A Phase I Study to Evaluate the Safety/Tolerability and Pharmacokinetics of GFH018 with Single/Multiple Ascending Dose Patients with Advanced Solid Tumors

GFH018X1101

S tatisicial Analysis Plan

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Abbreviations List

Abbreviations	Definition / Expansion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspertate Aminotransferase
AUC	Area Under the Concentration-Time Curve
$AUC_{(0-t)}$	Area Under the Curve (0-t hour)
BOR	Best of Response
CRF	Case Report Form
C_{max}	maximum concentration
CL	Clearance
CR	Complete response
d，D	day
DCR	Disease Control Rate
DLT	Dose Limited Toxiciyy
DOR	Duration of Response
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviations	Definition / Expansion
h	Hour
ICH	International Conference on Harmonization
kg	Kilogram
L	liter
LLN	Low Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OR	Objective Response
ORR	Objective Response Rate
PD	Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
PS	Physical performance
PR	Partial Response
RP2D	Recommended phase 2 dose
SAE	Severe Adverse Event

Abbreviations	Definition / Expansion
SAP	Satistical Analysis Plan
SD	Stable Disease
$T_{1/2}$	half-time
TEAE	Treatment-emergent Adverse Event
T_{max}	Time to maximum concentration
TTP	Time to Progression
ULN	Upper Limit of Normal

1. INTRODUCTION

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 1.6 (February 26, 2021)
- electronic Case Report Form, Version 6.0 (October 14, 2021)

2. STUDY OBJECTIVES

Primary Objectives

- To evaluate the safety and tolerability of single/multiple administration of GFH018 in patients with advanced solid tumors
- Determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of GFH018

Secondary Objectives

- To evaluate the pharmacokinetic characteristics of GFH018 after single/multiple administration in patients with advanced solid tumors
- To evaluate the preliminary efficacy of GFH018 in patients with advanced solid tumors
- To evaluate the expression level of TGF-β in the peripheral blood of patients with different solid tumors, and analyze whether it is related to the clinical response of subjects to GFH018

Exploratory Objectives

- Evaluate possible blood pharmacodynamic markers

3. OVERALL STUDY DESIGN

This is the first-in-human trial of GFH018, using an open-label, non-randomized, single/multi-dose dosing design to evaluate the safety, tolerability, pharmacokinetics, and preliminary anti-tumor efficacy of GFH018 in subjects with advanced solid tumors.

This study is divided into two parts: a dose-escalation part aimed at determining MTD and/or RDE followed by a dose expansion part to confirm the safety of RDE and RP2D and explore the preliminary efficacy of GFH018 in the potentially benefited population. The RDE will be determined for exploration in expansion. Different dosing regimens will be explored, RDE dose and optimal dosing regimen will be further confirmed, and RP2D will be obtained. Both parts were divided into three periods: screening, treatment, and follow-up.

Part I Dose Escalation

The study schema is shown in Figure1 **(14-day on/14-day off regimen).**

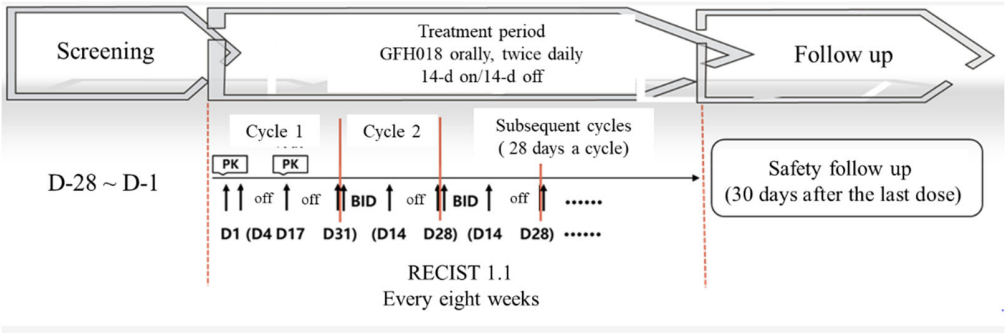

Fig 1 Study Schema (Dose Escalation Part)

This part is a safety, tolerability, and pharmacokinetic study with a modified 3+3 design to determine MTD and/or RDE. According to preclinical data, the starting dose is selected as 10 mg/day (5 mg administered twice daily). In the first cycle, each group of subjects is given a single dose (5 mg as the starting dose) on day 1 and taken serial PK sampling. After the first dose on day 1, serial PK blood samples will be collected up to 72 h post-dose to obtain the complete PK profile of a single dose (the collection point design may be modified based on preliminary PK results). Subjects will be administered with GFH018 BID, 14d-on/14d-off from day 4. Four to six dose levels are planned (refer to Table 1). The first cycle is defined as 31 days, and subsequent cycles are all defined as 28 days. After the last dose of cycle 1 (day 17), serial PK blood samples will be collected to obtain PK characteristics at steady state. Starting from the third dose level, urine samples from steady state will also be collected for PK studies to fully understand GFH018 PK characteristics.

Table 1 Dose escalation regimen (provisional dose level)

Dose level	Regimen	Incremental percentage (%)
1	5 mg bid, 14-d on/14-d off	-
2	10 mg bid, 14-d on/14-d off	100
3	20 mg bid, 14-d on/14-d off	100
4	30 mg bid, 14-d on/14-d off	50
5	40 mg bid, 14-d on/14-d off	33
6	50 mg bid, 14-d on/14-d off	25

During the study, a Safety Monitoring Committee (SMC) composed of principal investigators, representatives of contract research organizations (CROs) and sponsor representatives will be established to review the safety data generated in the study, mainly including Dose Limiting Toxicity (DLTs) and all other grade 2 and above adverse events per CTCAE v5.0, as well as pharmacokinetic and pharmacodynamic data, to determine whether to escalate to the next dose level. For a more specific dose escalation decision process and definition of DLT, see Section 5.4 of Protocol V1.6, "**Study Drug Dose Escalation Methods**".

The MTD is defined as the highest dose ≤ 1/3 of the incidence of DLT. Once the MTD is reached, the dose will not be escalated under this dosing regimen (even if not all planned dose groups have been completed), and the SMC will review and decide whether to explore alternative dosing regimens, such as 7d-on/7d-off, or daily or other dose regimens (if the total daily dose is higher than or equal to the MTD within 28 days, the dose level needs to be lowered for daily or other dosing regimen exploration); On the other hand, if the MTD is not reached by escalating to the current highest dose level, the SMC will comprehensively evaluate all the data obtained to decide whether to proceed with a higher dose level exploration, such as 65 mg BID, 85 mg BID, etc.

The RDE will be determined by SMC based on comprehensive data such as safety and tolerability, PK, pharmacodynamics, and preliminary antitumor efficacy obtained during the dose escalation part.

At the end of the dose escalation, at least six evaluable subjects in the MTD/RDE group should be ensured.

Part II Dose Expansion

The primary objective of this part is to confirm the safety of RDE dose and explore different dose regimens to ultimately determine RP2D. The secondary objective is to initially explore the efficacy in potentially benefited populations.

The 14d-on/14d-off and 7d-on/7d-off dose regimens under RDE dose will be explored based on the data from the dose escalation part, while the SMC will review the safety, PK, and biomarker data then decide whether to also explore other dose regimens at RDE, such as daily dosing. This part will further confirm the safety of RDE dose and optimal dose regimen and obtain RP2D. At least 12 subjects (including subjects receiving the same dose during the dose escalation part) are required to be enrolled to determine the final RP2D.

Potential benefited tumor types will be selected for dose expansion part based on the mechanism of action of the drug and preliminary efficacy data in dose escalation part, including hepatocellular carcinoma, cholangiocarcinoma/gallbladder cancer, colorectal cancer, urothelial cancer, pancreatic, cervical, head and neck squamous cell or esophageal cancer, and nasopharyngeal carcinoma.

4. STUDY ENDPOINTS

4.1. Safety Variables

4.1.1. Adverse Events

Adverse events (AEs)

The definition of AEs can be found in the section 8.1 of protocol. AEs should be collected from the time of informed consent through follow-up. The follow-up period was 30 days (± 3 days) after discontinuation of study treatment. SAEs occurring during the follow-up period should be reported to the sponsor by routine methods.

Treatment emergent adverse events (TEAEs)

TEAEs are defined as adverse events that worsened or occurred following the first dose date of study treatment and within 30 days of the last treatment. If missing dates or time prevent a clear determination as to whether AE is treatment emergent, the adverse event will be regarded TEAE.

Treatment related adverse events

Treatment related AEs are defined as TEAEs definitely related, possibly related to study treatment, and the relationship unable to determine.

Serious adverse events (SAEs)

The definition of AEs can be found in the section 8.2 of protocol.

Treatment related SAEs

Treatment related SAEs are defined as SAEs definitely related, possibly related to study treatment, and the relationship unable to determine.

Adverse event of special interest (AESI)

According to the toxicological results of GFH018, ASEIs include elevated cardiac biomarkers BNP or troponin, and abnormal cardiac ultrasound.

Adverse events leading to interruption of study treatment

Adverse events leading to dose reduction of study treatment

Adverse events leading to discontinuation of study treatment

Severity of adverse events

Severity of all AEs will be graded according to CTCAE v5.0 with grade 1 to 5.

4.1.2. Laboratory Tests

Please see Table 2 for the laboratory tests parameters.

Table 2 Laboratory tests parameters

Laboratory tests	Parameters
Hematology	Red blood cell count (RBC), hemoglobin concentration (HGB), hematocrit (HCT), mean red blood cell volume (MCV), mean red blood cell hemoglobin content (MCH), mean red blood cell hemoglobin concentration (MCHC), white blood cell count (WBC), platelet count (PLT), neutrophil count (ANC), lymphocyte (LY) count, monocytes (MO) count, eosinophil (EO) count, Basophil (BA) count, percentage neutrophils, percentage lymphocytes, percentage monocytes, percentage eosinophils, percentage basophils
Urinalysis	Urine leukocytes (LEU), urine nitrite (NIT), urine pH, urine specific gravity (SG), urine protein (PRO), urine glucose (GLU), urine ketone bodies (KET), urine bilinogen (UBG), urine bilirubin (BIL), urine occult blood (BLD), 24-hour protein*
Coagulation function	Prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR)
Chemistry	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), glutamyl transpeptidase (GGT), urea (UREA)/urea nitrogen, blood creatinine (CREA), total protein (TP), albumin (ALB), white globular ratio (A/G ratio), total bilirubin (TBIL), direct bilirubin (DBIL), creatine kinase (CK), pancreatic amylase (AMY), fasting blood glucose (FPG), total cholesterol (TCHO), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), bicarbonate, phosphate, calcium, sodium, chloride, potassium
Virus testing	Hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV), HIV antibody, treponemal antibody
Thyroid function tests	Free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH).
Cardiac markers	Hypertroponin T (or Hypertroponin I), brain natriuretic peptide (BNP), hs-CRP, cysteine protease inhibitor (Cystatin C)
Pregnancy test	Serum β-HCG pregnancy test (blood pregnancy test in women of childbearing age)

* For routine urinalysis, if the result of the fibrine test strip for urine protein is ⩾2+, a 24-hour urine sample should be collected for analysis.

4.1.3. Electrocardiogram (ECG)

ECG includes hearts rate, PR, QRS, QT, QTcF, and the clinical interpretation.

4.1.4. Echocardiography

Include left ventricular ejection fraction, heart valve function, and clinical interpretation.

4.1.5. Physical Examination

Physical examination includes General condition, skin condition, head/neck, lungs, cardiovascular, liver, kidneys, gastrointestinal, lymphatic system, musculoskeletal system, limbs, larynx; and weight.

4.1.6. Vital Signs

Vital signs include temperature, blood pressure, heart rate, and respiratory rate.

4.1.7. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

4.2. Efficacy Variables

The clinical efficacy will be evaluated by investigator per RECIST (Response Evaluation Criteria in Solid Tumors) 1.1. The efficacy variables including:

- Best overall response (BOR) is defined as the best overall response recorded from the start of treatment until disease progression or the last tumor assessment, whichever occurs earlier.
- Overall response rate (ORR) is defined as the proportion of subjects with BOR of complete response (CR) or partial response (PR).
- Disease control rate (DCR) is defined as the proportion of subjects with a BOR of CR, PR, or stable disease (SD).
- Duration of response (DOR) is defined as the time from first evidence of CR or PR to disease progression or death from any cause, whichever occurs first.

- Progression free survival (PFS) is defined as the time from start of study treatment until disease progression or death from any cause, whichever occurs first.
- Time to progression (TTP) is defined as the time from start of study treatment until disease progression.

4.3. Pharmacodynamic Biomarkers

Pharmacodynamic biomarkers includes TGF-β and pSMAD2/3.

4.4. Pharmacokinetic Parameters

Single-dose paremeters include: Cmax， Tmax， AUC_{0-12h}， AUC_{0-24h}， AUC_{0-inf}， $T_{1/2}$， CL/F，Vd/F. Steady-state parameters include: $C_{max,ss}$， $C_{min,ss}$， $T_{max,ss}$，AUC_{tau}， $T_{1/2}$， CL/F，Vd/F，CLr， Racc.

5. STATISTICAL HYPOTHESIS

No statistical hypothesis will be tested in this study.

6. SAMPLE SIZE

Dose escalation part:

Subjects will be enrolled and treated in cohort of size 3-6. Approximately 20-40 subjects are planned to be enrolled. Additional subjects may be enrolled if more dose levels or alternative dosing regimens are to be explored.

Dose expansion part:

6-12 subjects are planned to be enrolled in each treatment. A minimum of 12 subjects should be included in the cohort of RP2D (subjects who have received the same treatment regimen will be counted).

7. ANALYSIS DATASETS

7.1. Screening Set

Screening set: consists of subjects who signed the informed consent.

7.2. Full Analysis Set (FAS)

FAS: consists of all subjects who have received at least one dose of study treatment.

7.3. Safety Set (SS）

SS: consists of all subjects who have received at least one dose of study treatment and had at least one valid post-baseline safety assessment.

7.4. Phamacokinetic Analysis Set (PKAS)

PKAS: consists of all subjects who take at least one dose of study treatment and have at least one blood sample providing evaluable concentration data.

7.5. Dose-determining Set (DDS)

DDS: consists of all subjects who have received at least 80% of the total planned dose of GFH018, are considered to have sufficient safety evaluation during the 31-day-observation period or developed DLT during the first cycle.

7.6. Protocol Deviation

Protocol deviations will be defined on a Data Review Meeting prior to the final database lock.

8. STATISTICAL METHOD

8.1. General Statistical Consideration

The statistical analysis plan be finalized prior to data base lock. All analyses and data presentations will be generated using SAS® Version 9.4 or higher software

Descriptive summary

Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum and maximum values.

The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean and median values will be displayed to one more decimal than the source data, and the SD value will be displayed to two more decimals than the source data for the specific variable.

Categorical variables: Descriptive statistics will include counts and percentages per category. The denominator in all percentage calculations will be the number of participants in the relevant analysis set, unless otherwise specified. Percentages will be displayed to one decimal place with the following exceptions: 1) percentages will not be displayed for zero frequencies; 2) percentages will be displayed as “100%” when percentage is 100%.

ORR and DCR will be calculated, the corresponding two-sided 90% confidence intervals will be estimated by the Clopper-Pearson method.

Baseline

Baseline is defined as the last non-missing measurement collected on or before first study drug administration. For ECGs, the average of the ECG parameters should be used.

Censor rule

Table 3 below shows the censor rule for PFS：

Table 3 Censor rule for PFS

No.	Situation	Event or Censor / Analyais date
1	PD or death	Event / PD date or death date
2	Have at least one post-baseline assessment, no PD, no Death	Censor / Last imaging date
3	No post-baseline assessment and no Death	Censo r/ First dosing date

Only subjects with the BOR of CR or PR will be included for DOR analysis. DOR will apply the same consor rule as PFS.

Best overall response (BOR) is the best measured response at any time post treatment. Subject without any post-treatment assessments will be treated as non-responder.

8.2. Subjects in Study

8.2.1. Subjects Dispostion

From screening to study completion, the following summaries will be provided:

- Summary of the number of patients who screen success for entry into the study and screen failure, respectively, and the number of subjects treated with at least 1 dose of GFH018 (All enrolled population)

- Summary of the number and percentage of treatment withdraws by primary reason and overall (full analysis set) and the number and percentage of study discontinuation by primary reason and overall (full analysis set).

A by-subject listing of reasons for screen failure reason(s), treatment discontinuation, study discontinuation with date and reasons for discontinuation.

8.2.2. Protocol Deviation

Deviations will be defined on a Data Review Meeting shortly prior to the final database lock. The major protocol deviation will be summarized in the number and percentage of subjects with a major protocol deviation by type of deviation based on the FAS.

Additionally, major protocol deviations will be provided in a data listing.

8.2.3. Demographics and Baseline Characteristics

The following demographics and baseline characters will be summarized based on FAS:

- Age (years) at baseline

- Sex
- Race
- Height (cm)
- Weight (kg) at baseline
- BMI (kg/m2) at baseline
- ECOG Performance Status
- Smoking history
- Alcohol history

The following baseline characters of Tumor Diagnosis will be summarized:

- Disease diagnosis
- Primary site of cancer
- Time from initial diagnosis to start of study treatment
- TMN stage at screening
- Disease stage
- Any metastatic sites

8.2.4. Medical History/Current Medical Conditions

Medical history and current medical conditions will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. Medical history is the medical condition ended before the first dose date of study drug and the current medical condition is the medical condition ended on or after the first dose date of study drug.. For the FAS, medical history and current medical conditions will be summarized descriptively by System Organ Class (SOC) and Preferred Term (PT). The corresponding data listing will also be provided.

8.2.5. Prior Anti-Tumor Therapy

Prior anti-tumor drug therapies will be coded using World Health Organization Drug Dictionary (WHO DD) version 202203 B3.

Based on the FAS, prior anti-tumor therapies will be summarized, and prior anti-cancer drug therapies will be summarized by Anatomical Therapeutic Chemical (ATC) Grade 4 and Preferred Term (PT).

Based on the FAS, a detailed listing of prior anti-tumor therapies will be provided.

8.2.6. Prior and Concomitant Medications and Surgeries/Procedures

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO DD) version 202203 B3. Prior and concomitant surgeries and procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0.

<u>Prior and concomitant medications</u>

Prior medications include non-study medications that started and ended prior to the first dose of study medication. Concomitant medications include non-study medications with start date on or after the date of the first dose of study medication and no later than 30 days after the last dose of study medication. Medications will be considered both prior and concomitant if the start date of the medication is prior to the first dose of study medication and the end date is on or after the first dose of study medication.

If the start date and/or end date of a non-study medication is missing or partially missing, the non-complete date should be compared to the first dose date of study medication whenever possible. Non-study medication will be considered as concomitant medication unless there is clear evidence that the start date of the non-study medication is earlier than the first dose date of study medication. If there is clear evidence that the start date of the non-study medication is earlier than the first dose date of study medication, the non-study medication will be considered both prior and concomitant unless there is clear evidence that the end date is earlier than the first dose date of study medication. If there is clear evidence that the end date of the non-study medication is earlier than the first dose date of study medication, then the non-study medication will be considered as prior medication.

Prior and concomitant medications will be summarized by Anatomic Therapeutic Chemical (ATC) Grade 4 and Preferred Term (PT) and listed in detail for subjects in the FAS.

Prior and concomitant surgeries/procedures

Prior surgeries/procedures include surgeries/procedures (that are not prior anti-cancer therapies) with both start and end dates prior to the first dose date of study drug. Concomitant surgeries/procedures included surgeries/procedures with start date on or after the first dose date of study medication and no later than 30 days after the last dose date of study medication. If the start date of a surgery/procedure is before the first dose date of study medication and the end date is on or after the first dose date of study medication, then it will be considered both prior and concomitant. If the start date and/or end date are missing or partially missing, the criteria for judging whether a surgery/procedure is prior or concomitant are the same as for prior and concomitant medications.

Prior and concomitant surgeries/procedures will be summarized by SOC and PT for subjects in the FAS and listed in detail.

8.3. Treatment Compliance and Exposure

Investigate the exposure of study treatment and calculate the duration and amount of exposure, as well as dose intensity, of the study treatment GFH018 for subjects in each dose group.

Duration of exposure

Duration of exposure (days) = last dose date − first dose date + 1

Actual dose intensity

Actual dose intensity (mg/day) = actual total cumulative dose (mg) / actual cumulative days with treatment administered (days)

Treatment compliance

Planned cumulative dose: total planned dose before the decision of treatment discontinuation.

Actual cumulative dose: total actual dose before the decision of treatment discontinuation.

Treatment compliance (%) = actual cumulative dose / planned cumulative dose × 100%

Summarize actual total cumulative dose (mg), duration of exposure (days), actual dose intensity (mg/day), and treatment compliance (%) for subjects in the SS, and summarize treatment interruptions. Categorize treatment compliance by < 80%, 80% to 120%, and > 120%, and summarize the number and percentage of subjects under each category. List in detail subjects' first and last dose dates, duration of exposure, treatment adjustments, and reasons for the adjustments.

8.4. Safety Analysis

All safety analyses will be based on the safety set (SS), except for the DLT analysis which will be based on the dose-determining set (DDS). Baseline definition for safety analyses are provided in Section 8.1.

8.4.1. Adverse Events

Adverse events (AEs) will be coded using MedDRA version 25.0 .

AE summary tables will include only TEAEs, while listings will include all AEs; AE incidence will be calculated based on the number of subjects with adverse events, and when a subject experiences multiple occurrences of the same AE under the same SOC and PT, the occurrence with the most severe grade will be counted. The following summaries and listings will be provided for AEs:

- Summarize the number and percentage of subjects with TEAEs, TEAEs with CTCAE Grade ⩾ 3, treatment-related adverse events (TRAEs), TRAEs with CTCAE Grade ⩾ 3, serious adverse events (SAEs), treatment-related serious adverse events (TRSAEs), AESI , DLT, TEAEs leading to treatment interruption, TRAEs leading to treatment interruption, TEAEs leading to dose reduction, TRAEs leading to dose reduction, TEAEs leading to treatment discontinuation, and TRAEs leading to treatment discontinuation.
- Summary of TEAEs by SOC, PT, and CTCAE Grade
- Summary of TRAEs by SOC, PT, and CTCAE Grade
- Summary of SAEs by SOC, PT, and CTCAE Grade
- Summary of TRSAEs by SOC, PT, and CTCAE Grade
- Summary of AESIs by SOC, PT, and CTCAE Grade
- Summary of TEAEs of Grade 3 or Higher by SOC, PT, and CTCAE Grade
- Summary of TRAEs of Grade 3 or Higher by SOC, PT, and CTCAE Grade
- Summary of DLTs by SOC, PT, and CTCAE Grade
- Summary of TEAEs leading to treatment interruption by SOC, PT, and CTCAE Grade
- Summary of TRAEs leading to treatment interruption by SOC, PT, and CTCAE Grade
- Summary of TEAEs leading to dose reduction by SOC, PT, and CTCAE Grade

- Summary of TRAEs leading to dose reduction by SOC, PT, and CTCAE Grade
- Summary of TEAEs leading to treatment discontinuation by SOC, PT, and CTCAE Grade
- Summary of TRAEs leading to treatment discontinuation by SOC, PT, and CTCAE Grade
- Summary of TEAEs by PT and CTCAE Grade, ordered in descending frequency
- Summary of TRAEs by PT and CTCAE Grade, ordered in descending frequency
- Summary of cause of death
- Listing of adverse events
- Listing of SAEs
- Listing of AESIs
- Listing of DLTs
- Listing of TEAEs leading to treatment interruption
- Listing of TEAEs leading to treatment discontinuation
- Listing of deaths

8.4.2. Laboratory Evaluations

By-visit descriptive summary will be provided for hematology, blood biochemistry, urinalysis (quantitative measurements), coagulation, thyroid function, and their changes from baseline.

For hematology, blood biochemistry, coagulation, and cardiac markers, changes in CTCAE grade from baseline (Grade 0 to 4, where Grade 0 is non-missing value other than Grade 1-4) to worst CTCAE grade after treatment starts (Grade 0 to 4, where Grade 0 means normal) will be summarized using shift tables. Test results from both scheduled and unscheduled visits will be included. For the tests without corresponding CTCAE grades, results in shift tables will be categorized into “lower than normal values and higher than normal values (i.e., both higher than normal values and lower than normal values occurred after first dose of treatment)”, “lower than normal values”, “normal values”, and “higher than normal values”. CTCAE grading reference ranges for laboratory tests are detailed in Appendix I.

Qualitative descriptive summaries will be provided for urinalysis (qualitative) results measured at each visit. A shift table will also be provided by normal, abnormal without clinical significance, and abnormal with clinical significance. For urine protein, a shift table by CTCAE grade will also be provided.

Laboratory test results will be listed separately for hematology, urinalysis, coagulation, blood biochemistry, virology, thyroid function, cardiac markers, and pregnancy test.

8.4.3. Vital Signs

By-visit descriptive summary will be provided for vital sign measurements (body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure) and their changes from baseline. Changes from baseline to worst post-baseline measurements will be summarized in shift table according to the table below (Table 4). The number and percentage of subjects with significant changes in vital sign measurements will be summarized for each group.

Table 4 Criteria for Significant Changes in Vital Signs from Baseline

	Above Normal	Below Normal
Systolic Blood Pressure (mmHg)	increase > = 20 from baseline, and > = 160	Decrease > = 20 from baseline, and < = 80
Diastolic Blood Pressure (mmHg)	increase > = 15 from baseline, and > = 100	Decrease > = 15 from baseline, and < = 50
Heart Rate (beats/min)	increase > = 15 from baseline, and > = 100	Decrease > = 15 from baseline, and < = 60
Respiratory rate (breaths/min)	> 24	< 8
Body Temperature (ºC)	> = 39.1	-

Vital signs for each subject will be listed in detail, and values with significant changes from baseline will be flagged.

8.4.4. 12-Lead Electrocardiogram

Descriptive summaries will be provided for each electrocardiogram (ECG) parameter measured at each visit and their corresponding changes from baseline (averaged over the three measurements).

According to Table 5, the number and percentage of subjects with abnormal changes in ECG parameters after treatment start will be summarized, and summaries will be provided in shift table for the worst change from baseline. ECG results for each subject will be listed in detail.

Table 5 Criteria for Significant Changes in ECG Indicators from Baseline

	Above Normal	**Below Normal**
QTcF (ms)	> 450 and < = 480	-
	> 480 and < = 500	-
	> = 501, or > 60 increase from baseline	-
QT (ms)	> 450 and < = 480	-
	> 480 and < = 500	-
	>= 501, or > 60 increase from baseline	-
Heart Rate (beats/min)	> 25% increase from baseline and value >= 100	> 25% decrease from baseline and value <= 50
PR (ms)	> 25% increase from baseline and value > 200	> 25% decrease from baseline and value < 120

	Above Normal	Below Normal
QRS (ms)	> 25% increase from baseline and value > 110	-

8.4.5. Physical Examination

Worst changes from baseline in physical examination (normal, abnormal but not clinically significant, and abnormal and clinically significant) will be summarized using shift tables. Physical examination records will be listed in detail.

8.4.6. ECOG Score

ECOG scores will be listed in detail for all subjects.

8.4.7. Echocardiography

Descriptive summary will be provided for left ventricular ejection fraction (LVEF) measured at each visit and their changes from baseline. Number and percentage of subjects in the following categories will be provided: LVEF from 40% ~ 50% or with 10% ~ 19% decrease from baseline, LVEF from 20% ~ 39% or with >20% decrease from baseline, and post-baseline LVEF < 20%.

Worst changes from baseline in valve function measurement (normal, abnormal but not clinically significant, and abnormal and clinically significant) will be summarized using shift tables.

Echocardiography records will be listed in detail.

8.5. Efficacy Analysis

Efficacy analyses will be performed for subjects in the FAS based on RECIST evaluation.

A waterfall plot will be presented for the best percentage change from baseline in the sum of target lesion diameters. Swim plots will be prepared for all subjects to present subject drug exposure and efficacy evaluations at each visit.

The best overall response (BOR) will be determined and statistically analyzed based on evaluations at all visit, and the number and percentage of subjects with BOR of CR, PR, SD, PD, NE, and Non-CR/Non-PD will be summarized. Participants with BOR of unknown or none (i.e. no valid record of post-baseline tumor assessments) will be considered non-responsive. ORR (CR or PR) and DCR (CR, PR or SD) will be calculated based on BOR, respectively, and the Clopper-pearson method will be used to estimate ORR and DCR and their 2-sided 90% confidence intervals.

Time to progression (TTP), duration of response (DOR), and progression-free survival (PFS) will be analyzed using the Kaplan-Meier method, with their median and 90% confidence interval will be provided. If the number of subjects in a group is less than 10, only DOR, TTP and PFS listings will be provided for each subject.

Assessments of target lesion, non-target lesion, new lesion, and overall response will be listed in detail for each subject and each visit.

8.6. Pharmacokinetic Analysis

Plasma concentration of study drug will be provided by the central laboratory, and the plasma concentration data will be analyzed by the CRO MOSIM in the enterprise version WinNonlin software using non-compartmental model to calculate the pharmacokinetic parameters and reported independently. Analysis details are presented in the PK Statistical Analysis Report.

8.7. Pharmacodynamic Analysis

Detailed listings of pharmacodynamic markers and pSMAD2/3 in PBMCs (peripheral single cells) and TGF-β measured at each visit will be provided.

9. INTERIM ANALYSIS

No formal interim analysis is planned.

10. REFERENCES

NA.

11. ATTACHMENT

NA.

12. APPENDIX I

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
Blood biochemistry	Aspartate aminotransferase (AST)	Increased	1	ULN < value ⩽ 3.0 x ULN (baseline normal) or 1.5 x baseline value ⩽ value ⩽ 3.0 x baseline value (baseline abnormal)
			2	3.0 xULN < value ⩽ 5.0 xULN (baseline normal) or 3.0 times baseline value < value ⩽ 5.0 times baseline value (baseline abnormal)

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
			3	5.0 xULN < value ⩽ 20.0 xULN (baseline normal) or 5.0-fold baseline value < value ⩽ 20.0-fold baseline value (baseline abnormal)
			4	Value > 20.0 xULN (normal baseline) or value > 20.0 x baseline (abnormal baseline)
	Alanine aminotransferase (ALT)	Increased	1	ULN < value ⩽ 3.0 x ULN (baseline normal) or 1.5 x baseline value ⩽ value ⩽ 3.0 x baseline value (baseline abnormal)
			2	3.0 xULN < value ⩽ 5.0 xULN (baseline normal) or 3.0 times baseline value < value ⩽ 5.0 times baseline value (baseline abnormal)
			3	5.0 xULN < value ⩽ 20.0 xULN (baseline normal); 5.0-fold baseline value < value ⩽ 20.0-fold baseline value (baseline abnormal)
			4	Value > 20.0 xULN (normal baseline) or value > 20.0 x baseline (abnormal baseline)
	Alkaline phosphatase (ALP)	Increased	1	ULN < value ⩽ 2.5 xULN (baseline normal) or 2.0 times baseline value ⩽ value ⩽ 2.5

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
				times baseline value (baseline abnormal)
			2	2.5 xULN < value ⩽ 5.0 xULN (baseline normal) or 2.5 times baseline value < value ⩽ 5.0 times baseline value (baseline abnormal)
			3	5.0 xULN < value ⩽ 20.0 xULN (baseline normal) or 5.0-fold baseline value < value ⩽ 20.0-fold baseline value (baseline abnormal)
			4	Value > 20.0 xULN (normal baseline) or value > 20.0 x baseline (abnormal baseline)
	Glutamyl transpeptidase (GGT)	Increased	1	ULN < value ⩽ 2.5 xULN (baseline normal) or 2.0 times baseline value ⩽ value ⩽ 2.5 times baseline value (baseline abnormal)
			2	2.5 xULN < value ⩽ 5.0 xULN (baseline normal) or 2.5 times baseline value < value ⩽ 5.0 times baseline value (baseline abnormal)
			3	5.0 xULN < value ⩽ 20.0 xULN (baseline normal) or 5.0-fold baseline value < value ⩽ 20.0-fold baseline value (baseline abnormal)

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
			4	Value > 20.0 xULN (normal baseline) or value > 20.0 x baseline (abnormal baseline)
	Serum creatinine (CREA)	Increased	1	ULN < value ⩽ 1.5 xULN
			2	1.5 xULN < value ≤ 3.0 xULN or 1.5 times baseline value < value ≤ 3.0 times baseline value
			3	3.0 xULN < value ≤ 6.0 xULN or value > 3.0 baseline
			4	Value > 6.0 xULN
	Albumin (ALB)	Decreased	1	3 g/dL ⩽ value < LLN or 30 g/L ⩽ value < LLN
			2	2 g/dL ⩽ value < 3 g/dL or 20 g/L ⩽ value < 30 g/L
			3	Values < 2 g/dL or values < 20 g/L
	Total bilirubin (TBIL)	Increased	1	ULN < value ⩽ 1.5 xULN (baseline normal) or 1 x baseline value < value ⩽ 1.5 x baseline value (baseline abnormal)
			2	1.5 xULN < value ⩽ 3.0 xULN (baseline normal) or 1.5 times baseline value < value ⩽ 3.0 times baseline value (baseline abnormal)

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
			3	3.0 xULN < value ⩽ 10.0 xULN (baseline normal) or 3.0 times baseline value < value ⩽ 10.0 times baseline value (baseline abnormal)
			4	Value > 10.0 xULN (normal baseline) or value > 10.0 times baseline value (abnormal baseline)
	Creatine kinase (CK)	Increased	1	ULN < value ⩽ 2.5 xULN
			2	2.5 xULN < value ⩽ 5.0 xULN
			3	5.0 xULN < value ⩽ 10.0 xULN
			4	Value > 10.0 xULN
	Total cholesterol (TCHO)	Increased	1	ULN < value ⩽ 300 mg/dL or ULN < value ⩽ 7.75 mmol/L
			2	300 mg/dL < value ⩽ 400 mg/dL or 7.75 mmol/L < value ⩽ 10.34 mmol/L
			3	400 mg/dL < value ⩽ 500 mg/dL or 10.34 mmol/L < value ⩽ 12.92 mmol/L
			4	Value > 500 mg/dL or value > 12.92 mmol/L
	Triglycerides (TG)	Increased	1	1.71 mmol/L ⩽ value < 3.42 mmol/L or 150

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
				mg/dL ⩽ value < 300 mg/dL
			2	3.42 mmol/L ⩽ value < 5.7 mmol/L or 3 00 mg/dL ⩽ value < 500 mg/dL
			3	5.7 mmol/L ⩽ value < 11.4 mmol/L or 5 00 mg/dL ⩽ value < 1000 mg/dL
			4	Value > 11.4 mmol/L or value > 1000 mg/dL
	Blood glucose	Decreased		
			1	3. 0 mmol/L ⩽ value < LLN or 5 5 mg/dL ⩽ value < LLN
			2	2 . 2 mmol/L ⩽ value < 3 . 0 mmol/L or 4 0 mg/dL ⩽ value < 5 5 mg/dL
			3	1 . 7 mmol/L ⩽ value < 2 . 2 mmol/L or 3 0 mg/dL ⩽ value < 40 mg/dL
			4	Value < 1 . 7 mmol/L or Value < 30 mg/dL
	Calcium	Increased		
			1	ULN < value ⩽ 2.9 mmol/L or ULN < value ≤ 11.5 mg/dL
			2	2.9 mmol/L < value ⩽ 3.1 mmol/L or 11.5 mg/dL < value ≤ 12.5 mg/dL

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
			3	3.1 mmol/L < value ≤ 3.4 mmol/L or 12.5 mg/dL < value ⩽ 13.5 mg/dL
			4	Value > 3.4 mmol/L or Value > 13.5 mg/dL
		Decreased	1	2.0 mmol/L ⩽ value < LLN or 8 . 0 mg/dL ⩽ value < LLN
			2	1.75 mmol/L ⩽ value < 2.0 mmol/L or 7. 0 mg/dL ⩽ value < 8 . 0 mg/dL
			3	1.5 mmol/L ⩽ value < 1.75 mmol/L or 6. 0 mg/dL ⩽ value < 7 . 0 mg/dL
			4	Value < 1.5 mmol/L or Value < 6. 0 mg/dL
	Sodium	Increased	1	ULN < value ≤ 150 mmol/L
			2	150 mmol/L < value ⩽ 155 mmol/L
			3	155 mmol/L < value ⩽ 160 mmol/L
			4	Value > 160 mmol/L
		Decreased	1	130 mmol/L ⩽ value < LLN
			3	120 mmol/L ⩽ value ⩽ 130 mmol/L
			4	Value < 120 mmol/L

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
	Potassium	Increased	1	ULN < value ≤ 5 . 5 mmol/L
			2	5.5 mmol/L < value ⩽ 6.0 mmol/L
			3	6.0 mmol/L < value ⩽ 7.0 mmol/L
			4	Value > 7.0 mmol/L
		Decreased	1	3 . 0 mmol/L ⩽ value < LLN
			3	2.5 mmol/L ⩽ value < 3.0 mmol/L
			4	Value < 2.5 mmol/L
Blood routine	Eosinophil (EO) count	Increased	1	Value > ULN and value > baseline
	Hemoglobin concentration (HGB)	Increased	1	ULN < value ⩽ ULN + 2 g/d L
			2	ULN + 20 g/L < value ⩽ ULN + 40 g/L
			3	Value > ULN + 40 g/L
		Decreased	1	100 g/L ⩽ value < LLN or 10 . 0 g/dL ⩽ value < LLN or 6 .2 mmol/L ⩽ value < LLN
			2	8 0 g/L ⩽ value < 100 g/L or 8. 0 g/dL ⩽ value < 10 . 0 g/dL or 4 .9 mmol/L ⩽ value < 6 .2 mmol/L

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
			3	Value < 80 g/L or value < 8. 0 g/dL or value < 4.9 mmol/dL
	Lymphocyte (LY) count	Increased	2	20,000/mm ^{3} ⩽ value < 4000/mm ^{3} or 20 - < 4 x 10 ^{9}/L
			3	Value > 20,000/mm ^{3} or > 20 x 10 ^{9}/L
		Decreased	1	800/mm ^{3} ⩽ value < LLN or < LLN - 0.8 x 10 ^{9}/L
			2	500/mm ^{3} ⩽ value < 800/mm ^{3} or < 0.8 - 0.5 x 10 ^{9}/L
			3	200/mm ^{3} ⩽ value < 500/mm ^{3} or < 0.5 - 0.2 x 10 ^{9}/L
			4	Value < 200/mm ^{3} or < 0.2 x 10 ^{9}/L
	Neutrophil count (ANC)	Decreased	1	1.5 x 10 ^{9}/L ⩽ value < LLN or 1 500/mm ^{3} ⩽ value < LLN
			2	1.0 x 10 ^{9}/L ⩽ value < 1.5 x 10 ^{9}/L or 1 000/mm ^{3} ⩽ value < 1 500/mm ^{3}
			3	0.5 x 10 ^{9}/L ⩽ value < 1.0 x 10 ^{9}/L or 5 00/mm ^{3} ⩽ value < 1 000/mm ^{3}
			4	Value < 0.5 x 10 ^{9}/L or Value < 5 00/mm ^{3}

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
	Platelet count (PLT)	Decreased	1	75.0 x 10^9/L ⩽ value < LLN or 75000/mm^3 ⩽ value < LLN
			2	50.0 x 10^9/L ⩽ value < 75.0 x 10^9/L or 5 0000/mm^3 ⩽ value < 75000/mm^3
			3	25.0 x 10^9/L ⩽ value < 50.0 x 10^9/L or 2 5000/mm^3 ⩽ value < 50000/mm^3
			4	Value < 25.0 x 10^9/L or value < 2 5000/mm^3
	White blood cell count (WBC)	Decreased	1	3.0 x 10^9/L ⩽ value < LLN or 3 000/mm^3 ⩽ value < LLN
			2	2.0 x 10^9/L ⩽ value < 3.0 x 10^9/L or 2 000/mm^3 ⩽ value < 3000/mm^3
			3	1.0 x 10^9/L ⩽ value < 2.0 x 10^9/L or 1 000/mm^3 ⩽ value < 2000/mm^3
			4	Value < 1.0 x 10^9/L or value < 1 000/mm^3
Coagulation function	Activated partial thromboplastin time (APTT)	Increased	1	ULN < value ⩽ 1.5 xULN
			2	1.5 xULN < value ⩽ 2.5 xULN
			3	Value > 2.5 xULN

Laboratory Test Category	Laboratory test indicators	Altered (increased/decreased)	CTCAE Grade	Criteria for judgment
	International normalized ratio (INR)	Increased	1	1.2 < value ⩽ 1.5
			2	1.5 < value ⩽ 2.5
			3	Value > 2.5
Urine routine	Urine protein	Increased	1	1 +
			2	2 +, 3 +
			3	4 +

Note: LLN means lower limit of normal; ULN means upper limit of normal.