STATISTICAL ANALYSIS PLAN

An open-label, phase I/II clinical study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation

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Sponsor:	GenFleet Therapeutics (Shanghai) Inc.
CRO:	ClinChoice Enterprise Management (Shanghai) Co., Ltd.
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Signature Page

WRITTEN BY:

Author

Name Heng Chen

Title Senior Statistician _____

ClinChoice Enterprise Management (Shanghai) Co., Ltd. Signature

Date: _____

Reviewer

Name Chengguqiu Dai

Title PK Statistician _____

ClinChoice Enterprise Management (Shanghai) Co., Ltd. Signature

Date: _____

Reviewer

Name Hui He

Title Director of Statistics _____

ClinChoice Enterprise Management (Shanghai) Co., Ltd. Signature

Date: _____

Approver

Name: Shuang Wang

Title: Principal Statistician _____

GenFleet Therapeutics (Shanghai) Inc. Signature

Date: _____

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List of Abbreviations

Abbreviation	Term
AE	Adverse event
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the curve
BICR	Blinded Independent Central Review Committee
BID	Twice daily
BMI	Body mass index
BOIN	Bayesian Optimal Interval
BOR	Best overall response
BQL	Below lower limit of quantification
BSA	Body surface area
C_{max}	Maximum concentration
$C_{max,ss}$	Steady-state maximum concentration
$C_{trough,ss}$	Steady-state trough concentration
CI	Confidence interval
CL/F	Apparent clearance
CL/F_{ss}	Steady-state apparent clearance
CR	Complete response
CRC	Colorectal carcinoma
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CV	Coefficient of variation
DCR	Disease control rate
DDS	Dose Determination Set
DLT	Dose-limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FAS	Full Analysis Set
GCV	Geometric coefficient of variation
HR	Heart rate
LLOQ	Lower limit of quantification
KRAS	Kirsten ratsarcoma viral oncogene homolog
MedDRA	Medical Dictionary for Regulatory Activities
NE	Not evaluable
NSCLC	Non-small cell lung cancer
MRT	Mean residence time
MTD	Maximum tolerated dose
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PDAC	Ductal adenocarcinoma of pancreas

Abbreviation	Term
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PN	Preferred name
PPS	Per-Protocol Set
PPoS	Predictive probability of success
PR	Partial response
PT	Preferred term
Q1	First quartile
Q3	Third quartile
QD	Once daily
R^2adj	Adjusted coefficient of determination
R_{ac_AUC}	Accumulation ratio based on $AUC_{0\text{-}tau}$
R_{ac_Cmax}	Accumulation ratio based on C_{max}
$R_{ac\_Ctrough}$	Accumulation ratio based on C_{trough}
RECIST	Response Evaluation Criteria in Solid Tumors
RED	Recommended expansion dose
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SMC	Safety Monitoring Committee
SOC	System organ class
SS	Safety Set
$t_{1/2}$	Elimination half-life
T_{max}	Time to maximum concentration
TEAE	Treatment-emergent adverse event
TTR	Time to response
V_z/F	Apparent volume of distribution
V_z/F_{ss}	Steady-state apparent volume of distribution
WHODrug	World Health Organization Drug Dictionary
λ_z	Terminal elimination rate constant

1 Introduction

This study (Study No. GFH375X1101) is an open-label, phase I/II clinical study to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation. Based on the clinical study protocol (Version: V2.0, 2025-1-24), this Statistical Analysis Plan (SAP) details the specific statistical methods and data handling principles for analyzing and reporting participant safety assessments, efficacy assessments, PK assessments, and biomarker assessments.

This document will be gradually supplemented and improved to reflect protocol amendments, regulatory and other important changes. The final SAP will be archived after sponsor approval and before database lock. Any deviations from the final SAP will be noted in the clinical study report.

1.1 Study Objectives and Endpoints

Table 1 Objectives and Endpoints of the Phase I Part

Study Objectives	Study Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs); changes in vital signs, electrocardiogram (ECG), and laboratory tests
• To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of GFH375	• Incidence of dose-limiting toxicity (DLT) events
Secondary Objectives	**Secondary Endpoints**
• To evaluate the PK characteristics of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Plasma concentrations and PK parameters of GFH375, including but not limited to C_{max}, T_{max}, AUC, $t_{1/2}$, CL/F, Vz/F, C_{trough}
• To evaluate the preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
	• Overall survival (OS)
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms related to treatment sensitivity or drug resistance	• Mutation analysis of circulating tumor DNA (ctDNA) in blood at baseline and at the end of treatment

Table 2 Objectives and Endpoints of the Phase II Part

Study Objectives	Study Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced non-small cell lung cancer (NSCLC), advanced pancreatic carcinoma (PDAC), advanced colorectal cancer (CRC), and other solid tumors with	• ORR as assessed by RECIST 1.1

KRAS G12D mutation

Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation using other efficacy endpoints	• Best overall response (BOR), DoR, DCR, TTR, and PFS as assessed by RECIST 1.1 • OS
• To evaluate the safety of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation	• Incidence and severity of AEs and SAEs; changes in vital signs, ECG, and laboratory tests
• To evaluate the PK characteristics of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation	• Plasma concentrations of GFH375
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms related to treatment sensitivity or drug resistance	• Mutation analysis of blood ctDNA at baseline and at the end of treatment
• For PDAC participants: Relationship between carbohydrate antigen 19-9 (CA19-9) and treatment response	• For PDAC participants: Change from baseline in serum CA19-9

1.2 Study Overview

1.2.1 Overall Study Design

This is a study to evaluate the safety/tolerability, PK, and efficacy of GFH375 monotherapy in patients with advanced solid tumors with KRAS G12D mutation. The primary objective of the Phase I part is to evaluate the safety/tolerability, PK, and preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation, and to determine the MTD and/or RP2D of GFH375. The primary objective of the Phase II part is to evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation.

Phase I Part

According to the BOIN design, 3-6 participants will be enrolled in each dose cohort (except during accelerated titration) to receive oral administration of GFH375, with each treatment cycle lasting 21 days. Participants will be enrolled into sequential dose-escalation cohorts, with a starting dose of 100 mg once daily (QD). A total of 7 or more dose levels are expected to be evaluated in the dose-escalation part, and the planned dose escalation is shown in Table 3. The GFH375 dosing regimen will be comprehensively evaluated during dose escalation. If necessary, dose exploration with a twice daily (BID) dosing frequency will be conducted. Dose escalation for QD and BID dosing regimens can be conducted independently and in parallel.

Based on the data obtained, including safety, PK, and preliminary efficacy results, BID dose exploration may be conducted. The starting dose for BID will be selected from one of the dose cohorts in the table below, and the total daily dose will be consistent with the QD dose being explored.

Table 3 Dose Escalation

Dose Cohort	Planned QD Dose Escalation Cohorts for Phase I[1]
Dose Cohort 1	100 mg QD
Dose Cohort 2	200 mg QD
Dose Cohort 3	400 mg QD
Dose Cohort 4	600 mg QD
Dose Cohort 5	750 mg QD
Dose Cohort 6	1000 mg QD
Dose Cohort 7	1200 mg QD
Dose Cohort	**Potential BID Dose Exploration Cohorts for Phase I[2]**
Dose Cohort 1	100 mg BID
Dose Cohort 2	150 mg BID
Dose Cohort 3	200 mg BID
Dose Cohort 4	300 mg BID
Dose Cohort 5	400 mg BID

Note: [1] Intermediate doses of the above doses, such as 150 mg, 300 mg, 500 mg, 800 mg, 900 mg, 1100 mg QD, etc., may be explored during the escalation process based on the clinical data obtained, including safety, PK, and possible efficacy.
[2] Intermediate doses of the above doses, such as 250 mg BID, etc., may be explored.

Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling. These participants will be treated with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is considered to have potential clinical benefit by the investigator and sponsor, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. If the safety of the 750 mg QD dose cohort has been explored and confirmed, backfilling of the 700 mg QD dose cohort may also be conducted. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be treated in each GFH375 dose cohort (including participants enrolled in the BOIN dose-escalation phase).

The study schematic is shown in Figure 1.

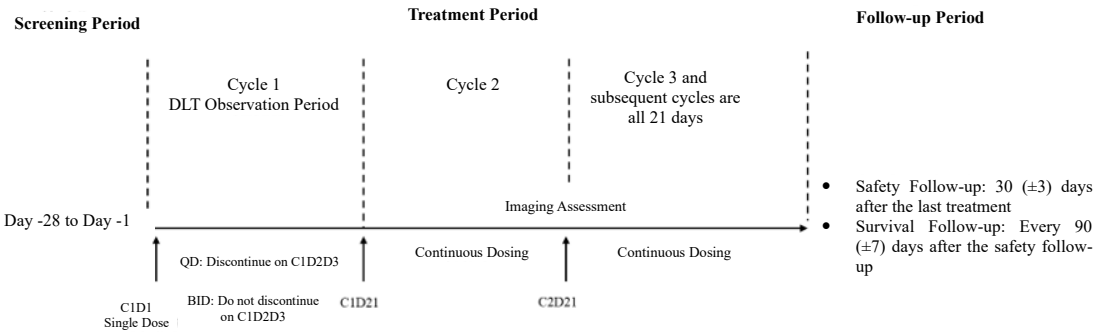

Figure 1 Phase I Part Schematic

Phase II Part

Based on all safety, tolerability, PK, and efficacy data from all patients in dose escalation and some of the backfilled participants in Phase I part, the RP2D was determined to be 600 mg QD.

The Phase II part is an open-label, multicenter study. The overall study plan is shown in Figure 2. The objective is to evaluate the efficacy, safety, and PK characteristics of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation. The Phase II part will enroll approximately 317 participants with advanced solid tumors with KRAS G12D mutation to receive continuous monotherapy with GFH375 at the RP2D, with 21-day treatment cycles , until progressive disease (PD), unacceptable toxicity, or discontinuation of study treatment for other reasons.

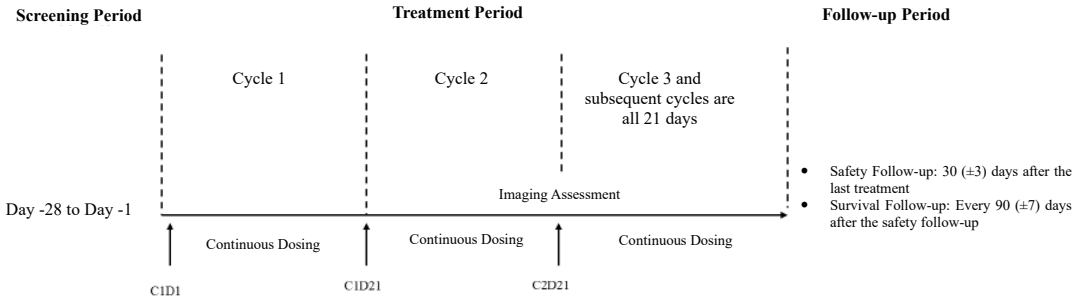

Figure 2 Phase II Part Schematic

1.2.2 Randomization and Blinding

This is a single-arm, open-label study, so randomization and blinding are not applicable.

1.2.3 Sample Size

1.2.3.1 Phase I Part: Dose Escalation

According to the BOIN design, 3-6 participants will be enrolled in each dose cohort (except during accelerated titration) to receive treatment. Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for

backfilling. These participants will be treated with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is considered to have potential clinical benefit by the investigator and sponsor, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be treated in each GFH375 dose cohort (including participants enrolled in the BOIN dose-escalation phase). If more dose cohorts or alternative dosing regimens need to be explored, additional participants may be enrolled.

1.2.3.2 Phase II Part

A total of approximately 317 participants are expected to be enrolled, including approximately 73 participants with advanced NSCLC, approximately 94 participants with advanced PDAC, 50 participants with advanced CRC, and 100 participants with other advanced solid tumors.

Table 5 Phase II Part Sample Size

Tumor Type	Historical Control ORR	Expected ORR	Sample Size
NSCLC	23%	40%	73
PDAC	15%	30%	94
CRC	10%	30%	50
Other			100
Total			317

For second-line advanced NSCLC, the historical control ORR is 23%, and the expected ORR in this study is 40%. The study will be considered successful if the lower limit of the 95% confidence interval (CI) for the observed ORR is not less than the historical control of 23%. With a one-sided $\alpha = 0.025$, 73 participants are required to achieve 89% power. When at least 25 of the 73 participants have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 23%. With 25 CR/PRs, the ORR = 34.2%, with a 95% CI of (23.5%, 46.3%).

For second-line advanced PDAC, the historical control ORR is set at 15%. The expected ORR with GFH375 treatment is 30%. If the lower limit of the 95% CI for ORR after GFH375 treatment is greater than 15%, the efficacy of GFH375 will be considered statistically significant. With a one-sided $\alpha = 0.025$, 94 participants will provide 95% power to ensure that the lower limit of the 95% CI for the ORR is greater than 15%. Approximately 94 participants with PDAC are planned for enrollment. When 22 responses (PR/CR) are observed in 94 participants, the exact 95% CI for the observed ORR is (15.29%, 33.26%). Therefore, if ≥22 responses are observed in 94 participants, the efficacy of GFH375 will be considered statistically significant.

For third-line CRC, the historical control ORR is 10%, and the expected ORR in this study is 30%. The study will be considered successful if the lower limit of the 95% CI for the observed ORR is not

less than the historical control of 10%. It is planned to enroll 50 participants, which will provide 96% power with a one-sided $\alpha = 0.025$. When at least 10 of the 50 participants have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 10%. With 10 CR/PRs, the ORR = 20.0%, with a 95% CI of (10.0%, 33.7%).

For other solid tumors: Approximately 100 participants with advanced solid tumors with KRAS G12D mutation, such as bile duct cancer and appendix cancer with KRAS G12D mutation, are planned for enrollment.

The above sample size and ORR (and its 95% exact CI) calculations were performed using the R software. Among them, the sample size was calculated using the "nBinomial1Sample()" function in the "gsDesign" package (option: conservative = TRUE); the ORRs and their 95% exact CIs were calculated using the "binom.exact()" function in the "epitools" package (with default options).

2 Basic Considerations for Statistical Analysis

2.1 General Rules

All statistical analyses will be performed using SAS version 9.4 or later.

For continuous variables, the number of participants, mean, standard deviation, median, minimum, and maximum will be summarized. For categorical variables, the number of participants and percentage for each category will be summarized. Time-to-event variables will be analyzed using the Kaplan-Meier method, survival curves will be plotted, and the median survival time and its corresponding two-sided 95% CI will be calculated. Table 6 shows the number of decimal places to be retained for each statistical parameter.

Table 6 Number of Decimal Places for Statistical Parameters

Statistic	**Number of Decimal Places to Retain**
Arithmetic mean, geometric mean, median, Q1, Q3, CI	One more decimal place than the original data, with a maximum of 3 decimal places
Standard deviation, standard error, coefficient of variation (CV%), and geometric coefficient of variation (GCV%)	Two more decimal places than the original data, with a maximum of 3 decimal places.
Maximum, minimum	Same number of decimal places as the original data, with a maximum of 3 decimal places
Percentage	Retain one decimal place. If the percentage is 100%, it will be expressed as "100". If the percentage is 0, it will be expressed as "0"
P-value	Retain 3 decimal places. If the P-value is less than 0.001, it will be expressed as "<0.001". If the P-value is greater than 0.999, it will be expressed as ">0.999".

2.2 Definition of Analysis Sets

- Full Analysis Set (FAS): All participants who have received at least one dose of GFH375.

- Safety Set (SS): All participants who have received at least one dose of GFH375 and have at least one valid post-baseline safety assessment.
- Dose Determination Set (DDS): All participants in the Phase I SS who received unreduced GFH375 for at least 15 cumulative days during the DLT observation period and had adequate safety assessments, or who experienced a DLT during the DLT observation period. The DDS does not include backfilled participants.
- Per-Protocol Set (PPS): All Phase II participants in the FAS who are compliant with the protocol. The study team will review all protocol deviations before the final database lock and exclude participants with major protocol deviations that affect the efficacy evaluation from the PPS.
- Pharmacokinetic Analysis Set (PKAS): All participants who have received at least one dose of GFH375 and have at least one blood sample providing evaluable PK data.

2.3 Data Handling Principles

2.3.1 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing assessment result (including scheduled and unscheduled visits) before the first dose of GFH375. If a participant does not have an assessment result as defined above, the baseline will be treated as missing. When the assessment occurs on the same day as the first dose of GFH375, if it cannot be confirmed that it occurred after the first dose of GFH375, it will be considered as baseline data by default. However, for a record of AE, concomitant medication/therapy, etc., when its start date is the same as the date of the first dose of GFH375, if it cannot be confirmed that it occurred before dosing, the AE, concomitant medication/therapy, etc., will be considered to have occurred post-baseline.

2.3.2 Definition of Study Day

The study day is calculated with the date of the first dose of GFH375 as the reference to obtain the time interval (in days) between the date of the event or assessment and the date of the first dose. The study day is calculated as follows:

- If the event or assessment occurs on or after the day of the first dose of GFH375, the study day is: Date of event or assessment - Date of first dose of GFH375 + 1;
- If the event or assessment occurs before the first dose of GFH375, the study day is: Date of event or assessment - Date of first dose of GFH375.

2.3.3 Definition of Analysis Window

All statistical analyses of study data will be based on the nominal visits recorded in the case report

form (CRF), and no analysis windows will be set.

2.3.4 Last Known Date of Survival

For participants who are not known to be dead as of the analysis date, their last known date of survival will be determined based on the last recorded non-missing date from the following data:

- The dates of all assessments (e.g., vital signs, physical examination, Eastern Cooperative Oncology Group (ECOG) assessment, laboratory tests, ECG, etc.). If the assessment involves sample collection, the collection date will be used;
- The start and end dates of GFH375 administration, concomitant medications, concomitant non-drug therapies, and new anti-tumor therapies;
- The end date of an AE with an outcome other than "death";
- The date of the last survival follow-up contact when the participant's status was "alive" during survival follow-up;
- The date of last contact before being lost to follow-up.

2.3.5 Rules for Handling Missing Data

Unless otherwise specified, missing data in this study will not be imputed.

2.3.5.1 Date of Initial Pathological Diagnosis

Imputation rules for the date of initial pathological diagnosis:

- If the year is missing (or the entire date is missing), it will not be imputed;
- If only the day is missing, it will be imputed as the 1st of that month;
- If both the month and day are missing, it will be imputed as July 1st.

If the imputed date is after the date of informed consent, the imputed date will be revised to the date of informed consent - 1 day.

2.3.5.2 Date of Death

Applicable only to confirmed deaths, the date of death will be imputed using the following rules:

- If the year is missing (or year, month, and day are all missing), the date of death will be imputed as the last known date of survival + 1 day.
- If both the day and month are missing, July 1st of that year will be imputed as the date of death.
- If only the day is missing, the 1st day of that month will be used as the imputed date of death.

If the imputed date of death is before the last known date of survival, the imputed date will be revised to the last known date of survival + 1 day.

2.3.5.3 Date of Prior/Concomitant Therapy

Prior/concomitant therapy includes drug and non-drug therapies. The imputation rules for the dates of prior/concomitant therapy are as follows. If both the start and end dates of a prior/concomitant therapy are missing, the end date will be imputed first, followed by the start date.

End Date of Prior/Concomitant Therapy

- Imputation will only be performed for prior/concomitant therapies for which "No" was selected for "Ongoing";
- If only the day is missing, it will be imputed as the last day of that month;
- If both the month and day are missing, it will be imputed as December 31st of that year;

If the imputed end date of the prior/concomitant therapy is after the study termination date, the end date of the prior/concomitant therapy will be revised to the study termination date.

Start Date of Prior/Concomitant Therapy

- If only the day is missing, it will be imputed as the 1st of that month;
- If both the month and day are missing, it will be imputed as January 1st of that year;
- If the year, month, and day are all missing, it will be imputed as the date of the first dose of GFH375;

If the imputed start date of the prior/concomitant therapy is later than its end date, it will be revised to the end date of the prior/concomitant therapy.

2.3.5.4 End Date of Prior Anti-tumor Therapy

Prior anti-tumor therapy includes drug therapy, surgery, and radiotherapy. The imputation rules for the end date of prior anti-tumor therapy are as follows:

- If only the day is missing, it will be imputed as the last day of that month;
- If both the month and day are missing, it will be imputed as December 31st of that year;
- If the year, month, and day are all missing, no imputation will be performed;

If the imputed date is after the date of informed consent, the imputed date will be revised to the date of informed consent - 1 day.

2.3.5.5 Date of Progressive Disease on Last Line of Prior Therapy

The imputation rules for the date of PD on the last line of prior therapy are as follows:

- If only the day is missing, it will be imputed as the last day of that month;
- If both the month and day are missing, it will be imputed as December 31st of that year;
- If the year, month, and day are all missing, no imputation will be performed;

If the imputed date is after the date of informed consent, the imputed date will be revised to the date

of informed consent - 1 day.

2.3.5.6 Start Date of Adverse Events

Imputation rules for the start date of an AE:

- If the AE start date is completely missing, it will be imputed as the date of the first dose of GFH375;
- If the AE start date is partially missing, the imputation rules are as follows:
  - If the year and month are known and are the same as the year and month of the first dose of GFH375, it will be imputed as the date of the first dose of GFH375;
  - If the year and month are known but are different from the year and month of the first dose of GFH375, it will be imputed as the 1st of that month;
  - If only the year is known and is the same as the year of the first dose of GFH375, it will be imputed as the date of the first dose of GFH375;
  - If only the year is known but is different from the year of the first dose of GFH375, it will be imputed as January 1st of that year.

If the AE end date is not missing and the imputed AE start date is after the AE end date, the AE start date will be imputed as the AE end date.

2.3.5.7 End Date of Investigational Product

If the end date of the last record (i.e., last dose) is missing, it will be imputed with the earliest, complete date from the following that is closest to the start date of that record:

- The last day of the month (if only the day is missing)
- The start time of the AE for which the action taken with study treatment was “drug withdrawn” in the AE record
- Date of decision to end study treatment - 1 day
- Date of death
- Data cutoff date

Missing end date during the study treatment period (not the last dose):

- Start date of the next nearest medication record - 1 day

2.3.6 Other Data Handling Principles

For laboratory test items, all results to be summarized will be presented in tables and listings using SI units. If laboratory test results contain “>” or “<”, the upper or lower limit of the test result will be used as the analysis value for tabulation and summary (the “>” or “<” will be retained in listings). For example, if the test result is “>100”, the analysis value will be assigned as 100.

Unless otherwise specified, only data from scheduled visits will be summarized. However, for the summary analysis of the best/worst post-baseline assessment results, results from both scheduled and unscheduled visits will be included. Results from both unscheduled and scheduled visits will be presented in listings. With the exception of ECG-related assessments, if, during a scheduled visit, an assessment item is tested two or more times within the same visit, the last non-missing result will be used for tabulation analysis; for multiple measurements of ECG-related parameters within the same visit, the mean value will be used for tabulation analysis. If multiple identical best/worst post-baseline assessment results occur, the last assessment result will be used for tabulation analysis. Multiple assessment results from both unscheduled and scheduled visits will be presented in listings.

2.4 Multiplicity Comparison

This study does not involve multiple comparisons.

2.5 Subgroup Analysis

For Phase II part participants with PDAC and NSCLC, a subgroup analysis of ORR will be performed based on the results assessed by Blinded Independent Central Review Committee (BICR) where CR/PR requires confirmation.

Subgroups for PDAC include:

- Age (<65 years, ≥65 years);
- Sex (male, female);
- ECOG PS score (0, 1);
- Number of metastatic sites (<2, ≥2);
- CA19-9 level (<40 U/mL, ≥40 U/mL);
- Albumin (<40 g/L, ≥40 g/L);
- Prior radiotherapy (yes, no);
- Prior surgery (yes, no);
- Tumor stage (III, IV, other);
- Metastases to liver (yes, no);
- Body mass index (BMI) (<median, ≥median);
- Number of prior lines of drug therapy (0, 1, 2, 3);
- Duration of disease (<median, ≥median);
- Time from PD on last line of prior therapy to first treatment (<median, ≥median, <1 month, 1-3 months, 3-6 months, ≥6 months);
- Prior treatment with gemcitabine/gemcitabine hydrochloride (yes, no);

- Prior treatment with albumin-bound paclitaxel/paclitaxel (yes, no);
- Prior treatment with irinotecan (yes, no).

Subgroups for NSCLC include:

- Age (<60 years, ≥60 years, <65 years, ≥65 years);
- Sex (male, female);
- ECOG PS score (0, 1);
- Smoking history (never smoked, former smoker, current smoker);
- Brain metastasis (yes, no);
- Metastases to liver (yes, no);
- Metastases to adrenals (yes, no);
- Metastases to bone (yes, no);
- Number of prior lines of drug therapy (1, 2, 3);
- Prior treatment with anti-PD-1/PD-L1 drugs (yes, no);
- Prior treatment with platinum-containing drugs (yes, no);
- Prior treatment with anti-PD-1/PD-L1 and platinum-containing drugs (yes, no);
- PD-L1 expression level (low expression, medium expression, high expression).

2.6 Pooling of Study Centers

This is a multicenter trial, and data from all centers will be pooled for analysis, without considering center effects.

3 Definition and Derivation Rules for Variables

3.1 Participant Demographics

3.1.1 Prior/Concomitant Medical History

Prior medical history refers to medical history that had resolved at screening, while concomitant medical history refers to medical history that was ongoing at screening. This is determined by the "Ongoing" field on the "Other Medical History" page in the CRF.

3.1.2 Prior/Concomitant Medications

Prior medications refer to non-investigational treatments that were discontinued before the first dose of GFH375.

Concomitant medications refer to non-investigational treatments that meet one of the following conditions:

- Started before the first dose of GFH375 and continued after the first dose of GFH375;
- Started on or after the day of the first dose of GFH375.

In addition, if "Yes" is selected for "Ongoing" on the "Prior/Concomitant Medications" page of the CRF, then it is regarded as concomitant medication.

3.1.3 Prior/Concomitant Non-drug Therapies

Prior non-drug therapies refer to non-drug therapies with end date before the first dose of GFH375.

Concomitant non-drug therapies refer to non-drug therapies that meet one of the following conditions:

- Started before the first dose of GFH375 and continued after the first dose of GFH375;
- Started on or after the day of the first dose of GFH375.

In addition, if "Yes" is selected for "Ongoing" on the "Prior/Concomitant Non-drug Therapies" page of the CRF, then it is regarded as concomitant non-drug therapy.

3.2 Efficacy Endpoints

The efficacy endpoints in this study are assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Best overall response (BOR) is the best response from the start of the first dose of GFH375 until PD, death from any cause, or the start of new anti-tumor therapy (whichever occurs first). If the start date of the new anti-tumor therapy is the same as the assessment date, the assessment will be considered to have occurred before the start of the new anti-tumor therapy. If a participant has no record of PD or new anti-tumor therapy, all assessment results can be used to determine the BOR. The confirmation criteria for best overall response (BOR) are as follows:

- Confirmed CR: Assessed as CR at least once, and confirmed as CR again in a subsequent assessment (at least 4 weeks later), with no evidence of PD in between.
- Confirmed PR: Assessed as PR at least once, and confirmed as PR or CR again in a subsequent assessment (at least 4 weeks later), with no evidence of PD in between.
- Stable Disease (SD): To be assessed as SD, the participant must have had at least 6 weeks (42 days) of follow-up after the first dose of GFH375, and not meet the criteria for CR or PR. If the minimum time criterion is not met, SD will not be recognized. For example, if a patient is assessed as SD on Day 30, the BOR cannot be regarded as SD because the condition of ≥42 days is not met.
- PD: Not assessed as confirmed CR, PR, or SD before PD, PD occurs before new anti-tumor therapy, and PD occurs before 91 days (2*6 weeks + 1 week) after the first dose of GFH375.
- NE: No post-baseline tumor assessment; post-baseline tumor assessments have been performed, but none can be decided to be CR, PR, SD, or PD; post-baseline tumor assessments have been performed, but occur after new anti-tumor therapy; SD does not meet the minimum of 6 weeks after the first dose of GFH375 and there is no subsequent tumor

assessment; PD occurs after 91 days (2*6 weeks + 1 week) after the first dose of GFH375, and there is no tumor assessment during this period.

3.2.1 Objective Response Rate (ORR)

For the definition of ORR, see section **4.2.1**.

3.2.2 Disease Control Rate (DCR)

For the definition of DCR, see section **4.2.2**.

3.2.3 Progression-Free Survival (PFS)

For the definition of PFS, see section **4.2.3**.

The calculation of PFS will always be based on the imaging examination date corresponding to the efficacy assessment, not the visit or efficacy assessment date. The calculation of TTR and DoR is similar. If imaging examinations within a visit are completed on multiple dates, the following rules will be applied to select the analysis date:

- The date of PD will be determined by the earliest date of the imaging examination of the lesion corresponding to the PD event. For example, for PD based on a new lesion according to RECIST v1.1 criteria, the PD date is the date of the imaging examination where the new lesion was first detected.
- For participants who have not experienced PD, the censor date will be determined by the latest imaging examination date within that visit.

For participants who experience PD or death, the PFS is calculated as: PFS (months) = (Date of earliest imaging examination corresponding to PD or date of death - Date of first dose of GFH375 + 1) / 30.4375.

For censored participants, the PFS is calculated as: PFS (months) = (Censor date - Date of first dose of GFH375 + 1) / 30.4375. The censoring rules are shown in Table 7:

Table 7 PFS Censoring Rules

#	Scenario	Event or Censor Date	Outcome
1	No post-baseline tumor assessment, and death occurs within the first two tumor assessment cycles	Date of death	Event
2	No post-baseline tumor assessment, and no death within the first two tumor assessment cycles	Date of first dose of GFH375	Censor
3	With post-baseline tumor assessment, no PD or death	Date of last valid imaging examination	Censor
4	With post-baseline tumor assessment; PD at first assessment, and the assessment date is more than two consecutive assessment cycles after the first dose date	Date of first dose of GFH375	Censor
5	With post-baseline tumor assessment; PD at first assessment, and the date of first progression is less than or equal to two consecutive assessment cycles after the	Date of PD	Event

	first dose		
6	With post-baseline tumor assessment; PD occurs (not at first assessment), but the date of first PD is more than two consecutive assessment cycles after the date of the previous imaging examination	Date of the last valid imaging examination before the date of PD	Censor
7	With post-baseline tumor assessment; PD occurs (not at first assessment), and the date of first PD is less than or equal to two consecutive assessment cycles after the date of the previous imaging examination	Date of PD	Event
8	With post-baseline tumor assessment; death before PD, and the date of death is more than two consecutive assessment cycles after the date of the previous imaging examination	Date of the last valid imaging examination before death	Censor
9	With post-baseline tumor assessment; death before PD, and the date of death is less than or equal to two consecutive assessment cycles after the date of the previous imaging examination	Date of death	Event
10	Received new anti-tumor therapy before PD or death	Date of the last valid imaging examination on or before the day of receiving new anti-tumor therapy (if no imaging examination, then the date of the first dose of GFH375)	Censor

The rule for determining two consecutive missing/invalid tumor assessment visits is as follows:

- If there is no tumor assessment after the first dose of GFH375, two consecutive missing/invalid tumor assessments are defined as 91 days (2*6 weeks + 7-day window) after the first dose of GFH375;
- If there are tumor assessments after the first dose of GFH375:
  - If PD/death occurs within 48 weeks of the first dose of GFH375, two consecutive missing/invalid tumor assessments are 98 days (2*(6 weeks + 7-day window)) after the previous tumor assessment;
  - If PD/death occurs after 48 weeks of the first dose of GFH375, but the last imaging assessment before PD/death occurred within 48 weeks of the first dose of GFH375, two consecutive missing/invalid tumor assessments are 140 days (6 weeks + 7-day window + 12 weeks + 7-day window) after the previous tumor assessment;
  - If PD/death occurs after 48 weeks of the first dose of GFH375, and the last imaging assessment before PD/death also occurred after 48 weeks of the first dose of GFH375, two consecutive missing/invalid tumor assessments are 182 days ([2*(12 weeks + 7-day window)]) after the previous tumor assessment.

3.2.4 Duration of Response (DoR)

For the definition of DoR, see section **4.2.4**. The end date of DoR should be consistent with the date

of PFS event, including PD and death due to any cause. For participants who meet the response criteria and do not experience subsequent PD, the censor date for their DoR is the same as their PFS censor date (see Section 3.2.3).

For participants with BOR of confirmed CR or PR, the DoR is calculated as: DoR (months) = (Date of PD or death or censor date - Date of imaging examination corresponding to the first confirmed CR or PR + 1) / 30.4375. DoR will also be calculated without requiring CR or PR confirmation.

3.2.5 Time to Response (TTR)

For the definition of TTR, see section **4.2.5**.

For participants with BOR of confirmed CR or PR, the TTR is calculated as: TTR (months) = (Date of imaging examination corresponding to the first confirmed CR or PR - Date of first dose of GFH375 + 1) / 30.4375. TTR will also be calculated without requiring CR or PR confirmation.

3.2.6 Overall Survival (OS)

For the definition of OS, see section **4.2.6**.

Overall survival (months) = (Date of death/censor date - Date of first dose of GFH375 + 1) / 30.4375.

3.3 PK Endpoints

The non-compartmental analysis module in Phoenix WinNonlin (version 8.2 or later) software will be used to calculate PK parameters from blood concentration data based on actual sampling times. PK parameters include: C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, T_{max}, T_{last}, $t_{1/2}$, V_z/F, CL/F, λ_z, MRT, $AUC_{\%\_Extrap}$, $C_{trough,ss}$, $C_{max,ss}$, $AUC_{0\text{-}t,ss}$, $AUC_{0\text{-}tau,ss}$, $AUC_{0\text{-}inf,ss}$, CL/F_{ss}, V_z/F_{ss}, R_{ac_Cmax}, $R_{ac\_Ctrough}$, R_{ac_AUC}. For specific definitions and calculation methods of PK parameters, see Table 11 in section **4.4.2**. The planned PK blood sampling time points are shown in Table 8 and Table 9.

Table 8 Phase I Part PK Sample Collection Schedule

Cycle	Day	Planned Sampling Time Point (h)	Time Window
1	1	Predose	-1 h
1	1	1 h postdose	±5 min
1	1	2 h postdose	±10 min
1	1	4 h postdose	±15 min
1	1	6 h postdose	±30 min
1	1	8 h postdose	±30 min
1	1[1]	12 h postdose	±30 min
1	2[2]	24 h postdose	±1 h
1	3[2]	48 h postdose	±2 h
1	4[2]	72 h postdose (collected before dosing on D4)	±3 h
1	8	Predose	-1 h
1	15	Predose	-1 h
1	21	Predose	-1 h
1	21	1 h postdose	±5 min
1	21	2 h postdose	±10min

1	21	4 h postdose	±15 min
1	21	6 h postdose	±30 min
1	21	8 h postdose	±30 min
1	21[1]	12 h postdose	±30 min
1	21[2]	24 h postdose	±1 h
2	10	Predose	-1 h
4	1	Predose	-1 h
5	1	Predose	-1 h
6	1	Predose	-1 h

1. If BID dosing is used, the PK samples at 12 h postdose on C1D1 and C1D21 must be collected before the second dose of the day.
2. Only applicable to QD dosing, collection is required before dosing.

Table 9 Phase II Part PK Sample Collection Schedule

Cycle	**Day**	**Planned Sampling Time Point (h)**	**Time Window**
1	10	Predose	-1 h
1	10	Postdose	2-4 h
2	1	Predose	-1 h
2	1	Postdose	1-3 h
3	1	Predose	-1 h
3	1	Postdose	2-4 h
4	1	Predose	-1 h
5	1	Predose	-1 h
6	1	Predose	-1 h

3.4 Safety Analysis

3.4.1 Study Treatment Exposure

- Actual exposure duration (months): (Date of last dose of GFH375 - Date of first dose of GFH375 + 1) / 30.4375
- Total actual exposure dose (mg): The total dose of GFH375 actually taken by the participant during the study, which is the sum of the total daily actual dose collected on the study drug administration record page in the eCRF.
- Number of dosing days (days): Actual exposure duration (days) - Number of days with zero actual dose (days)
- Average daily exposure (mg/day): Total actual exposure dose (mg) / Number of dosing days (days)
- Actual dose intensity (mg/day): Total actual exposure dose (mg) / Actual exposure duration (days)
- Relative dose intensity (%): 100% * Actual dose intensity (mg/day) / Planned dose intensity (mg/day). The planned dose intensity (mg/day) is the treatment dose group to which the

participant was assigned at enrollment. For example, the planned dose intensity for a participant assigned to the 100 mg QD dose group is 100 mg/day, and the planned dose intensity for a participant assigned to the 300 mg BID dose group is 600 mg/day.

- Dosing compliance (%): 100% * Total actual exposure dose (mg) / Total planned exposure dose (mg). The total planned exposure dose is the sum of the total daily planned dose collected on the study drug administration record page in the eCRF.

3.4.2 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event that was not present before treatment and occurred during the treatment period (defined as from the first dose of the study drug to within 30 days after the last dose) or worsened compared to the pre-treatment state. If the AE start date for a participant is incompletely recorded, the imputation rules in section 2.3.5.3 will be used to determine if it is a TEAE.

The relationship between a TEAE and the study treatment is assessed as related or not related. TEAEs related to the study treatment will be defined as TEAEs that the investigator considers related, probably related, or possibly related to the study treatment; TEAEs unrelated to the study treatment include TEAEs that are not related and unlikely related to the study treatment. If the relationship to the study treatment is missing, it will be considered "related" to the study treatment.

3.4.3 Laboratory Test Indicators

Laboratory tests in this study include hematology, blood chemistry, urinalysis, coagulation function, viral serology tests, and pregnancy tests.

When creating cross-tabulations of the clinical evaluation (normal, abnormal but not clinically significant, abnormal and clinically significant) for each test, the worst post-baseline result is defined as the worst clinical assessment of the participant at all post-baseline visits (including scheduled and unscheduled visits), with results ranked from best to worst as normal, abnormal but not clinically significant, and abnormal and clinically significant.

3.4.4 Vital Signs, Physical Examination, and ECGs

3.4.4.1 Vital Signs

Vital sign assessments include body temperature (°C), pulse (beats/min), respiration (breaths/min), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg).

When creating cross-tabulations of the clinical evaluation of vital signs (normal, abnormal but not clinically significant, abnormal and clinically significant), the worst post-baseline result is defined as the worst clinical assessment of the participant at all post-baseline visits (including scheduled and

unscheduled visits), where "normal" is better than "abnormal but not clinically significant", and "abnormal but not clinically significant" is better than "abnormal and clinically significant". In addition, whether there are abnormal changes in the participant's post-dosing vital sign indicators will be determined according to Table 10.

Table 10 Criteria for Determining Significant Changes in Vital Sign Indicators from Baseline

	Above normal	**Below normal**
Systolic blood pressure (mmHg)	Increase from baseline >=20 and value >=160	Decrease from baseline >=20 and value <=90
Diastolic blood pressure (mmHg)	Increase from baseline >=10 and value >=100	Decrease from baseline >=10 and value <=50
Pulse (beats/min)	Increase from baseline >25% and value >120	Decrease from baseline >25% and value <50
Respiration (breaths/min)	Measured value < 8	Measured value > 35
Body temperature (C)	Measured value >=39.1	-

3.4.4.2 Physical Examination

A complete physical examination includes general condition, skin, neck (thyroid), eyes, ears, nose, throat, chest (including lungs), heart, abdomen, back, lymph nodes, extremities, and vascular and nervous systems; breast, pelvic, rectal, and external genitalia examinations will be performed if clinically indicated. When creating cross-tabulations of the clinical evaluation of physical examinations (normal, abnormal but not clinically significant, abnormal and clinically significant), the worst post-baseline result is defined as the worst clinical assessment of the participant at all post-baseline visits (including scheduled and unscheduled visits), where "normal" is better than "abnormal but not clinically significant", and "abnormal but not clinically significant" is better than "abnormal and clinically significant".

3.4.4.3 ECGs

12-lead ECG assessments include: heart rate (HR), PR interval, QRS interval, QT interval, and QTcF (Fridericia's formula) interval, and overall clinical significance assessment.

If multiple assessments are performed during the same visit, the mean of the quantitative results will be used for analysis. In addition, all 12-lead ECG results will be listed.

When creating cross-tabulations of the clinical evaluation of ECGs (normal, abnormal but not clinically significant, abnormal and clinically significant), the best result of multiple measurements will be used for baseline, and the worst result of multiple measurements will be used for post-baseline visits. The worst post-baseline result is defined as the worst clinical assessment of the participant at all post-baseline visits (including scheduled and unscheduled visits), where "normal" is better than

"abnormal but not clinically significant", and "abnormal but not clinically significant" is better than "abnormal and clinically significant". In addition, whether there are abnormal changes in the participant's post-dosing ECG indicators will be determined according to Table 11.

Table 11 Criteria for Determining Significant Changes in ECG Indicators from Baseline

	Above normal	Below normal
QTcF (ms)	Value >450 and <=480	-
	Value >480 and <=500	-
	Value >=501	-
QTcF (ms) maximum change from baseline	Increase from baseline >30 and <=60	-
	Increase from baseline >60	-
Heart rate (beats/min)	Increase from baseline >25% and value >=100	Decrease from baseline >25% and value <=50
PR (ms)	Increase from baseline >25% and value >200	Decrease from baseline >25% and value <120
QRS (ms)	Increase from baseline >25% and value >110	-

3.4.5 Other Safety Indicators

Other safety indicators include the ECOG score.

3.5 Biomarker Indicators

Biomarker indicators include only CA19-9 for Phase II PDAC participants.

4 Statistical Analysis

Unless otherwise specified, the Phase I and Phase II data of this study will be analyzed separately. The Phase I data will be analyzed and summarized by different dose levels and dosing regimens; the Phase II data will be analyzed and summarized by tumor type. Unless otherwise specified, the same statistical methods will be used to analyze the Phase I and Phase II data.

4.1 Participant General Characteristics

4.1.1 Participant Disposition

Based on all participants who have signed the informed consent form, the number and percentage of participants who have been successfully screened and who failed screening will be summarized, and the reasons for screening failure will be summarized by category. Based on successfully screened participants, the number and percentage of participants in each analysis set will be summarized, and the number and percentage of participants in the Phase I dose-escalation and backfilling cohorts will also be summarized. In addition, based on the FAS, the main reasons for treatment discontinuation and study termination will be summarized by category. The above analyses will be summarized separately for Phase I and Phase II data.

A listing of screening and screening failure reasons, treatment discontinuation, and study termination will be provided for all participants.

4.1.2 Protocol Deviations

To measure how well the protocol is followed, all protocol deviations will be determined before database lock based on the information collected and in conjunction with the protocol requirements. These protocol deviations will be evaluated by the study team and classified as major or minor protocol deviations. Based on successfully screened participants, all major protocol deviations will be summarized.

In addition, based on successfully screened participants, a listing of all protocol deviations will be provided.

4.1.3 Demographics and Baseline Characteristics

Based on the FAS, descriptive statistics will be performed on the participants' demographics and baseline characteristics. The indicators to be counted include:

Demographics

- Sex
- Age
- Age group (<65 and >=65 years, <60 and >=60 years)
- Race: Han, Other
- Body height
- Baseline weight
- Baseline BMI = weight (kg) / (body height (cm) / 100)^2, rounded to 1 decimal place.

Baseline Characteristics

- Baseline tumor diagnosis information
  - Diagnosis name: non-small cell lung cancer (NSCLC), ductal adenocarcinoma of pancreas (PDAC), colorectal cancer (CRC), bile duct cancer, endometrial cancer, other
  - Pathological type (applicable to NSCLC, PDAC, and CRC)
  - Histological grade: G1 (well-differentiated), G2 (moderately differentiated), G3 (poorly differentiated), G4 (undifferentiated), not assessed, other
  - Tumor stage at enrollment
  - TNM stage at enrollment - T stage
  - TNM stage at enrollment - N stage
  - TNM stage at enrollment - M stage

- Presence of metastasis at enrollment
- Metastatic sites at enrollment

- Duration of disease (months) = (Date of first dose of GFH375 - Date of initial pathological diagnosis + 1) / 30.4375
- PD on last line of therapy: Yes, No
- Time from PD on last line of therapy to first treatment (months) = (Date of first dose of GFH375 - Date of last PD + 1) / 30.4375
- Time from PD on last line of therapy to first treatment category: <1 month, 1-3 months, 3-6 months, ≥6 months
- ECOG performance status score: 0, 1
- Smoking history: Never smoked, former smoker, current smoker (Phase II NSCLC participants)
- PD-L1 expression level at baseline (applicable to NSCLC): Low expression (TPS<1%), Medium expression (TPS 1-49%), High expression (TPS>=50%), Non-TPS, Unknown
- KRAS G12D mutation status: Negative, Positive, Unknown
- KRAS G12D mutation rate: <5%, 5-20%, 20-50%, ≥50%
- NRS score: 0, 1, 2, 3

In addition, based on the FAS, a listing of participant demographics and baseline characteristics will be provided.

4.1.4 Prior and Concomitant Medical History

The Medical Dictionary for Regulatory Activities (MedDRA version 26.0 or later) will be used to code the prior and concomitant medical history of participants. Based on the FAS, the number and percentage of participants in each disease category will be summarized by System Organ Class (SOC) and Preferred Term (PT).

Based on the FAS, a listing of all prior and concomitant medical history details will be provided.

4.1.5 Prior and Concomitant Therapies

4.1.5.1 Prior and Concomitant Medications

The World Health Organization Drug Dictionary (WHODrug, version B3 March 1, 2023 or later) will be used to code the prior and concomitant medications of participants. Based on the FAS, the number and percentage of participants will be calculated according to the Anatomical Therapeutic Chemical (ATC) classification level II and Preferred Name (PN).

Based on the FAS, listings of prior and concomitant medication data will be provided.

4.1.5.2 Prior/Concomitant Non-drug Therapies

MedDRA version 26.0 or later will be used to code all prior/concomitant non-drug therapies for participants. Based on the FAS, prior and concomitant non-drug therapies will be summarized by SOC and PT.

In addition, a listing of all prior/concomitant non-drug therapy information will be provided.

4.1.5.3 Prior Anti-tumor Therapy History

Based on the FAS, the following prior anti-tumor therapy categories will be summarized.

- Summary of prior anti-tumor drug therapy history:
  - History of prior anti-tumor therapy: Yes, No
  - Total number of prior lines of drug therapy: 0, 1, 2, 3, ≥4
  - Type of last line of drug therapy: 1st line, 2nd line, 3rd line, 4th line, 5th line, ≥6th line, adjuvant, neoadjuvant, unknown, other
  - Best response to last line of drug therapy: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Assessed (NA), Not Evaluable (NE), Unknown (UN)
  - Reason for discontinuation of last line of drug therapy: Completed treatment plan, PD/relapse, intolerable toxicity, other
  - Time from end of last line of drug therapy to first dose of GFH375 (months)
- Summary of prior anti-tumor surgery history (excluding surgery for diagnostic purposes):
  - History of prior anti-tumor surgery: Yes, No
  - Purpose of last surgery: Palliative, curative, other
  - Time from last surgery to first dose of GFH375 (months)
- Summary of prior anti-tumor radiotherapy history:
  - History of prior anti-tumor radiotherapy: Yes, No
  - Site of prior radiotherapy
  - Purpose of prior radiotherapy: Neoadjuvant, adjuvant, palliative, curative, other
  - Best response to last radiotherapy: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Assessed (NA), Not Evaluable (NE), Unknown (UN)
  - Reason for discontinuation of last radiotherapy: Completed treatment plan, PD/relapse, intolerable toxicity, other
  - Time from end of last radiotherapy to first dose of GFH375 (months)

The World Health Organization Drug Dictionary (WHODrug, version B3 March 1, 2023 or later) will be used to code the prior anti-tumor therapy drugs of participants. Based on the FAS, the number and percentage of participants will be calculated according to the ATC classification level II and PN.

MedDRA version 26.0 or later will be used to code all prior anti-tumor surgery for participants. Based on the FAS, prior anti-tumor surgery will be summarized by SOC and PT. In addition, a listing of all prior anti-tumor therapy related information for participants will be provided.

4.1.5.4 Subsequent Anti-tumor Therapy

Based on the FAS, information related to participants' new anti-tumor therapies will be summarized, including:

- Number and percentage of participants who received subsequent new anti-tumor therapy
- Time from end of study treatment to start of new anti-tumor therapy (months) = (Start date of new anti-tumor therapy - Date of last dose of GFH375 + 1) / 30.4375
- Therapy category: drug therapy, radiotherapy, surgery

The World Health Organization Drug Dictionary (WHODrug, version B3 March 1, 2023 or later) will be used to code the subsequent anti-tumor therapy drugs of participants. Based on the FAS, the number and percentage of participants will be calculated according to the ATC classification level II and PN.

MedDRA version 26.0 or later will be used to code all subsequent anti-tumor surgery for participants. Based on the FAS, subsequent anti-tumor surgery will be summarized by SOC and PT.

In addition, a listing of detailed information on participants' subsequent anti-tumor therapies will be provided.

4.2 Efficacy Analysis

4.2.1 Objective Response Rate (ORR)

4.2.1.1 Primary Analysis

The same analysis method will be used for Phase I and Phase II participants.

Definition of Estimand:

- **Treatment:** GFH375.
- **Study Population:** Participants with advanced solid tumors with KRAS G12D mutation (FAS).
- **Variable:** Whether confirmed CR or PR is achieved, as assessed by RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant will be considered a non-responder. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the

results will be based on the investigator's assessment.

- **Intercurrent Events and Handling Strategy:**

Intercurrent Event		**Handling Strategy**
Inc1	Start of new anti-tumor therapy	On-treatment strategy (Assessment results after the start of anti-tumor therapy will not be included in the analysis)

- **Population-level Summary:** ORR and its 90% and 95% CIs.

Analysis Method of Estimand:

The BOR of participants will be summarized, the number of participants who have achieved confirmed CR or PR and the ORR of participants will be summarized, and the Clopper-Pearson exact method will be used to estimate the 90% and 95% CIs for the ORR. At the same time, BOR and ORR will be summarized without requiring confirmation of CR or PR, and the 90% and 95% CI for ORR will be provided. BOR and ORR will be analyzed based on participants with measurable lesions at baseline as assessed by the investigator or BIRC. In addition, a swimmer plot of efficacy assessment results during treatment for all participants, a waterfall plot of the minimum percentage change from baseline in the sum of diameters of target lesions, and a spider plot of the percentage change from baseline in the sum of diameters of target lesions at different time points during treatment for all participants will be generated.

For NSCLC and PDAC participants, the consistency of BOR results between BICR and investigator assessments will be summarized.

4.2.1.2 Supportive Analysis

1) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC participants in the FAS.
- **Variable:** Whether confirmed CR or PR is achieved, as assessed by the investigator according to RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant will be considered a non-responder.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

2) Adjustments to the study population

- **Study Population:** Phase II participants with advanced solid tumors with KRAS G12D mutation (PPS).
- **Other Attributes:** Same as the primary analysis.

Except for plotting, the analysis method is the same as the primary analysis.

3) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC participants in the Phase II PPS.
- **Variable:** Whether confirmed CR or PR is achieved, as assessed by the investigator according to RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant will be considered a non-responder.
- **Other Attributes:** Same as the primary analysis.

Except for plotting, the analysis method is the same as the primary analysis.

4.2.1.3 Subgroup Analysis

For Phase II PDAC and NSCLC participants, a subgroup analysis of ORR will be performed based on the results assessed by BICR where CR/PR requires confirmation, and the results of the subgroup analysis will be displayed in a forest plot. For specific subgroups, see section **2.5**.

4.2.2 Disease Control Rate (DCR)

4.2.2.1 Primary Analysis

The same analysis method will be used for Phase I and Phase II participants.

Definition of Estimand:

- **Variable:** The percentage of participants who have achieved confirmed CR or PR, SD, as assessed by RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant will be considered as not having achieved CR/PR/SD. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Population-level Summary:** DCR and its 90% and 95% CIs.
- **Other Attributes:** Same as the estimand for the primary analysis of objective response rate.

Analysis Method of Estimand:

The number of participants who have achieved confirmed CR or PR, SD in BOR, and the DCR will be summarized. The Clopper-Pearson exact method will be used to estimate the two-sided 90% and 95% CI for the DCR. At the same time, without requiring confirmation of CR or PR, the number of participants who have achieved CR or PR, SD in BOR, and the DCR will be summarized, and the 90% and 95% CI for the DCR will be provided. BOR and DCR will be analyzed based on participants with measurable lesions at baseline as assessed by the investigator or BIRC.

4.2.2.2 Supportive Analysis

1) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC participants in the FAS.
- **Variable:** Whether confirmed CR or PR, SD is achieved, as assessed by the investigator according to RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant will be considered as not having achieved CR/PR/SD.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

2) Adjustments to the study population

- **Study Population:** Phase II participants with advanced solid tumors with KRAS G12D mutation (PPS).
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

3) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC participants in the Phase II PPS.
- **Variable:** Whether confirmed CR or PR, SD is achieved, as assessed by the investigator according to RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant will be considered as not having achieved CR/PR/SD.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

4.2.3 Progression-Free Survival (PFS)

4.2.3.1 Primary Analysis

The same analysis method will be used for Phase I and Phase II participants.

Definition of Estimand:

- **Treatment:** GFH375.
- **Study Population:** Participants with advanced solid tumors with KRAS G12D mutation (FAS).
- **Variable:** Time from the first dose of GFH375 to the first occurrence of PD or death from any cause, whichever occurs first. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Intercurrent Events and Handling Strategy:**

Intercurrent Event		**Handling Strategy**
Inc2	Participants who have received new anti-tumor therapy without PD or death.	Hypothetical strategy (Censored at the date of the last valid imaging

		examination before the start of new anti-tumor therapy)
Inc3	The date of PD or death is more than two consecutive assessment cycles after the date of the previous imaging examination	Hypothetical strategy (Censored at the date of the last valid imaging examination before two or more consecutive missing assessments; if there are no prior valid imaging examination results, censored at the date of the first dose of GFH375)

- **Population-level Summary:** Quartiles of PFS and PFS rates at different time points.

Analysis Method of Estimand:

The occurrence of events and censoring for participants will be summarized. The Kaplan-Meier method will be used to estimate the quartiles of PFS and the two-sided 90% and 95% CI estimated using the Brookmeyer and Crowley method, and the PFS rate and its two-sided 90% and 95% CI at each time point will be calculated. The Kaplan-Meier survival curve will be plotted.

In addition, the Reverse Kaplan-Meier method will be used to estimate the median follow-up time for PFS and the two-sided 90% and 95% CI will be estimated using the Brookmeyer and Crowley method. The follow-up time for PFS refers to the time from the first dose of GFH375 to the last tumor assessment. If PD or death occurs, the PFS follow-up time will be censored at the date of PD or death (whichever occurs first).

For the Phase I stage, when the sample size of the analysis group is less than 10, PFS will be listed individually for each participant and will not be analyzed using the Kaplan-Meier method.

4.2.3.2 Supportive Analysis

1) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC participants in the FAS.
- **Variable:** Based on the investigator's assessment, the time from the first dose of GFH375 to the first occurrence of PD or death from any cause, whichever occurs first.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

4.2.4 Duration of Response (DoR)

4.2.4.1 Primary Analysis

Definition of Estimand:

- **Treatment:** GFH375.
- **Study Population:** Participants in the FAS who have achieved confirmed CR or PR in BOR. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be

based on the investigator's assessment.

- **Variable:** Time from the first achievement of CR or PR to the first occurrence of PD or death from any cause, whichever occurs first. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Intercurrent Events and Handling Strategy:** Same as for PFS.
- **Population-level Summary:** Quartiles of DoR and DoR rates at different time points.

Analysis Method of Estimand:

The occurrence of events and censoring for participants will be summarized. The Kaplan-Meier method will be used to estimate the quartiles of DoR and the two-sided 90% and 95% CI estimated using the Brookmeyer and Crowley method, and the DoR rate and its two-sided 90% and 95% CI at each time point will be calculated. The Kaplan-Meier survival curve will be plotted. DoR will be analyzed based on participants with measurable lesions at baseline as assessed by the investigator or BIRC.

For the Phase I stage, when the sample size of the analysis group is less than 10, DoR will be listed individually for each participant and will not be analyzed using the Kaplan-Meier method.

4.2.4.2 Supportive Analysis

1) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC participants in the FAS who have achieved confirmed CR or PR in BOR, based on the investigator's assessment.
- **Variable:** Based on the investigator's assessment, the time from the first achievement of CR or PR to the first occurrence of PD or death from any cause, whichever occurs first.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

2) Adjustments to the study population

- **Study Population:** Participants in the FAS who have achieved CR or PR in BOR, where CR and PR do not require confirmation according to RECIST 1.1 rules. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

3) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC participants in the FAS who have achieved CR or PR in BOR based on the investigator's assessment, where CR and PR do not require confirmation according to RECIST 1.1 rules.
- **Variable:** Based on the investigator's assessment, the time from the achievement of CR or PR to the first occurrence of PD or death from any cause, whichever occurs first.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

4.2.5 Time to Response (TTR)

4.2.5.1 Primary Analysis

Definition of Estimand:

- **Treatment:** GFH375.
- **Study Population:** Participants in the FAS who have achieved confirmed CR or PR. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Variable:** Time from the start of study drug administration to the first achievement of confirmed CR or PR, based on the earliest time CR or PR is observed. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Intercurrent Events and Handling Strategy:** Same as for ORR.
- **Population-level Summary:** Mean, standard deviation, median, Q1, Q3, minimum, and maximum.

Analysis Method of Estimand:

A descriptive analysis of TTR will be performed, including the number of participants who have achieved CR or PR, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

For the Phase I stage, when the sample size of the analysis group is less than 10, TTR will be listed individually for each participant.

4.2.5.2 Supportive Analysis

1) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC participants in the FAS who have achieved

confirmed CR or PR in BOR, based on the investigator's assessment.

- **Variable:** Based on the investigator's assessment, the time from the start of study drug administration to the first achievement of confirmed CR or PR, based on the earliest time CR or PR is observed.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

2) Adjustments to the study population

- **Study Population:** Participants in the FAS who have achieved CR or PR in BOR, where CR and PR do not require confirmation according to RECIST 1.1 rules. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

3) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC participants in the FAS who have achieved CR or PR in BOR based on the investigator's assessment, where CR and PR do not require confirmation according to RECIST 1.1 rules.
- **Variable:** Based on the investigator's assessment, the time from the start of study drug administration to the first achievement of confirmed CR or PR, based on the earliest time CR or PR is observed.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

4.2.6 Overall Survival (OS)

Definition of Estimand:

- **Treatment:** GFH375.
- **Study Population:** Participants with advanced solid tumors with KRAS G12D mutation (FAS).
- **Variable:** Time from the start of study drug administration to death from any cause. For participants in whom a death event is not observed, they will be censored at the last known date of survival.
- **Intercurrent Events and Handling Strategy:**

Intercurrent Event		Handling Strategy
Inc1	Start of new anti-tumor therapy	Treatment policy strategy (If death occurs, it will be treated as a death event; if no death, it will be censored at the last known date of survival)

- **Population-level Summary:** Quartiles of OS and PFS rates at different time points.

Analysis Method of Estimand:

The occurrence of events and censoring for participants will be summarized. The Kaplan-Meier method will be used to estimate the quartiles of OS and the two-sided 90% and 95% CI estimated using the Brookmeyer and Crowley method, and the OS rate and its two-sided 90% and 95% CI at each time point will be calculated. The Kaplan-Meier survival curve will be plotted.

In addition, the Reverse Kaplan-Meier method will be used to estimate the median OS follow-up time and the two-sided 90% and 95% CI will be estimated using the Brookmeyer and Crowley method. OS follow-up time refers to the time from the start of study drug administration to the last known date of survival. If death occurs, the OS follow-up time will be censored at the date of death.

For the Phase I stage, when the sample size of the analysis group is less than 10, OS will be listed individually for each participant and will not be analyzed using the Kaplan-Meier method.

4.3 Safety Analysis

DLT analysis will be based on the DDS, and all other safety analyses will be based on the SS.

4.3.1 Drug Exposure

Descriptive statistics will be performed on the actual exposure duration (months), total actual exposure dose (mg), number of dosing days (days), average daily exposure (mg/day), actual dose intensity (mg/day), relative dose intensity (%), and dosing compliance (%) of GFH375. Relative dose intensity and dosing compliance will be categorized and summarized as < 80%, 80% to 120%, and >120%.

The number and percentage of participants who have planned dose adjustments and dose reductions will be summarized, and the corresponding reasons will be provided. A planned dose adjustment refers to a change in the planned dose compared to the previous planned dose. A planned dose reduction refers to a planned dose that is less than the previous non-zero planned dose (i.e., the comparison between two planned doses does not consider drug holidays in between), and the reduced planned dose is not zero. The number and percentage of participants whose actual administered dose is inconsistent with the planned dose will be summarized, and the corresponding reasons will be provided.

The number of occurrences of planned dose reductions and planned dose interruptions will be summarized, and the number and percentage of participants for different numbers of occurrences will

also be summarized.

The GFH375 medication status of participants will be listed.

4.3.2 Dose-Limiting Toxicities (DLTs)

The number and percentage of participants who have experienced DLTs in the Phase I part will be summarized, and the types of DLTs will also be summarized.

DLTs will be coded using MedDRA version 26.0 or later. The number and percentage of DLTs will be summarized by SOC, PT, and severity.

Based on a prior non-informative probability distribution of $beta$ (0.05, 0.05), the posterior probability distribution for the DLT rate in each group is $beta$ $(y_j + 0.05, n_j - y_j + 0.05))$, and the posterior mean DLT rate for each group is then calculated. The formula for calculating the posterior mean DLT rate is $p_j = \frac{y_j+0.05}{n_j+0.1}$, where n_j is the number of participants in each group, and y_j is the number of participants who have experienced a DLT in each group.

The DLT rate and the posterior mean DLT rate for each group will be estimated using isotonic regression, where the weight for the DLT rate is the number of participants in each group, and the weight for the posterior mean DLT rate is the reciprocal of the posterior distribution variance (according to the BOIN design)$w_j = \frac{(n_j+0.1)^2\ (n_j+0.1+1)}{(y_j+0.05)(n_j-y_j+0.05)}$, where n_j is the number of participants in each group, and y_j is the number of participants who have experienced a DLT in each group.

All DLTs will be listed.

4.3.3 Adverse Events

AEs will be coded using MedDRA version 26.0 or later, and the severity of AEs will be graded based on NCI CTCAE V5.0. TEAEs will be summarized in tables and all AEs will be listed.

The number and percentage of participants will be summarized based on the following categories:

- TEAE
  - Any TEAE
  - TEAE of CTCAE Grade 3 or higher
  - TEAE leading to dose reduction of GFH375
  - TEAE leading to dose interruption of GFH375
  - TEAE leading to discontinuation of GFH375
  - Treatment-emergent serious adverse event (TESAE)
  - TEAE of CTCAE=Grade 5

- TEAE meeting Hy's Law criteria

- TEAE related to GFH375 (TRAE)
  - Any TRAE
  - TRAE of CTCAE Grade 3 or higher
  - TRAE leading to dose reduction of GFH375
  - TRAE leading to dose interruption of GFH375
  - TRAE leading to discontinuation of GFH375
  - Treatment-related serious adverse event during treatment (TRSAE)
  - TRAE of CTCAE=Grade 5
  - TRAE meeting Hy's Law criteria

The number and percentage of participants who have experienced the following types of events will be summarized by SOC, PT, and severity:

- TRAE
- TEAE
- TEAE of CTCAE Grade 3 or higher
- TRAE of CTCAE Grade 3 or higher
- TESAE
- TRSAE
- TEAE leading to dose reduction of GFH375
- TRAE leading to dose reduction of GFH375
- TEAE leading to dose interruption of GFH375
- TRAE leading to dose interruption of GFH375
- TEAE leading to discontinuation of GFH375
- TRAE leading to discontinuation of GFH375
- TEAE meeting Hy's Law criteria
- TRAE meeting Hy's Law criteria

The number and percentage of participants who have experienced the following types of events will be summarized by SOC and PT:

- TEAE
- TRAE
- TESAE of CTCAE Grade 3 or higher
- TRSAE of CTCAE Grade 3 or higher

- TEAE of CTCAE Grade 3 or higher leading to dose reduction of GFH375
- TRAE of CTCAE Grade 3 or higher leading to dose reduction of GFH375
- TEAE of CTCAE Grade 3 or higher leading to dose interruption of GFH375
- TRAE of CTCAE Grade 3 or higher leading to dose interruption of GFH375
- TEAE of CTCAE Grade 3 or higher leading to discontinuation of GFH375
- TRAE of CTCAE Grade 3 or higher leading to discontinuation of GFH375
- TEAE of CTCAE=Grade 5
- TRAE of CTCAE=Grade 5

The number and percentage of participants who have experienced the following types of events will be summarized by PT:

- TEAE with an incidence of ≥10% in any group
- TRAE with an incidence of ≥10% in any group
- TEAE of CTCAE Grade 3 or higher with an incidence of ≥5% in any group
- TRAE of CTCAE Grade 3 or higher with an incidence of ≥5% in any group

The number and percentage of participants who have experienced hepatotoxicity will be summarized by PT, including alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic function abnormal, hyperbilirubinaemia, liver injury, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, and blood lactate dehydrogenase increased.

When counting the number of AE occurrences, if a participant experiences the same AE (same PT) more than once, it will be counted only once under that PT. Similarly, if a participant experiences more than one AE in the same SOC classification, it will be counted only once under that SOC classification. When summarizing AEs by severity, if the same AE occurs more than once in the same participant during the study, the one with the highest grade will be used for calculation.

All AEs will be presented in a listing. In addition, SAEs and AEs with an outcome of death will be listed separately.

4.3.4 Laboratory Tests

Viral serology test and pregnancy test results will only be listed. For other test items, the results from each visit will be analyzed with descriptive statistics and listed.

For quantitative test results, summaries will be provided for each scheduled visit and their change from baseline, calculating statistics such as number of participants, mean, standard deviation, median, minimum, and maximum. For qualitative results of clinical assessments, a cross-tabulation will be

used to show the change of the worst post-baseline result relative to the baseline result and the result at the last post-baseline visit.

For laboratory test parameters whose abnormalities can be graded for severity according to NCI CTCAE (version 5.0) (Grade 0 to 4, where Grade 0 indicates normal), such as hematology, blood chemistry, and coagulation function, a cross-tabulation will be used to summarize the maximum change in CTCAE grade from baseline and the result at the last post-baseline visit. The increase in CTCAE grade for laboratory test parameters post-baseline will be summarized. See Appendix 1 for the CTCAE grading rules for laboratory test parameters to be evaluated. For quantitative parameters from hematology, blood chemistry, urinalysis, and coagulation function that do not have a corresponding CTCAE grade, they will be categorized according to their normal range (below normal, normal, above normal, below & above normal [both below and above normal values occurred post-baseline]). A cross-tabulation will be used to summarize the change of the worst post-baseline situation from baseline and the result at the last post-baseline visit.

Based on the liver function-related test results from blood chemistry, the number and percentage of participants in the following categories post-baseline will be summarized (ULN: upper limit of normal):

ALT > 3 * ULN, ALT > 5 * ULN, ALT > 10 * ULN, ALT > 20 * ULN;

AST > 3 * ULN, AST > 5 * ULN, AST > 10 * ULN, AST > 20 * ULN;

(ALT or AST) > 3 * ULN, (ALT or AST) > 5 * ULN, (ALT or AST) > 10 * ULN, (ALT or AST) > 20 * ULN;

TBIL > 2 * ULN;

AKP > 1.5 * ULN;

Concurrent ALT > 3 * ULN and TBIL > 2 * ULN;

Concurrent AST > 3 * ULN and TBIL > 2 * ULN;

Concurrent (ALT or AST) > 3 * ULN and TBIL > 2 * ULN;

Concurrent (ALT or AST) > 3 * ULN and TBIL > 1.5 * ULN;

Concurrent (ALT or AST) > 3 * ULN, TBIL > 2 * ULN, and AKP ≥ 2 * ULN;

Concurrent (ALT or AST) > 3 * ULN, TBIL > 2 * ULN, and (AKP < 2 * ULN or missing).

4.3.5 Vital Signs, Physical Examination, and ECGs

4.3.5.1 Vital Signs

The observed values of vital sign test items at each scheduled visit and their change from baseline will be summarized. Based on the overall clinical evaluation of vital signs (normal, abnormal but not

clinically significant, abnormal and clinically significant), a cross-tabulation of the worst post-baseline evaluation (including unscheduled visits) and the last visit relative to baseline will be summarized.

In addition, the number and percentage of participants with abnormal changes in post-dosing ECG indicators (Table 10) will be summarized (based on the worst post-dosing result).

In addition, all vital signs measurement results for participants will be listed.

4.3.5.2 Physical Examination

For the clinical evaluation results of physical examinations (normal, abnormal but not clinically significant, abnormal and clinically significant), a cross-tabulation of the worst post-baseline result (including unscheduled visits) and the change from baseline result at the last visit will be created.

In addition, all physical examination results for participants will be listed.

4.3.5.3 ECGs

For quantitative test results, the observed values at each scheduled visit and their change from baseline will be summarized. For clinical significance (normal, abnormal but not clinically significant, abnormal and clinically significant), a cross-tabulation of the worst post-baseline assessment result (including scheduled and unscheduled visits) and the result relative to the baseline examination at the last visit will be created.

In addition, the number and percentage of participants with abnormal changes in post-dosing ECG indicators (Table 11) will be summarized (based on the worst post-dosing result).

All ECG results will be presented in listings.

4.3.6 Death

The number of deceased participants and the cause of death will be summarized by study observation period (during the study, on-treatment period, post-treatment period), and the death cases will be listed.

Deaths during the study are classified by study observation period as:

- Death during the study: Death occurring from the first study treatment to the end of the study (including survival follow-up).
- On-treatment death: Death occurring from the first study treatment to within 30 days after the last study drug administration;
  - Death after initiation of new anti-tumor therapy.
- Post-treatment death: Death occurring from more than 30 days after the last study drug administration until the end of the study.

4.3.7 Other Safety Analyses

For ECOG performance status, a cross-tabulation of the status at each scheduled visit, the worst post-baseline assessment result (including scheduled and unscheduled visits), and the result at the last visit relative to the baseline examination will be created. In addition, all ECOG score results for participants will be listed.

4.4 PK Analysis

PK analysis will be based on the PKAS. Data below the lower limit of quantification (LLOQ) will be marked as BQL.

PK analysis will be handled according to the following rules:

- PK parameters will be calculated based on actual sampling times;
- All blood drug concentration values below the lower limit of quantification (LLOQ) will be treated as "0" before T_{max} and as missing after T_{max} for PK parameter calculation and plotting; however, for descriptive statistical analysis, all will be treated as "0", and the number of BQLs at each time point will be noted;
- When calculating descriptive statistics for concentrations at each time point, out-of-window data will not be included; statistics such as mean, standard deviation, and coefficient of variation will only be calculated if at least two-thirds of the individual data at a specific sampling time point are at or above BQL, otherwise the descriptive statistics for that sampling point will not be calculated and will be represented as "NC". When plotting the mean drug concentration-time curve, out-of-window data will not be included; if at least one-third of the individual data at a specific post-dose sampling time point are below BQL, that point will not be displayed on the graph.

For each PK sampling cycle, if a participant meets the following conditions, the blood drug concentration data for that PK sampling cycle will not be included in the summary analysis (including descriptive statistics by group and plotting of the mean blood drug concentration-time curve), but individual blood drug concentration-time curves still need to be plotted and listed. PK parameters calculated based on this blood drug concentration data will not be included in the analysis, but will only be listed and marked.

- If the participant experiences vomiting within 3 hours after taking the investigational drug;
- Other protocol deviations or AEs that significantly affect the PK evaluation.

4.4.1 Blood Drug Concentration Analysis

In the PK analysis, concentrations will be as provided by the laboratory. Concentration data and units

will be presented as the raw data received from the laboratory.

Descriptive statistics will be performed on the GFH375 blood drug concentration data according to the sampling times specified in the protocol. The Phase I summary will be presented by different dose groups and dosing frequencies, and the Phase II summary will be presented by different tumor types, including number of participants, number of BQLs, arithmetic mean, standard deviation, arithmetic coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric coefficient of variation (GCV%).

Drug concentration-time curves for Phase I blood drug concentration data will be plotted, including drug concentration-time curves after the first dose and multiple doses. Mean blood drug concentration-time curves (linear and semi-logarithmic) will be plotted based on planned blood sampling time points; individual blood drug concentration-time curves (linear and semi-logarithmic) will be plotted based on actual blood sampling time points.

The formula for calculating GCV% is as follows:

$$GCV\%=\sqrt{\exp^{(\ln(\text{Geo SD}))^2}-1}\times 100\%$$

The reference SAS program for GCV% is as follows:

GCV%=sqrt(exp(SD**2)-1)*100, where SD is the standard deviation of the natural logarithm of the original data.

The blood drug concentration-time data will be listed for all participants, and BQL will be marked in the listing.

4.4.2 PK Parameter Analysis

PK parameter analysis is only for Phase I data. PK parameters will be summarized and analyzed by different dose groups and dosing frequencies, including number of participants and missing cases, arithmetic mean, standard deviation, arithmetic coefficient of variation (CV%), median, Q1, Q3, minimum, maximum, as well as geometric mean and geometric coefficient of variation (GCV%). However, T_{max} and T_{last} will only be described by number of participants and missing cases, median, Q1, Q3, minimum, and maximum. For specific PK parameters, see Table 12.

Table 12 List of PK Parameters

Parameter	WNL Term	Definition	Calculation Method
C_{max}	Cmax	Maximum concentration	Obtained directly from observed data
AUC_{0-t}	AUC_{last}	Area under the drug concentration-time curve from time 0 to the last measurable concentration collection time t	Linear-up/log-down trapezoidal method†

$AUC_{0\text{-}tau}$	$AUC_{0\text{-}12h}$ or $AUC_{0\text{-}24h}$	Area under the drug concentration-time curve from time 0 to 12 h (BID group) or 24 h (QD group)	Linear-up/log-down trapezoidal method†
$AUC_{0\text{-}inf}$	AUCINF_obs	Area under the drug-time curve from time 0 extrapolated to infinity	$AUC_{0\text{-}inf} = AUC_{0\text{-}t} + C_t/\lambda_z$, where C_t is the blood drug concentration corresponding to the last measurable time point
T_{max}	T_{max}	Time to maximum concentration	Obtained directly from observed data
T_{last}	T_{last}	Time of last measurable concentration	Obtained directly from observed data
$t_{1/2}$	HL_Lambda_z	Elimination half-life	$t_{1/2} = \ln(2)/\lambda_z$, Note: Only data points in the log-linear decline phase can be used in the regression
V_z/F	Vz_F_obs	Apparent volume of distribution	$V_z/F = Dose/(AUC_{0\text{-}inf} * \lambda_z)$
CL/F	Cl_F_obs	Apparent clearance	Single dose: $CL/F = Dose/AUC_{0\text{-}inf}$
λ_z	Lambda_z	Terminal elimination rate constant	Calculated by linear regression of the elimination phase of the log concentration-time curve
MRT	MRTINF_obs	Mean residence time	$MRT=AUMC_{0\text{-}inf} / AUC_{0\text{-}inf}$
$AUC_{\%\_Extrap}$	AUC_%Extrap_obs	Percentage of area extrapolated	$AUC_{\%\_Extrap} = (AUC_{0\text{-}inf} - AUC_{0\text{-}t}) / AUC_{0\text{-}inf} *100\%$
$C_{trough,ss}$	C_{tau}	Steady-state trough concentration	Obtained directly from observed data
$C_{max,ss}$	C_{max}	Steady-state maximum concentration	Obtained directly from observed data
$AUC_{0\text{-}t,ss}$	AUC_{last}	Area under the steady-state plasma concentration-time curve from time zero to the time of the last quantifiable concentration (C0-t)	Linear-up/log-down trapezoidal method†
$AUC_{0\text{-}tau,ss}$	AUC_TAU	Area under the plasma concentration-time curve from time zero to tau, where tau is the dosing interval.	Linear-up/log-down trapezoidal method†
$AUC_{0\text{-}inf,ss}$	AUCINF_obs	Area under the steady-state plasma concentration-time curve from time zero extrapolated to infinity	$AUC_{0\text{-}inf,ss} = AUC_{0\text{-}t,ss} + C_{ss,last}/\lambda_z$, where $C_{ss,last}$ is the plasma concentration corresponding to the last measurable time point (T_{last})
$T_{max,ss}$	T_{max}	Time to steady-state peak concentration	Obtained directly from observed data
CL/F_{ss}	CLss_F	Steady-state apparent clearance	$CL/F_{ss} =Dose/ AUC_{0\text{-}tau,ss}$
V_z/F_{ss}	V_z_F	Steady-state apparent volume of distribution	$V_z/F_{ss} = MRT_{0\text{-}inf}* CL/F_{ss}$
R_{ac_Cmax}	R_{acCmax}	Accumulation ratio based on C_{max}	$R_{ac\_Cmax} = C_{max,ss}$ (multiple doses)/C_{max} (first dose)

$R_{ac\_Ctrough}$	$R_{acCtrough}$	Accumulation ratio based on C_{trough}	$C_{trough,ss}$ (multiple doses)/C_{trough} (first dose)
R_{ac_AUC}	R_{acAUC}	Accumulation ratio based on $AUC_{0\text{-}tau}$	R_{ac_AUC} = $AUC_{0\text{-}tau}$ (multiple doses)/$AUC_{0\text{-}tau}$ (first dose)

†For the ascending concentration phase, the area under the curve will be calculated using the linear trapezoidal rule, and for the descending concentration phase, the log-linear trapezoidal rule will be used (linear-up/log-down trapezoidal rule).

The calculation of λ_z follows the following rules:

- The elimination phase has at least 3 measurable sampling points (the first sample point must be after T_{max});
- The concentration is decreasing (λ_z must be a positive value);
- Adjusted coefficient of determination (R^2_{adj}) ≥ 0.8;
- $AUC_{\%\_Extrap}$ ≤20%.

When $R^2_{adj} < 0.8$ or $AUC_{\%\_Extrap} > 20\%$, or when the λ_z value cannot be accurately calculated (missing), λ_z and other related PK parameters ($t_{1/2}$, $AUC_{0\text{-}inf}$, CL/F, V_z/F, $AUC_{\%\_Extrap}$, MRT) will not be summarized, but will still be presented in the listing and marked.

4.4.3 Dose Proportionality Analysis

Dose proportionality analysis is only for Phase I data. Using the Power model, a linear regression model will be fitted after natural logarithmic transformation of the PK parameters (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$) and dose for both single and multiple doses to analyze the linear relationship between drug exposure and dose.

The formula for the Power model is:

$\ln [PK]=\alpha+\beta*\ln [Dose] +\varepsilon$

where PK represents the PK parameters above, α is the intercept, β is the slope, ε is the random error, and Dose is the administered dose group.

The reference SAS program is as follows:

```
proc glm data = pkdata;
model ln[pk] = ln[dose] / clparm alpha=0.1;
ods output parameterestimates=parameterestimates;
run;
```

The CI method will be used to evaluate the linear relationship between PK parameters and dose. The 90% CI of the slope (β) will be compared with the decision region. If the 90% CI of β falls completely within the decision region, the linear relationship between the PK parameter and dose is considered

to be established, i.e.:

$$1+\frac{\ln(\theta_L)}{\ln(r)} < \beta < 1+\frac{\ln(\theta_H)}{\ln(r)}$$

where θ_L=0.8, θ_H=1.25, and r is the ratio of the highest dose group to the lowest dose group.

4.5 Biomarker Analysis

For Phase II PDAC participants, CA19-9 will be summarized. For quantitative indicators, the number of participants, mean, standard deviation, median, minimum, and maximum will be summarized; for categorical indicators, the number of participants and percentage for each category will be summarized.

CA19-9 will be presented in a listing.

5 Interim Analysis and Safety Monitoring Committee (SMC)

5.1 Interim Analysis

A futility interim analysis will be performed separately for NSCLC, PDAC, and CRC. For each tumor type, it is planned to be conducted when approximately 35 participants (including Phase I participants treated with RP2D and Phase II participants) have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early. Due to practical clinical operational reasons, the number of participants at the time of the interim analysis is allowed to differ from the planned number. During the interim analysis, enrollment will not be stopped.

At the interim analysis, a futility analysis will be conducted on ORR for NSCLC, PDAC, and CRC, respectively, using the Bayesian predictive probability method. Early termination of the study for the corresponding tumor type due to lack of efficacy evidence is permitted (but not mandatory).

The predictive probability of success (PPoS) will be calculated based on the observed number of participants who have achieved a response (CR/PR). If the PPoS is < 0.2, early termination of enrollment due to lack of efficacy evidence is permitted (but not mandatory). The corresponding termination criteria for PPoS < 0.2 are shown in the table below:

Tumor Type	Number of Participants	Recommended to terminate the cohort when the number of responders is ≤
NSCLC	20 ~ 21	3
	22 ~ 25	4
	26 ~ 29	5
	30 ~ 33	6
	34 ~ 37	7
	38 ~ 41	8
	42 ~ 45	9
PDAC	25 ~ 26	2
	27 ~ 33	3
	34 ~ 39	4

	40 ~ 45	5
CRC	20 ~ 23	1
	24 ~ 30	2
	31 ~ 37	3
	38 ~ 43	4
	44 ~ 48	5

*Number of participants: Number of Phase I participants treated with RP2D and Phase II participants who have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early (at least one of the two is met).

The interim analysis planned above is not mandatory. If there is sufficient comprehensive safety and efficacy data to support it before the planned time point for the interim analysis, this interim futility analysis may be omitted.

5.2 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) composed of investigators and the sponsor will be established for this study. The SMC will continuously review safety data from the first dose of the first participant until the end of the study. During the dose-escalation and expansion phases, SMC members will review safety data, PK data, etc., to decide on enrollment for the next dose or to explore other potential dose cohorts, and to recommend the appropriate RDE and RP2D.

During the study, if both the investigator and the sponsor believe that a participant is at a safety risk or has reached the limit of tolerability, dose escalation or study treatment will be stopped immediately. For details, please refer to the SMC charter.

6 Modifications to the Original Analysis Plan

None.

7 References

None.

Appendix 1 CTCAE (V5.0) Grading Rules for Laboratory Test Parameters to be Evaluated

Parameter	CTCAE V5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin concentration (HGB)	Anemia	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-
Haemoglobin concentration (HGB)	Hemoglobin increased	Increase of 0 - 2 g/dL relative to ULN	Increase of 2 - 4 g/dL relative to ULN	Increase of >4 g/dL relative to ULN	-
White blood cell count (WBC)	Leukocyte count decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000 - 1000/mm^3; <2.0 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
White blood cell count (WBC)	Leukocytosis	-	-	>100,000/mm^3;	
Lymphocyte (LY) count	Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
Lymphocyte (LY) count	Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3, >4 x 10^9/L - 20 x 10^9/L	>20,000/mm^3; >20 x 10^9/L	-
Neutrophil count (ANC)	Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000 - 500/mm^3; <1.0 - 0.5 x 10^9 /L	<500/mm^3; <0.5 x 10^9 /L
Platelet count (PLT)	Thrombocyte count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9 /L	<25,000/mm^3; <25.0 x 10^9 /L
Alanine aminotransferase (ALT)	Alanine aminotransferase increased	>ULN - 3.0 × ULN (if baseline normal); 1.5-3.0 × baseline (if baseline abnormal)	>3.0 - 5.0 × ULN (if baseline normal); 3.0-5.0 × baseline (if baseline abnormal)	>5.0 - 20.0 × ULN (if baseline normal); 5.0 - 20.0 × baseline (if baseline abnormal)	>20.0 × ULN (if baseline normal); >20.0 × baseline (if baseline abnormal)
Aspartate aminotransferase (AST)	Aspartate aminotransferase increased	>ULN - 3.0 × ULN (if baseline normal); 1.5-3.0 × baseline (if baseline abnormal)	>3.0 - 5.0 × ULN (if baseline normal); 3.0-5.0 × baseline (if baseline abnormal)	>5.0 - 20.0 × ULN (if baseline normal); 5.0 - 20.0 × baseline (if baseline abnormal)	>20.0 × ULN (if baseline normal); >20.0 × baseline (if baseline abnormal)
Alkaline phosphatase (ALP)	Alkaline phosphatase increased	>ULN - 2.5 × ULN (if baseline normal); 2.0-2.5 × baseline (if baseline abnormal)	>2.5 - 5.0 × ULN (if baseline normal); 2.5 - 5.0 × baseline (if baseline abnormal)	>5.0 - 20.0 × ULN (if baseline normal); 5.0 - 20.0 × baseline (if baseline abnormal)	>20.0 × ULN (if baseline normal); >20.0 × baseline (if

Parameter	CTCAE V5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
					baseline abnormal)
Creatine kinase (CK)	Creatine phosphokinase increased	> ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10 x ULN
Blood creatinine (CREA)	Creatinine increased	>ULN - 1.5 x ULN;	>1.5 - 3.0 × ULN; >1.5 - 3 × baseline	>3.0 - 6.0 × ULN; >3 × baseline	>6.0 x ULN
Total bilirubin (TBIL)	Blood bilirubin increased	>ULN - 1.5 × ULN (if baseline normal); >1-1.5 × baseline (if baseline abnormal)	>1.5 - 3.0 × ULN (if baseline normal); 1.5 - 3.0 × baseline (if baseline abnormal)	>3.0 - 10.0 × ULN (if baseline normal); 3.0 - 10.0 × baseline (if baseline abnormal)	>10.0 × ULN (if baseline normal); >10.0 × baseline (if baseline abnormal)
Total cholesterol (TCHO)	Hypercholesteremia	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92mmol/L
Gamma-glutamyltransferase (GGT)	Gamma-glutamyltransferase increased	>ULN - 2.5 × ULN (if baseline normal); >2-2.5 × baseline (if baseline abnormal)	>2.5 - 5.0 × ULN (if baseline normal); 2.5 - 5.0 × baseline (if baseline abnormal)	>5.0 - 20.0 × ULN (if baseline normal); 5.0 - 20.0 × baseline (if baseline abnormal)	>20.0 × ULN (if baseline normal); >20.0 × baseline (if baseline abnormal)
Triglycerides (TG)	Hypertriglyceridaemia	>150 - 300 mg/dL; >1.71 - 3.42 mmol/L	>300 - 500 mg/dL; >3.42 - 5.7 mmol/L	>500 - 1000 mg/dL; >5.7 - 11.4 mmol/L	
Potassium	Hyperkalaemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Potassium	Kaliopenia	-	<LLN - 3.0 mmol/L	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Sodium	Hypernatraemia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Sodium	Hyponatraemia	<LLN - 130 mmol/L	<125 - 129 mmol/L	<120 - 124 mmol/L	<120 mmol/L
Blood glucose	Hypoglycaemia	<lower limit of normal (LLN) - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Albumin (ALB)	Hypoalbuminaemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	-
International normalised ratio (INR)	INR increased	>1.2-1.5; >1-1.5 × baseline	>1.5-2.5; >1.5-2.5 × baseline	>2.5; >2.5 × baseline	-

Parameter	CTCAE V5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Activated partial thromboplastin time (APTT)	Activated partial thromboplastin time prolonged	> ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 × ULN;	-
Eosinophils	Eosinophilia	For baseline visit: AVAL > ANRHI; For post-baseline visit: AVAL > ANRHI and AVAL > BASE	-	-	-
Lactate dehydrogenase	Blood lactate dehydrogenase increased	AVAL> ANRHI	-	-	-
Calcium (mmol/L)	Hypocalcaemia	2.0 mmol/L<=AVAL<ANRLO	1.75 mmol/L<=AVAL<2.0 mmol/L	1.5 mmol/L<=AVAL<1.75 mmol/L	AVAL<1.5 mmol/L
Calcium (mmol/L)	Hypercalcaemia	ANRHI<AVAL<=2.9 mmol/L	2.9 mmol/L<AVAL<=3.1 mmol/L	3.1 mmol/L<AVAL<=3.4 mmol/L	AVAL>3.4 mmol/L