive of ILD is observed, the case should be reported to Haihe PV Team as described in 8.3.2 even if none of the serious criteria is met. The investigator should complete a questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters) and send the questionnaire together with the SAE form to the sponsor within 24hours.

QTc Interval Prolongation

If a mean QTcF > 500 ms or > 60 ms from the baseline is confirmed by the cardiologist, the case should be reported to sponsor within 24 hours as required in 8.3.2. The subject's medical history, concomitant medications, electrolytes (including sodium, potassium, calcium and magnesium et al) and PK information should be collected in the report.

Pancreatitis

Subjects experiencing lipase/amylase elevation of Grade ≥ 3 will undergo clinical and imagological evaluation for the presence of pancreatitis. Any pancreatitis identified during the study should be reported to sponsor within 24 hours according to procedure described in section 8.3.2, and all relevant medical information and risk factors should be included in the report.

Note: Haihe SAE report form would be used for the special safety events, and if none of the SAE criteria is met for the reported case, the criterion 'AESI' should be ticked in the form.

8.5 Follow up of adverse events (AEs) and serious adverse events (SAEs)

Investigators should perform follow up to patients with AE or SAEs to protect patients' safety, and to collect as much related information as possible. Investigators should proactively understand the detailed disease condition, provide necessary treatment to the patient, collect complete case information and report follow-up report in a time manner. If an AE or an SAE related to the study drug still remains after the study completion or when the patient proposes withdrawal of the study, it shall be followed up until any of the followings is reached:

- Resolved or improved to baseline status;
- No further anticipated improvement will present according to the investigator;
- Death of patients;
- Patient lost to follow-up;
- The patient starts new anti-cancer treatment;
- End of study.

9. Statistical Considerations

9.1 General Methods

Except as specified, descriptive statistics and summary of study data will be conducted in accordance with the following general principles.

Continuous data will be descriptively summarized by statistics including the number of cases, mean, standard deviation, median, minimum and maximum.

Categorical data will be descriptively summarized by statistics including frequency and percentage, and 95% confidence interval of percentage if necessary.

Missing data in the trial will not be imputed but censored.

All statistical analyses will be performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA) or above version.

9.2 Analysis Set

Analysis Set

The *safety analysis set (SAS)* will include all patients who received at least one dose of Glumetinib.

This analysis set will be the primary analysis set for safety evaluation.

The *PK analysis Set* will consist of patients who have received at least one dose of Glumetinib and have at least one Glumetinib evaluable plasma concentration data. All such patients will be evaluated for PK unless major protocol deviations have impacted the data or key dosing information is missing. Changes to the procedures, which may impact the quality of PK data, will be considered "PK relevant protocol deviations". Examples include sample process errors that lead to inaccurate bioanalytical results and/or inaccurate dosing on the day of PK sampling.

Analysis sets will be used for efficacy analysis are defined as follows:

Phase Ib:

F*ull analysis Set (FAS)* will include all treated patients (same as the safety analysis set)

Phase II:

Full analysis set (FAS) will include all treated patients (same as the safety analysis set).

Efficacy analysis set will include all NSCLC patients with sponsor-designated central laboratory confirmed *MET*ex14 skipping mutation treated at RP2D (including patients in Safety Run-in part of phase II) and have valid baseline tumor assessment.

9.3 Estimation of Sample Size

Phase Ib:

Approximately 90 patients will be enrolled in China. Sample size considerations are exploratory and not based on hypothesis test. Based on the assumption of the observed ORR for each cohort, the corresponding 95% CI are presented in the following table for the given sample size.

Cohorts	Sample size	Observed ORR	95% CI
Patients with *MET*ex14 skipping mutation who had previously treated by other MET inhibitor(s)	25	15%	(4.0%, 34.9%)
Patients with *MET*ex14 skipping mutation who had received 3 or more lines prior systemic therapies without MET inhibitor for the advanced NSCLC	25	15%	(4.0%, 34.9%)
Patients with *MET* amplification (GCN ≥ 4 or *MET*/CEP7 ratio ≥ 2)	20	13%	(2.3%, 35.5%)
Patients with MET over-expression (IHC 2+)	20	13%	(2.3%, 35.5%)

Sponsor can decide the priority of the cohorts, and adjust the sample size among the cohorts according to the safety and preliminary efficacy data and registration strategy.

Phase II:

Approximately 78 evaluable NSCLC patients with *MET*ex14 skipping mutation, will be treated at RP2D. Sample size considerations are based on differentiating a historic control ORR of 30% or less with a target ORR of 45% based on patient data in the current study and clinical activity of other MET

inhibitors. Assuming the true ORR is 45%, the study has approximately 80% power to reject the null hypothesis that the true ORR is ≤ 30%, considering a 2-sided alpha of 5%.

In addition, Table 9-1, summeraizes the 95% exact CI for the target ORRs ranging from 41 – 45% with sample size of 78. At observed ORR = 41%, the lower boundary of the 95% CI excludes 30%, which is the null hypothesis ORR. This translates into observing at least 32 responders of the 78 efficacy evaluable patients (ORR of 41% with 95% CI (30.0% – 52.7%).

Table 9-1 95% Exact CIs Corresponding to Given ORR (n=78)

Practical ORR（%）	95% Exact CI
41%	(0.300,0.527)
43%	(0.318,0.547)
45%	(0.337,0.567)

Enrollment in other countries may be increased per country specific health authority request.

9.4 Statistical Analysis

9.4.1 Interim Analysis

Interim analysis of safety will be performed for the Phase II part of the study when approximately 25%, 50% and 75% of patients are enrolled and treated for at least for one cycle (21 days). These interim analysis will be reviewed by an Independent Data Monitoring Committee (IDMC). A complete description of the composition of the IDMC and details on the interim analysis process will be provided in a separate IDMC charter. In addition, the Sponsor will share safety data from the study with all primary investigators throughout the conduct of the study.

9.4.2 Primary Analysis

The objective of the primary analysis for the phase II part is to confirm ORR. The primary efficacy analysis will be based on subjects from the efficacy analysis set.

The primary analysis will be triggered after all patients complete at least 6 months of follow-up or withdraw consent or die, whichever occurs earlier. Secondary endpoints will also be analyzed simultaneously. Analysis may be performed earlier to support country specific health authority interaction if deemed necessary by the sponsor.

9.4.3 Final Analysis

The objective of final analysis for the phase II part is to update the secondary endpoints based on the follow-up data. The final analysis will occur after all the enrolled patients complete the long-term follow-up according to protocol.

9.5 Statistical Analysis Method

9.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint of the Phase II part of the study is ORR assessed by BIRC. ORR is defined as the proportion of patients achieve CR/PR after treatment with Glumetinib.

For the primary endpoint ORR, the 95% exact CI (as per Clopper-Pearson method) will be calculated. Patients, whose corresponding response data after administration are missing, may be deleted from the calculation and undergo sensitivity analysis. There is no multiplicity correction plan for efficacy endpoints.

9.5.2 Secondary Efficacy Endpoints

The secondary endpoints include ORR assessed by investigator, DOR, DCR, TTR, PFS, 6-month PFS rate assessed by BIRC and investigator and OS.

- Duration of Response (DOR): CR/PR time will be calculated from the first onset of CR/PR per RECIST 1.1 until the documented PD, or death due to any cause, whichever occurs first. The subjects still alive and relapse-free will be censored at the date of last tumor assessment prior to the date that triggers the analysis.
- Disease Control Rate (DCR): DCR is defined as the proportion of patients achieve confirmed CR, PR or continued SD no less than 6 weeks (±7days) after treatment with Glumetinib per RECIST 1.1.
- Time to response (TTR): TTR is defined as the time from the start of treatment with Glumetinib to the first objective tumor response observed for patients who achieve CR or PR per RECIST 1.1.
- Progression-free survival (PFS): PFS is defined as the time from the start of treatment with Glumetinib to disease progression per RECIST 1.1 or death from any cause, whichever occurs first. The subjects still alive and relapse-free will be censored at the date of last tumor assessment prior to the date that triggers the analysis.
- 6-month PFS rate: 6-month PFS rate is the proportion of patients who are alive and progression free at 6 months.
- Overall survival (OS): OS time will be calculated from the time of the start of treatment with Glumetinib until death due to any cause. Subjects still alive will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

For the efficacy analysis (DOR, TTR, PFS and OS) in the secondary endpoints, survival curves will be plotted by the Kaplan-Meier method, and the median survival and its 95% CI will be provided. The 6-month PFS rate will be calculated by the Kaplan-Meier method. For the DCR, the 95% exact CI (as per Clopper-Pearson method) will be calculated.

9.5.3 Safety Endpoints

For safety analysis in the secondary endpoints, the frequency and incidence, duration, and severity of treatment-emergent AEs and SAEs and their relationship with the study drug will be performed with descriptive statistical analysis. The changes from baseline in other measures (e.g.: physical examination results, clinical laboratory parameters, vital signs and ECG, etc.) will also performed with shift tables.

9.5.4 Pharmacokinetic Endpoints

The PK data of this study will be pooled with the PK analysis data from other studies of Haihe Biopharma Co., Ltd. and undergo population pharmacokinetic (Pop PK) analysis, but the corresponding analysis results will not be reported in the clinical study report.

Please refer to the Statistical Analysis Plan for the specific analysis methods.

10. Data Collection and Management

10.1 Data Collection

The electronic case report form (eCRF) will be adopted for study data collection and management. Investigators shall truthfully, completely and in a timely manner, record relevant data of each patient in the trial and confirm and sign the record. Information for all patients who have signed an informed consent shall be collected in the Case Report Form.

The sponsor or the data management party entrusted by the sponsor will provide the EDC system to study sites and conduct EDC training. Relevant personnel will apply for a corresponding account to login to the EDC system after training. The investigator at each site will enter the data generated in the trial in the corresponding eCRF in accordance with the eCRF completion guidelines. Finally, the principal investigator or personnel authorized by the principal investigator shall sign via electronic signature for the confirmed data.

10.2 Data Review

The CRA will periodically monitor the source data to guarantee the consistency with that recorded in the eCRF. The medical monitors will review eCRF data from the medical perspective, and data management personnel will check the integrity and logicality of eCRF data.

In terms of problems found during the data review, relevant audit personnel will create and send data queries in the EDC system to study sites, and personnel at site will answer the queries and make necessary changes to the data. All records of data revision and relevant operations are tracked in the EDC system.

10.3 Database Locking and Archiving

After trial data are collected and cleaned and locking conditions are reached through data review, database will be locked. Locked data will be sent to statistical analysts for analysis.

After the completion of the study, patient eCRF in PDF form shall be generated from EDC and saved on non-rewritable compact discs which will be submitted to and kept by the sponsor and each site for audit. Trial documents shall be kept and managed in accordance with the requirements addressed in GCP.

11. Committee

11.1 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will be established in phase Ib. SMC is to oversee the safety, MTD or RP2D determination and other pivotal study decisions. However, in the event of any discrepancy between the sponsor and SMC, the decision process will be described in the regulations of

SMC. The SMC will consist of members as follows: the principal investigator, one PK specialist, drug safety physician, medical monitor, and one statistician.

11.2 Blinded Independent Review Committee

A Blinded Independent Review Committee (BIRC) will be established for phase II study and the BIRC will perform tumor imaging evaluation data (CT or MRI) in a blinded manner in accordance with RECIST 1.1.

11.3 Independent Data Monitoring Committee

An independent data Monitoring committee (IDMC) will comprise at a minimum:

- At least one independent investigator and 1 independent statistician, none of whom are directly involved in the conduct or analysis of the study; and
- There is a total of at least 3 (always an odd number) members in the IDMC

A complete description of the composition of the IDMC and details of its responsibility will be provided in a separate IDMC charter.

12. Ethical Considerations

12.1 Ethical Principles

The study will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki, the guideline for ICH E6 GCP, and other appropriate local regulations to provide patients with safety protection to the largest extent.

12.2 The Informed Consent Form of the Patients

Each patient (and/or the patient's legally representative) shall voluntarily sign the informed consent form prior to starting any prescreening, screening or other study-related procedures. Investigators must obtain the informed consent by designated procedures. Importantly, investigators or personnel designated by investigators shall explain the clinical study to each potential patient, and patients must voluntarily sign and date the approved informed consent form. Patients must have opportunities to ask investigators questions and may also ask other qualified personnel questions if required by local regulations. Investigators must provide patients with a copy of the written informed consent form in a language understandable to them.

The informed consent form must abide by all applicable local laws, and patients shall be informed of study objectives, procedures, requirements and limitations, and any known risks and potential benefits related to the study drug, compensations and confidentiality clauses of personal health information. Patients shall be told that they voluntarily participate in the study and be informed of contact information when they have questions or concerns during the study. Patients shall also be informed that their records can be reviewed by appropriate institutions and personnel designated by the sponsor and the Health Authority. Investigators must retain the original signed informed consent form and provide a copy to each patient.

Any changes and modifications to the informed consent form shall be submitted to the Ethics Committee for approval. Any revised informed consent shall be carried out in compliance with local

laws and regulations after receiving the approval opinion of the Ethics Committee, except for the purpose of immediately eliminating injury to patients who participate in the study. The new version shall be signed and dated by all patients or witnesses involved in modifications of informed consent form and by investigators who conducted the informed consent discussion. Patients shall receive a copy of signed informed consent form.

12.3 Ethics Committee (EC)/Institutional Review Board (IRB)

The trial protocol, informed consent form, any other written information provided to patients and any advertisement for patient recruitment shall be approved by the Ethics Committee/Institution Review Board (EC/IRB). Investigators must provide approval documents of EC/IRB to the sponsor. The approval letter must be dated and include appropriate trial protocol, revised version (if any), informed consent form, all appropriate recruitment documents, written information provided to patients and compensation plan to patient. The Investigator's Brochure, any periodical safety updates and local regulations, or other and all information required by EC/IRB shall be provided to EC/IRB. At the end of the study, investigators shall notify EC/IRB that the study has ended. Premature termination shall be reported to EC/IRB. Finally, investigators shall report study progress to EC/IRB at intervals as required by EC/IRB.

12.4 Confidentiality of Study data

Health information of patients obtained during the study shall be confidential. No information can be disclosed prior to obtaining the written agreement. Individual data shall be handled in compliance with data protection laws of countries or regions the study conducted. Investigators must guarantee that patients' identity is not disclosed. Patients shall not be identified with names in CRF and other documents submitted to the sponsor or its Contract Research Organization (CRO). Instead, patients will be identified only with assigned enrollment numbers to guarantee the confidentiality of all study documents. Patients will be identified by their I.D. number only throughout the study.

To follow guidelines of authorities and to ensure patients' safety, the sponsor and its representative, CRO personnel, local institution review board or authorities, which are related to the study, shall have authority to audit patients' medical records. The enrollment number of a patient in CRF is the only way to identify the patient, but the full name of the patient can be available to drug regulatory institution or other authorized governmental organizations or medical staff (if necessary) and personnel designated by the sponsor.

Documents (e.g. informed consent form) that are not submitted to the sponsor will be kept by investigators in an absolute confidential way. Documents in which patients can be identified by their names shall be kept at study sites, and patients identify will remain confidential in all publications related to the study.

12.5 Termination of the Study

The sponsor and investigators may terminate the study at any time. To ensure patients' best interests and medical and ethical considerations, premature termination of the study can be conducted after receiving the approval of investigators and the sponsor. The sponsor, CRO and investigators will take full consideration of the protection of patients' interests while terminating the study.

12.6 Insurance

The sponsor will strictly abide by any applicable laws and cover insurance in compliance with local and specific policies. All insurance-related documents will be included in documents submitted to administrative departments as required.

13. Study Records, Monitoring and Management

13.1 Retention of Study Documents and Records

According to sponsor's requirements, the investigator shall retain the latest and complete documents related to the clinical study as part of the study monitoring, and the sponsor will review the investigator's files. Financial information is not covered by regulatory inspections and should be kept separately.

In addition, investigators must retain study records and source documents until receiving the sponsor's written approval of destruction. If investigators do not undertake the responsibility of retention of study records because of retirement, resignation or any other reasons, they must notify the sponsor and appropriately arrange the retention of study records and source documents in accordance with China, Japan and US's regulations. The sponsor shall also keep the clinical trial documents according to applicable regulatory requirements or special regulations of the sponsor. The sponsor will be responsible for informing investigators of the specific retention duration of these documents.

13.2 Protocol Deviation

The investigators must completely read the protocol and comply with it, except for emergency conditions requiring immediate intervention for patients' protection, safety and health at the discretion of the investigator or professional personnel (sub-investigator) designated by the investigator.

The investigator or personnel designated by the investigator shall contact monitors as soon as possible in case of major protocol deviations due to emergency conditions, accidents or negligence. As a result, investigators and the sponsor can make a decision as soon as possible on whether or not to continue the study in the patient.

13.3 Study Monitoring

After qualification of clinical study sites and/or visit initiation, the sponsor or personnel designated by the sponsor shall regularly monitor visits and close-out visits at clinical study sites. In accordance with GCP and ICH GCP, investigators must provide assistance to monitors and allocate enough time and space to make them able to inspect patients' original records, CRF, query forms, laboratory normal ranges (if applicable), and disposition records of the study drug.

The purposes of trial monitoring are to verify that:

- The rights and well-being of patients are protected.
- The reported trial data are accurate, complete, and verifiable from source documents.
- All data are collected and followed by study sites and submitted to the sponsor or personnel designated by the sponsor, including evaluation of unscheduled visits and omission.
- The reported data are consistent with all source data (e.g. laboratory test values, safety and clinical database).

- The conduct of the trial is in compliance with the currently approved protocol/amendment, with GCP, and with the applicable regulatory requirements.

Investigators must allow National Medical Products Administration (China) or other applicable regulatory institutions to inspect study sites and records as required. If NMPA or relevant regulatory institution notifies investigators of inspection of the study, investigators must immediately notify the sponsor.

13.4 Audit and Inspection

The sponsor's authorized representative, regulatory institution and Ethics Committee can audit or inspect study sites, including verification of source data. Investigators will allow the sponsor's auditors, regulators, representative of the Ethics Committee to inspect the storage area and inventory of the study drug, count records of drugs, patients' records, source documents of the study and other records related to the clinical study. The purposes of audit and inspection are to systemically, independently inspect all activities and documents related to the clinical study, and evaluate whether or not these activities are conducted, and whether the data are recorded, analyzed and accurately reported in compliance with the clinical trial protocol, ICH GCP guidelines and any applicable regulatory requirements. Investigators shall immediately notify the sponsor of the notification of a regulatory institution on inspection.

13.5 Publication Policy

The sponsor shall take full responsibility for this and retain exclusive ownership of the study results and may use them as appropriate.

Because this is a multinational, multicenter study, papers can be published only after data are collected from some sites and analyzed by the sponsor. Except with the prior written consent of the other investigators and the sponsor, an investigator shall not publish or communicate part of the study results of his or her sites or other sites until complete study results are made publicly available.

Any study-related contents to be published and (or) communicated and (or) study data obtained during the study or at the end of the study shall be submitted to the sponsor for audit at least 30 days (full text) or 15 days (abstract) prior to the estimated publication or communication date. The sponsor shall evaluate the full text within 15 days and evaluate the abstract within 7 days. Investigators who propose publication plans shall take into account the sponsor's requirements. An investigator who proposes a plan shall submit a written report and explain reasons to the sponsor if he or she decides not to revise according to the sponsor's opinions at any time.

However, when the sponsor is patenting the study results, approval for publication or communication can be delayed until after the patent is registered.

13.6 Protocol Amendment

In accordance with ICH GCP E6 (R1) guidelines, investigators shall not deviate from or alter the protocol prior to receiving the sponsor's approval and the written approval of the Ethics Committee on protocol amendment. The only exception is in order to eliminate injury to patients in the study, or to make minor logistic or administrative changes involving the study (e.g. changes in monitors and telephone number).

Any revision of the protocol shall be handled in accordance with protocol amendment. Any potential revision shall obtain the approval of the sponsor. Written revisions must be submitted to relevant regulatory departments and the competent EC/IRB. Investigators may not implement relevant changes prior to obtaining the approval of EC/IRB on protocol amendment, except for vitally necessary changes for immediately eliminating obvious current injury to patients, which shall be notified to EC/IRB within 5 days after carrying out changes.

All protocol amendments must be approved in writing by relevant regulatory institutions and EC/IRB except for administrative amendments which only require a notification. Protocol amendment and guidance for adding amendment to the protocol will be sent to all receptors of the original protocol after being approved.

If protocol amendments, at the discretion of local EC/IRB, investigator and/or the sponsor, have changed the study design, procedures and/or increased potential risks to patients, the written informed consent form will be revised. The revised informed consent form shall be audited and approved by the sponsor, relevant regulatory institutions and EC. In such case, informed consent of subjects enrolled into the study shall be obtained again prior to continuing the study.

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15. Appendices

Appendix 1 RECIST 1.1

Interpretation

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable lesions

Tumor lesions: must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ⩾15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ⩾10mmto <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by pharmacological exam that is not measurable by reproducible imaging techniques, and cystic lesions.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions;
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above;
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered

as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts;

- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ⩾ 10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next). If new lesions are identified by

ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in at least first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and progressive disease.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of target and non-target lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not

lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ⩾ 15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm·× 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ⩾10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference of baseline diseases.

All other lesions including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions	
Complete response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have short axis <10 mm.
Partial response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions:

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retro peritoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mmshould be assigned in this circumstance as well.) This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

The table below provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions.

Evaluation of non-target lesions	
Complete response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. Notes: the appearance of one or more new lesions is also considered

progression).

Special notes on assessment of progression of non-target disease:

The concept of progression of non-target disease requires additional explanation as follows: When the patient also has measurable disease to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. furthermore, depending on the nature of the study, the protocol requirements and confirmatory measurement standard of results. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the best overall response.

Time point response

The table below provides evaluation for patients with target lesions and patients with non-target lesions only (no target lesion).

Time point response: patients with target (+/- non-target) lesions

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = non-evaluable.

Time point response: patients with non-target lesions only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Not evaluated
Equivocal PD	Yes or No	PD
Any	Yes	PD

Note: 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease. Since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised. For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Missing assessments and non-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Best overall response

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). See the following table for further information.

Best Overall Response when Confirmation of CR and PR Required

Overall response First time point	Overall response Subsequent time point	Best overall response

CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable. a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix 2 ECOG performance status score

Grade	Performance Status
0	Asymptomatic, fully active, able to carry on all pre-disease activities without restriction.
1	Symptomatic but completely ambulatory, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work.
2	Symptomatic, ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours, < 50% in bed during the day.
3	Symptomatic, capable of only limited self-care, confined to bed or chair 50% or more of waking hours, but not bedbound.
4	Completely disabled, cannot carry on any self-care, bedbound.
5	Death.

References: Oken, M.M., Creech, R.H., Tormey, D.C., et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 3 Women of child-bearing potential and contraceptive measures

Women of child-bearing potential (WOCBP) refer to any women who have experienced menarche, not experienced surgical sterilization (hysterectomy or bilateral ovariectomy or tubal ligation performed at least 6 weeks) and not yet reached menopause. Menopause refers to 12-month menostasis of women aged over 45 years in circumstance of lacking other biological or physiological causes for patients with amenorrhea due to anti-tumor agents, even amenorrhea over 12 months, a pregnancy test is necessary). In addition, menopause can be confirmed only serum follicle-stimulating hormone (FSH) level in women aged below 55 years > 40 mIU/mL.

* Women receiving hormone replacement therapy (HRT) may have artificially inhibited FSH levels. Therefore, a wash-out period may be required to reach the physiological FSH level. The duration of wash-out period is associated with the functions of HRT. Wash-out duration recommended by the guideline is as follows. An investigator shall inspect serum FSH level at his or her discretion. If serum FSH level at any time of the whole wash-out period > 40 mIU/ml, the woman will be regarded as menopause:

- At least one week of using vaginal hormone products (pessulum, ointment, gel)
- At least four weeks of using transdermal products
- At least eight weeks of using products for oral administration

Patients (including sexual partners of male patients) of child-bearing potential shall take full contraceptive measures and avoid donating eggs and sperms between the date of signing an informed consent form and month 6 after the last dose. Patients will be provided with information on relevant acceptable contraceptive measures during patients' inform consent process.

<u>Acceptable Effective Contraception</u>

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injection
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner with documentation of the success of the vasectomy
- Complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)
- Male patients with partners who are WOCBP should use a combination of male **condom** with cap, diaphragm, or sponge with spermicide during the trial and for 6 months after the last dose of Glumetinib.

Appendix 4 New York Heart Association (NYHA) Functional Classification

I	Patients have heart disease, but no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pectoris.
II	Patients have heart disease and slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in undue fatigue, palpitation, dyspnea or angina pectoris.
III	Patients have heart disease leading to marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes undue fatigue, palpitation, dyspnea or angina pectoris.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix 5 QTc Fridericia's formula

$$QT_F = \frac{QT}{\sqrt[3]{RR}}$$

QT refers to the interval from the start of the Q wave to the end of the T wave.
RR refers to the interval from the occurrence of QRS wave group to the occurrence of the next QRS wave.

Appendix 6 CYP3A4/CYP2C8/CYP2C9 inhibitor and CYP3A4 inducer

CYP3A4 inhibitor	CYP3A4 inducer
Strong: ● Protease inhibitor Ritonavir Crizotinib Indinavir Darunavir Nelfinavir Delavirdine Saquinavir Dronedarone Danoprevir Elvitegravir Fosamprenavir Amprenavir ● Macrolides antibiotics Clarithromycin Telithromycin ● Chloramphenicol (antibiotics) ● Azole antifungals Ketoconazole Itraconazole ● Nefazodone (antidepressant) **Moderate:** ● Aprepitant (antiemetic) ● Calcium channel blockers Verapamil Diltiazem ● Macrolides antibiotics Erythromycin ● Azole antifungals Fluconazole ● Bergamottin (grapefruit juice) ● Valerian **Weak:** ● Fluoxetine/norfluoxetine ● Cimetidine (H2-antagonist) ● Buprenorphine (analgesic) ● Cafestol (unfiltered coffee) ● Orphenadrine	**Strong:** ● Apalutamide, ● Carbamazepine ● Enzalutamide ● Mitotane ● Phenytoin ● Rifampin ● St. John's wort (*hypericum perforatum* L.) **Moderate:** ● Bosentan, ● Efavirenz ● Etravirine ● Phenobarbital ● Primidone **Weak:** ● Armodafinil ● Modafinil ● Rufinamide
CYP2C8 inhibitor **Strong:** ● Gemfibrozil **Moderate:** ● Clopidogrel ● Deferasirox ● Teriflunomide **Weak:** ● Trimethoprim	

CYP2C9 inhibitor

Moderate:

- Amiodarone
- Fluconazole
- Miconazole
- Piperine

Weak:

- Diosmin
- Disulfiram
- Fluvastatin
- Fluvoxamine
- Voriconazole

For updated information please refer https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Appendix 7 Substrates or inhibitors of transporters

Substrates of transporters	
Transporter	**Substrate**
P-gp	Dabigatran etexilate, digoxin, fexofenadine
BCRP	Rosuvastatin, sulfasalazine
OATP1B1 OATP1B3	Asunaprevir, atorvastatin, bosentan, danoprevir, docetaxel, fexofenadine, glyburide, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rosuvastatin, simvastatin acid
OAT1 OAT3	Adefovir, cefaclor, ceftizoxime, famotidine, furosemide, ganciclovir, methotrexate, oseltamivir carboxylate, penicillin G
METE1 METE-2K OCT2	Metformin
Inhibitors of transporters	
Transporter	**Inhibitor**
P-gp	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP	Curcumin, cyclosporine A, eltrombopag
OATP1B1 OATP1B3	Atazanavir and ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir and ritonavir, rifampin (single dose), simeprevir
OAT1 OAT3	P-aminohippuric acid, probenecid, teriflunomide
METE1 METE-2K	Cimetidine, dolutegravir, isavuconazole, ranolazine, trimethoprim, vandetanib
For updated information please refer https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers	

Appendix 8 List of known drugs that can prolong QT interval or may be associated with torsade de pointes

For drugs that can prolong QT interval or may be associated with torsade de pointes, http://www.crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=All is accessible.

Appendix 9 Summary of Changes

Amendment 1 Key changes (Version 1.0 to Version 2.0)
- The study purpose and rationale was added in Protocol Synopsis. - Study introduction was updated to summarize the emerging clinical data. - The study objectives and endpoints were updated. - Phase II part of this study changed from a China only study to a global study including sites in Japan and US, and added a safety run-in of Glumetinib in patients in the US. - Add the DLT definition for safety run-in part of the study. - The study population was modified to clarify the prior systematic treatment for the advanced NSCLC and the MET alterations. - The inclusion and exclusion criteria were updated for clarification and the participation of Japan and US, including MET alteration eligibility, renal and liver function, heart function (NYHA and QTcF), malignancies history, infection, comorbidities, etc. - Revised treatment guidelines, including clarification of administration, revision of dose modification (dose reduction and interruption criteria, and required follow-up for toxicities). - Revised "Concomitant medications" accordingly in Appendix 6. - Study Flowchart was updated for clarification, adjustment in procedure, such as ECG timepoint, frequency of tumor assessment, and PK samples collection time. - Revised "Molecular Pre-screening of Tumor or ctDNA Samples for MET Alterations": local lab testing results of MET alteration was added for eligibility and ctDNA was added for both pre-screening and MET alterations (exploratory objective). - The sample size was updated. - An interim analysis for efficacy was added. - Safety monitoring by the SMC was replaced by ISAC for Phase II. - Sections with duplicated contents are deleted or merged.
Key changes (Version 2.0 to Version 2.1)
- Add strong inhibitor for CYP2C8 and/or CYP2C9 and substrate or inhibitor for transporter as prohibited concomitant therapy in safety run-in part of the study and closely monitoring for AE in patients co-administer these drugs in phase 2 part of the study.
Key changes (Version 2.1 to Version 2.2)
- Add rationale for determination of whether 400 mg will be evaluated in US or globally; - Remove intra-patient dose-escalation in safety run-in; - Revise DLT criteria; - Add requirements for patients who could be treated with SCC244 after RECIST-defined

radiological progression of disease in Section 4.3.1

- Add section 4.4 Study Stopping Criteria;
- Revise inclusion criterion 4 for stage of NSCLC;
- Revise exclusion criteria:
  - Exclusion criterion 1: exclude patients with BRAF mutation and NTRK fusion;
  - Exclusion criterion 2: add maximum dose requirement for stable dose of steroids used for CNS metastases;
  - Exclusion criterion 7: revise the exclusion criteria for HIV infection in the US;
- Remove footnote “a” and “d” from Table 6-2 in Section 6.3.2;

Key changes (Version 2.2 to Version 2.3)

- Updated the requirements of tumor samples which are sent to central laboratory during pre-screening for testing (tumor tissue sample must be available and ctDNA is optional)
- Added the clarification on investigational product starting dose for Phase Ib and Phase II respectively;
- Added the information of study SCC244-102 in section 2.3 Clinical Development of Glumetinib;
- Added the criteria of evaluable patient for Phase II study in section 4.1 Overall Study Design
- Changed the time point of 1 of 3 occasions to assess MET alterations in ctDNA from screening to pre-screening;
- The time window for 28-day safety follow up visit from ±7 days to + 7 days;
- Typos corrections

Key changes (Version 2.3 to Version 3.0)

- Update the non-clinical and clinical PK data according to the newly acquired data; improved the rationale for RP2D selection.
- Update the study background based on the updating NCCN guideline and the new published study results of other MET-TKIs.
- Modification of the subject number of phase Ib (from 15 to 90) and phase II (from 90 to 78); modification of the study population of phase Ib, adding NSCLC patients harboring *MET*ex14 skipping and having received 3 or more lines prior systemic therapies without MET inhibitor and updating the criteria for other three cohort and add the sample size and observed ORR for each cohort. The sample size of phase II was re-calculated based on updated observed ORR according to communication results with authority.
- Update the study objectives and endpoints and the PK analysis; the PK evaluation was modified to population PK analysis; delete the exploratory objectives and endpoints and the procedure regarding ctDNA; update the statistical analysis sets and definition of endpoints for clarification.

- Modification of inclusion/exclusion criteria to clarify the requirements on prior systematic antitumor therapy, adding the definition of treatment failure, lines and (neo)adjuvant therapy.
- Modification of the study procedure including modification of ECG and PK sampling timepoints, updating the requirement of vital sign/X-ray/HRCT/lung function/ SpO_2, adding the troponin T, lipase and amylase in blood biochemistry, modification of the PR/CR confirmation window from week 4 (+7 days) to at least 4 weeks, etc.
- Re-location of the section "End of treatment Discontinuation Criteria" and add the "Criteria for Early Withdraw from Study" in line with protocol template/unify version.
- Adding the criteria for continuing study treatment after progressive disease.
- Modification of the SAE reporting procedure in line with the updates of regulations and global study needs.
- Modification of the safety follow-up for QTcF and Pancreas and "Special safety monitoring" (ILD with special reporting requirement, QTc Prolongation and Pancreatitis added).
- Remove the interim analysis of efficacy.
- Add "Rationale for the Dose and Frequency of Administration in Patient".
- Add Safety Monitoring Committee in phase Ib and the ISAC was changed to IDMA in phase II for safety monitoring.
- Sections with duplicated contents are deleted or merged, adjust the section location and typo correction.

Key changes (Version 3.0 to Version 3.1)

- Table 6-3 Required Follow-up for Toxicities, follow-up evaluation for Non-laboratory toxicity was updated to "Patients who experience non-laboratory Grade 3 or 4 AEs must be evaluated at least once a week until the event resolution or stabilization of the AE".
- Inconsistent or format or typos corrections or delete duplication: table 1-1 (delete PK sampling in EOT), section 4.1 (delete duplication content), section 5.2 (correction to keep consistent with synopsis), section 9.2 (typos), section 11.3 (format correction).

Key changes (Version 3.1 to Version 3.2)

- Section 4.3 the measures taken after the completion of the study was updated to "After the completion of the study, if a patient still not reaches disease progression, the patients requires administration of Glumetinib and which has been assessed as beneficial per the investigator, the Sponsor will continue to provide Glumetinib in the form of a complimentary medication. At that time, patients will follow and complete the procedures described in the Study Schedules for the EOT Visit and Safety Follow-up procedures before entering the drug donation process. Subsequently all the data will not be collected and recorded in the EDC, but if any SAE happened during the medication, it's still required to report to Sponsor as per section 8.3.2."

Key changes (Verson 3.2 to Version 3.3)

- Section 1.2: The flow chart has been modified to reflect changes in sections 4.1 and 8.3 (See below).
- Section 4.1: a paragraph has been added that after the approval of new drug application in Japan, the remaining Japanese patients will be rolled over to a post marketing clinical part of this study in accordanc with GVP and GPSP in Japan. This part will continue until the product is commersially available in Japan and accessible to the enrolled patients.
- Section 8.3: a paragraph has been added that after the approval of new drug application in Japan, the Sponsor becomes obliged to safety reporting to the regulatory authority in accordance with GVP and GPSP in Japan.

Signature Page for VV-CLIN-001313 v1.0

Approval	Yiming Du(杜一鸣) RA 16-Apr-2024 05:33:42 GMT+0000

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Signature Page for VV-CLIN-001313 v1.0

Shanghai Haihe Biopharma Co., Ltd.

A Phase Ib/II, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Glumetinib (SCC244), a Selective MET Inhibitor in Patients with Advanced Non-Small Cell Lung Cancer Harboring MET-alterations

Study Number: SCC244-108

Statistical Analysis Plan

Version Number: 3.1

Date: 29Jun2022

1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations or terminology	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
BOR	Best overall response
CI	Confidence interval
c-MET/MET	Cellular-mesenchymal to epithelial transition factor
CR	Complete response
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
IDMC	Independent Data Monitoring Committee
BIRC	Blinded Independent Review Committee
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred Term
QD	Once daily

QT	The timemeasuredfrom the start of QRS complex to the end of the Twaveon the ECG
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase II dose
SAE	Serious adverse event
SAS	Safety analysis set
SD	Stable disease
SMQ	Standard MedDRA query
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTR	Time to response
ULN	Upper limit of normal
WHO	World Health Organization

3. INTRODUCTION

This document presents the statistical analysis plan (SAP) for Protocol SCC244-108: A Phase Ib/II, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Glumetinib (SCC244), a Selective MET Inhibitor in Patients with Advanced Non-Small Cell Lung Cancer Harboring MET-alterations (Version 3.0, dated 07Dec2020) and approved case report forms (CRFs) (Version 3.0, dated 20Feb2021), and contains definitions of analysis populations, derived variables, imputation rules for missing values, and statistical methods for the analysis of efficacy and safety parameters. Pharmacokinetics (PK) analysis methods will be included in a separate SAP document.

4. STUDY OBJECTIVES and ENDPOINTS

Table 1 Study objectives and endpoints

Study objectives	Study endpoints
Phase Ib	
Primary objective: 1. To evaluate the tolerability and safety of Glumetinib in patients with locally advanced or metastatic NSCLC.	Primary endpoint: 1. Tolerability and safety: incidence, duration and severity of adverse events (AEs), physical examination, laboratory data, vital signs and electrocardiogram (ECG) changes.
Secondary objectives: 1. Preliminary efficacy of Glumetinib in patients with local advanced or metastatic NSCLC harboring *MET*-aberrations.	Secondary endpoints: 1. Object Response Rate (ORR), Duration of Response (DOR), Disease Control Rate (DCR), Time to Response (TTR), Progression-Free Survival (PFS), 6-month

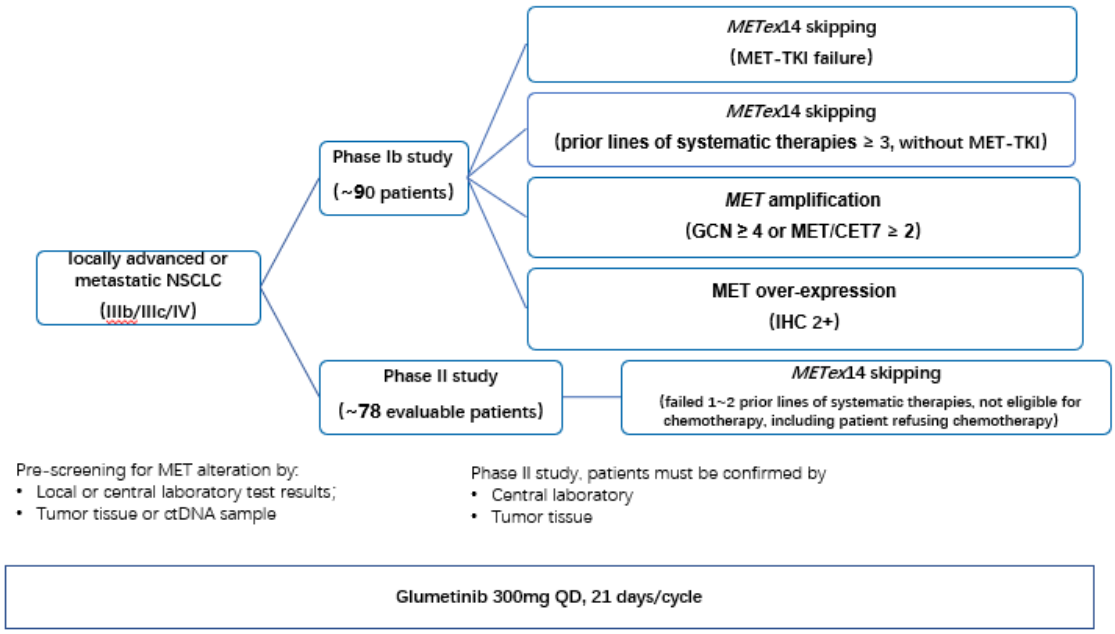
2. To evaluate the pharmacokinetic (PK) characteristics of Glumetinib with Population PK analysis.	PFS rate assessed by investigator and Overall Survival (OS).
Phase II	
Primary objective: 1. To evaluate the antitumor efficacy of Glumetinib (confirm ORR by BIRC) in locally advanced or metastatic NSCLC harboring METex14 skipping mutation.	Primary endpoint: 1. ORR will be based on the blinded independent review committee (BIRC). Tumor response assessments will be made based on RECIST 1.1.
Secondary objectives: 1. To evaluate ORR (by investigator); DOR, DCR, TTR, PFS, 6-month PFS rate by BIRC and by investigator; and OS. 2. To investigate the safety and tolerability of Glumetinib. 3. To evaluate the PK characteristics of Glumetinib with Population PK analysis.	Secondary endpoints: 1. ORR assessed by investigator. 2. DOR, DCR, TTR, PFS, 6-month PFS rate by BIRC and by investigator and OS. 3. Safety: incidence, duration and severity of AEs, physical examination, laboratory data, vital signs and ECG changes.

5. STUDY DESIGN

5.1. *Overall design*

This is an open-label, multicenter phase Ib/II study including two parts: Phase Ib in NSCLC patients with *MET* alterations and Phase II study in patients with locally advanced or metastatic NSCLC (stage IIIb, IIIc or IV) harboring *MET*ex14 skipping mutation.

Figure 1 Study Design



Glumetinib will be administered orally in continuous once daily (QD) 21-day treatment cycles until disease progression, unacceptable AE or withdrawal of consent. There are no breaks in dosing between cycles. Patients should follow the instructions of the treating physician on study drug administration during treatment. Patients are required to fast for at least 2 hours before and 1 hour after administration of Glumetinib.

5.2. *Phase Ib (China only)*

Patients with locally advanced or metastatic NSCLC including PSC (stage IIIb, IIIc or IV) who have the MET alteration that has been pre-screened by local or Sponsor-designated central laboratory as listed below and meet the inclusion/exclusion criteria in the protocol will be enrolled.

- Patients with *MET*ex14 skipping mutation who had previously treated by and later progressed or intolerance to other MET inhibitor(s)
- Patients with *MET*ex14 skipping mutation who had received 3 or more lines prior systemic therapies without MET inhibitor for the advanced NSCLC or

- Patients with *MET* amplification (GCN ≥ 4 or MET/CEP7 ratio ≥ 2)
- Patients with MET over-expression (IHC 2+)

During the phase Ib study, MTD or RP2D will be confirmed based on the latest clinical study data of Glumetinib. The phase II study will be started once the MTD or RP2D is confirmed. Phase Ib study will be continued to further evaluate the tolerability, safety, preliminary efficacy and pharmacokinetics of Glumetinib in the specified subgroup of NSCLC patients. Glumetinib will be administered orally continuous once daily (QD) in 21-day treatment cycles until disease progression, unacceptable AE or withdrawal of consent. A total of approximately 90 patients will be enrolled. The purpose of the Phase Ib study is to assess the tolerability, safety, preliminary efficacy and pharmacokinetics of Glumetinib in the specified subgroup of NSCLC patients.

5.3. *Safety Run-in (US only)*

In order to evaluate potential variations in Glumetinib drug exposure in different ethnic groups, there will be a safety run-in of Glumetinib at the dose of 300 mg in patients from the US while China and other countries continues enrolling patients at 300 mg. A minimum of 6 patients with *MET*-alterations (meeting the eligibility for either Phase Ib or Phase II) from the US will be enrolled. Once the first 6 patients at 300 mg are evaluated for DLT and no more than one of 6 DLT-evaluable patients experiencing DLT, additional patients could be enrolled in Phase 2. If > 1/6 patients experience DLT at 300 mg, 200 mg will be evaluated. In addition, based on the evaluation of safety, PK and efficacy, 400 mg may be evaluated according to the same evaluation criteria for DLT set forth for 300 mg. If > 1/6 patients experience DLT at 400 mg, 400 mg will be deemed not tolerated and no additional patients will be treated at 400 mg for the study. If no more than 1 of the 6 patients who have been treated at 400 mg and evaluated for DLT experiences a DLT, a comprehensive review of all available safety, PK, and efficacy data from ongoing SCC244 studies will be performed. Based on this review, a final RP2D will be selected to continue further enrollment until meeting the prespecified sample size for Phase II at all sites globally.

A DLT-evaluable patient is defined as either experienced a DLT during the first 21-day of the treatment or has received at least 80% of the assigned doses (i.e.17 of the 21 days of Glumetinib doses). DLT is defined as below:

A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that meets any of the following criteria assessed using the NCI-CTCAE Version 5.0 and reported to be at least possibly related to the study drug by the Principal Investigator and/or the Sponsor during the DLT evaluation period. The DLT observation period starts on Day 1 up to Day 21 of Cycle 1 (21 days).

- Hematological toxicity:
  - CTCAE Grade 4 neutropenia (absolute neutrophil count < $0.5x10^9$/L)
  - CTCAE Grade 4 thrombocytopenia (platelet count< 25 $x10^9$/L)
  - CTCAE Grade 3 thrombocytopenia accompanied by clinically significant bleeding tendency (platelet count < 50 $x10^9$/L)
  - ≥ CTCAE Grade 3 febrile neutropenia (absolute neutrophil count <$1.0x10^9$/L with a single temperature of > 38.3°C or a sustained temperature of ≥ 38 °C for more than one hour)
- Non-hematological toxicity, ≥ CTCAE Grade 3*. Additionally, the following will be judged to be a DLT:
  - Liver transaminase elevation (AST or ALT) >3 x the upper limit of normal (ULN) with concurrent increase in total bilirubin >2 x ULN without evidence of cholestasis or alternative explanations (e.g., viral hepatitis, disease progression in the liver)
  - Liver transaminase (ALT or AST) elevation >8 x ULN or total bilirubin > 5 x ULN
  - CTCAE Grade 4 vomiting, diarrhea, and constipation, regardless of duration
  - CTCAE Grade 4 electrolyte disturbance, regardless of duration
  - CTCAE Grade 3 electrolyte disturbances that require hospitalization
  - CTCAE Grade 2 pneumonitis lasting > 7 days or recurring in the same cycle
- Other adverse events:

- Any death not clearly due to the underlying disease or extraneous causes
- Any adverse events that is unrelated to disease progression, intercurrent illness, or concomitant medications requiring permanent discontinuation of the study drug
- Any grade toxicity that is clinically significant and/or unacceptable and is judged to be a DLT by the Investigator and/or Sponsor

*The following CTCAE Grade 3 adverse event or laboratory abnormalities will not be considered as DLT:

- Nausea/vomiting, diarrhea, and constipation return to grade 2 by appropriate supportive treatment within 3 days
- Fatigue for less than 7 days after proper supportive treatment
- Headache for less than 7 days after proper supportive treatment
- Laboratory abnormalities without clinical significance that are not already specified in the DLT criteria above will not be considered as DLT (e.g., Grade 3 elevations in serum amylase or lipase that are not associated with symptoms or clinical manifestations of pancreatitis)

In the absence of clinical abnormality, repeat laboratory testing should be performed to confirm significant laboratory findings prior to designation as a DLT. However isolated laboratory changes of any grade without clinical sequelae or clinical significance are not considered DLTs.

5.4. *Phase II (globally)*

The phase II study is a single-arm study. Patients with locally advanced or metastatic NSCLC including PSC (stage IIIb, IIIc or IV) harboring *MET*ex14 skipping mutation that have been pre-screened by local or Sponsor-designated central laboratory, who are not eligible for chemotherapy or refuse chemotherapy after well-informed or have failed one or two prior lines of systemic therapies and have not had prior MET inhibitor for the advanced NSCLC, and meet the inclusion/exclusion criteria in the protocol, will be enrolled.

Approximately 78 evaluable NSCLC patients with *MET*ex14 skipping mutation will be enrolled to evaluate the antitumor efficacy of Glumetinib [to confirm ORR by a Blinded Independent Review Committee (BIRC)]. Secondary objectives are to evaluate DOR, DCR, TTR, PFS, 6-month PFS rate, OS, safety and PK. An evaluable patient must meet the following criteria: 1. *MET*ex14 skipping mutation confirmed by analysis at sponsor designated central lab; 2. treated at RP2D dose; 3. at least have valid baseline tumor assessment.

Enrollment in other countries may be increased per country specific health authority request.

Phase Ib and Phase II will enroll patients concurrently.

5.5. *Estimation of sample size*

Phase Ib:

Approximately 90 patients will be enrolled in China. Sample size considerations are exploratory and not based on hypothesis test.

Based on the assumption of the observed ORR for each cohort, the corresponding 95% CI are presented in the following table for the given sample size.

Cohorts	Sample size	Observed ORR	95% CI
Patients with *MET*ex14 skipping mutation who had previously treated by other MET inhibitor(s)	25	15%	(4.0%, 34.9%)
Patients with METex14 skipping mutation who had received 3 or more lines prior systemic therapies without MET inhibitor for the advanced NSCLC	25	15%	(4.0%, 34.9%)

Patients with *MET* amplification (GCN ≥ 4 or *MET*/CEP7 ratio ≥ 2)	20	13%	(2.3%, 35.5%)
Patients with MET over-expression (IHC 2+)	20	13%	(2.3%, 35.5%)

Sponsor can decide the priority of the cohorts, and adjust the sample size among the cohorts according to the safety and preliminary efficacy data and registration strategy.

Phase II:

Approximately 78 evaluable NSCLC patients with METex14 skipping mutation, will be treated at RP2D. Sample size considerations are based on differentiating a historic control ORR of 30% or less with a target ORR of 45% based on patient data in the current study and clinical activity of other MET inhibitors. Assuming the true ORR is 45%, the study has approximately 80% power to reject the null hypothesis that the true ORR is <=30%, considering a 2-sided alpha of 5%.

In addition, Table 2, summeraizes the 95% exact CI for the target ORRs ranging from 41 – 45% with sample size of 78. At observed ORR = 41%, the lower boundary of the 95% CI excludes 30%, which is the null hypothesis ORR. This translates into observing at least 32 responders of the 78 efficacy evaluable patients (ORR of 41% with 95% CI (30.0% – 52.7%).

Table 2 95% Exact CIs Corresponding to Given ORR (n=78)

Practical ORR（%）	95% Exact CI
41%	(0.300,0.527)
43%	(0.318,0.547)
45%	(0.337,0.567)

Enrollment in other countries may be increased per country specific health authority request.

6. ANALYSIS SETS

The *safety analysis set (SAS)* will include all patients who received at least one dose of Glumetinib. This analysis set will be the primary analysis set for safety evaluation.

The *PK analysis Set* will consist of patients who have received at least one dose of Glumetinib and have at least one Glumetinib evaluable plasma concentration data. All such patients will be evaluated for PK unless major protocol deviations have impacted the data or key dosing information is missing. Changes to the procedures, which may impact the quality of PK data, will be considered "PK relevant protocol deviations". Examples include sample process errors that lead to inaccurate bioanalytical results and/or inaccurate dosing on the day of PK sampling.

Analysis sets will be used for efficacy analysis are defined as follows:

Phase Ib:

F*ull analysis Set (FAS)* will include all treated patients (same as the safety analysis set)

Phase II:

Full analysis set (FAS) will include all treated patients (same as the safety analysis set).

Efficacy analysis set will include all NSCLC patients with sponsor-designated central laboratory confirmed *MET*ex14 skipping mutation treated at RP2D (including patients in Safety Run-in part of phase II) and have valid baseline tumor assessment.

Subgroup analysis

Definition of subgroups are presented below for phase Ib and phase II respectively.

Phase Ib:

Tumor Tissue Biomarker:

- MET14 skipping (MET-TKI failure)
- MET14 skipping (Prior lines of systematic therapies >=3, without MET-TKI)
- MET amplification
- Met over-expression

Age Group:

- < 65
- >= 65

Sex:

- Male
- Female

Subject Disposition, Demographics and Baseline Characteristics and Efficacy Analysis will be summarized by tumor tissue biomarker subgroup.

Forest plot for ORR will be provided base on all other subgroups by tumor tissue biomarker.

Phase II:

Treatment Status at Baseline:

- Treatment Naive
- Pre-treated

Age Group:

- < 65
- >= 65

Sex:

- Male
- Female

Country:

- China
- Japan
- US

Brain Metastasis:

- Yes
- No

Smoking Status:

- Never
- Current
- Former

Subject Disposition, Demographics and Baseline Characteristics and Efficacy Analysis will be summarized by treatment status at baseline.

Forest plot for ORR will be provided base on all other subgroups by treatment status at baseline. The subgroups can be modified according to the actual number of subjects in subgroups, for example, the subgroup of US can be combined into other subgroups or deleted if the actual number of subjects is very small or zero.

7. STATISTICAL ANALYSIS

7.1. *General Considerations*

Phase Ib and Phase II will be summarized and listed sepearately.

Continuous variables will be summarized (by dose group and visit, if applicable) using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max). The number of subjects (n) will represent the number with non-missing data on the continuous variable under consideration. The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures, and derived listings. Unless otherwise specified, min and max values will be reported with the same precision as the units of measure; the mean, median will be reported to 1 greater decimal place, the SD will be reported to 2 greater decimal places, all of them will not be greater than 4 decimal places. Any values that require transformation

to standard units (metric or International System [SI]) will be converted with the appropriate corresponding precision.

Categorical variables will be summarized using frequencies and percentages (95% confidence interval of percentage if necessary). Percentages will be presented to 1 decimal place unless otherwise specified.

Dose group indicates the dose level of glumetinib (unless otherwise specified, summarize for all the assigned dose level respectively, e.g., 200mg QD, 300mg QDand total).

Baseline value, unless otherwise specified, will be defined as the last non-missing measurement (scheduled or unscheduled) collected prior to the initial administration of study drug. For example, if an assessment was performed at screening and Day 1 prior to initial dosing of study drug, then Baseline is the Day 1 measurement if the Day 1 value is not missing; if the Day 1 value is missing, then the screening value is Baseline, and so forth.

Change (absolute change) from baseline will be calculated as post-baseline value - baseline value.

Unscheduled visits: Subject data for safety or efficacy assessments (such as unscheduled labs) will be incorporated into the cycle windows appropriate to the scheduled visits. For summary by visit tables and figures, only scheduled visits will be included in the analysis, but for worst post baseline summary table, both scheduled and unscheduled visits should be included.

Incomplete/missing data: Unless otherwise specified, for efficacy and safety analysis, no imputation will be used. Missing data (e.g., dates) will remain as missing, and conservative conventions established, as required.

Lab Data Handling: For Lab values, will minus 0.0001 if contains '<' or '<=', and will plus 0.0001 if contains '>' or '>=', and will use the mean if it is a range (such as: will use 7 for "6 – 8") for analysis use.

Replicated observations: Measurements recorded more than once at a scheduled visit per protocol, are defined as replicated observations. If a subject has replicated measurements at a

scheduled visit per protocol (may span from one day to more than one day), the mean value may be used for data analysis.

All statistical analyses will be performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA) or above version.

7.2. *Background Characteristics*

7.2.1. Subject Disposition

For phase Ib and phase II, the number and percentage of subjects in the following disposition categories will be summarized:

- All subjects who signed main informed consent form
- Screen failure (with the reasons for screen failure):
- Enrolled
- Reciceved at least one dose of study drug
- Still on treatment
- Discontinued treatment (with a breakdown of the reasons for treatment discontinuation)
- Completed the Safety Follow-up Visit
- Entered Radiologic Progression Follow-up
- Entered Survival Follow-up
- Discontinued study (with a breakdown of the reasons for study discontinuation)

The disposition summary will be based on the All Subjects Set. Percentages of screen failure is based on the number of subjects who signed main informed consent form, percentages of screen failure reasons are based on the number of subjects who screen failure, percentages of treated are based on the number of subjects who enrolled, else percentages are based on the number of subjects who treated.

7.2.2. Demographics and Baseline Characteristics

For phase Ib and phase II, demographics and baseline characteristics will be summarized for the Full Analysis Set. The demographics table will include the following variables:

- Sex
- Race
- Age
- Age Group (< 65, >= 65 and < 75, >= 75 and < 85, >= 85)
- Weight, height, BMI ((weight in kg)/ (height in meter) ^2)
- Country

The baseline characteristics table will include the following variables:

- ECOG performance status (PS)
- Pathological type
- TNM Stage at initial diagnosis
- Stage at initial diagnosis
- TNM Stage at current
- Stage at current
- Number of target lesions based on BIRC assessment
- Number and location of metastases at current
- Clinical/radiographic status of disease at study entry
- Smoking status
- Subject received any prior systemic anti-tumor therapy
    - Number of prior lines of therapy
    - Number of prior regimens of therapy
    - Treatment type
    - Best overall response
- Subject received any radiotherapy for Tumour

- Prior diagnostic or therapeutic procedures (including surgery and biopsy)
    - Purpose of procedure
- Tumor biomarker.

7.2.3. Medical history

Medical history will be coded according to MedDRA (Version 23.0 or above). The number and percentage of subjects experiencing a medical history will be summarized by the MedDRA System Organ Class and Preferred Term.

Subjects reporting more than one condition/diagnosis within a System Organ Class will be counted only once for that System Organ Class.

7.2.4. Prior and Concomitant Medications

Medication summaries will be based on the Full Analysis Set. All medications will be coded using WHOdrug global B3, 202003.

Medications used in the study will be classified in two parts:

1. Prior medication: medication that ended before the first dose date of study drug, regardless of when dosing of the medication started.
2. Concomitant medication: medication that ended on or after the first dose date of study drug, or medication with missing stop date.

Missing or partial dates will be imputed for medication. Algorithm for missing or partial start date is:

Missing day: first day of the month is imputed;

Missing month: January is imputed (01 January if day is also missing);

Missing year: not imputed.

Algorithm for missing or partial end date is:

Missing day: last day of the month is imputed;

Missing month: December is imputed (31 December if day is also missing);

Missing year: not imputed.

Missing data algorithms will be reviewed to ensure the algorithm works. For example, end date will not be before the start date after the imputation.

Rule for determining prior and concomitant status of medications see Table 3, and only concomitant medications will be summarized by ATC2 and Preferred Name and only by Preferred Name in the table, all medications will be listed in an individual subject data listing, including Prior and Concomitant Medications. All summaries will be tabulated using frequency counts and percentages.

Table 3 Rule for determining prior and concomitant status of medications

End Date of Medication	Start Date of Medication		
	Missing	< 1st dose date	≥ 1st dose date
Missing	Concomitant Meds	Concomitant Meds	Concomitant Meds
< 1st dose date	Prior Meds	Prior Meds	Data error
≥ 1st dose date	Concomitant Meds	Concomitant Meds	Concomitant Meds

7.2.5. Study Drug Exposure

The study drug exposure will be summarized based on the Safety Analysis Set.

Treatment duration (weeks) is defined as (last dose date – first dose date +1)/7. Total cumulative dose (mg) is the sum of the actual doses that the subject receives across cycles. Dose intensity (mg/day) is defined as Total cumulative dose (mg) / Treatment duration (days). Relative dose intensity is defined as follows:

Relative dose intensity = Actual dose intensity (mg/day) / Planned dose intensity (mg/day) *100%.

Treatment duration (days), total cumulative dose (mg), actual dose intensity (mg/day), relative dose intensity categorized as < 80%, ≥ 80% and < 120%, >120% will be summarized for each component of the dosing regimen for phase Ib and phase II, Swimmer plot of treatment duration (days) for each subject will be provided.

Dose modification (reduction and interruption), duration from first dose date to fisrt dose modification date and dose modified reasons will be summarized and listed.

7.2.6. Subsequent Therapies

Anti-tumor therapy medicationsinitiated after discontinuation of study drug will be listed.

Anti-tumor therapy since discontinuation of study treatment will be summarized by setting (post-treatment diagnostic or therapeutic procedures, Treatment reason, Procedures (Surgery or biopsy), Best Overall Response, post-treatment radiotherapy, post-treatment anti-tumor medication therapy and Treatment Type).

Missing values for starting date of subsequent therapies will be imputed. If day of diagnosis is missing, the 15th of the month will be used. If month is missing, later date of EOT and July 1st of diagnosis year will be imputed first, then earlier date of this date, death date and EOS date will be used for subsequent therapy starting date.

7.3. *Protocol Deviations*

Protocol deviations will be identified throughout the study. Major protocol deviations are defined as those deviations from the protocol likely to have a significant impact on the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

A summary of the number and percentage of subjects with a major protocol deviation by type of deviation will be provided using the safety analysis set. Individual subject listings of protocol deviations will be provided.

COVID 19 has been spreading in the world during the clinical trial. If subjects have missing visits or protocol deviations due to the pandanmic, they will be described in the relevant sections in the CSR.

7.4. *Safety assessments*

Safety variables include: adverse event, clinical laboratory parameters (hematology and urinalysis, blood biochemistry, coagulation function, etc), vital signs, physical examination, ECOG Performance Status (PS), Echocardiogram and 12-led ECG.

Unless otherwise specified, safety analyses will be performed by dose group. Safety analysis will be conducted for the Safety Analysis Set. Safety data will be presented in the individual subject data listings based on Safety Analysis Set. Only descriptive analysis of safety will be performed (i.e., no statistical hypothesis testing will be performed).

7.4.1. Analysis of Adverse Events

AEs will be coded according to MedDRA (Version 23.0 or above). In the coded preferred term (PT), the PT with similar definition will be merged and de duplicated based on PT, and the merging rules will be defined in the programming specific document. The severity of adverse events will be judged in accordance with NCI CTCAE 5.0. The number and percentage of subjects experiencing an AE will be summarized by the MedDRA System Organ Class and Preferred Term. AEs will be classified as pretreatment or treatment-emergent.

Pretreatment AEs are defined as AEs that were reported or worsened after signing the main ICF up to the start of study drug dosing.

Treatment-emergent AEs (TEAEs) are defined as AEs that were reported or worsened on or after the start of study drug dosing up to 28 days after the last dose of study drug, or up to end of the study for treatment-related SAEs.

PTs will be grouped (Grouped PT) base on medical concepts with similar or same definitions. The Grouped PT including the following:

Grouped Terms	PTs
Oedema	Face oedema, Swelling face, Periorbital oedema, orbital oedema, eye swelling, Periorbital swelling, swelling of eyelid, eyelid oedema, Oedema, Swelling, Generalised oedema, Oedema peripheral, Peripheral swelling, fluid overload, eye oedema, localised oedema, oedema genital, vulval oedema
Fatigue	Fatigue, Asthenia
Leukopenia	Leukopenia, White blood cell count decreased
Proteinuria	Proteinuria, Protein urine present, Albuminuria, Albumin urine present
Thrombocytopenia	Thrombocytopenia, Platelet count decreased
Haematuria	Haematuria, Red blood cells urine positive
Hypoalbuminaemia	Hypoalbuminaemia, Hypoproteinaemia,
Neutropenia	Neutropenia, Neutrophil count decreased
Blood bilirubin increase	Blood bilirubin increase, hyperbilirubinaenmia, Blood bilirubin conjugated increased, Blood bilirubin unconjugated increased

All the analyses for TEAEs will base on Grouped PT.

For missing or partial AE start/end date, use the imputation rules below for the purpose of determining whether an AE is treatment-emergent. The imputed dates will not be displayed in the listing outputs.

- For the start date:

1) If year and month are known of an AE, and:

a. If year and month of the AE < the year and month of the first dose date of study drug, then use the last day of the month.

b. If year and month of the AE = the year and month of the first dose date of study drug, then use the day of first dose date of study drug.

c. If year and month of the AE > the year and month of the first dose date of study drug, then use the first day of the month.

2) If only the year is known of an AE, and:

a. If year of the AE < the year of the first dose date of study drug, then use December 31.

b. If year of the AE = the year of the first dose date of study drug, then use the day and month of first dose date of study drug.

c. If year of the AE > the year of the first dose date of study drug, then use January 1.

3) If year, month, and day are missing, then use the first dose date of study drug.

- For the end date:

1) If year and month are known of an AE, then use the last day of the month.

2) If year is known of an AE, then use December 31.

3) If year, month, and day are missing, then not impute the end date.

Only TEAEs will be summarized in tables unless otherwise specified.

The overall TEAE summary will include the following:

- All TEAEs (regardless of relationship to study drug)
- Treatment–related TEAE
- Grade ≥ 3 TEAEs
  - Grade =3
  - Grade =4
  - Grade=5
- Treatment –related Grade ≥ 3 TEAEs
  - Grade =3
  - Grade =4
  - Grade=5
- Serious TEAEs

- Treatment –related serious TEAEs
- TEAEs leading to study drug dose reduction
- Treatment –related TEAEs leading to study drug dose reduction
- TEAEs leading to study drug interruption
- Treatment –related TEAEs leading to study drug interruption
- TEAEs leading to study drug discontinuation
- Treatment –related TEAEs leading to study drug discontinuation
- TEAEs leading to death
- Treatment –related TEAEs leading to death

The overall QTc interval prolongation (see detailed search strategy for QT-Prolongation in special safety concerns part) TEAE summary will include the following:

- All TEAEs (regardless of relationship to study drug)
- Treatment–related TEAE
- Grade ≥ 3 TEAEs
  - Grade =3
  - Grade =4
- Serious TEAEs
- TEAEs leading to study drug dose reduction
- TEAEs leading to study drug interruption
- TEAEs leading to study drug discontinuation

The TEAE, Treatment–related TEAE, Serious TEAEs, Treatment –related serious TEAEs, TEAEs leading to study drug dose reduction, Treatment–related TEAEs leading to study drug dose reduction, TEAEs leading to study drug interruption, Treatment–related TEAEs leading to study

drug interruption, TEAEs leading to study drug discontinuation and Treatment–related TEAEs leading to study drug discontinuation, Incidence rate >10% TEAEs will be summarized by MedDRA system organ class, preferred term and maximum grade using frequency counts and percentages in descending order of frequency separately.

Grade ≥ 3 TEAEs, Treatment–related Grade ≥ 3 TEAEs, TEAEs leading to Death, Treatment–related TEAEs leading to Death will be summarized by system organ class and preferred term in descending order of frequency separately.

All AEs (including pretreatment AEsSerious AEs and AEs leading to Death, TEAEs leading to study drug discontinuation, TEAEs leading to study drug interruption, TEAEs leading to study drug dose reduction will be listed in an individual subject data listing.

Some rules that will apply to the summarization of AEs are:

- a subject with multiple occurrences of the same adverse event or a continuing adverse event will only be counted once;
- only the maximum toxicity grade will be presented in the summary by CTCAE grade table; missing toxicity grade will be presented if there is no toxicity grade;

Special Safety Concerns and Special Safety Monitoring

Special Safety concerns refer to safety risks which sponsor would pay close attention and monitoring to the SCC244, and would analyze in details by the risks. Treatment –related adverse events for each risk would be retrieved using pre-defined case retrevall strategy, including SMQ, SOC or PT groups.

Special safety monitoring refers to safety risks which sponsor would pay close attention and monitoring to the SCC244 during the trial.

Special safety concerns and its search criteria and special safety monitoring standard of SCC244 are listed below:

Special Safety Concerns	**Search Criteria**		**Events for Special Safety**
	CMQ	**MedDRA Code**	

			Monitoring Standard
Liver Toxicity	Drug related hepatic disorders - comprehensive search (SMQ) exclude Hypoalbuminaemia, Ascites	20000006 (exclude 10020942,10003445)	Refer to protocol section 8.4.3
Hemotology Toxicity	Haematopoietic cytopenias (SMQ)-Broad	20000027	NA
	Haematopoietic erythropenia (SMQ)-Broad	20000029	
	Haematopoietic leukopenia (SMQ)-Broad	20000030	
	Haematopoietic thrombocytopenia (SMQ)	20000031	
QT-Prolongation	Torsade de pointes/QT prolongation (SMQ)-Broad	20000001	Refer to protocol section 8.4.3
Renal Dysfunction	Acute renal failure (SMQ)-Broad	20000003	NA
ILD	Interstitial lung disease (SMQ)-Broad	20000042	Refer to protocol section 8.4.3
Pancreatitis	Acute pancreatitis (SMQ)-Narrow	20000022	Refer to protocol section 8.4.3
	Amylase abnormal (PT)	10072327	
	Amylase increased (PT)	10002016	
	Blood trypsin increased (PT)	10064751	
	Computerised tomogram pancreas abnormal (PT)	10082936	
	Hyperamylasaemia (PT)	10062770	
	Hyperlipasaemia (PT)	10067725	
	Lipase abnormal (PT)	10054821	
	Lipase increased (PT)	10024574	
	Pancreatic enzyme abnormality (PT)	10033619	
	Pancreatic enzymes abnormal (PT)	10061899	
	Pancreatic enzymes increased (PT)	10061900	

	Ultrasound pancreas abnormal (PT)	10078673	
Central Neorological Symptoms	Nervous System Disorders (SOC)	10029205	NA
	Psychiatric disorders (SOC)	10037175	
Oedema	Oedema	10030095	NA
	Swelling	10042674	
	Oedema peripheral	10030124	
	Generalised oedema	10018092	
	Peripheral swelling	10048959	
	fluid overload	10016803	
	Face oedema	10016029	
	Swelling face	10042682	
	Periorbital oedema	10034545	
	orbital oedema	10031051	
	eye swelling	10015967	
	Periorbital swelling	10056647	
	swelling of eyelid	10042690	
	eyelid oedema	10015993	
	eye oedema	10052139	
	localised oedema	10048961	
	oedema genital	10030104	
	vulval oedema	10047763	
Gastrointestinal Disorders	Gastrointestinal disorders (SOC)	10017947	NA
	Decreased appetite (PT)	10061428	
Headache	Headaches (HLGT)	10019231	NA

Treatment–related TEAEs for each special safety concern which with high incidence rate will be summarized by preferred term and maximum grade using frequency counts and percentages in descending order of frequency. Time to first occurrence for each Treatment–related TEAEs and each CTCAE grade >= 3 Treatment–related TEAEs will be summarized by special safety concerns.

The categories of special safety concern that to be analyzed will be determined according to the clinical considerations and the amount of data.

Some additional analysis related to special safety monitoring events should refer to SAP section 7.4.3 and section 7.4.4.

Management of AEs of special safety concerns

Duration of each special safety concerns of a subject is defined as the average duration of all special safety concern events which outcome is "Recovered/resolved" and have start date and end date completed of the subject. The average duration of a special safety concern is defined as the sum of duration of each special safety concerns of all subject divide by the total number of the special safety concerns. Proportion of time on Glumetinib is defined as the average duration of the event that is between the first and last dose of Glumetinib divided by the patient's total duration of treatment with Glumetinib, multiplied by 100. Average number of special safety concern is defined as the total number of the events divide by the number of subjects that experience the event.

The above information of treatment-related AE of special safety concern will be summaried.

7.4.2. Analysis of Death

All death, death wihin 28 days after last dose date and primary reason of deaths will be summarized and listed.

7.4.3. Analysis of Laboratory Data

Hematology, blood biochemistry and urinalysis will be conducted in the screening period, treatment period and follow-up period according to study procedures, and examination frequency will be increased according to clinical indications.

Specific evaluation items include:

● **Hematological test**: red blood cell count, hemoglobin, hematocrit, reticulocyte count or percentage, platelet count and absolute leukocyte differential count (neutrophil, lymphocyte, eosinophils, monocyte, basophils);

● **Blood biochemical test** (including cardiac enzymes): Total protein, albumin, blood glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, alkaline phosphatase, total bilirubin, direct bilirubin or indirect bilirubin, aspartate aminotransferase, alanine aminotransferase, glutamyl transpeptidase; creatinine, urea or urea nitrogen, creatinine

clearance, uric acid; electrolytes (potassium, sodium, calcium, phosphorus); LDH; cardiac enzymes (troponin T/I and CPK), lipase and amylase;

● **Urinalysis**: specific gravity, pH, urine glucose, protein, urinary cast, ketone bodies, white blood cell (quantitative) and red blood cell (quantitative). 24-hour urinary protein quantitative test should be conducted in case of urinary protein positive;

● **Coagulation function test**: prothrombin time, activated partial thromboplastin time and international normalized ratio;

● **Pregnancy test** (applicable to non-menopausal women);

● **HBV, HCV and HIV tests**: HBsAg, HBsAb, HBcAb, HBV DNA (tested in patients with HBsAg positive), HCV-Ab, HCV RNA (tested in patients with HCV antibody positive), and HIV antibody (in Chinese and Japanese patients only);

For serum chemistry, hematology and urinalysis data, a shift table between the worst post-baseline clinical significance and baseline clinical significance will be provided by dose group.

New or worsened abnormal laboratory results will be graded according to NCI CTCAE version 5.0, if applicable. The worst post-baseline abnormalities based on NCI CTCAE grade will be summarized. A shift table between baseline and post-baseline maximum grade will also be provided. The CTCAE grade will be determined only by numberic value if both numeric value and clinical assessments are in the CTCAE grading criteria.

For liver safety, summaries of the liver chemistry elevations will be presented in the table according to Table 4.

Table 4 Categary for liver chemistry elevations

Test	**Categary**
ALT or AST increased	≥3 * ULN
	≥5 * ULN
	≥ 10 * ULN
	≥ 20 * ULN
ALT increased	≥ 3 * ULN
	≥ 5 * ULN

	≥ 10 * ULN
	≥ 20 * ULN
AST increased	≥ 3 * ULN
	≥5 * ULN
	≥ 10 * ULN
	≥ 20 * ULN
TBIL increased	≥ 1.5 * ULN
	≥ 2 * ULN
ALP increased	≥ 1.5 * ULN

In additional, ALT or AST ≥ 3 * ULN and TBIL ≥ 2 * ULN and ALP < 2*ULN, ALT or AST ≥ 3 * ULN and TBIL ≥ 2 * ULN, ALT and AST ≥ 3 * ULN and TBIL ≥ 1.5 * ULN will also presented in this table.

The listing for abnormal findings in laboratory data will be provided.

7.4.4. Analysis of 12-lead ECG

12-lead ECG: Including heart rate, P-R interval, QRS interval, QT interval, QTcF interval and diagnosis

For 12-lead ECG diagnosis, a shift table between the worst post-baseline clinical significance and baseline clinical significance will be provided by dose group.

The number and percentage of patients with notable ECG values will be presented by dose group, A new ECG notable value is defined as a post-baseline value that meets the criterion but did not meet the criterion at baseline.

- QTcF

- New value of > 450 and ≤ 480 ms

- New value of > 480 and ≤ 500 ms

- New value of > 500 ms

- Increase from Baseline of > 30 ms to ≤ 60ms

- Increase from Baseline of > 60 ms to ≤ 90ms

- Increase from Baseline of > 90 ms

• HR

- Increase from baseline >25% and to a value > 100 bpm

- Decrease from baseline >25% and to a value < 50 bpm

• PR

- Increase from baseline >25% and to a value > 200 ms

- New value of > 200 ms

• QRS

- Increase from baseline >25% and to a value > 120 ms

- New value of > 120 ms

Clinically significant abnormal findings will be reported as AEs.

7.4.5. Analysis of Echocardiogram

Echocardiogram: including left ventricular ejection fraction and diagnosis.

A shift table between the worst post-baseline clinical significance and baseline clinical significance will be provided by dose group.

7.4.6. Analysis of Vital Signs

For vital signs data (blood pressure, pulse, respiratory rate, temperature and weight), change from baseline summaries will be provided by scheduled visit and dose group using descriptive statistics.

Clinically notable elevated values are defined as:

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline.
- Body temperature: ≥ 39.1°C

- Weight: increase from baseline of ≥ 10%
- Pulse rate: ≥ 100 bpm with increase from baseline of ≥25%

Clinically notable below normal values are defined as:

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Body temperature: ≤ 35°C or ≥ 39.1 °C
- Weight: decrease from baseline of ≥ 10%
- Pulse rate: ≤ 50 bpm with decrease from baseline of ≥ 25%

Notable post baseline vital sign values will be summarized in table.

Baseline values (Low/high) are defined as:

- Systolic BP: ≤ 90 mmHg; Systolic BP: ≥ 180 mmHg
- Diastolic BP: ≥ 105 mmHg; Diastolic BP: ≤ 50 mmHg
- Pulse rate: ≤ 50 bpm; Pulse rate: ≥ 100 bpm

Vital signs shift table based on values classified as notable low, normal, notable high at baseline and worst post-baseline will be produced for pulse rate, diastolic BP and systolic BP, the related absolute change from baseline bigger then the result worse if a subject both have post baseline notable high and post baseline notable low results. Patients with clinically notable vital sign abnormalities will be listed.

7.4.7. Analysis of Physical Examination

Physical examination: including head, eyes, ears, nose, throat, neck, heart, chest (including lungs), abdomen, extremities, skin, lymph nodes, nervous system, and general condition of patients.

For each physical examination, a shift table between the worst post-baseline clinical significance and baseline clinical significance will be provided by dose group.

Clinically significant abnormal findings in PEs will be reported as AEs.

7.4.8. Analysis of ECOG

ECOG Performance Status (PS): ECOG evaluation is recommended to be conducted by the same investigator throughout the study;

A shift table between the worst post-baseline ECOG Performance Status and baseline ECOG Performance Status will be provided by dose group.

7.5. *Efficacy assessments*

The efficacy analysis will be base on Full Analysis Set and Efficacy Analysis Set seperatly.

In phase Ib, efficacy analysis will be summarized by assessed as per investigator only. In phase II, efficacy analysis will be summarized by both assessed as per investigator and determined by BIRC.

Tumors will be evaluated according to RECIST1.1. Tumor assessment will be conducted once every 6 weeks ± 7 days for the first 8 cycles, then every 9 weeks ± 7days (or according to clinical need). Imaging evaluation method of tumors, at the investigator's discretion, may adopt CT or MRI, but evaluation method, instrument and technical parameters should be consistent throughout the study.

Target, non-target lesions and bone metastatic lesions will be identified at screening. Target, non-target, new lesions, and bone metastatic lesions will be evaluated at subsequent disease assessment visits. The applicable overall response category for each disease assessment visit (Complete Response [CR], Partial Response [PR], Stable Disease [SD], Progressive Disease [PD], Not Evaluable [NE] and Missing), based on interpretation of CT/MRI scan using RECIST 1.1 criteria by the investigator or radiologist of each study site, will be recorded in the electronic case report form (eCRF).

Efficacy Analysis will be analysed for phase Ib and phase II separately unless otherwise specified.

7.5.1. Definition of Study Endpoint

Best Overall Response (BOR) is defined as the best overall response recorded from the start of treatment until disease progression/recurrence or initiation of alternative therapy or end of study.

ORR is defined as the percentage of patients who have at least one confirmed response of CR or PR defined by RECIST 1.1 prior to any evidence of progression. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any CR or PR which occurred after a further anticancer therapy was received will not be included in numerator of the ORR calculation.

CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10mm to be considered nonpathological) and no new lesions have developed since baseline. A PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.

PFS is defined as the time from the start of treatment with Glumetinib to disease progression per RECIST 1.1 or death from any cause, whichever occurs first. The subjects still alive and relapse-free will be censored at the date of last tumor assessment prior to the date that triggers the analysis, See Appendix 1 for detailed rule of Censore date for PFS.

TTR is defined as the time from the start of treatment with Glumetinib to the first objective tumor response observed for patients who achieve CR or PR per RECIST 1.1.

OS is defined as the interval between the date of first dose and the date of patient death due to any cause. Patients who have not died at the time of the statistical analysis will be censored at the time they were last known to be alive.

DoR is defined as the time from the date of first documented response, (that is subsequently confirmed) until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

DCR is defined as the proportion of patients achieve confirmed CR, PR or continued SD no less than 6 weeks after treatment with Glumetinib per RECIST 1.1.

7.5.2. Analysis of Efficacy Variables

Analyses of efficacy variables will be based on the overall response category entered into eCRF by investigators, or the result from BIRC for phase II. For subjects continuing on treatment after documentation of PD, tumor assessments performed post-PD (assessed as per investigator or determined by BIRC, which later) will not be included in any efficacy summaries.

7.5.2.1. Best Overall Response

A summary of subjects achieving a best overall response in a given category (CR, PR, SD, PD, NE and NA) will be provided for phase Ib and phase II.

Swimmer plot for individual subject efficacy evaluation results and Waterfall plot for best percentage change from baseline on sum of tumor diameter will be provided base on both assessed as per investigator and determined by BIRC.

For ORR nad DCR, the summary will be provided base on both assessed as per investigator and determined by BIRC, and 95%CI will be also provided using Clopper-Pearson method based on exact binomial distribution.

Forest plot of ORR with 95% CI will be provided base on both assessed as per investigator and determined by BIRC separately by subgroup variable which defined in section 6.

A concordance table for BOR between assessed as per investigator and assessed by BIRC will be provided for phase II.

7.5.2.2. Progression-Free Survival and Overall Survival

For time-to-event endpoints (PFS and OS), the survival curve will be estimated by the Kaplan-Meier estimate, the proportion of subjects with event (and event type) or censored and the median survival and its 95% CI, 25^{th} and 75^{th} percentiles and Kaplan-Meier estimated probabilities with

corresponding 95% CIs at several time points (such as at 3 months, 6 months, 9 months…) will be provided. The listing of PFS and OS will be provided.

7.5.2.3. Duration of Response and Time to Response

For Duration of Response (DoR), only subjects with BOR is CR/PR during the study treatment will be calculated. DoR = min (last adequate tumor assessment before last follow-up date, progression or death date, last adequate tumor assessment before initiation of alternative anti-cancer therapy) – first date of documented CR/PR + 1. See Appendix 1 for detailed rule of Censore date for DoR.

Time to Response (TTR) is measured from the date of first study treatment to the date of initial response (CR, or PR). only subjects with BOR are CR/PR during the study treatment will be calculated. TTR = first date of documented CR/PR – first date of study treatment + 1.

DoR will be described by the Kaplan-Meier estimates same with PFS. TTR will be analysed by summary statistics. A listing will be provided both for DoR and TTR.

KM plot will be provided for PFS/DOR/OS.

8. Summary of Primary, Final, Interim and IDMC Analyses

8.1. *Primary Analysis*

The objective of the primary analysis for the phase II part is to confirm ORR. The primary efficacy analysis will be based on subjects from the efficacy analysis set.

The primary analysis will be triggered after the enrolment meet the criteria of estimated sample size in protocal and all patients complete at least 6 months of follow-up or withdraw consent or die, whichever occurs earlier. Secondary endpoints will also be analyzed simultaneously. Analysis may be performed earlier to support country specific health authority interaction if deemed necessary by the sponsor.

8.2. *Final Analysis*

For phase II, the objective of final analysis is for the primary and secondary endpoints based on the follow-up data. The final analysis might be occurred after all the enrolled subjects complete the long-term follow-up according to protocol, or occurred according to the requirement of declaration or the communication with health regulatory authorities in particular countries.

8.3. *Interim Analyses*

Interim analysis of safety will be performed for the Phase II part of the study when approximately 25%, 50% and 75% of patients are enrolled and treated for at least for one cycle (21 days). These interim analyses will be reviewed by an Independent Data Monitoring Committee (IDMC). A complete description of the composition of the IDMC and details on the interim analysis process will be provided in a separate IDMC charter. In addition, the Sponsor will share safety data from the study with all primary investigators throughout the conduct of the study.

8.4. *Safety run-in*

Safety run-in analysis will be performed in safety run-in subjects with US MET-alterations (meeting the eligibility for either Phase Ib or Phase II) for DLT. The analysis will occur once enough US subjects at 300mg are evaluable for DLT.

9. Summary of Changes

9.1. *Summary of Changes Between Previous Version and the Current Version*

This current SAP is the third version for Study SCC244-108, compared to the previous version, the major changes are listed as below:

Amendment from Version 1.0 to Version 2.0:

- In section 6, for Phase II, deleted the condition “(Investigator and BIRC independently)” for baseline tumor assessment; deleted the description of “Kaplan-Miere plot for PFS will be provided by all subgroups base on efficacy analysis set.”; added the description of subgroup

"The subgroups can be modified according to the actual number of subjects in subgroups, for example, the subgroup of US can be combined into others subgroups or deleted if the actual number of subjects is very small or zero.".In section 7.2.1, deleted the description of the category of enrolled but not treated.

- In section 7.2.4, updated "Safety Analysis Set" to "Full Analysis Set".
- In section 7.2.6, deleted the description of "Subsequent therapies received by patients after progression will be summarized. Anti-tumor therapy medications initiated after discontinuation of study drug will be summarized by Anatomical Therapeutic Chemical (ATC) class 2, preferred name."; added the imputed rules for missing starting date of subsequent therapies.
- In section 7.4.1, for grouped PT, combined "Face oedema, Eye swelling, Oedema" into one grouped PT "oedema" to one and added a new group term "Blood bilirubin increase"; for TEAE, added the summary of "Incidence rate ≥10% TEAEs" by SOC and PT and maximum grade, and deleted the summary of "Incidence rate ≥10% TEAEs, Incidence rate ≥10% Treatment-related TEAEs" and "Non-TEAEs" by SOC and PT, and deleted the listing of "treated-related TEAEs, grade ≥3 TEAEs", and added the listing of "TEAEs leading to study drug discontinuation, TEAEs leading to study drug interruption, TEAEs leading to study drug dose reduction"; for Special Safety Concerns and Special Safety Monitoring, deleted the "Type" column in the table; for "Management of AEs of special safety concerns", added the definition of Average number of special safety concern and denoted the summary only for the "treatment-related AE" and added the condition "(only the longest duration of the event will be used if the event occurs multiple times for one subject)" for the duration of each special safety concerns.
- In section 7.4.3, added the description "The CTCAE grade will be determined only by numberic value if both numeric value and clinical assessments are in the CTCAE grading criteria.".
- In section 7.5.1, for DCR definition, deleted the condition of "(±7 days)".
- In section 7.5.2.1, added the description of summary for ORR and DCR.

- In section 7.5.2.2, deleted the summary for censor reason and concordance of PFS between BIRC and Investigator Assessment.
- Deleted the section 7.5.2.4.
- In section 8.1, added the condition “the enrolment meet the criteria of estimated sample size in protocal” for the primary analysis.
- In section 8.2, added the “primary endpoints”, and added the other case of finaly analysis “the requirement of declaration or the communication with health regulatory authorities in particular countries.”.

Amendment from Version 2.0 to Version 3.0:

- In section 7.1, for “incomplete/missing data”, deleted the imputing rule for calculation of duration.
- In section 7.4.1, for grouped PT, added new terms “eye oedema, efinitio oedema, oedema genital, vulval oedema” into grouped PT “oedema”, for "Management of AEs of special safety concerns", modified the definition of duration of each special safety concerns, and deleted the condition “(only the longest duration of the event will be used if the event occurs multiple times for one subject)” for the duration of each special safety concerns.”.

10. References:

(1) Oken, M.M., Creech, R.H., Tormey, D.C., et al. Toxicity and Response Criteria of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

(2) Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial, Biometrika. 1934; 26(4):404-413.

11. Appendix

Appendix 1： Censor rule for PFS and DoR

No.	Situation	Events or Censor	Analysis date*
1	No baseline assessment	Censor	First dose date
2	No post-baseline assessment, no Death	Censor	First dose date
3	Any kind of Death (except #5, #7)	Events (Death)	Death date
4	PD during the study (except #5, #7)	Events (PD)	PD date
5	PD or Death after missed two consecutive assessments	Censor	Last assessment date before the missed two consecutive assessments
6	Have at leatest one post-baseline assessment, no PD, no Death	Censor	Last assessment date
7	Initiating alternative anti-cancer therapy	Censor	Last assessment date before initiating alternative anti-cancer therapy

* If there are multiple assessment date on one tumor assessment, choose the earliest assessment date when overall response is PD, and choose the latest assessment date when overall response is CR/PR/SD.