Clinical Study Protocol

Study Title:	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
Protocol Number:	GFH375X1101
Version Number and Version Date:	Version 2.0 / January 24, 2025
Product Name:	GFH375
Study Phase:	Phase I/II
Sponsor:	GenFleet Therapeutics (Shanghai) Inc.
Sponsor Contact:	Huaqiang Zhu, Vice President of Medical Science Tel: 15601727272 Email: hqzhu@genfleet.com

Sponsor Signature Page

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Position	Name	Signature (Printed)	Date
Vice President of Medical Science	Huaqiang Zhu	Huaqiang Zhu	Jan. 24, 2025

Investigator Signature Page

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By signing this protocol signature page, the investigator confirms and agrees to the following:

I have read the above study protocol and its appendices. I have fully discussed the contents of this protocol with the sponsor, GenFleet Therapeutics (Shanghai) Inc. I agree to conduct the study in accordance with this study protocol and to fulfill the relevant responsibilities in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP), local regulations, and other applicable regulations. I agree to ensure that all staff involved in this study are aware of their obligations in fulfilling the above commitments.

This document contains confidential information and shall not be disclosed to anyone other than those directly involved in the conduct of the study or in ethical/regulatory review, without the written authorization of the sponsor.

I have read the entire content of this study protocol and guarantee to conduct this study as required:

Investigator's Signature: _____ Date: _____

Printed Name: _____

Investigator's Title: _____

Contact Number: _____

Site Name/Address: _____

_____

_____

Summary of Protocol Amendments

Version Number	Version Date	Summary of Protocol Amendments
1.0	March 15, 2024	Not applicable
1.1	April 08, 2023	Main reason for amendment: To clarify the requirements for prior anti-tumor therapy for participants enrolled in Phase I to avoid ambiguity. • Updated inclusion criterion #3 regarding prior anti-tumor therapy for participants enrolled in Phase I: Either of the following criteria is met: 1) PD after standard of care and no other standard of care is available; or 2) standard of care has been confirmed to be ineffective, intolerable, or considered unsuitable.
1.2	September 13, 2024	Main reason for amendment: To clarify the dose exploration of twice daily (BID) dosing regimen in the original protocol. • Clarified the study design, operational procedures, and PK sampling related to BID dose regimen. • Made the definitions of individual DLT entries more operational. • Optimized some study operational procedures. • Corrected inconsistencies throughout the text.
1.3	November 18, 2024	Main reason for amendment: Adjusted the Phase I protocol design, increased the number of participants for dose level backfilling. • Removed the Phase Ib expansion period. • Adjusted the maximum dose for QD. • Added ctDNA testing in the Phase I stage. • Revised the GFH375 PK blood sampling time points. • Revised the list of prohibited medications in the appendix. • Corrected errors and adjusted inconsistencies.
2.0	January 24, 2025	Main reason for amendment: Completed the Phase I dose escalation part, added the rationale for RP2D selection; further refined the inclusion/exclusion criteria for PDAC and NSCLC in Phase II and added Blinded Independent Central Review (BICR) assessment for efficacy evaluation. • Added the rationale for RP2D selection. • Further refined the inclusion/exclusion criteria for PDAC and NSCLC participants enrolled in Phase II. • Added BICR efficacy assessment to the primary endpoint analysis for PDAC and NSCLC enrolled in Phase II. • Increased the sample size for Phase II participants with PDAC and other advanced solid tumors. • Added an exploratory objective for PDAC participants enrolled in Phase II to explore the relationship between CA19-9 and treatment response.

Protocol Synopsis

<table>
<tr><td>Protocol Number:</td><td>GFH375X1101</td></tr>
<tr><td>Sponsor</td><td>GenFleet Therapeutics (Shanghai) Inc.</td></tr>
<tr><td>Investigational Product</td><td>Code: GFH375</td></tr>
<tr><td>Study Title</td><td>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</td></tr>
<tr><td>Brief Title</td><td>A Phase I/II Study to Evaluate GFH375 in Patients with Solid Tumors with KRAS G12D Mutation</td></tr>
<tr><td>Phase</td><td>Phase I/II</td></tr>
<tr><td>Version Number/Date</td><td>V2.0 / January 24, 2025</td></tr>
<tr><td>Study Duration</td><td>Approximately 48 months</td></tr>
<tr><td>Study Objectives and Endpoints</td><td>This is a Phase I/II study.
Phase I objectives and endpoints include:
<table>
<tr><th>Study Objectives</th><th>Study Endpoints</th></tr>
<tr><td>Primary Objectives</td><td>Primary Endpoints</td></tr>
<tr><td>To evaluate the safety and tolerability of GFH375 in patients with advanced solid tumors with KRAS G12D mutation</td><td>• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs); changes in vital signs, electrocardiogram (ECG), and laboratory tests</td></tr>
<tr><td>• To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of GFH375</td><td>• Incidence of dose-limiting toxicity (DLT) events</td></tr>
<tr><td>Secondary Objectives</td><td>Secondary Endpoints</td></tr>
<tr><td>• To evaluate the pharmacokinetic (PK) characteristics of GFH375 in patients with advanced solid tumors with KRAS G12D mutation.</td><td>• Plasma concentrations and PK parameters of GFH375, including but not limited to C_{max}, T_{max}, AUC, $t_{1/2}$, CL/F, V_z/F, C_{trough}</td></tr>
<tr><td>• To evaluate the preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation</td><td>• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) as assessed according to Response</td></tr>
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	Evaluation Criteria in Solid Tumors (RECIST) 1.1.
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
Phase II objectives and endpoints:	
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 ductal adenocarcinoma of pancreas (PDAC), advanced colorectal cancer (CRC), and other solid tumors with KRAS G12D mutation.	• ORR as assessed by RECIST 1.1
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	• Mutation analysis of circulating tumor DNA (ctDNA) in blood at

	treatment sensitivity or drug resistance	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
Study Background	The RAS family is responsible for regulating signaling pathways related to cell growth, migration, survival, and differentiation. RAS proteins typically switch between GTP- and GDP-bound conformations, corresponding to the "on" and "off" states of the kinase, respectively. In various malignant tumors, oncogenic mutations in RAS lead to the inhibition of GTP hydrolysis, leaving the kinase in a constitutively active state, which results in malignant cell proliferation and changes in biological behavior. KRAS is the most common mutation type in the RAS family, accounting for approximately 90% of ductal adenocarcinomas of the pancreas, 50% of colorectal cancers, and 30% of lung adenocarcinomas. Therefore, KRAS is considered a driver oncogene for the development of many malignant tumors and for tumor metastasis. KRAS G12D is one of the most common KRAS mutation types. It is estimated that in lung adenocarcinoma, data from the United States show that the G12D mutation accounts for 4.9%, while a large-sample analysis of domestic NSCLC patients shows a KRAS G12D mutation frequency of approximately 2.2%. In pancreatic carcinoma, approximately 37% of patients carry the KRAS G12D mutation, suggesting the importance of this mutant allele at the population level in patients with pancreatic carcinoma. Preclinical studies have confirmed in multiple PDAC xenograft transplant models that KRAS G12D acts as a persistent oncogenic driver in PDAC, and KRAS G12D inhibitors have shown significant anti-tumor activity in PDAC models. In colorectal cancer, the KRAS mutation rate is approximately 40%, with KRAS G12D accounting for about 28%. In addition, studies have shown that KRAS mutation is a common factor for acquired drug resistance to cetuximab in colorectal cancer, and acquired KRAS G12D mutations have been observed in metastatic CRC tissue samples after treatment with cetuximab (or in combination with chemotherapy). Currently, several selective KRAS G12D inhibitors (such as MTRX1133 and HRS-4642) have entered clinical development, administered either orally or intravenously, but no therapy specifically targeting KRAS G12D-mutated tumors has been approved. Patients with advanced NSCLC, PDAC, CRC, and other solid tumors carrying the KRAS G12D mutation are usually first treated with chemotherapy, immunotherapy, or anti-angiogenic drugs in combination. After treatment failure with standard of care, there is a lack of effective treatment options. For example, in advanced NSCLC, although patients positive for driver genes such as EGFR and ALK can choose targeted therapies and achieve good efficacy, KRAS G12D rarely co-exists with these driver genes. Therefore, chemotherapy, such as docetaxel, remains the main treatment after failure of standard systemic therapy, with recently reported ORRs of 7.1-16.0% and a median PFS of 2.6-4.5 months. The Phase III NAPOLI-1 study, which enrolled patients with metastatic PDAC (mPDAC), showed that for mPDAC patients who had failed prior gemcitabine-based chemotherapy regimens, treatment with liposomal irinotecan in combination with 5-FU/LV (5-fluorouracil + leucovorin) resulted in significantly improved efficacy compared to those receiving only 5-FU/LV (5-fluorouracil + leucovorin): median overall survival (mOS) was 6.1 months (vs 4.2 months, HR 0.67), median PFS was 3.1 months (vs 1.5 months, HR 0.56), and ORR was 16% (vs 1%, $p < 0.0001$) . In other Phase II studies conducted in mPDAC participants who had received ≥ 1 line of therapy (most participants had received ≥ 2 lines of therapy), the reported ORR was 0%-10.7%. In CRC participants, TAS-102 +/- bevacizumab, regorafenib, and fruquintinib are common third-line treatment options, with an ORR of only 1-4%. Therefore, there is currently a lack of effective treatment methods for	

	NSCLC, PDAC, and CRC after failure of standard of care, representing a huge unmet clinical need. KRAS G12C inhibitors (sotorasib, adagrasib) have been approved for the indication of NSCLC, demonstrating good efficacy and safety in this patient population. Compared to other KRAS-mutated lung cancers, KRAS G12D mutation-positive tumors have different clinical, genomic, and immunological features. For example, in NSCLC, KRAS G12D mutation-positive status may be associated with low tumor mutation burden and low PD-(L)1 expression, often being "immune cold," which promotes tumor cell drug resistance to immunosuppressants. Clinically, separate studies are needed for these populations, and KRAS G12D inhibitors provide a great research opportunity that may bring potential benefits to these patients. GFH375 is a highly selective, oral, non-covalent small molecule inhibitor targeting the KRAS G12D mutation. In preclinical *in vitro* studies, GFH375 has shown potent inhibitory effects on KRAS-dependent signal transduction and cancer cell viability, and has demonstrated significant anti-tumor efficacy in animal models of KRAS G12D-mutated tumors. The above results support the further evaluation of the safety and efficacy of GFH375 in patients with advanced solid tumors carrying the KRAS G12D mutation.
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. A Safety Monitoring Committee (SMC), composed of investigators and the sponsor, will be established during the study. For details, please refer to Chapter 10 and the SMC Charter for this study. **Phase I Part** According to the BOIN design, 3-6 participants will be enrolled in each dose cohort for treatment (except during accelerated titration). Additional participants may be enrolled if more dose levels or alternative dosing regimens need to be explored. After enrollment, participants will receive oral administration of GFH375, with each treatment cycle being 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. The planned escalating doses are shown in the **table below**. The GFH375 dosing regimen will be comprehensively evaluated during dose escalation. If necessary, dose exploration with a twice daily (BID) dosing regimen will be conducted. Dose escalation can be conducted independently and in parallel for QD and BID dosing regimens. The first cycle after the first administration will serve as the DLT observation period. A DLT-evaluable case must meet one of the following two conditions: ▪ The participant experiences a DLT event, or ▪ The participant does not experience a DLT event and has received at least 15 days of the planned dosing of GFH375 in the first cycle. If no DLT event occurs, the participant will continue treatment, with dose adjustments permitted as allowed by this protocol, until progressive disease (PD), unacceptable toxicity, or discontinuation of study treatment for other reasons. If a participant experiences a DLT event during the DLT observation period, and if the investigator and sponsor assess that the participant can benefit from continuing treatment with GFH375, treatment with GFH375 will be resumed after the relevant adverse event (AE) has resolved. Refer to the corresponding section in the main text for the criteria for resumption of dosing. Participants enrolled in Phase I will undergo intensive PK sampling and have matching

ECGs collected with PK sampling to evaluate the PK characteristics and safety of GFH375. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the Informed Consent Form (ICF), initiation of other anti-tumor therapy, or the end of the study.

	Phase I QD Dose Cohorts with Planned/Completed Escalation *
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

Note: Intermediate dose exploration of the above doses, such as 150 mg, 300 mg, 500 mg, 800 mg, 900 mg, 1100 mg QD, etc., may be conducted during the escalation process based on the clinical data obtained, including safety, PK, and possible efficacy.

Based on the data obtained, including safety, PK, and preliminary efficacy results, BID dose regimen 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.

	Phase I Possible BID Dose Cohorts for Exploration*
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: Intermediate dose exploration of the above doses, such as 250 mg BID, etc., may be conducted.

DLT Definition

A DLT is an AE that occurs within 21 days after the first dose, is related to the investigational drug GFH375, and meets the following severity criteria. The severity of AEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:

- Grade ≥ 4 absolute neutrophil count (ANC) decreased for ≥ 5 days;
- Grade ≥ 3 febrile neutropenia (ANC $<1.0 \times 10^9$/L with a single body temperature > 38.3°C or a sustained body temperature ≥38°C for more than 1 hour);
- Grade ≥ 4 platelet count decreased for ≥ 5 days;
- Grade ≥ 3 platelet count decreased with Grade ≥ 2 hemorrhage;
- Grade ≥ 4 anemia;
- If baseline ALT or AST is Grade ≤ 1: Grade ≥ 3 serum transaminases increased (ALT or AST) lasting > 7 days is considered a DLT; if baseline ALT or AST is Grade 2, then ALT or AST > 10×ULN lasting > 7 days is considered a DLT;
- Grade ≥ 3 serum bilirubin increased;
- According to Hy's Law, AST or ALT > 3×ULN (if baseline metastases to liver are

present, then > 3 times the baseline value is required), with concurrent total bilirubin > 2×ULN (causes such as biliary obstruction or other causes like hepatitis, intrahepatic tumor progression, etc., must be excluded);

- Grade ≥ 3 other toxicities (non-hepatic, non-hematologic), with the exception of the following:
  - Grade 3 nausea or vomiting, diarrhea, lasting no more than 3 days with/without symptomatic supportive care;
  - Grade 3 fatigue, lasting no more than 3 days with/without symptomatic supportive care;
  - Asymptomatic Grade 3 abnormal laboratory results lasting no more than 7 days with intervention, such as elevated cholesterol, elevated triglycerides, gamma-glutamyl transferase (GGT) increased, alkaline phosphatase (ALP) increased, blood amylase increased, etc.

Toxicities meeting the above criteria that occur after the DLT observation period will also be considered important factors in the safety evaluation. In addition, other treatment-related toxicities that may be assessed as DLTs will be determined after discussion between the sponsor and the investigator.

During the first cycle (DLT observation period), AEs that meet the DLT criteria should be reported to the sponsor within 24 hours of awareness of their occurrence.

Dose Escalation Rules and MTD Definition

Accelerated titration is permitted for the first two dose levels of the QD dosing regimen, meaning the first participant will receive treatment at the first dose level. If no Grade ≥2 treatment-related AE is observed in participants in the first two dose cohorts during the DLT observation period, 3-6 participants will be enrolled at the next higher dose level, and the BOIN design will be used for this cohort and subsequent dose escalations. Conversely, if any Grade ≥2 treatment-related AE or DLT event is reported in the first or second dose cohort, the study will switch directly to the BOIN design, starting from the lowest dose cohort where the Grade ≥2 treatment-related AE or DLT event was observed. Provided that accelerated titration is completed for the first dose, the decision on whether to use accelerated titration for the second dose level will be made by the SMC based on discussion of the PK and safety data from the first dose level. Subsequent dose levels will use the BOIN design to determine the MTD, with a target toxicity probability of 0.3. If dose exploration of the BID dosing regimen is required, the BOIN design will be used for dose escalation, with a target toxicity probability of 0.3. Each dose level will enroll 3-6 participants for treatment. Additional participants may be enrolled if more dose levels or other dosing regimens need to be explored.

The BOIN design will assign the dose level for the next group of participants according to the dose escalation/de-escalation rules shown in the table below.

Decision	Total number of participants treated at the current dose						
	3	**4**	**5**	**6**	**7**	**8**	**9**
Escalate, if number of participants with DLT is ≤	0	0	1	1	1	1	2
De-escalate, if number of participants with DLT is ≥	2	2	2	3	3	3	4
Eliminate dose, if number of participants with DLT is ≥	3	3	4	4	5	5	5

For specific rules, please see Section 3.1.1.2 of the main text.

After the dose escalation part is completed, isotonic regression analysis will be used based on the dose determination set (DDS) to determine the MTD. The online BOIN software at

	http://www.trialdesign.org will be used to perform isotonic regression analysis to obtain the isotonic estimates of the toxicity probability for each dose level. The dose level closest to the target toxicity rate of 0.3 is the MTD. If there are 2 or more dose levels that meet the condition simultaneously, the highest dose level with an isotonic estimate <0.3 or the lowest dose level with an isotonic estimate ≥0.3 will be selected. **Backfilling of Participants in the Dose Escalation Part** 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 doseescalation part). Backfilled participants will complete the relevant visits according to the Phase I part Schedule of Activities and the Phase I part PK blood sampling schedule. **Intra-participant Dose Escalation** In principle, intra-participant dose escalation will not be performed during the dose escalation part. For participants enrolled in Phase I, after agreement from the investigator and sponsor, intra-participant dose adjustment to receive RP2D monotherapy is permitted after the RP2D for this protocol has been confirmed. **Determination of RP2D** Based on all safety, tolerability, PK, and efficacy data from the Phase I dose escalation part and some backfilled participants, the RP2D was determined to be 600 mg QD. **Phase II Part** The Phase II part is an open-label, multicenter study. The overall study plan is shown in Figure 3 of the main text. The objective is to evaluate the efficacy, safety, and PK characteristics of GFH375 in patients with advanced non-small cell lung cancer, advanced pancreatic carcinoma, colorectal cancer, 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 GFH375 monotherapy at the RP2D, with a treatment cycle of 21 days. Participants enrolled in this part will undergo sparse PK sampling according to the Phase II part PK blood sampling schedule and have matching ECGs collected with PK sampling. • Advanced NSCLC participant cohort: Approximately 73 participants with advanced NSCLC carrying the KRAS G12D mutation are planned for enrollment. • Advanced PDAC participant cohort: Approximately 94 participants with advanced PDAC carrying the KRAS G12D mutation are planned for enrollment. • Advanced CRC participant cohort: Approximately 50 participants with advanced CRC carrying the KRAS G12D mutation are planned for enrollment. • Other advanced solid tumor participant cohort: Approximately 100 participants with other advanced solid tumors carrying the KRAS G12D mutation are planned for enrollment, such as bile duct cancer, appendix cancer, etc., carrying the KRAS G12D mutation. Eligible participants who are screened will receive GFH375 monotherapy until PD, unacceptable toxicity, or discontinuation of study treatment for other reasons. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days

	thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the ICF, initiation of other anti-tumor therapy, or the end of the study.
Inclusion Criteria	**Participants must meet all of the following criteria to participate in this study:** 1. Participants who voluntarily participate in the study and sign the ICF. 2. Male or female, aged 18 - 75 years at the time of signing the ICF. 3. Participants with histologically or cytologically confirmed locally advanced or metastatic malignant tumor, who must meet the following criteria: （1）Phase I Part: Either of the following criteria is met: 1) PD after standard of care and no other standard of care is available; or 2) standard of care has been confirmed to be ineffective, intolerable, or considered unsuitable. （2）Phase II Part: a) Advanced NSCLC: ✓ Participants who have progressed after prior treatment with anti-PD-(L)1 therapy and/or platinum-based chemotherapy (unless contraindicated or intolerant), and have received no more than 3 prior lines of therapy; ✓ If prior adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy. b) Advanced PDAC: Participants who have progressed after adequate treatment with a gemcitabine-based chemotherapy regimen or FOLFIRINOX/mFOLFIRINOX regimen, or are unsuitable for standard of care due to reasons such as unacceptable toxicity, and have received no more than 3 prior lines of therapy. Those with high microsatellite instability (MSI-H) and/or deficient mismatch repair (dMMR) must have progressed after at least one prior line of anti-PD-1 therapy. If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy. c) Advanced CRC: Participants who have progressed after at least two lines of standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity. Participants must have experienced PD or recurrence during or after treatment with fluorouracil, irinotecan, and oxaliplatin for metastatic disease, unless the investigator considers the participant unsuitable for the above treatment regimens. Those with known MSI-H and/or dMMR must have received prior treatment with an immune checkpoint inhibitor (if applicable). If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy. d) Other solid tumors: Participants who have progressed after standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity. 4. Participants enrolled in this study must provide a written test report confirming KRAS G12D mutation-positive status. NSCLC and PDAC participants enrolled in Phase II must provide a compliant archived tumor tissue sample or undergo a biopsy during the screening period before enrollment. If a tumor tissue sample cannot be provided and a biopsy cannot be performed during the screening period, the investigator must communicate with the sponsor's medical monitor and obtain their consent before

	enrollment. 5. According to RECIST 1.1, participants enrolled in Phase I must have at least one evaluable lesion, and participants enrolled in Phase II must have at least one measurable lesion. 6. Toxicities from prior anti-tumor therapy must have resolved to baseline level (excluding alopecia) or ≤ Grade 1 (for neurological toxicity, ≤ Grade 2). 7. Investigator-assessed life expectancy ≥ 12 weeks. 8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 (see Appendix 2 for scoring criteria). 9. Adequate organ function, including: • Hematopoietic function: Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 75 × 10^9/L, hemoglobin ≥ 9 g/dL, with no transfusion or treatment with granulocyte colony-stimulating factor, thrombopoietin, or erythropoietin within 14 days before the blood test. • Liver function: ➢ Both AST and ALT < 2.5×ULN; for participants with baseline metastases to liver, both AST and ALT < 5×ULN; ➢ Total bilirubin (TBIL) < 1.5×ULN; for participants with Gilbert's syndrome: TBIL < 2×ULN. • Renal function: Creatinine clearance (CrCl) ≥ 50 mL/min (calculated by Cockcroft-Gault formula, see Appendix 3). • Coagulation function: Prothrombin time (PT) or activated partial thromboplastin time (APTT) < 1.5×ULN, international normalized ratio (INR) < 1.5×ULN or within the target range for anticoagulant therapy. • Albumin level ≥30 g/L (for Phase II PDAC participants only). 10. Women of childbearing potential (WOCBP) and male participants with partners who are WOCBP must agree to use effective methods of contraception from the time of signing the ICF until 30 days after the last study treatment. WOCBP must have a negative serum pregnancy test result within 7 days before dosing. 11. Participants who are able to communicate well, adhere to the follow-up schedule, and comply with the protocol requirements in the investigator's judgment.
Exclusion Criteria	**Participants who meet any of the following criteria cannot be enrolled in this study:** 1. Other malignant tumor that has progressed or required treatment within 3 years prior to enrollment, with the exception of adequately treated carcinoma in situ, basal cell carcinoma, or squamous cell carcinoma of skin. 2. Patients with unstable brain metastasis as judged by the investigator. Patients with incidentally detected brain metastasis during screening may be enrolled if they are asymptomatic and do not require therapeutic intervention; enrollment is permissible if the investigator judges the brain metastasis to be stable, the hormone dose is stable, and the prednisone dose is ≤10 mg/d (or an equivalent dose if other steroid drugs are used). 3. Phase II Part: a) Advanced NSCLC: Exclusion of known other driver gene mutations or fusions, such as EGFR, ALK, BRAF (V600E), HER2, MET (exon 14), ROS1, RET, KRAS G12C, or NTRK1/2/3 b) Advanced CRC: Exclusion of known other driver gene mutations, amplifications, or fusions, such as BRAF (V600E), HER2, NTRK, or RET c) Advanced PDAC: Exclusion of known other driver gene mutations or fusions, such as BRAF (V600E), BRCA, NTRK, or RET 4. Prior targeted therapy against KRAS G12D or pan-KRAS (with primary targeting

	effect on KRAS G12D). 5. Receipt of palliative radiation within 14 days before administration of the study drug. 6. Receipt of other anti-tumor therapy within 28 days or 5 half-lives (whichever is shorter) before dosing, including chemotherapy, targeted therapy, endocrine therapy, immunotherapy, Chinese patent medicines with definite anti-tumor effects, and other investigational drugs or devices, with the exception of endocrine maintenance therapy. 7. Concomitant clinically significant severe cardiovascular disorder: • Clinically significant severe cardiovascular events within 6 months before the first study treatment, such as myocardial infarction, angina unstable, symptomatic cardiac failure congestive (New York Heart Association Class III or IV), severe arrhythmia requiring drug therapy, or receipt of angioplasty, stenting, and coronary artery bypass graft surgery, etc. • Clinically significant QT/QTcF prolongation (based on the average of three QTcF values during the screening period, QTcF > 470 ms) or a family history of QT interval prolongation. • Hypertension that remains poorly controlled after standard treatment. 8. Stroke or other severe cerebrovascular disorder within 6 months prior to enrollment. 9. History of deep vein thrombosis or any other severe thromboembolism within 3 months prior to enrollment. 10. Concomitant pleural effusion, ascites, or pericardial effusion requiring repeated drainage or causing significant symptoms. 11. Concomitant superior vena cava syndrome. 12. History of gastrointestinal perforation and/or fistula within 6 months before the first dose of study drug that has not healed after surgery; current unstable or active gastrointestinal ulcer or other high-risk gastrointestinal hemorrhage diseases; presence of biliary or pyloric obstruction, or persistent recurrent vomiting (≥3 episodes within 24 hours); high risk of rupture, hemorrhage, or gastrointestinal/respiratory fistula due to tumor invasion of surrounding vital structures (e.g., major blood vessels, trachea); or other gastrointestinal dysfunction or diseases that may significantly affect the absorption of GFH375, or inability or unwillingness to swallow tablets. 13. Concomitant clinically significant interstitial lung disease, radiation pneumonitis, or immune-related pneumonitis requiring treatment. 14. Concomitant major acute or chronic infectious diseases, including: • Active infection requiring intravenous antibiotic therapy within 7 days prior to enrollment. • Positive for human immunodeficiency virus antibody (HIV-Ab) at baseline. • Active hepatitis b virus infection (HBsAg positive with positive HBV-DNA). • Active hepatitis c virus infection (HCV-Ab positive with positive HCV-RNA). • Active tuberculosis. 15. Other poorly controlled systemic diseases, such as diabetes mellitus. 16. Undergone or planning to undergo major surgery as judged by the investigator within 28 days before the first dose (excluding needle biopsy). 17. History of organ transplant or preparing to receive an organ transplant. 18. Need for acid-suppressing drugs, including proton pump inhibitors and novel acid-suppressing drugs (e.g., potassium-competitive acid blockers), within 7 days before or during the administration of the study drug. 19. Receipt of strong inhibitors or inducers of CYP3A or P-gp within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug. 20. Receipt of known sensitive substrates of CYP3A or OAT1 within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug. Unless

	agreed for enrollment after review by the investigator and sponsor. 21. Known allergy to the study drug or its components. 22. Severe mental or psychological illness, or history of drug abuse or severe alcoholism. 23. Pregnant or lactating women. 24. Other conditions that, in the investigator's judgment, make the participant unsuitable for the study. 25. **Phase II PDAC participants:** Numeric Rating Scale (NRS) for pain score ≥4 after standardized treatment with analgesics.
Statistical Analysis	**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 post-treatment safety assessment. • Dose Determination Set (DDS): All Phase I participants who have received undiminished doses of GFH375 for at least 15 cumulative days during the DLT observation period and had adequate safety assessments, or who have 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 provided at least one blood sample for evaluable PK data. **Statistical Analysis Methods** Data from Phase I and Phase II will be analyzed and summarized separately. Data from the Phase I stage will be analyzed and summarized by different dose levels and dosing regimens; data from the Phase II stage will be analyzed and summarized separately by tumor type. **Safety Analysis** The incidence of AEs, treatment-related AEs, and SAEs will be summarized by System Organ Class (SOC), Preferred Term (PT), and severity. For the Phase I part, the incidence of various types of DLTs will be summarized based on the DDS, and the DLTs will be listed. Descriptive summaries will be provided for laboratory tests, vital signs, and ECGs. **Efficacy Analysis** Best overall response (BOR), ORR, and DCR will be calculated, and the two-sided 95% confidence interval (CI) for ORR and DCR will be estimated using the Clopper-Pearson method. The median DoR, PFS, and OS and their 95% Brookmeyer-Crowley CIs will be estimated using the Kaplan-Meier method. TTR will be summarized descriptively. For the Phase I stage, when the sample size of an analysis group is less than 10, DoR, TTR, PFS, and OS will be listed individually by participant, and the Kaplan-Meier method will not be used for analysis. For the Phase II stage, the primary estimand is set as follows:

Study Population	Participants with advanced solid tumors with KRAS G12D mutation
Treatment	GFH375
Endpoint	Percentage of participants who achieve CR or PR as assessed by RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant is considered a non-responder**.**

	Note: For NSCLC and PDAC, this will be the percentage of participants with confirmed CR or PR based on Blinded Independent Central Review (BICR) assessment.
Intercurrent Event	Start of new anti-tumor therapy (Handling strategy: Treatment policy strategy, assessment results after the start of new anti-tumor therapy are not included in the analysis.)
Population-level Summary	ORR

PK Analysis

Plasma concentration data of GFH375 will be listed and summarized descriptively according to the sampling times specified in the protocol. The summaries will be presented by study phase, dose group, and dosing regimen. Individual participant plasma concentration-time curves of GFH375 and corresponding summary curves (mean + standard deviation) will be plotted using linear and semi-logarithmic coordinates, by study phase, dose group, and dosing regimen. Planned PK sampling times will be used to calculate summary statistics and plot summary curves (mean + standard deviation); actual PK sampling times will be used to plot individual participant curves.

Phoenix WinNonlin software (version v8.2 or later, Certara USA, Inc., New Jersey, US) will be used to perform non-compartmental analysis (NCA) to calculate the PK parameters of GFH375 based on actual blood sampling time points. The PK parameters of GFH375 after single and multiple doses in participants in the Phase I dose escalation part will be summarized descriptively, with summaries presented by dose group and dosing regimen.

Sample Size Calculation

Phase I Part

According to the BOIN design, 3-6 patients will be enrolled in each dose group for treatment (except during accelerated titration). 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-escalationpart).

Additional patients may be enrolled if more dose levels or alternative dosing regimens need to be explored.

Phase II Part

A total of approximately 317 participants are planned for enrollment, including approximately 73 patients with advanced NSCLC, approximately 94 patients with advanced PDAC, approximately 50 patients with advanced CRC, and approximately 100 patients with other advanced solid tumors.

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

	<table><tr><td>Total</td><td></td><td></td><td>317</td></tr></table> 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% 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.
Interim Analysis	A futility interim analysis will be performed separately for NSCLC, PDAC, and CRC. For each tumor type, the analysis is planned 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 Phase II 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: <table><tr><th>Tumor Type</th><th>Number of Participants*</th><th>Recommended to terminate the cohort when the number of responders is ≤</th></tr><tr><td rowspan="5">NSCLC</td><td>20 ~ 21</td><td>3</td></tr><tr><td>22 ~ 25</td><td>4</td></tr><tr><td>26 ~ 29</td><td>5</td></tr><tr><td>30 ~ 33</td><td>6</td></tr><tr><td>34 ~ 37</td><td>7</td></tr></table>

	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: The sum 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 these must be 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.

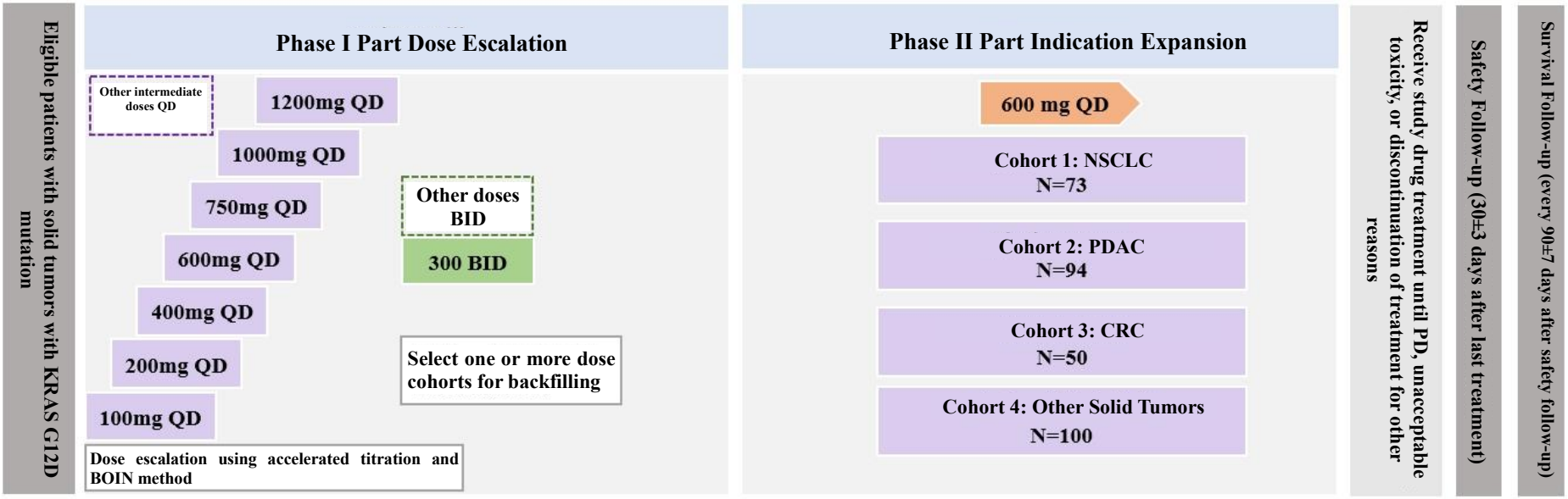

Figure 1 Overall Study Design

Abbreviations: QD: once daily; BID: twice daily; NSCLC: non-small cell lung cancer; PDAC: ductal adenocarcinoma of pancreas; CRC: colorectal cancer; BOIN: Bayesian Optimal Interval.

Schedule of Activities for Phase I Treatment Stage

Study Stage	Screening Period	Treatment Period							Remarks
		Cycle 1				Cycle 2		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**0**	**±3**	**±3**	**-1 ~ 3**	**±3**	**±3**	
Informed Consent	×								
Inclusion/Exclusion Criteria	×	×							Inclusion/exclusion criteria must be reviewed again on C1D1.
Demographics	×								Includes sex, age, ethnicity, etc.
Body Height/Weight	×	×				×		×	Body height is measured only once during the screening period.
Tumor History	×								Includes information on tumor diagnosis, time of diagnosis, metastatic sites, etc. For advanced NSCLC, data on prior PD-L1 expression levels should be collected (if available)
Other Medical History	×								All active medical conditions and any conditions the investigator considers clinically significant will be collected.
Prior Anti-tumor Therapy History	×								All prior anti-tumor therapy history for the study disease, including therapeutic drugs, start time, end time, best overall assessment, reason for discontinuation, etc. will be collected.
Other Prior/Concomitant Therapy	×								All prior/concomitant medications and therapeutic procedures from 30 days before the first dose until the end of the safety follow-up will be collected.
Virus Serology	×								Includes hepatitis b surface antigen (HBsAg), hepatitis b surface antibody (HBsAb), hepatitis b core antibody (HBcAb), HCV antibody, HIV antibody, and HBV-DNA and HCV-RNA tests (if necessary).
Pregnancy Test	×	×						×	Female participants of childbearing potential must undergo a serum pregnancy test within 7 days before the first dose, followed by a pregnancy test urine on D1 of every 2 cycles. If a negative urine pregnancy result cannot be confirmed, a serum pregnancy test is required.

Study Stage	Screening Period	Treatment Period							Remarks
		Cycle 1				Cycle 2		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**0**	**±3**	**±3**	**-1 ~ 3**	**±3**	**±3**	
Physical Examination	×	×	×	×		×	×	×	
ECOG PS	×	×				×		×	If assessed within 72 hours before the first dose, it does not need to be repeated on C1D1.
Vital Signs	×	×	×	×	×	×	×	×	
Hematology	×	×	×	×	×	×	×	×	If laboratory test results are available within 7 days before the first dose, they do not need to be repeated on C1D1. If the participant's clinical status changes significantly, laboratory tests must be repeated on C1D1.
Blood Chemistry	×	×	×	×	×	×	×	×	
Urinalysis	×	×			×	×	×	×	
Coagulation Function	×	×			×	×	×	×	
Electrocardiogram	×	×	×	×	×	×	×	×	1. If other trial procedures are combined, an ECG should be performed first to avoid the impact of study procedures on the ECG results. 2. The ECG should be performed after the participant has rested quietly for at least 10 minutes. Three ECGs will be performed at each visit during the study, with an interval of at least 5 minutes between each. 3. For ECG collection that matches PK sampling, please refer to the PK blood collection form for specific requirements.
Tumor Imaging Assessment	×	×							Compliant examination results from within 4 weeks before the first dose can be accepted as baseline and do not need to be repeated. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks.
GFH375 Administration		×							GFH375 tablets will be dispensed to participants on specified visit days and taken orally as scheduled. **Participants receiving QD**

Study Stage	Screening Period	Treatment Period							Remarks
		Cycle 1				Cycle 2		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**0**	**±3**	**±3**	**-1 ~ 3**	**±3**	**±3**	
									dosing should skip the dose on Day 2 and Day 3 of the first cycle; participants receiving BID dosing do not need to skip.
PK Blood Sampling		×							See PK Collection Form
Blood ctDNA	×	×							Blood samples will be collected at baseline (if collected during the screening period, no need to repeat on C1D1) for next-generation sequencing (NGS) testing
AE/SAE	×	×							AEs/SAEs will be collected from signing of ICF until 30 days after the last dose

Abbreviation: C1D1: Cycle 1 Day 1. ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; PK: Pharmacokinetics; AE/SAE, Adverse Event/Serious Adverse Event.

Schedule of Activities for Phase II Treatment Stage

Study Stage	Screening Period	Treatment Period			Remarks
		Cycle 1		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**±3**	**±3**	
Informed Consent	×				
Inclusion/Exclusion Criteria	×	×			Inclusion/exclusion criteria must be reviewed again on C1D1.
Demographics	×				Includes sex, age, ethnicity, etc.
Body Height/Weight	×	×		×	Body height is measured only once during the screening period.
Tumor Tissue Sample	×				Phase II NSCLC and PDAC participants must provide an archived formalin-fixed paraffin-embedded (FFPE) sample or a biopsy sample.
Tumor History	×				Includes information on tumor diagnosis, time of diagnosis, metastatic sites, etc. For patients with advanced NSCLC, data on prior PD-L1 expression levels should be collected (if available).
Other Medical History	×				All active medical conditions and any conditions the investigator considers clinically significant will be collected.
Prior/Concomitant Therapy	×				All prior/concomitant medications and therapeutic procedures from 30 days before the first dose until the end of the safety follow-up will be collected.
NRS Pain Score	×	×			For PDAC participants only; if assessed within 72 hours before the first dose, it does not need to be repeated on C1D1.
Virus Serology	×				Includes hepatitis b surface antigen (HBsAg), hepatitis b surface antibody (HBsAb), hepatitis b core antibody (HBcAb), HCV antibody, HIV antibody, and HBV-DNA and HCV-RNA tests (if necessary).

Study Stage	Screening Period	Treatment Period			Remarks
		Cycle 1		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**±3**	**±3**	
Pregnancy Test	×	×		×	Female participants of childbearing potential must undergo a serum pregnancy test within 7 days before the first dose, followed by a pregnancy test urine on D1 of every 2 cycles. If a negative urine pregnancy result cannot be confirmed, a serum pregnancy test is required.
Physical Examination	×	×	×	×	
ECOG PS Score	×	×		×	If assessed within 72 hours before the first dose, it does not need to be repeated on C1D1.
Vital Signs	×	×	×	×	
Hematology	×	×	×	×	If laboratory test results are available within 7 days before the first dose, they do not need to be repeated on C1D1. If the participant's clinical status changes significantly, laboratory tests must be repeated on C1D1.
Blood Chemistry	×	×	×	×	
Urinalysis	×	×	×	×	
Coagulation Function	×	×	×	×	
Electrocardiogram	×	×	×	×	1. If other trial procedures are combined, an ECG should be performed first to avoid the impact of study procedures on the ECG results. 2. The ECG should be performed after the participant has rested quietly for at least 10 minutes. Three ECGs will be performed at each visit during the study, with an interval of at least 5 minutes between each. 3. For ECG collection that matches PK sampling, please refer to the PK blood collection form for specific requirements.

Study Stage	Screening Period	Treatment Period			Remarks
		Cycle 1		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**±3**	**±3**	
CA19-9	×	×			For PDAC participants only; tested at baseline (if collected during the screening period, no need to repeat on C1D1) and every 6 ± 1 weeks during the treatment period.
Tumor Imaging Assessment	×	×			Compliant examination results from within 4 weeks before the first dose can be accepted as baseline and do not need to be repeated. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks.
GFH375 Administration		×			GFH375 tablets will be dispensed to participants on specified visit days and taken orally as scheduled
PK Blood Sampling		×			See PK Collection Form
Blood ctDNA	×	×			Blood samples will be collected at baseline (if collected during the screening period, no need to repeat on C1D1) for next-generation sequencing (NGS) testing
AE/SAE	×	×			AEs/SAEs will be collected from signing of ICF until 30 days after the last dose

Abbreviation: C1D1: Cycle 1 Day 1. ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; PK: Pharmacokinetics; AE/SAE, Adverse Event/Serious Adverse Event.

Phase I and II Parts: Schedule of Activities for End of Treatment Visit and Long-term Follow-up Visit

	End of Treatment (EOT) Visit	Safety Follow-up Visit	Survival Visit	Remarks
Visit	**Decision to end study treatment**	**30 days after last dose**	**Every 90 days after safety visit**	
Time Window (days)	+7	±3	±7	
Pregnancy Test	×	×		Pregnancy test urine will be performed; serum test will be used if necessary.
Physical Examination	×	×		
ECOG PS Score	×			
Vital Signs	×	×		
Weight	×	×		
Blood ctDNA	×			
Hematology	×	×		Tests performed within 7 days after the last dose do not need to be repeated at the EOT visit, but AE-related tests should be reviewed at the investigator's discretion
Blood Chemistry	×	×		
Urinalysis	×	×		
Coagulation Function	×	×		
Electrocardiogram	×	×		
CA19-9	×			For PDAC participants enrolled in Phase II only; no need to repeat if tested within 4 weeks before the end of treatment visit.
Imaging Assessment	×			Imaging tests performed within 4 weeks before the end of treatment visit do not need to be repeated; participants who discontinue treatment for reasons other than PD/due to PD and have not started other anti-tumor therapy need to undergo scheduled tumor imaging until PD, start of new anti-tumor therapy, or withdrawal from the study.

	End of Treatment (EOT) Visit	Safety Follow-up Visit	Survival Visit	Remarks
Visit	**Decision to end study treatment**	**30 days after last dose**	**Every 90 days after safety visit**	
Time Window (days)	**+7**	**±3**	**±7**	
Concomitant Therapy	×			Concomitant medications and therapeutic procedures will be collected
AE/SAE	×			AEs/SAEs will be collected from signing of ICF until 30 days after the last dose or start of new anti-tumor therapy
Subsequent Anti-tumor Therapy	×			Includes subsequent anti-tumor therapy, start/end time, reason for discontinuation, and BOR
Survival Status	×			

Phase I Part PK Sample and 12-Lead ECG Collection Schedule (QD/BID)

Cycle	Day	Planned Sampling Time Point (h)	Time Window	PK Sampling[1,2]	12-Lead ECG[3]
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[4]**	12 h postdose	±30 min	√	
1	**2[5]**	24 h postdose	±1 h	√	
1	**3[5]**	48 h postdose	±2 h	√	
1	**4[5]**	72 h post-dose (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	±10 min	√	√
1	21	4 h postdose	±15 min	√	√
1	21	6 h postdose	±30 min	√	√
1	21	8 h postdose	±30 min	√	
1	**21[4]**	12 h postdose	±30 min	√	
1	**21[5]**	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. When a patient experiences a drug-related SAE, a blood sample for GFH375 plasma concentration measurement should be collected immediately upon the investigator's awareness of the event, if possible.
2. If a PK sample cannot be obtained at a planned visit, it can be postponed to the next visit for collection. It is sufficient to accurately record the dose administered, time of administration, and time of sampling.
3. ECGs matching the PK samples will be collected at qualified sites. It is recommended to perform the ECG first, then the PK blood draw. If it cannot be completed before the blood sample collection, the ECG should be performed after resting quietly for 10 minutes after the blood draw. Meanwhile, the interval between the ECG and PK sampling time needs to be kept within 30 minutes. All planned 12-ECGs should be performed after the participant has rested quietly for at least 5 min. Three measurements should be taken at each time point, with an interval of 1-2 min between each.
4. **If BID dosing, the 12 h post-dose PK samples on C1D1 and C1D21 should be collected before the second dose of the day.**
5. **Only applicable to QD dosing, collection is required before dosing.**

Phase II Part PK Sample and 12-Lead ECG Collection Schedule (QD/BID)

Cycle	Day	Planned Sampling Time Point (h)	Time Window	PK Sampling[1,2]	12-Lead ECG[3]
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	√	√

1. When a patient experiences a drug-related SAE, a blood sample for GFH375 plasma concentration measurement should be collected immediately upon the investigator's awareness of the event, if possible.
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List of Abbreviations

Abbreviation	Full Term
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the curve
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
BID, bid	Bis in die
BOIN	Bayesian Optimal Interval
BOR	Best of Response
C_{max}	Maximal concentration
C_{trough}	Trough concentration
CA19-9	Carbohydrate Antigen 19-9
CI	Confidence Interval
CL	Clearance
CL_r	Renal Clearance
CNS	Central Nervous System
Cr	Creatinine
CR	Complete Response
CRC	Colorectal Cancer
CRO	Contract Research Organization
CSCO	Chinese Society of Clinical Oncology
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450 Proteins
D	Day
DCR	Disease Control Rate
DDS	Dose Determination Set
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DRF	Dose Range Finding
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
G12D	Gly12Asp

Abbreviation	Full Term
GAP	GTPase-Activating Protein
GCP	Good Clinical Practice
GDP	Guanosine Diphosphate
GEF	Guanine Nucleotide Exchange Factor
GGT	Gamma-Glutamyl Transpeptidase
GTP	Guanosine Triphosphate
GLP	Good Laboratory Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
HR	Hazard Ratio
ICH-GCP	International Council for Harmonization
INR	International Normalized Ratio
LLOQ	Lower Limit of Quantification
K^+	Serum Potassium
KRAS	Kirsten Rat Sarcoma Viral Oncogene
MAPK	Mitogen-Activated Protein Kinase
MATE1	Multidrug and toxin extrusion 1
MATE2-K	Multidrug and toxin extrusion 2-K
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRSD	Maximal Recommended Starting Dose
MSI-H	High Microsatellite Instability
MTD	Maximum Tolerated Dose
NGS	Next Generation Sequencing
NOAEL	No-Observed-Adverse-Effect Level
NRS	Numerical Rating Scale
NSCLC	Non-Small Cell Lung Cancer
OATP1B1	Organic anion transporting polypeptide 1b1
OATP1B3	Organic anion transporting polypeptide 1b3
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OCT2	Organic cation transporter 2
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression Disease
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression Free Survival
P-gp	P-glucoprotein
PLT	Blood Platelet
PK	Pharmacokinetic
PKS	Pharmacokinetic Set

Abbreviation	Full Term
PO, po, p.o.	Oral Administration
PPoS	Predictive Probability of Success
PPS	Per Protocol Set
PR	Partial Response
PRO	Protein in Urine
PS	Physical performance
PT	Preferred Term
PT	Prothrombin Time
QD, qd	Quaque die
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SS	Safety Set
STD10	Severely Toxic Dose in 10% of the Animals
$t_{1/2}$	Elimination half-life
T_{max}	Time to reach maximum concentration
TEAE	Treatment Emergent Adverse Event
TRAE	Treatment Related Adverse Event
T-BIL	Total Bilirubin
TTP	Time to Progression
TK	Toxicokinetics
TTR	Time to Response
ULN	Upper Limits of Normal
V_d	Volume of distribution
V_{dss}	Volume of distribution at steady state

1. Introduction

1.1. Disease Background

1.1.1 Biological Mechanism of KRAS and KRAS G12D Mutation

RAS proteins are guanine nucleotide-binding proteins with GTPase enzyme activity. Their activity is switched by binding to either guanosine diphosphate (GDP) or guanosine triphosphate (GTP). They are in an inactive state when bound to GDP and become activated when bound to GTP. In cells, RAS is located at a relatively central position in signaling pathways and activates multiple downstream signaling pathways. By regulating gene transcription and protein regulation processes, RAS proteins are responsible for intercellular signaling pathways for cell growth, migration, survival, and differentiation. RAS is the most widely mutated oncogene in tumors, with approximately 30% of tumors containing RAS mutations. Mutations in all three subtypes, KRAS, HRAS, and NRAS, have been found in tumors, with KRAS mutations being the most common. KRAS mutations are most common in pancreatic carcinoma, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC), reaching up to 90% in pancreatic carcinoma. KRAS mutations mainly occur at three sites: glycine (Gly, G) at positions 12 and 13, and glutamine (Gln, Q) at position 61, with the highest mutation rate at the G12 position. More than 10 different types of mutations can occur at the Gly12 position of KRAS, with mutations to aspartic acid (G12D), valine (G12V), and cysteine being the most frequent[1-3]. The role of KRAS in tumors is widely recognized, but its protein structure and extremely high affinity for GTP have hindered the development of targeted drugs against KRAS. Recent breakthroughs in covalent inhibition strategies for KRAS have led to the successful development and clinical validation of innovative small molecule drugs targeting KRAS. Among them, KRAS G12C inhibitors (sotorasib, adagrasib) have been approved for the treatment of patients with KRAS G12C-mutated NSCLC, with confirmed efficacy and an acceptable safety profile.

1.1.2 KRAS G12D-mutated Tumors

KRAS mutations are common in CRC (approx. 45% in the US, 49% in China), pancreatic carcinoma (approx. 90% in the US, 87% in China), and NSCLC (adenocarcinoma: approx. 35% in the US, 13% in China)[3]. Among them, KRAS G12D is one of the most common mutation types, with high expression in various solid tumors, including NSCLC, pancreatic carcinoma, CRC, and bile duct cancer.

Advanced NSCLC

Lung cancer is the second most common cancer and the leading cause of cancer death worldwide. NSCLC accounts for approximately 84% of lung cancer cases, and most NSCLC patients are

diagnosed at an advanced stage. Global cancer statistics reported by the International Agency for Research on Cancer show an estimated 820,000 new lung cancer diagnoses and 715,000 lung cancer-related deaths in China in 2020[4]. KRAS G12D is one of the common mutations in NSCLC. A study based on data from the American Association for Cancer Research (AACR) Project GENIE showed that the G12D mutation accounts for an estimated 4.9% of all lung adenocarcinomas in the United States[3]. A retrospective study analyzed NGS data from 150,327 NSCLC cases in the Lung Cancer Big Data Precision Treatment Collaborative Group (LANDSCAPE) project, in which the frequency of KRAS G12D mutation was approximately 2.2%[5].

The treatment of advanced NSCLC varies depending on the presence of driver gene mutations. If positive for driver genes such as EGFR, ALK, ROS, etc., corresponding targeted drugs or platinum-based doublet chemotherapy, as well as chemotherapy combined with immunotherapy, anti-angiogenic therapy, etc., can be selected. Since KRAS G12D rarely co-exists with the above-mentioned driver genes, chemotherapy, such as docetaxel, remains the main treatment after failure of standard systemic therapy, with recently reported ORRs of 13.2-16.0% and a median PFS of 2.6-4.5 months [6-8]; the ORRs for prior chemotherapy and chemotherapy plus anti-angiogenic drugs were 8.5-18.3% and 8.6%-22.9%, respectively; PFS was 2.8-4.2 months and 4.8-5.4 months, respectively; and OS was 6-11.4 months and 9.9-12.6 months, respectively[9-13]. Considering the potential for increased toxicity with combination therapy, the tolerability of patients to doublet chemotherapy and other combination therapies needs to be fully assessed in second-line and above treatments. Data on immune checkpoint inhibitor treatment for KRAS-mutated NSCLC patients mainly come from subgroup analysis reports of large Phase III clinical studies. Among them, the CheckMate057 and OAK studies reported that compared to docetaxel monotherapy, patients with KRAS mutations could achieve better overall survival (OS) benefits from nivolumab or atezolizumab treatment[14,15]. However, since most patients have already received immune checkpoint inhibitors in first-line treatment, they are not the primary choice for second-line treatment.

KRAS G12C targeted inhibitors have achieved good efficacy as monotherapy or in combination in advanced NSCLC, and it is expected that drugs targeting KRAS G12D will bring new treatment options for the subgroup of patients with this targetable mutation.

Advanced PDAC

Ductal adenocarcinoma of pancreas (PDAC) is one of the most malignant tumors with poor treatment efficacy. It is projected that pancreatic carcinoma will become the second leading cause of death from all malignant tumor by 2030, with an overall 5-year survival rate of only 10%. Furthermore, the

disease burden of pancreatic carcinoma is expected to increase globally[16]. Most PDAC patients present with metastatic disease at their initial visit and require more effective systemic therapy. With the exception of patients carrying the germline breast cancer susceptibility gene (BRCA), very few targetable mutations in PDAC have been identified to date. KRAS mutation is an early genetic driver event in its tumorigenesis process and is closely related to key biological features such as inflammation, immune evasion, and metabolic changes[17]. It is estimated that 37% of pancreatic carcinomas carry the KRAS G12D mutation, suggesting the importance of this mutant allele at the population level. Some PDAC xenograft models have shown that KRAS G12D acts as a consistent and strong oncogenic driver in PDAC, and KRAS G12D inhibitors have demonstrated significant anti-tumor activity in ductal adenocarcinoma of pancreas models.

The progress of drug therapy for PDAC has been very limited overall, especially with the limited efficacy of targeted drugs and immunotherapy. The Phase III NAPOLI-1 study, which enrolled patients with metastatic PDAC (mPDAC), showed that for mPDAC patients who had failed prior gemcitabine-based chemotherapy regimens, treatment with liposomal irinotecan in combination with 5-FU/LV (5-fluorouracil + leucovorin) resulted in significantly improved efficacy compared to those receiving only 5-FU/LV (5-fluorouracil + leucovorin): median overall survival (mOS) was 6.1 months (vs 4.2 months, HR 0.67), median PFS was 3.1 months (vs 1.5 months, HR 0.56), and ORR was 16% (vs 1%, $p < 0.0001$)[18]. Currently, there is a lack of standard or recommended treatment options for third-line therapy, with most being the reuse of first- or second-line chemotherapy drugs. A recently published French cohort study showed that among 676 patients with advanced pancreatic carcinoma who received at least one line of chemotherapy, only 37% received third-line chemotherapy, with a median PFS of only 2.03 months and a median overall survival of only 5.5 months[19,20]. Therefore, there is an urgent clinical need for effective therapeutic drugs. Currently, targeted inhibitors against KRAS G12C have achieved good efficacy in previously treated PDAC, with ORRs for sotorasib, adagrasib, and glecirasib monotherapy being 21.0%, 33.3%, and 46.4%, respectively, and median PFS being 4.0 months, 5.4 months, and 5.5 months, respectively[21-23]. It is expected that drugs targeting KRAS G12D can also provide new treatment options for the patient population with this targetable mutation.

Advanced CRC

Colorectal cancer (CRC) is currently the third most common cancer by incidence, with an estimated 1,931,590 new cases annually worldwide. CRC is also the second leading cause of cancer death, with 935,173 deaths globally in 2020. Approximately 20% of CRC patients have metastasis at diagnosis,

while up to 50% of patients with initial local disease will develop metastasis[19]. In CRC, the KRAS mutation rate is approximately 40%, with KRAS G12D accounting for about 28% [24,25]. CRC with KRAS mutations is associated with advanced disease state, poor tumor differentiation, distant metastasis, and lower survival rates, potentially indicating a poorer prognosis for PFS and OS, which has been validated in real-world clinical practice[25]. In addition, studies have shown that KRAS mutation is a common driver of acquired drug resistance to cetuximab in colorectal cancer, and acquired KRAS G12D mutations have been observed in metastatic CRC tissue samples after treatment with cetuximab (or in combination with chemotherapy)[26,27]. Targeting KRAS mutations in CRC patients holds the promise of potentially providing more effective targeted therapy and a better safety profile in this highly selected patient population.

The treatment of advanced CRC also varies depending on the presence of gene mutations such as RAS, BRAF, and HER2. When both RAS and BRAF are wild-type, the treatment used is monochemotherapy or polychemotherapy combined with cetuximab (for left-sided lesions) or bevacizumab (for right-sided lesions). Although immunotherapy has been approved for the treatment of MSI-H CRC patients, the proportion of MSI-H patients in CRC is low, and there remains a huge unmet clinical need. In the third-line or later setting, there are fewer treatment options available for patients, including palliative care, participation in clinical trials, or approved drugs (regorafenib, trifluridine/tipiracil +/- bevacizumab, and fruquintinib). However, in the late-line treatment of CRC, the currently recommended standard therapies (regorafenib, trifluridine/tipiracil, and fruquintinib) offer only limited efficacy in mCRC patients who have failed at least 2 lines of therapy, with an ORR of 1-4.7%, a median PFS of 1.9-3.7 months, and a median OS of 6.4-9.3 months[28-30]. Recently, based on a Phase III part (the SUNLIGHT study, NCT01607957), the FDA approved trifluridine/tipiracil + bevacizumab as one of the third-line treatment options. Compared to trifluridine/tipiracil monotherapy, the use of trifluridine/tipiracil combined with bevacizumab showed improved OS and PFS, but the ORR remained low at only 6.1%[31]. Therefore, there remains a significant unmet medical need in third-line and later mCRC patients. In patients with advanced CRC, the KRAS G12C-targeted inhibitors sotorasib and adagrasib have shown preliminary efficacy as monotherapy, with ORRs of 9.7% (95% CI 3.6, 19.9) and 19% (95% CI 8, 33), respectively[32,33]. Combination with an anti-EGFR antibody can further improve their efficacy. The ORR achieved with sotorasib combined with panitumumab was 26.4%-30%, with a median PFS of 5.6-5.7 months[34]. The ORR for adagrasib combined with cetuximab was 46% (95% CI 28, 66), with a median PFS of 6.7 months[33]. In addition to NSCLC, CRC, and PDAC, KRAS G12D has a high mutation frequency in various solid tumors,

including bile duct cancer, gastric cancer, and esophageal cancer. For these patients who lack effective treatment options, there are no targeted drugs against KRAS available yet.

1.1.3 Development of Drugs Targeting KRAS G12D Mutation

Currently, no therapy specifically targeting KRAS G12D-mutated tumors has been approved for marketing. Several selective KRAS G12D inhibitors are in clinical development, including MTRX1133, HRS-4642, and INCB161734.

Among them, only partial clinical data for HRS-4642, developed by Hengrui, has been disclosed. HRS-4642 is a liposomal formulation administered by intravenous injection. A total of 18 participants were enrolled in the FIH trial and treated with 15 mg QW to 300 mg QW. The overall safety was good, and preliminary efficacy was observed [37].

1.2. Investigational Product: GFH375

1.2.1 Preclinical Studies of GFH375

GFH375 is a KRAS G12D inhibitor independently developed by the sponsor, GenFleet. Comprehensive preclinical studies have been conducted, and a summary is provided below. For more detailed information, please refer to the GFH375 Investigator's Brochure.

1.2.1.1 Summary of Pharmacology Studies

GFH375 has demonstrated high activity and high selectivity in *in vitro* studies. *In vitro* biochemical studies have shown that GFH375 can effectively inhibit the transition of KRAS G12D mutant or wild-type protein from the inactive state (GDP-bound) to the active state (GTP-bound), with half-maximal inhibitory concentrations (IC_{50}) of 6 nM and 9 nM, respectively. GFH375 can also directly block the binding of activated KRAS G12D or wild-type protein to its downstream effector protein RAF1, with IC_{50} values of 2 nM and 7 nM, respectively. GFH375 has shown high activity in multiple KRAS G12D-mutated tumor cell lines, with an IC_{50} of 0.2-0.9 nM for inhibiting the phosphorylation level of the downstream pathway protein ERK1/2, and an anti-tumor cell proliferation IC_{50} of 1-10 nM. In other KRAS mutation types (KRAS G12C, G12V) of tumor cell lines, as well as KRAS wild-type and KRAS function-dependent tumor cell lines, the activity of GFH375 is relatively weak, with anti-tumor cell proliferation IC_{50} values of 159-1895 nM and 17-75 nM, respectively. GFH375 has only very weak activity in other RAS protein mutations (NRAS G12D, Q61H, HRAS Q61L) and KRAS-independent cell lines (anti-cell proliferation IC_{50}: 1636 nM-7873 nM), indicating very low off-target non-specific cytotoxicity.

Preclinical *in vivo* studies have shown that GFH375 demonstrates excellent *in vivo* activity and anti-tumor efficacy in animal models of KRAS G12D-mutated tumors. In a human pancreatic carcinoma

Panc 04.03 xenograft tumor mouse model, a single dose of GFH375 (100 mg/kg) produced strong and durable inhibition of intratumoral ERK1/2 phosphorylation levels. In the Panc 04.03 and another human pancreatic carcinoma AsPC-1 xenograft tumor mouse model, GFH375 (10 mg/kg, 30 mg/kg, and 100 mg/kg) administered orally twice daily for 14 consecutive days demonstrated dose-dependent anti-tumor efficacy, with effective doses of 5 mg/kg and 10 mg/kg, respectively, and caused significant tumor regression at the high dose (100 mg/kg).

GFH375 has high selectivity for the KRAS G12D target, with a low potential risk of off-target effects. At 10 μM, GFH375 showed no inhibitory activity against 72 representative human kinases and no inhibitory activity against 38 of 44 important safety-related targets, including G protein-coupled receptors (GPCRs), ion channels, and enzymes. For the 6 affected targets, the predicted IC_{50} concentration of GFH375 is at least >1000 nM, which is much higher than the aforementioned IC_{50} concentrations for ERK1/2 phosphorylation inhibition and anti-tumor cell proliferation in KRAS G12D cells.

The safety pharmacology studies of GFH375 included *in vitro* effects on the hERG potassium channel current and *in vivo* effects on the central nervous, respiratory, and cardiovascular systems in rats and beagle dogs, respectively.

At concentrations of 3, 6, 12, and 24 μM, GFH375 showed a concentration-dependent inhibitory effect on the hERG potassium channel current expressed in transfected human embryonic kidney cells (HEK293), with an IC_{50} value of 9.65 μM.

SD rats were given single oral gavage doses of 50, 100, and 200 mg/kg of GFH375, and the effects of the test article on the central nervous system were evaluated through a functional observation battery (FOB) while simultaneously measuring forelimb grip strength and body temperature. The results showed that the no observed adverse effect level (NOAEL) of GFH375 on the central nervous system was 200 mg/kg.

SD rats were given single oral gavage doses of 50, 100, or 200 mg/kg of GFH375, and the effects on the respiratory system were assessed using a whole-body plethysmography system. The results showed that the no observed adverse effect level (NOAEL) of GFH375 on the respiratory system in this study was 200 mg/kg.

Beagle dogs were given oral gavage doses of 5, 10, and 25 mg/kg of GFH375 according to a "crossover design", and the effects on the cardiovascular system were evaluated using telemetry. The results showed that the NOAEL of GFH375 on the cardiovascular system of Beagle dogs was 25 mg/kg/day.

1.2.1.2 Summary of PK Studies

GFH375 showed low permeability in Caco-2 cells with significant efflux transport. It can be administered orally, with a preclinical absolute bioavailability of 8.40-16.3% across species, and systemic exposure increased with increasing oral doses. There was no significant sex difference overall after administration in dogs, while there was some sex difference in rats; after repeated dosing in rats, there was no accumulation at PK doses, but accumulation was observed in female rats at TK doses; accumulation was observed in dogs after repeated dosing.

GFH375 showed very high binding in mouse plasma, high binding in rat and dog plasma, and moderate binding in monkey and human plasma. The steady-state volume of distribution (Vd_{ss}) in rats and dogs ranged from 15.7-22.5 L/kg, both showing high distribution. Total radioactivity of [^{14}C]GFH375 was widely distributed in rats, with C_{max} in descending order in the stomach wall, intestinal wall, liver, spleen, kidney, lung, heart, ovary/uterus, body fat, skeletal muscle, whole blood, and plasma. Radioactivity levels were low in the whole brain and testis/epididymis, with no significant red blood cell binding.

The main metabolic pathway of [^{14}C]GFH375 in rats was glucuronidation, with minor pathways including mono-oxidation, dehydrogenation, defluorination, cysteine conjugation, glycine conjugation, and acetylation. In beagle dog plasma, the main metabolic pathways were oxidation, dehydrogenation, defluorination, dealkylation, glucuronidation, and glutathione conjugation followed by hydrolysis to remove glutamic acid. CYP3A is its main metabolic enzyme, and the *in vivo* and *in vitro* metabolic profiles are basically consistent.

GFH375 showed moderate and low clearance in male and female rat plasma, respectively, and high clearance in dog plasma. It has a long half-life in rats and dogs, ranging from 8.18-14.3 h. Total radioactivity of [^{14}C]GFH375 in rats was mainly excreted directly in feces or via bile into feces, with urine being a minor excretion route.

GFH375 showed no inhibitory effect on CYP1A2 and CYP2C9, but had an inhibitory effect on CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP3A (with midazolam as substrate), and CYP3A (with testosterone as substrate), with IC_{50} values of 42.8, 93.2, 42.6, 26.2, 6.40, and 7.95 μM, respectively. GFH375 has significant time-dependent inhibition on CYP3A (with midazolam and testosterone as substrates, respectively). GFH375 is not an inducer of CYP1A2 and CYP2B6, but its potential as an inducer of CYP3A4 at the gene level cannot be excluded. GFH375 is not a substrate of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide 1B1 (OATP1B1), or organic anion-transporting polypeptide 1B3 (OATP1B3) transporters, but it is a substrate of P-gp. GFH375 showed

no inhibitory effect on BCRP, OATP1B1, organic cation transporter 2 (OCT2), or multidrug and toxin extrusion protein 2-K (MATE2-K), but had an inhibitory effect on P-gp, OATP1B3, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), and multidrug and toxin extrusion protein 1 (MATE1), with IC_{50} values of 16.9, 17.4, 2.56, 24.4, and 15.6 μM, respectively. This suggests that GFH375 has potential for drug-drug interactions.

1.2.1.3 Summary of Toxicology Studies

In 14-day repeated-dose toxicity dose-range finding studies conducted in SD rats and beagle dogs, the results showed that the severe toxicity dose in 10% of animals (STD_{10}) in SD rats was greater than 150 mg/kg/day. The highest non-severely toxic dose (HNSTD) in beagle dogs was 100 mg/kg/day.

In a 4-week repeated-dose Good Laboratory Practice (GLP) toxicity study in SD rats, doses of 50, 100, 200 mg/kg/day of GFH375 or blank vehicle [5% (v/v) LABRASOL + 5% (v/v) PEG400 + 90% sterile water for injection] were administered by oral gavage once daily for 28 consecutive days. At a dose of 100 mg/kg/day, 1 female animal death was observed; at a dose of 200 mg/kg/day, 2 male and 3 female animal deaths were observed. Surviving animals in the 200 mg/kg/day dose group also showed test article-related clinical signs, changes in hematology and serum chemistry parameters, and histopathological changes. At the end of the recovery period, all the above changes were reversed. Under the conditions of this study, the STD_{10} of the test article was 100 mg/kg/day.

In a 4-week repeated-dose GLP toxicity study in beagle dogs, doses of 5, 10, 25 mg/kg/day of GFH375 or blank vehicle [5% (v/v) LABRASOL + 5% (v/v) PEG400 + 90% sterile water for injection] were administered by oral gavage once daily for 28 consecutive days. No animal deaths were observed during the study. Test article-related clinical signs, changes in hematology and serum chemistry parameters, and histopathological changes were observed. After the recovery period, the changes were reversible or showed a trend toward recovery. Under the conditions of this study, the HNSTD of GFH375 for beagle dogs was 25 mg/kg/day.

The genotoxicity of GFH375 was evaluated using a standard battery of genotoxicity tests, and the results were negative.

1.3. Rationale for Study Design

1.3.1 Dose Selection

1.3.1.1 Rationale for Starting Dose Selection

The selection of the starting dose in the Phase I part is based on the results of preclinical toxicology studies, and the starting dose is calculated according to the recommendations of the ICH S9 guideline on the maximum recommended starting dose (MRSD) method.

Pivotal 4-week toxicology studies compliant with GLP were conducted in SD rats and beagle dogs. The study doses in rats were 50, 100, and 200 mg/kg/day, and the study doses in dogs were 5, 10, and 25 mg/kg/day. The study results showed that the severe toxicity dose in 10% of animals (STD10) in rats was 100 mg/kg/day, and the HNSTD in dogs was 25 mg/kg/day. According to ICH S9, based on 1/10 of the rodent STD10 or 1/6 of the non-rodent HNSTD, calculated for a patient weight of 60 kg, the corresponding human MRSDs are approximately 100 mg and 140 mg/day, respectively.

Pharmacodynamic studies showed that in an *in vivo* anti-tumor efficacy study conducted in the Panc 04.03 human pancreatic carcinoma CDX tumor mouse model, the effective dose of GFH375 was 5 mg/kg BID for 14 days. In the AsPC-1 human pancreatic carcinoma CDX tumor mouse model, the effective dose of GFH375 was 10 mg/kg BID for 14 days.

In summary, based on the safety indicated by the toxicology study results, and in combination with the GFH375 tablet strength, a dose level of 100 mg/day was selected as the starting dose for the first-in-human trial of GFH375.

1.3.1.2 Rationale for Phase II Dose Selection

After the completion of Phase I dose escalation and backfilling, the safety and RP2D will be confirmed based on a comprehensive assessment of preclinical *in vitro* and *in vivo* activity, clinical PK, clinical safety, and clinical efficacy data, and this dose will be used for the Phase II part.

1.3.2 Risk-Benefit Assessment

1.3.2.1 Potential Risks

Currently, a few small molecule inhibitors targeting KRAS G12D are in the clinical trial stage, with limited disclosure of safety and efficacy data. Among them, HRS-4642 is a KRAS G12D small molecule developed by Hengrui, administered intravenously for the treatment of patients with advanced solid tumors with KRAS G12D mutation. In its first-in-human Phase I part, a total of 18 participants were enrolled. The overall safety was good. Treatment-related AEs with a higher incidence (>2 cases) included blood cholesterol increased, infusion related reaction, proteinuria, anemia, hypertriglyceridemia, lipase increased, hypoproteinemia, blood glucose increased, alanine aminotransferase increased, platelet count decreased, hypercalcemia, hypocalcemia, pyrexia, fatigue, neutrophil count decreased, leucopenia, and aspartate aminotransferase increased[33].

Preclinical toxicology data for GFH375 suggest that its potential toxicities may include liver function impairment and gastrointestinal system adverse reactions. Based on the preclinical study results of GFH375 and data from other KRAS G12D inhibitors, the potential risks of GFH375 are as follows:

- Hepatic impairment

- Gastrointestinal system adverse reactions

1.3.2.2 Potential Benefits

The target population for this study is patients with KRAS G12D mutation-positive advanced NSCLC, PDAC, CRC, and other solid tumors. For such patients, there are no effective treatment options, and chemotherapy or chemotherapy combined with immunotherapy remains the main treatment regimen. No therapeutic drug targeting this mutation has been approved for marketing.

Currently, drugs targeting KRAS G12D have entered clinical studies and have shown preliminary clinical results. Preliminary efficacy data for the KRAS G12D small molecule inhibitor HRS-4642 show that among 18 enrolled participants with advanced solid tumors, 7 participants had target lesion shrinkage. Among them were 10 participants with NSCLC, and 5 of these participants had target lesion shrinkage.

Preclinical studies of GFH375 showed that in a human pancreatic carcinoma tumor animal model carrying the KRAS G12D mutation, a single oral gavage dose of GFH375 resulted in dose-dependent inhibition of ERK1/2 protein phosphorylation, a downstream protein in the KRAS pathway, observed in the tumor. Long-term oral gavage administration (twice daily for 14 consecutive days) showed significant anti-tumor efficacy, with an effective dose of 5-10 mg/kg, and tumor regression was observed at a high dose (100 mg/kg).

In summary, it is expected that GFH375 is worthy of further clinical research in this population to provide a new anti-tumor treatment option for these patients.

1.3.2.3 Risk-Benefit Assessment

Based on the biological characteristics of the KRAS G12D target, the product characteristics of GFH375, and the non-clinical data obtained for GFH375 as described above, this protocol has designed corresponding inclusion/exclusion criteria, lifestyle requirements, and safety examination and follow-up procedures. Through rigorous protocol design, selection of study sites, collection of drug safety information, and timely updating and communication of drug safety information, the risks to participants will be minimized as much as possible. Based on clinical data from products with the same mechanism of action, it is expected that participants who meet the inclusion/exclusion criteria are likely to benefit from GFH375 monotherapy. The overall benefit/risk assessment supports the conduct of this study.

2 Study Objectives and Endpoints

This is a Phase I/II study. The study objectives and endpoints are summarized below.

The objectives and endpoints of the Phase I part of the study include:

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 pharmacokinetic (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, V_z/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 the investigator according to 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

The objectives and endpoints of the Phase II part of the study include:

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 KRAS G12D mutation	• ORR as assessed by RECIST 1.1
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	• Incidence and severity of AEs and SAEs • Changes in vital signs, ECGs, and laboratory tests

CRC, and other advanced solid tumors with KRAS G12D mutation	
• 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 associated with 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

3 Study Design

3.1. Overall 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 carrying the KRAS G12D mutation, and to determine the MTD and 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.

A Safety Monitoring Committee (SMC), composed of investigators and the sponsor, will be established during the study. For details, please refer to Chapter 10 and the SMC Charter for this study.

3.1.1 Phase I Part Dose Escalation

Phase I will enroll patients with KRAS G12D-positive advanced solid tumors. The study schematic is shown in Figure 2.

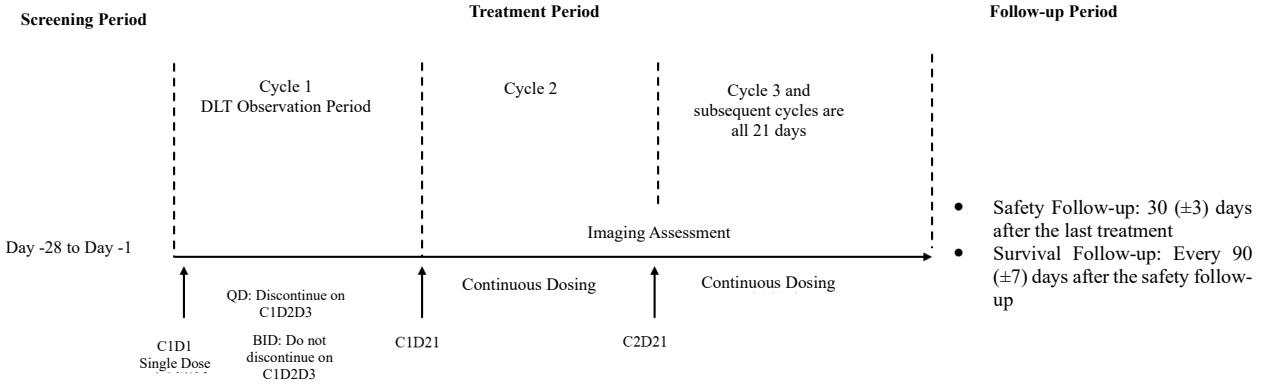

Figure 2 Phase I Part Schematic

According to the BOIN design, 3-6 participants will be enrolled in each dose cohort (except during accelerated titration) for 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 receive treatment with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is assessed by the investigator and sponsor as potentially clinically beneficial, 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).

Additional participants may be enrolled if more dose levels or alternative dosing regimens need to be explored.

After enrollment, participants will receive oral administration of GFH375, with each treatment cycle being 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. The planned escalating doses are shown in Table 1.

The GFH375 dosing regimen will be comprehensively evaluated during dose escalation. If necessary, dose exploration with a twice daily (BID) dosing regimen will be conducted. Dose escalation for QD and BID dosing regimens can be conducted independently and in parallel.

The first cycle after the first administration will serve as the DLT observation period. A DLT-evaluable case must meet one of the following two conditions:

- The participant experiences a DLT event, or
- The participant does not experience a DLT event and has received at least 15 days of the planned dosing of GFH375 in the first cycle.

If no DLT event occurs, the participant will continue treatment, with dose adjustments permitted as allowed by this protocol, until progressive disease (PD), unacceptable toxicity, or discontinuation of study treatment for other reasons. If a participant experiences a DLT event during the DLT observation period, and if the investigator and sponsor assess that the participant can benefit from continuing treatment with GFH375, treatment with GFH375 will be resumed after the relevant adverse event (AE) has resolved. Refer to Table 4 and Table 5 for the criteria for resumption of dosing.

Participants enrolled in Phase I will undergo intensive PK sampling and have matching ECGs collected with PK sampling to evaluate the PK characteristics and safety of GFH375. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the Informed Consent Form (ICF), initiation of other anti-tumor therapy, or the termination of the study.

Table 1 Phase I Part QD Dose Cohorts with Planned/Completed Escalation

	Phase I Part QD Dose Cohorts with Planned/Completed Escalation *
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

Note: Intermediate dose exploration of the above doses, such as 150 mg, 300 mg, 500 mg, 800 mg, 900 mg, 1100 mg QD, etc., may be conducted during the escalation process based on the clinical data obtained, including safety, PK, and possible efficacy.

Based on the data obtained, including safety, PK, and preliminary efficacy results, BID dose regimen 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 2 Phase I Part Possible BID Dose Cohorts for Exploration

	Phase I Part Possible BID Dose Cohorts for Exploration*
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: Intermediate dose exploration of the above doses, such as 250 mg BID, etc., may be conducted.

3.1.1.1 DLT Definition

A DLT is an AE that occurs within 21 days after the first dose, is related to the investigational drug GFH375, and meets the following severity criteria. The severity of AEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:

- Grade ≥ 4 absolute neutrophil count (ANC) decreased for ≥ 5 days;
- Grade ≥ 3 febrile neutropenia (ANC $<1.0 \times 10^9$/L with a single body temperature > 38.3°C or a sustained body temperature ≥38°C for more than 1 hour);
- Grade ≥ 4 platelet count decreased for ≥ 5 days;
- Grade ≥ 3 platelet count decreased with Grade ≥ 2 hemorrhage;
- Grade ≥ 4 anemia;
- If baseline ALT or AST is Grade ≤ 1: Grade ≥ 3 serum transaminases increased (ALT or AST) lasting > 7 days is considered a DLT; if baseline ALT or AST is Grade 2, then ALT or AST >

10×ULN lasting > 7 days is considered a DLT;

- Grade ≥ 3 serum bilirubin increased;
- According to Hy's Law, AST or ALT > 3×ULN (if baseline metastases to liver are present, then > 3 times the baseline value is required), with concurrent total bilirubin > 2×ULN (causes such as biliary obstruction or other causes like hepatitis, intrahepatic tumor progression, etc., must be excluded);
- Grade ≥ 3 other toxicities (non-hepatic, non-hematologic), with the exception of the following:
  - Grade 3 nausea or vomiting, diarrhea, lasting no more than 3 days with/without symptomatic supportive care;
  - Grade 3 fatigue, lasting no more than 3 days with/without symptomatic supportive care;
  - Asymptomatic Grade 3 abnormal laboratory results lasting no more than 7 days with intervention, such as elevated cholesterol, elevated triglycerides, gamma-glutamyl transferase (GGT) increased, alkaline phosphatase (ALP) increased, blood amylase increased, etc.

Toxicities meeting the above criteria that occur after the DLT observation period will also be considered important factors in the safety evaluation. In addition, other treatment-related toxicities that may be assessed as DLTs will be determined after discussion between the sponsor and the investigator.

During the first cycle (DLT observation period), AEs that meet the DLT criteria should be reported to the sponsor within 24 hours of awareness of their occurrence.

3.1.1.2 Dose Escalation Rules and MTD Definition

Accelerated titration is permitted for the first two dose levels of the QD dosing regimen, meaning the first participant will receive treatment at the first dose level. If no Grade ≥2 treatment-related AE is observed in participants in the first two dose cohorts during the DLT observation period, 3-6 participants will be enrolled at the next higher dose level, and the BOIN design will be used for this cohort and subsequent dose escalations. Conversely, if any Grade ≥2 treatment-related AE or DLT event is reported in the first or second dose cohort, the study will switch directly to the BOIN design, starting from the lowest dose cohort where the Grade ≥2 treatment-related AE or DLT event was observed. Provided that accelerated titration is completed for the first dose, the decision on whether to use accelerated titration for the second dose level will be made by the SMC based on discussion of the PK and safety data from the first dose level. Subsequent dose levels will use the BOIN design to

determine the MTD, with a target toxicity probability of 0.3. If dose exploration of the BID dosing regimen is required, the BOIN design will be used for dose escalation, with a target toxicity probability of 0.3. Each dose level will enroll 3-6 participants for treatment. If more dose levels or dosing regimens need to be explored, additional participants may be enrolled.

The BOIN design will assign the dose level for the next group of participants according to the dose escalation/de-escalation rules shown in Table 3.

Table 3 BOIN Design Dose Escalation/De-escalation Rules

Decision	Total number of participants treated at the current dose						
	3	**4**	**5**	**6**	**7**	**8**	**9**
Escalate, if number of participants with DLT is ≤	0	0	1	1	1	1	2
De-escalate, if number of participants with DLT is ≥	2	2	2	3	3	3	4
Eliminate dose, if number of participants with DLT is ≥	3	3	4	4	5	5	5

The specific rules are as follows:

- If the decision based on the rules in the table above is neither to escalate, de-escalate, nor eliminate the dose, then continue treating the next group of participants at the current dose.
- "Eliminate dose" in the table above means to eliminate the current and higher doses from the study.
- If the current dose is eliminated, the dose will be automatically de-escalated to the next lower level to treat participants.
- If the lowest dose level is eliminated, the study will be terminated early to ensure participant safety. In this case, the MTD cannot be determined.
- If the current dose is the lowest dose level and the rule suggests de-escalation, the next group of participants will still be treated at the current lowest dose.
- If the current dose is the highest dose level and the rule suggests escalation, newly enrolled participants will still be treated at the highest dose.
- The dose escalation part can be terminated when there are ≥6 evaluable participants at the recommended next dose level.
- There must be at least 6 evaluable participants treated at the RP2D.

After the dose escalation part is completed, isotonic regression analysis will be used based on the DDS to determine the MTD. The online BOIN software at http://www.trialdesign.org will be used to

perform isotonic regression analysis to obtain the isotonic estimates of the toxicity probability for each dose level. The dose level closest to the target toxicity rate of 0.3 is the MTD. If there are 2 or more dose levels that meet the condition simultaneously, the highest dose level with an isotonic estimate <0.3 or the lowest dose level with an isotonic estimate ≥0.3 will be selected.

3.1.1.3 Backfilling of Participants in the Dose Escalation Part

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 receive treatment with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is assessed by the investigator and sponsor as potentially clinically beneficial, 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 level (including participants enrolled in the BOIN dose escalation part).

Backfilled participants will complete the relevant visits according to the Phase I part Schedule of Activities and the Phase I part PK blood sampling schedule.

3.1.1.4 Intra-participant Dose Escalation

In principle, intra-participant dose escalation will not be performed during the dose escalation part. For participants enrolled in Phase I, after agreement from the investigator and sponsor, intra-participant dose adjustment to receive RP2D monotherapy is permitted after the RP2D for this protocol has been confirmed.

3.1.1.5 Rationale for Selection of Recommended Phase II Dose (RP2D)

As of January 17, 2025, a total of 33 participants have been enrolled in the Phase I part of this study (including 22 participants in the dose escalation part and 11 backfilled participants), and DLT observation has been completed for 7 dose cohorts: 100 mg, 200 mg, 400 mg, 600 mg, 750 mg, 900 mg QD, and 300 mg BID. Enrolled participants include 14 with pancreatic carcinoma, 11 with NSCLC, 5 with CRC, and 1 each with ampullary cancer, endometrial cancer, and bile duct cancer. Based on all available safety, tolerability, PK, and efficacy data, after discussion between the sponsor and key members of the SMC, the RP2D was determined to be 600 mg QD. The rationale for this selection is as follows:

Safety and tolerability:

No DLTs or Grade 5 AEs occurred in any dose cohort. In the 900 mg dose cohort, 2 of the 3 enrolled

participants discontinued treatment in Cycle 1 due to AEs and poor tolerability, indicating poor overall tolerability. The 750 mg dose cohort had a higher incidence of more severe gastrointestinal toxicity (Grade 2/3 diarrhea and vomiting), and the duration of vomiting was relatively long. In the 750 mg dose cohort, the incidence of Grade ≥2 diarrhea and Grade 2 vomiting were both 50%, including one case of Grade 3 diarrhea. In dose cohorts below 750 mg (QD), no Grade 3 diarrhea was observed, and the incidence of Grade 2 diarrhea was ≤20.0%. In the 300 mg BID dose cohort, the incidence of Grade 2 diarrhea and vomiting were 33.3% and 66.7%, respectively, which were higher than in the 600 mg QD dose cohort. The incidence of ≥ G3 treatment-emergent AEs (TEAEs) and treatment-related AEs (TRAEs) was higher in the 400 mg dose cohort than in the 600 mg QD dose cohort. There was no significant difference in the incidence of SAEs. The incidence of dose interruption due to TRAEs was also higher in the 400 mg QD dose cohort than in the 600 mg dose cohort. In the 600 mg dose cohort, only 1 participant discontinued dosing due to a TRAE, and no participants had a dose reduction due to a TRAE. The overall safety and tolerability of the 600 mg dose cohort were similar to or better than the 400 mg dose cohort. The 600 mg dose cohort was generally safe, manageable, and well-tolerated.

PK:

After oral administration of 100-900 mg of GFH375, exposure to GFH375 increased with increasing dose in the 100-400 mg range, but the increase in exposure was not significant in the 400-900 mg range. After QD oral administration of 400 mg-900 mg of GFH375, the median T_{max} was 2-4 h, the single-dose half-life was 18.5-21.6 h, and the accumulation ratio after continuous QD dosing was 0.859-1.30, with no significant accumulation observed. When the dose was higher than 400 mg, the mean trough concentration of GFH375 (34.4-50.2 ng/mL) could be sustained above the preclinical cellular IC_{90} (approximately 11 ng/mL). As mentioned earlier, overall, the safety and tolerability of the 400 mg and 600 mg cohorts were better than those of the 750 mg and 900 mg cohorts. However, the 400 mg cohort showed greater inter-individual variability (geometric CV% for C_{max} and AUC was 111%-127%). Compared to 400 mg, 600 mg can provide participants with higher and more stable exposure.

Efficacy:

Partial responses were observed in participants with pancreatic carcinoma and NSCLC starting from the 400 mg dose cohort. In the 400 mg dose cohort, the ORR and DCR for participants with pancreatic carcinoma were both 100% (2/2), while for participants with NSCLC, the ORR was 0 and the DCR was 50% (1/2). In the 600 mg QD and 300 mg BID dose cohorts, the ORR for pancreatic carcinoma was 25% (1/4) and the DCR was 100% (4/4). For NSCLC, the ORR was 75% (3/4) and the DCR was

100% (4/4). In the 750 mg dose cohort, the ORR for pancreatic carcinoma was 0 and the DCR was 100% (2/2). For NSCLC, both the ORR and DCR were 100% (1/1). In participants with NSCLC, the efficacy of the 600 mg dose cohort was superior to that of the 400 mg cohort.

Based on a comprehensive review of the above data, the RP2D was determined to be 600 mg QD.

3.1.2 Phase II Part

The Phase II part is an open-label, multicenter study. The overall study plan is shown in Figure 3. The objective is to evaluate the efficacy, safety, and PK characteristics of GFH375 in patients with advanced non-small cell lung cancer, advanced pancreatic carcinoma, colorectal cancer, 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 GFH375 monotherapy at the RP2D, with a treatment cycle of 21 days. All participants enrolled in this part will undergo sparse PK sampling according to the Phase II part PK blood sampling schedule and have matching ECGs collected with PK sampling.

- Advanced NSCLC participant cohort: Approximately 73 participants with advanced NSCLC carrying the KRAS G12D mutation are planned for enrollment.
- Advanced PDAC participant cohort: Approximately 94 participants with advanced PDAC carrying the KRAS G12D mutation are planned for enrollment.
- Advanced CRC participant cohort: Approximately 50 participants with advanced CRC carrying the KRAS G12D mutation are planned for enrollment.
- Participant cohorts with other solid tumors: Approximately 100 participants with other advanced solid tumors carrying the KRAS G12D mutation are planned for enrollment, such as bile duct cancer, appendix cancer, etc., carrying the KRAS G12D mutation.

Eligible participants who are screened will receive GFH375 monotherapy until PD, unacceptable toxicity, or discontinuation of study treatment for other reasons. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the Informed Consent Form (ICF), initiation of other anti-tumor therapy, or the termination of the study.

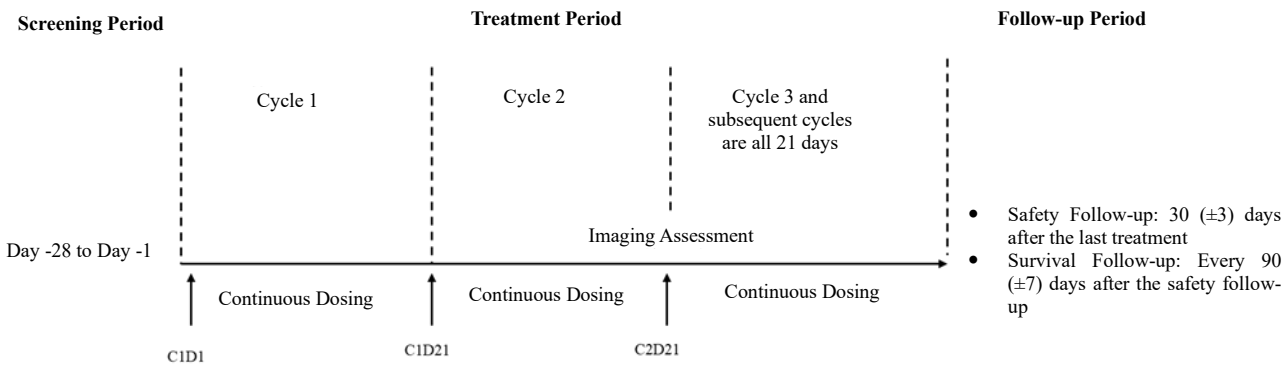

Figure 3 Phase II Part Schematic

3.2. Definition of End of Study

The end of the study is defined as the last participant having received at least 6 months of study treatment or having withdrawn early (whichever occurs first).

3.3. Early Termination of the Study

This study may be terminated or suspended early due to a decision by a regulatory authority, an opinion from an ethics committee (EC), or a judgment and decision made jointly by the sponsor and the investigator. In addition, the sponsor reserves the right to stop the development of GFH375.

Reasons for early termination or suspension of the study may include:

- Determination of an unexpected, significant, or unacceptable risk to participants;
- Existing efficacy results support early termination of the study;
- Low compliance with protocol requirements.

The party that decides to suspend/terminate the study will issue a written notice and record the reason for the study termination or suspension to the investigator, sponsor, and regulatory authorities. If the study is terminated or suspended early, the investigator should immediately notify the EC and the sponsor, and provide the relevant reasons.

Once the aforementioned issues leading to the suspension of the investigational drug, such as safety and protocol compliance, are resolved and with the consent of the sponsor, EC, and/or regulatory authorities, the study will be resumed.

4 Study Population

Participants must meet all inclusion criteria and not meet any of the exclusion criteria.

4.1. Inclusion Criteria

Participants must meet all of the following criteria to participate in this study:

1. Participants who voluntarily participate in the study and sign the ICF.
2. Male or female, aged 18 - 75 years at the time of signing the ICF.
3. Participants with histologically or cytologically confirmed locally advanced or metastatic malignant tumor, who must meet the following criteria:

（1） Phase I Part: Either of the following criteria is met: 1) PD after standard of care and no other standard of care is available; or 2) standard of care has been confirmed to be ineffective, intolerable, or considered unsuitable.

（2） Phase II Part:

a) Advanced NSCLC:

- ✓ Participants who have progressed after prior treatment with anti-PD-(L)1 therapy and/or platinum-based chemotherapy (unless contraindicated or intolerant), and have received no more than 3 prior lines of therapy;
- ✓ If prior adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy.

b) Advanced PDAC: Participants who have progressed after adequate treatment with a gemcitabine-based chemotherapy regimen or FOLFIRINOX/mFOLFIRINOX regimen, or are unsuitable for standard of care due to reasons such as unacceptable toxicity, and have received no more than 3 prior lines of therapy. Those with high microsatellite instability (MSI-H) and/or deficient mismatch repair (dMMR) must have progressed after at least one prior line of anti-PD-1 therapy. If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy.

c) Advanced CRC: Participants who have progressed after at least two lines of standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity. Participants must have experienced PD or recurrence during or after

treatment with fluorouracil, irinotecan, and oxaliplatin for metastatic disease, unless the investigator considers the participant unsuitable for the above treatment regimens. Those with known MSI-H and/or dMMR must have received prior treatment with an immune checkpoint inhibitor (if applicable). If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy.

d) Other solid tumors: Participants who have progressed after standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity.

4. Participants enrolled in this study must provide a written test report confirming KRAS G12D mutation-positive status. NSCLC and PDAC participants enrolled in Phase II must provide a compliant archived tumor tissue sample or undergo a biopsy during the screening period before enrollment. If a tumor tissue sample cannot be provided and a biopsy cannot be performed during the screening period, the investigator must communicate with the sponsor's medical monitor and obtain their consent before enrollment.
5. According to RECIST 1.1, participants enrolled in Phase I must have at least one evaluable lesion, and participants enrolled in Phase II must have at least one measurable lesion.
6. Toxicities from prior anti-tumor therapy must have resolved to baseline level (excluding alopecia) or ≤ Grade 1 (for neurological toxicity, ≤ Grade 2).
7. Investigator-assessed life expectancy ≥ 12 weeks.
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 (see Appendix 2 for scoring criteria).
9. Adequate organ function, including:
   - Hematopoietic function: Absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥ 75×10^9/L, hemoglobin ≥ 9 g/dL, with no transfusion or treatment with granulocyte colony-stimulating factor, thrombopoietin, or erythropoietin within 14 days before the blood test.
   - Liver function:
     - Both AST and ALT < 2.5×ULN; for participants with baseline metastases to liver, both AST and ALT < 5×ULN;
     - Total bilirubin (TBIL) < 1.5×ULN; for participants with Gilbert's syndrome: TBIL < 2×ULN.
   - Renal function: Creatinine clearance (CrCl) ≥ 50 mL/min (calculated by Cockcroft-Gault

formula, see Appendix 3).

- Coagulation function: Prothrombin time (PT) or activated partial thromboplastin time (APTT) < 1.5×ULN, international normalized ratio (INR) < 1.5×ULN or within the target range for anticoagulant therapy.
- Albumin level ≥30 g/L (for PDAC participants enrolled in Phase II only).

10. Women of childbearing potential (WOCBP) and male participants with partners who are WOCBP must agree to use effective methods of contraception from the time of signing the ICF until 30 days after the last study treatment. WOCBP must have a negative serum pregnancy test result within 7 days before dosing.
11. Participants who are able to communicate well, adhere to the follow-up schedule, and comply with the protocol requirements in the investigator's judgment.

4.2. Exclusion Criteria

Participants who meet any of the following criteria cannot be enrolled in this study:

1. Other malignant tumor that has progressed or required treatment within 3 years prior to enrollment, with the exception of adequately treated carcinoma in situ, basal cell carcinoma, or squamous cell carcinoma of skin.
2. Patients with unstable brain metastasis as judged by the investigator. Patients with incidentally detected brain metastasis during screening may be enrolled if they are asymptomatic and do not require therapeutic intervention; enrollment is permissible if the investigator judges the brain metastasis to be stable, the hormone dose is stable, and the prednisone dose is ≤10 mg/d (or an equivalent dose if other steroid drugs are used).
3. Phase II Part:
   a) Advanced NSCLC: Exclusion of known other driver gene mutations or fusions, such as EGFR, ALK, BRAF (V600E), HER2, MET (exon 14), ROS1, RET, KRAS G12C, or NTRK1/2/3
   b) Advanced CRC: Exclusion of known other driver gene mutations, amplifications, or fusions, such as BRAF (V600E), HER2, NTRK, or RET
   c) Advanced PDAC: Exclusion of known other driver gene mutations or fusions, such as BRAF (V600E), BRCA, NTRK, or RET
4. Prior targeted therapy against KRAS G12D or pan-KRAS (with primary targeting effect on KRAS G12D).
5. Receipt of palliative radiation within 14 days before administration of the study drug.
6. Receipt of other anti-tumor therapy within 28 days or 5 half-lives (whichever is shorter) before dosing, including chemotherapy, targeted therapy, endocrine therapy, immunotherapy, Chinese patent medicines with definite anti-tumor effects, and other investigational drugs or devices, with the exception of endocrine maintenance therapy.
7. Concomitant clinically significant severe cardiovascular disorder:
   - Clinically significant severe cardiovascular events within 6 months before the first study treatment, such as myocardial infarction, angina unstable, symptomatic cardiac failure congestive (New York Heart Association Class III or IV), severe arrhythmia requiring drug therapy, or receipt of angioplasty, stenting, and coronary artery bypass graft surgery, etc.
   - Clinically significant QT/QTcF prolongation (based on the average of three QTcF values

during the screening period, QTcF > 470 ms) or a family history of QT interval prolongation.

- Hypertension that remains poorly controlled after standard treatment.

8. Stroke or other severe cerebrovascular disorder within 6 months prior to enrollment.
9. History of deep vein thrombosis or any other severe thromboembolism within 3 months prior to enrollment.
10. Concomitant pleural effusion, ascites, or pericardial effusion requiring repeated drainage or causing significant symptoms.
11. Concomitant superior vena cava syndrome.
12. History of gastrointestinal perforation and/or fistula within 6 months before the first dose of study drug that has not healed after surgery; current unstable or active gastrointestinal ulcer or other high-risk gastrointestinal hemorrhage diseases; presence of biliary or pyloric obstruction, or persistent recurrent vomiting (≥3 episodes within 24 hours); high risk of rupture, hemorrhage, or gastrointestinal/respiratory fistula due to tumor invasion of surrounding vital structures (e.g., major blood vessels, trachea); or other gastrointestinal dysfunction or diseases that may significantly affect the absorption of GFH375, or inability or unwillingness to swallow tablets.
13. Concomitant clinically significant interstitial lung disease, radiation pneumonitis, or immune-related pneumonitis requiring treatment.
14. Concomitant major acute or chronic infectious diseases, including:
    - Active infection requiring intravenous antibiotic therapy within 7 days prior to enrollment.
    - Positive for human immunodeficiency virus antibody (HIV-Ab) at baseline.
    - Active hepatitis b virus infection (HBsAg positive with positive HBV-DNA).
    - Active hepatitis c virus infection (HCV-Ab positive with positive HCV-RNA).
    - Active tuberculosis.
15. Other poorly controlled systemic diseases, such as diabetes mellitus.
16. Undergone or planning to undergo major surgery as judged by the investigator within 28 days before the first dose (excluding needle biopsy).
17. History of organ transplant or preparing to receive an organ transplant.
18. Need for acid-suppressing drugs, including proton pump inhibitors and novel acid-suppressing drugs (e.g., potassium-competitive acid blockers), within 7 days before or during the administration of the study drug.
19. Receipt of strong inhibitors or inducers of CYP3A or P-gp within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug.

20. Receipt of known sensitive substrates of CYP3A or OAT1 within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug. Unless agreed for enrollment after review by the investigator and sponsor.
21. Known allergy to the study drug or its components.
22. Severe mental or psychological illness, or history of drug abuse or severe alcoholism.
23. Pregnant or lactating women.
24. Other conditions that, in the investigator's judgment, make the participant unsuitable for the study.
25. **Phase II PDAC participants:** Numeric Rating Scale (NRS) for pain score ≥4 after standardized treatment with analgesics.

5 Study Treatment

5.1 Treatment Regimen

Phase I

The initial dose of GFH375 is 100 mg QD, with each treatment cycle being 21 days. Participants will continue treatment until PD or the occurrence of unacceptable toxicity leading to treatment discontinuation.

Phase II

Participants in Phase II will receive GFH375 at the RP2D, dosed daily. Each treatment cycle is 21 days. Participants will continue treatment until PD, unacceptable toxicity, or other reasons leading to treatment discontinuation.

5.2 Investigational Product

5.2.1 Description of Investigational Product

Investigational Product	GFH375 tablets
Active Ingredient	GFH375
Excipients	Mannitol, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, film coating premix (enteric-coated) - Opadry, purified water
Type	Oral solid dosage form
Dosage Form	Tablet
Strength	25 mg, 100 mg
Route of Administration	Oral
Storage Requirements	Store protected from light, sealed, at no more than 25°C
Shelf Life	Tentatively 24 months
Packaging and Labeling	High-density polyethylene bottles for oral solid drugs and polypropylene child-resistant combination caps for oral solid drugs, with a desiccant in a high-density polyethylene non-woven (Tyvek) bag for solid drugs inside. Each bottle will be labeled according to relevant regulatory requirements.

5.2.2 Treatment Assignment and Drug Dispensing

When a participant signs the written ICF, they will be assigned a participant number, which will be used for all study documents and Case Report Forms (CRFs). After completing the screening process,

eligibility for formal enrollment in the study will be determined based on the inclusion/exclusion criteria. All enrolled participants will receive GFH375 treatment.

The investigator or their designee must ensure that all drugs or related items for study treatment are maintained under appropriate temperature conditions during transport. If any deviation occurs, the issue must be reported and resolved before administering the study treatment.

Only participants enrolled in the study may receive the study treatment, and only authorized site personnel may provide or manage the study treatment product. All investigational intervention drugs or related items must be stored according to the storage conditions specified on the label in a secure, environmentally controlled, and monitorable (manually or automatically) area, ensuring that only the investigator and authorized site personnel have access to the study treatment product.

5.2.3 Administration of Investigational Product

GFH375 will be dispensed to participants by site personnel at scheduled visits. The quantity of drug dispensed at one time will ensure that the participant has enough medication for self-administration outside the hospital for the specified period.

GFH375 tablets are administered orally. Participants must be instructed to swallow the tablets whole and not to chew or break them. Fasting is required from 2 h before to 1 h after taking the medication, and the dosing time should be kept as consistent as possible each day. If a PK blood sample needs to be drawn in the morning, the medication should be taken after the blood draw. When dosing twice daily (BID), it is recommended to schedule the doses around 8:00 AM and 8:00 PM.

If a dose is missed, it should be taken within 4 hours of the scheduled time, the actual time of administration should be recorded, and subsequent doses should be taken as originally scheduled. If more than 4 hours have passed, the missed dose should not be taken, and the next dose should be taken as originally scheduled. If vomiting occurs after taking the medication, the dose should not be retaken. All actual dosing times should be recorded in the participant's diary, or any unexpected situations such as "missed dose" should be recorded.

5.3 Dose Adjustment

5.3.1 Permitted Dose Adjustments

In principle, dose adjustments are not permitted for participants enrolled in Phase I during the DLT observation period. The safety of participants using the investigational drug should be closely monitored during the study. It is recommended to manage TRAEs with best supportive care according to the practice of the respective study site.

Phase I participants who have completed the DLT observation period and participants enrolled in Phase II may have their doses adjusted based on actual clinical needs. Dose reduction will be performed according to the dose level settings of Phase I. A maximum of 2 dose reductions are permitted for the same participant. For participants receiving 100 mg QD of GFH375, dose reduction is not permitted in principle; for participants receiving 200 mg QD of GFH375, dose reduction is only permitted to 100 mg QD in principle. In special cases, the investigator should discuss further with the sponsor to reach an agreement. For detailed principles of dose adjustment, refer to Table 4 and Table 5.

In principle, intra-participant dose escalation will not be performed during the dose escalation part. For participants enrolled in Phase I, after agreement from the investigator and sponsor, intra-participant dose adjustment to receive RP2D monotherapy is permitted after the RP2D for this protocol has been confirmed.

5.3.2 Dose Interruption and Permanent Discontinuation

During the study, if a participant experiences an event related to the study treatment that meets any of the permanent discontinuation criteria in Table 4 or Table 5, GFH375 treatment should be stopped, and the participant should be followed up until the event resolves or returns to baseline. If the participant has shown a tumor treatment response and the investigator judges that continuing treatment is beneficial, after full communication with the sponsor, study treatment may be resumed at the same dose or a lower dose after the toxicity has recovered to the following levels, while continuing to closely monitor the relevant toxicity.

Table 4 Dose Adjustment Principles for Hematologic Toxicity

Drug-related Adverse Event	**Severity**	**Dose Adjustment**
Neutrophil count (ANC) decreased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level;
	Grade 4	Interrupt dosing until recovery to ≤ Grade 1 or baseline, and reduce by 1 dose level;
	Grade 3 febrile ANC decreased	Interrupt dosing until recovery to ≤ Grade 1 or baseline, and reduce by 1 dose level;
	Grade 4 febrile ANC decreased	Interrupt dosing and withdraw from study treatment;
Platelet count (PLT) decreased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level; if accompanied by hemorrhage requiring clinical intervention, reduce by 1 dose level;

Drug-related Adverse Event	**Severity**	**Dose Adjustment**
	Grade 4	Interrupt dosing until recovery to ≤ Grade 1 or baseline, and reduce by 1 dose level or interrupt dosing and withdraw from study treatment;
Anemia	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 2 or baseline, resume at the same dose or reduce by 1 dose level;
	Grade 4	Interrupt dosing until recovery to ≤ Grade 2 or baseline, and reduce by 1 dose level or interrupt dosing and withdraw from study treatment;
Other	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 2 or baseline, resume at the same dose or reduce by 1 dose level;
	Grade 4	For non-life-threatening AEs that can be controlled with treatment, dosing may be interrupted, and resumed at a reduced dose after the AE recovers to ≤ Grade 1 or baseline. For life-threatening AEs, dosing should be terminated.

Table 5 Dose Adjustment Principles for Non-hematologic Toxicity

Drug-related Adverse Event	Severity	Dose Adjustment
ALT/AST increased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level; if ALT/AST >5×ULN for more than 2 weeks, or ALT/AST > 8×ULN, interrupt dosing and withdraw from study treatment;
	Grade 4/Meets Hy's Law	Interrupt dosing, withdraw from study treatment;
Blood bilirubin increased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline; if there is no concurrent elevation of transaminases or alkaline phosphatase, treatment can be resumed at the same dose or reduced by 1 dose level;
	Grade 4	Interrupt dosing, withdraw from study treatment;
Blood amylase/lipase increased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline; if asymptomatic, treatment can be resumed at the same dose or reduced by 1 dose level; if symptomatic, reduce by 1 dose level;
	Grade 4	Interrupt dosing until recovery to ≤ Grade 1 or baseline and reduce by 1 dose level, or interrupt dosing and withdraw from study treatment;
Pancreatitis	Grade 2	Interrupt dosing until amylase and imaging are normal or not clinically significant; Reduce by 1 dose level;
	Grade 3/4	Interrupt dosing, withdraw from study treatment;
Nausea/vomiting/diarrhea	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level; if there is no improvement after more than 3 days of symptomatic supportive care, reduce by 1 dose level;
	Grade 4	Interrupt dosing, withdraw from study treatment;
Hypodynamia	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 2 or baseline; If recovery time is ≤ 1 week, it is recommended to resume treatment at the same dose; if >1 week, it is recommended to reduce by 1 dose level
Other systemic AEs	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline; If recovery time is ≤ 1 week, it is recommended to resume treatment at the same dose; if recovery time is >1 week, it is recommended to reduce by 1 dose level
	Grade 4	For non-life-threatening AEs that can be controlled with treatment, dosing may be interrupted, and resumed at a reduced dose after the AE recovers to ≤ Grade 1 or baseline. For life-threatening AEs, dosing should be terminated.

When the above hematologic toxicities occur, it is recommended to repeat the hematology within 3 days and then continue to closely monitor recovery. Resumption of treatment may be considered if the following criteria are met: non-hematologic toxicity recovers to ≤ Grade 1 or baseline; hematologic toxicity recovers to ANC ≥1.0×10^9/L, PLT ≥ 75×10^9/L, Hb ≥8 g/dL.

If a TRAE does not recover to a level where dosing can be resumed within 4 weeks, or if the same toxicity requiring dose interruption recurs after resuming treatment, permanent discontinuation of treatment should be considered. For the follow-up study procedures after permanent discontinuation, please refer to Section 6.4.2 of the protocol.

5.4 Prior and Concomitant Therapies

5.4.1 Prior Therapies

For prohibited prior/concomitant therapies before a participant participates in this study, please refer to Section 4 of the protocol.

After the participant signs the ICF, information on each line of prior therapy for the study disease (advanced solid tumors) will be collected, as well as other prior medications/therapies within 30 days before the first dose in this study.

5.4.2 Concomitant Therapies

From the first study treatment until the safety follow-up visit, all concomitant therapies, blood products, and non-drug interventions (such as paracentesis) received by the participant will be recorded.

5.4.2.1 Permitted/Cautionary Concomitant Therapies

During the study, the investigator must follow the principles below and use concomitant medications with caution to maximize participant safety.

Palliative and best supportive care for disease symptoms are permitted during the study, but concomitant therapies during the DLT observation period should be avoided if they may interfere with the assessment of DLTs. Palliative and supportive care for disease-related symptoms will depend on the investigator's judgment and relevant guidelines (e.g., American Society of Clinical Oncology guidelines). For example, palliative local radiation to treat painful bone lesions for symptomatic relief is permitted, provided that these lesions were known to exist at enrollment and are not the only target lesions. Before initiating radiation therapy, the investigator should assess and document whether the use of radiation is related to PD.

If a participant develops other diseases during the study, the investigator should determine whether drug therapy is necessary and should, as much as possible, avoid drugs that could significantly affect

the interpretation of study results, so as not to interfere with the assessment of the participant's safety and tolerability. If a serious adverse reaction or SAE occurs, or if the original condition aggravates or other serious diseases develop, the investigator should promptly provide concomitant and active treatment. If the criteria for participant withdrawal from the study are met, arrangements should be made for the participant's proper withdrawal.

- If the investigator is unsure whether a concomitant therapy will affect participant safety, or whether its use will affect the assessment of participant safety and tolerability, or whether its use will affect the participant's eligibility for enrollment and the evaluability of the data, they should discuss with the sponsor and reach an agreement before using the concomitant therapy.

During the study, participants should use known H2 receptor antagonists and antacids with caution, including but not limited to cimetidine, famotidine, nizatidine, and roxatidine. Antacids include hydrotalcite chewable tablets, aluminum phosphate gel, aluminum hydroxide, magnesium hydroxide, calcium carbonate, etc. If the above drugs must be used, GFH375 should be administered at least 2 hours before or after the administration of these drugs.

5.4.2.2 Prohibited Concomitant Therapies

During the study, participants should not receive the following treatments:

1) Any other anti-tumor therapy besides the study treatment (chemotherapy, immunotherapy, biological products, extensive radiotherapy, hormone therapy, targeted therapy, surgery, Chinese medicines with approved anti-tumor indications), including investigational or approved therapies. Participants receiving gonadotropin-releasing hormone (GnRH) antagonists for prostate cancer, oral contraception, or hormone replacement therapy may continue their medication.
2) The use of Chinese medicine (including Chinese patent medicine) is prohibited within 7 days before the first dose, and is not recommended until the final PK collection of the study is completed. If Chinese medicine is required to manage AEs or diseases, its use must be reviewed and approved by the sponsor beforehand.
3) Use of granulocyte colony-stimulating factor drugs as prophylactic treatment. Such drugs may only be used for the treatment of AEs at the investigator's discretion.
4) Any other investigational drugs for ongoing clinical studies, other than the study treatment.
5) The use of known strong inhibitors and inducers of CYP3A and P-gp is prohibited within 14 days before the first dose or 5 half-lives (whichever is longer) until two weeks after the last dose (see Appendix 4).

6) The use of known sensitive substrates of CYP3A or OAT1 is prohibited within 14 days before the first dose of the study drug or 5 half-lives of the drug (whichever is longer) until two weeks after the last dose (see Appendix 4). Unless the drug is reviewed and approved by the investigator and the sponsor's medical monitor during the screening period.

7) The use of known proton pump inhibitors and novel acid-suppressing drugs (e.g., potassium-competitive acid blockers), including but not limited to omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, ilaprazole, and vonoprazan, is prohibited within 7 days before the first dose of the study drug or 5 half-lives (whichever is longer) until one week after the last dose.

5.5 Treatment Compliance

Participants will follow the investigator's instructions to return all unused GFH375 tablets and packaging from the previous cycle on the specified visit day, and hand in the completed participant diary. The quantity returned by the participant will be counted, recorded, and archived, and medication compliance will be calculated based on the actual drug usage.

5.6 Drug Management

5.6.1 Receipt and Accountability of Investigational Product

The sponsor will provide GFH375 according to the expected enrollment plan of the study site. GFH375 will be shipped to the study site by a third-party logistics company with transportation qualifications. Authorized personnel at the study site will sign the shipping manifest to confirm receipt of the drug.

GFH375 can only be used for this study and can only be managed by personnel authorized by the investigator. To fully control the dispensing and use of GFH375, a quantity record must be made at each visit.

5.6.2 Storage and Management of Investigational Product

The investigator or other authorized study site personnel (e.g., pharmacist) will ensure that all investigational products are stored in a secure, access-controlled area that meets the storage conditions described in Section 5.2.1 of the protocol and that their storage complies with applicable regulatory requirements. After receiving the GFH375 tablets, participants will follow the instructions of the investigator or authorized personnel for proper storage. If any non-compliant storage situation is found, the investigator should contact the sponsor for guidance.

5.6.3 Return and Destruction of Investigational Product

Unused investigational product and packaging will be returned to and destroyed by the sponsor after

accountability, or the sponsor may authorize the study site to destroy them. The sponsor or its authorized personnel will provide the study site with instructions on how to destroy unused investigational product. If authorized to destroy at the study site, the investigator must ensure that all returns and destructions are conducted and documented in accordance with relevant regulations, guidelines, and rules.

5.6.4 Investigational Product Records

Designated personnel at the study site must promptly record the receipt, dispensing, use, inventory, destruction, return, and damage of the investigational product in accordance with relevant regulations and guidelines, and the operational procedures of this study.

5.7 Complaint Handling

To ensure participant safety and monitoring quality, and to assist in process and drug improvement, the sponsor will collect product complaints related to the investigational product used in the clinical study. For complaints related to concomitant medications, they will be reported directly to the manufacturer according to the product instructions. The investigator or their designee is responsible for completing the following product complaint process in accordance with the relevant regulations of this study:

- Use the study-specific complaint form to record the reported product complaint and a complete description of it.
- Fax or email the completed product complaint form to the sponsor or their designee within 24 hours.

If the investigator is required to return the product for investigation, the investigator should return a copy of the product complaint form along with the product.

6 Study Procedures

Before initiating any study procedures required by this protocol, the participant must read and sign the ICF approved by the EC.

All procedures should be performed within the required time windows. If, in special circumstances, a study procedure cannot be completed on time or as required, the investigator should take all necessary measures to ensure the participant's safety and well-being, and document the reason and the measures taken. In addition, the investigator must promptly notify the study team of any unexpected situations that occur.

6.1 Screening Period

Screening Period: Day -28 to Day -1 before the first study drug administration. After the participant signs the ICF, they will provide relevant information and undergo relevant examinations as required by the protocol. Baseline is defined as the last examination result before dosing. All screening period examinations and confirmations must be completed according to the Schedule of Activities. NSCLC and PDAC participants enrolled in Phase II must provide a compliant archived tumor tissue sample or undergo a biopsy during the screening period before enrollment. If a tumor tissue sample cannot be provided and a biopsy cannot be performed during the screening period, the investigator must communicate with the sponsor's medical monitor and obtain their consent before enrollment.

A screening failure is defined as a participant who, for any reason, does not ultimately start the first study drug administration. Participants who fail screening may be re-screened. If re-screening a participant is considered, the investigator must contact the sponsor's medical monitor. Consent from the sponsor's medical monitor must be obtained for re-screening. When re-screening, the participant must re-sign the ICF and will be assigned a new identification number. Assessment results from the initial screening period that are still within the study-specified time frame and meet the inclusion/exclusion criteria are still acceptable and do not need to be repeated.

The inclusion/exclusion criteria must be strictly followed. If a participant who does not meet the inclusion/exclusion criteria is found to be enrolled, the sponsor's medical monitor and the investigator must discuss and determine whether the participant should continue to participate in the study, with or without the use of the study drug. If the investigator believes that it is medically appropriate for the participant to continue participating in the study, and the sponsor's medical monitor agrees with this decision, the participant may continue to participate in the study and receive treatment with the study drug. If the investigator believes it is medically appropriate for the participant to continue participating in the study, but the sponsor's medical monitor disagrees with this decision, the participant must not

continue to participate in the study (regardless of whether they receive study drug therapy). The investigator may only allow a participant who was accidentally enrolled in this study to continue participating after receiving written approval from the sponsor.

6.2 Treatment Period

Eligible participants will receive study treatment until PD (except for participants whom the investigator judges may still benefit from continued treatment), unacceptable toxicity, withdrawal of informed consent, termination of study or early termination, initiation of new anti-tumor therapy, or death, whichever occurs first. The treatment period begins on Day 1 of study drug administration, and each treatment cycle is 21 days. During the study, participants will complete scheduled visits regularly. PK samples will be collected at the time points specified in the protocol. Efficacy will be assessed by the investigator according to RECIST 1.1. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks.

6.3 Continued Dosing After PD

After PD, if the investigator judges that the participant will continue to benefit, continued treatment with GFH375 is permitted with the participant's full informed consent, until the criteria for treatment discontinuation are met (see protocol Section 6.4).

If dosing is continued after PD, data collection must continue according to the study-designed visits.

6.4 Participant Discontinuation of Treatment and Withdrawal from the Study

6.4.1 Participant Discontinuation of Treatment

Discontinuation of study treatment does not mean withdrawal from the study. Participants who discontinue study treatment should complete the end of treatment (EOT) visit and subsequent follow-up visits as required by the protocol. Possible reasons for discontinuing study treatment include:

1) The participant experiences PD requiring treatment discontinuation, if the investigator judges that the participant may still benefit from continued dosing, study treatment may be continued after discussion with the sponsor;
2) AEs;
3) The participant starts other anti-tumor therapy;
4) The participant has serious non-compliance with the study protocol requirements;
5) Participant pregnancy;
6) Participant is lost to follow-up;
7) Participant death;

8) The participant requests to discontinue treatment but agrees to subsequent follow-up;
9) The participant withdraws informed consent;
10) The investigator believes that discontinuing study treatment is in the participant's best interest;
11) The entire clinical study is terminated or suspended.

When the above situations occur, the end of treatment (EOT) visit should be completed within 7 days of the decision to end study treatment. Investigations performed within 7 days before the EOT visit do not need to be repeated, but AE-related examinations should be re-checked at the investigator's discretion.

6.4.2 Participant Withdrawal from the Study

Participants may voluntarily withdraw from the study at any time. Reasons for withdrawal from the study may include:

1) The participant withdraws informed consent, refuses to undergo study procedures, and refuses to be contacted for future information;
2) Participant death;
3) Participant is lost to follow-up;
4) The entire study is terminated or suspended.

If a participant does not return to the site for follow-up as scheduled, every effort should be made to contact the participant promptly and reschedule the missed visit as soon as possible. The investigator should inquire about the reason for withdrawal, ask the participant to return to the site to complete the visit if possible, and follow up on any unresolved AEs. In any case, every effort should be made to document the participant's outcome if possible.

If a participant refuses to come to the study site for further visits, their disease and survival status should still be tracked and collected, unless the participant withdraws informed consent (i.e., refuses to be contacted further). In this case, no further study evaluations should be performed, and no further data should be collected.

6.5 Lost to Follow-up

A participant will be considered lost to follow-up if they fail to return to the study site for 3 consecutive scheduled visits and the site staff are unable to contact them.

If a participant does not return to the study site for a required study visit, the following actions must be taken:

- The study site will attempt to contact the participant to reschedule the missed visit, explain

the importance of adhering to the visit schedule, and confirm whether the participant is willing and/or should continue to participate in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to re-establish contact with the participant (should attempt at least two phone calls, and if still unable to make contact, a letter should be sent to the participant's most recently updated contact address). These attempts to contact the participant should be documented in the participant's medical records or study files. Before the termination of this study, the investigator should still try to contact the participant.

If the participant still cannot be contacted, they will be considered lost to follow-up. All attempts to make contact should be recorded in the source documents.

6.6 Unscheduled Visits

If the investigator judges that it is necessary for safety assessment or AE follow-up, or if clinical symptoms suggestive of PD appear, the investigator may schedule a corresponding visit for further examination and assessment.

6.7 Follow-up Period

6.7.1 Safety Follow-up

After the end of treatment visit (including participants who have completed the end of treatment/withdrawal from study visit), the follow-up period begins. Thirty days (±3 days) after the last study drug administration, participants need to return to the study site for a safety follow-up, regardless of whether they have started new anti-tumor therapy.

After the safety follow-up visit, AEs will no longer be actively collected, but all treatment-related AEs must be followed up until resolution, return to baseline, or until the investigator judges them to be stable and irreversible.

6.7.2 PD Follow-up

Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the ICF, initiation of other anti-tumor therapy, or the end of the study.

6.7.3 Survival Follow-up

After the safety follow-up is completed, participants will enter survival follow-up. Participants will undergo a survival follow-up every 90 (±7) days. The investigator will obtain the participant's survival status, disease status, and subsequent anti-tumor therapy via telephone or email, etc.

7 Study Assessments

7.1 Safety Assessment

Participants will be recorded and assessed for the safety endpoint dataset starting from the screening/baseline period. Safety endpoint assessment indicators include the incidence, severity, and type of AEs, the participant's physical examination results, vital signs measurements, and clinical laboratory test results, with assessment time points according to the visit schedule. Adverse reactions will be graded according to CTCAE v5.0. For detailed information on AE collection and reporting, please refer to Chapter 8.0 Safety Reporting and Adverse Event Management.

7.1.1 Laboratory Tests

Hematology, urinalysis, blood chemistry, coagulation function, and pregnancy tests will be performed according to the Schedule of Activities. Viral serology tests are also required during the screening period to assess eligibility for enrollment. For details, please see Table 6 Laboratory Tests.

If a participant undergoes laboratory tests outside the study site and reports a related AE, the results of that laboratory test should also be collected and entered into the electronic Case Report Form (eCRF).

Table 6 Laboratory Tests

Test Item	Observation Parameter
ematology	Red blood cell count (RBC), hemoglobin concentration (HGB), haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell count (WBC), platelet count (PLT), absolute neutrophil count (ANC), lymphocyte (LY) count, monocyte (MO) count, eosinophil (EO) count, basophil (BA) count, neutrophil percentage, lymphocyte percentage, monocyte percentage, eosinophil percentage, basophil percentage
rinalysis	Urine white blood cells (LEU), urine nitrite (NIT), urine pH, urine specific gravity (SG), urine protein (PRO), urine glucose (GLU), urine ketone body (KET), urine urobilinogen (UBG), urine bilirubin (BIL), urinary occult blood (BLD); 24-hour urine protein (this test is required when protein urine is ≥2+)
oagulation Function	Prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR)
lood Chemistry	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), urea (UREA)/blood urea nitrogen, blood creatinine (CREA), protein total (TP), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), creatine kinase (CK), pancreatic amylase (AMY), fasting plasma glucose (FPG), total cholesterol (TCHO), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), calcium, sodium, chloride, potassium
irus Serology	Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), HBV-DNA (if necessary), hepatitis C virus antibody (HCV antibody), HCV-RNA (if necessary), HIV antibody

Test Item	Observation Parameter
·egnancy Test	Female participants of childbearing potential will undergo a serum β-HCG pregnancy test at baseline, and a urine pregnancy test at other visits

7.1.2 Physical Examination

Physical examinations will be performed at the time points specified in the corresponding Schedule of Activities.

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. A comprehensive physical examination will be performed during the screening period.

A brief physical examination will be performed before the first dose of GFH375 and at the time points specified in the protocol, based on clinical indications. The investigator may also increase the frequency of physical examinations as needed.

7.1.3 Vital Signs

The participant's vital signs (respiration, pulse, blood pressure, and body temperature) will be recorded.

7.1.4 Performance Status

Performance status assessment will be performed during the screening period, before the first dose, on D1 of each cycle, at EOT, and 30 days after the last treatment. If assessed within 72 hours before the first dose, it does not need to be repeated on C1D1. Performance status will be scored according to the Eastern Cooperative Oncology Group (ECOG) performance status scoring criteria (see Appendix 2).

7.1.5 Body Height and Weight

Body height is measured only once during the screening period. Weight will be measured during the screening period, on C1D1, C2D1, on D1 of each subsequent cycle, at EOT, and 30 days after the last treatment. Body height [centimeters (cm)] and weight [kilograms (kg), rounded to one decimal place, measured in indoor clothing without shoes] will be measured according to hospital standards.

7.1.6 12-Lead ECG

12-lead ECGs will be completed according to the date and time requirements specified in the Schedule of Activities.

The ECG examination should be performed after the participant has rested quietly for at least 10 minutes. During the screening period and the study, 3 ECG examinations will be performed, with an

interval of at least 5 minutes between each. If other trial procedures are combined, the ECG examination should be performed first to avoid the impact of trial procedures on the ECG results.

Heart rate (HR), PR interval, QRS interval, QT interval, and QTcF (Frederica's formula) interval should be assessed and collected.

12-ECG Collection of the Phase I Part Dose Escalation

Participants will undergo an ECG examination on C1D1 (pre-dose, 2 h post-dose, 4 h post-dose, 6 h post-dose), C1D4 (pre-dose, only for QD dosing), C1D8 (pre-dose), C1D15 (pre-dose), C1D21 (pre-dose, 2 h post-dose, 4 h post-dose, 6 h post-dose, 24 h post-dose [only for QD dosing]), C2D10 (pre-dose), C4D1 (pre-dose), C5D1 (pre-dose), and C6D1 (pre-dose).

12-ECG Collection of Phase II Part

Participants will undergo an ECG examination on C1D10 (pre-dose, 2-4 h post-dose), C2D1 (pre-dose, 1-3 h post-dose), C3D1 (pre-dose, 2-4 h post-dose), C4D1 (pre-dose), C5D1 (pre-dose), and C6D1 (pre-dose).

ECGs matching the PK samples will be collected at qualified sites. It is recommended to perform the ECG examination first, then the PK blood draw. If it cannot be completed before the blood sample collection, the ECG examination should be performed after resting quietly for 10 minutes after the blood draw. Meanwhile, the interval between the ECG and PK sampling time needs to be kept within 30 minutes. All planned 12-ECG examinations should be performed after the participant has rested quietly for at least 10 minutes. Three measurements should be taken at each time point, with an interval of 1-2 minutes between each.

7.1.7 Adverse Events and Concomitant Therapies

The assessment of an AE includes the event name, severity (graded according to CTCAE version 5.0), start and end time, whether it is an SAE, its relationship to the study treatment, the measures taken regarding the study treatment, and the outcome.

AEs occurring from the signing of the ICF until the completion of the study safety follow-up visit will be recorded in the source medical records and collected in the eCRF. Other drugs or treatments used by the participant during the study treatment period will be recorded as concomitant therapy in the source medical records and collected in the eCRF.

7.2 PK Assessment

7.2.1 Blood Sample Collection

Phase I Part Dose Escalation

Serial PK samples will be collected on C1D1 (single dose), C1D21 (steady state), C2D1, C2D10,

C4D1, C5D1, and C6D1 to assess the PKs of GFH375. For specific time points, see the **Phase I Part PK Sample and 12-Lead ECG Collection Schedule**.

Phase II Part

Enrolled participants will have PK samples collected pre-dose on C1D10, C2D1, C3D1, C4D1, C5D1, and C6D1. For details, see the **Phase II Part PK Sample and 12-Lead ECG Collection Schedule**.

- **Unscheduled PK Blood Draw**

When a participant experiences a drug-related SAE, a blood sample for GFH375 plasma concentration measurement should be collected immediately upon the investigator's awareness of the event, if possible.

- **Gastrointestinal AEs (Vomiting and Diarrhea) and PK Sampling**

During the study, it has been found that the incidence of gastrointestinal AEs is high after participants take GFH375, which may affect the participants' PK results. The time of occurrence and frequency of vomiting and diarrhea will be collected in the CRF for subsequent analysis.

7.2.2 Sample Analysis

The concentration of GFH375 will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Concentrations below the lower limit of quantitation (LLOQ) will be marked as LLOQ, and any missing samples will be marked accordingly. Sample testing will be conducted by Teddy Clinical Research Laboratory (Shanghai) Limited. Detailed information about the analysis will be recorded in the bioanalytical report.

The collection and processing methods for biological samples are detailed in the laboratory manual.

7.3 Efficacy Assessment

The assessment of tumor remission will include all known or suspected sites of disease. Imaging includes computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, or pelvis; brain CT or MRI for participants with known or suspected brain metastasis; bone scan and/or bone X-rays for participants with known or suspected metastases to bone.

A baseline CT/MRI scan should be performed within 28 days before the first administration . During the study, efficacy will be assessed by the Blinded Independent Central Review (BICR) or the investigator according to RECIST 1.1 criteria (efficacy for all participants must be assessed by the investigator, and PDAC and NSCLC participants enrolled in Phase II also require BICR assessment). Imaging and tumor assessment will be performed every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks thereafter. In subsequent tumor evaluations, the same imaging modality as used during the screening period should be used for the

same type of lesions, and the investigation should be performed on the same imaging equipment whenever possible. For participants in whom no corresponding lesions were found on baseline cranial imaging and bone scan, the investigator may decide to add corresponding examinations during the treatment period if clinically indicated.

Disease in remission assessment will be performed by the BICR or the investigator according to RECIST 1.1 (Appendix 1). All participants' radiological imaging examinations must comply with RECIST 1.1 criteria, and all data should be properly retained and be available for source verification and peer review.

If a participant discontinues study treatment for a reason other than PD and has not started subsequent other anti-tumor therapy, imaging examinations will continue until PD occurs, or subsequent anti-tumor therapy is initiated, or the participant withdraws from the study for other reasons.

7.4 Biomarker and Drug Resistance Mechanism Exploration

NSCLC and PDAC participants enrolled in Phase II must provide a compliant archived tumor tissue sample or undergo a biopsy during the screening period before enrollment, to have their baseline gene mutation status confirmed by testing at the central laboratory designated for this study (Burning Rock Biotech).

In Phase I and Phase II, blood samples will be collected from participants at baseline (if collected during the screening period, no need to repeat on C1D1) and at the end of treatment visit, and will be shipped to the central laboratory for ctDNA isolation and sequencing. The sequencing results will be correlated with efficacy to explore biomarkers related to treatment sensitivity or drug resistance.

PDAC participants enrolled in Phase II will have blood samples collected for CA19-9 testing at baseline (if collected during the screening period, no need to repeat on C1D1), every 6 ± 1 weeks during the treatment period, and at the end of treatment (no need to repeat if tested within 4 weeks before the end of treatment visit), to explore the correlation between its changes and treatment response.

7.5 Storage and Destruction of Biological Samples

Remaining samples will be disposed of or destroyed, and will be anonymized and pooled.

Sample flashback analysis (if performed) will be conducted concurrently with the bioanalysis of the study samples. These assessment results will not be reported in the Clinical Study Report (CSR), but will be provided separately in a bioanalytical report.

8. Safety Reporting and Adverse Event Management

8.1 Definition and Recording of Adverse Events

8.1.1 Definition of an Adverse Event

An AE is defined as any untoward sign, symptom, abnormal laboratory value or examination result, or medical condition that appears (or worsens) after the participant has signed the ICF, regardless of whether the event is considered to be related to the study drug. A TEAE is defined as an event that was not present before treatment and appears during the treatment period (defined as from the first dose of the study drug to 30±3 days after the last dose) or worsens relative to the pre-treatment state. AEs that begin or worsen after informed consent should be recorded in the AE eCRF. Conditions already existing at the time of informed consent should be recorded on the medical history page of the participant's eCRF. AE monitoring should continue for 30±3 days after the last dose of treatment, or until the start of new anti-tumor therapy. For details, see Section 8.2.3. AEs (including laboratory abnormalities that constitute an AE) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a definitive diagnosis cannot be made, each sign or symptom should be reported as a separate AE.

8.1.2 Criteria for Assessing the Severity of Adverse Events

AEs will be assessed using NCI-CTCAE version 5.0. If there is no corresponding AE in CTCAE v5.0, please refer to the following criteria (summarized from the grading criteria in CTCAE v5.0).

Table 7 Criteria for Assessing the Severity of Adverse Events

Grade	Clinical Description of Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), where instrumental ADL refers to preparing meals, shopping, using the telephone, managing money, etc.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; resulting in disability; limiting self-care ADL. Self-care ADL refers to bathing, dressing, undressing, eating, toileting, taking medications, etc., but not bedridden
4	Life-threatening; urgent intervention indicated
5	AE resulting in death

8.1.3 Recording and Management of Adverse Events

Each AE should be assessed as much as possible to determine:

- Name of the AE
- Severity grade
- Duration (start and end dates)
- Relationship to study treatment
- Action taken with study drug (none, dose reduced, drug interrupted, drug permanently discontinued, unknown, not applicable)
- Whether medication or treatment has been given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered, recovered, recovering, recovered with sequelae, fatal, unknown)
- Whether it is an SAE, as defined in Section **8.2** as an SAE

All AEs should be managed appropriately. If concomitant medication or non-drug therapy is given, it should be recorded in the AE eCRF. Once an AE is discovered, it should be followed up until it resolves, stabilizes, or is judged to be permanent, and changes in severity, relationship to study treatment, interventions required to treat the AE, and the outcome should be assessed at each visit (or more frequently if necessary).

8.2 Serious Adverse Events

8.2.1 Definition

An SAE is defined as an AE that occurs during any clinical study and meets one or more of the following criteria:

- Results in death;
- Is life-threatening, meaning the patient is at immediate risk of death, not that death might occur if the condition were to worsen in the future;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Other important medical events: Medical and scientific judgment must be used to decide whether to expedite reporting of other situations, such as important medical events that may not be immediately life-threatening, result in death, or require hospitalization, but are generally considered serious if medical intervention is required to prevent one of the above outcomes.

Hospitalization for the following reasons should not be reported as an SAE:

- Routine treatment or monitoring for the indication under study, not associated with any condition aggravated
- Elective or pre-planned treatment for a pre-existing disease not related to the indication under study, which has not worsened since signing the ICF
- Social reasons and respite care where there is no deterioration in the patient's general condition

Emergency outpatient treatment that does not result in hospitalization and involves an event that does not meet the above SAE definition is not an SAE.

8.2.2 Malignant Tumor Progression and Death

Clinical symptoms caused by malignant tumor progression may be recorded as an AE if it cannot be exclusively determined to be due to the progression of the study disease, or if the symptoms are inconsistent with the characteristics of the study PD. If it is clearly consistent with the suspected progression of the study disease, it is not recorded as an AE. Malignant tumor progression itself is not reported as an AE.

Clinical symptoms caused by malignant tumor progression that meet the SAE criteria and for which a relationship to the study drug cannot be completely ruled out must be reported as an SAE. If the event meets the SAE criteria (excluding death events) and is clearly consistent with the suspected progression of the study disease, it is not reported as an SAE. The collection period for SAE reporting is from the time the participant signs the ICF until 30 days after the last dose.

In a clinical study, if a participant dies during the safety follow-up period, it must be reported as an SAE, regardless of whether the investigator assesses it as possibly related to PD. The term 'death' should not be used as an SAE term, but as the outcome of an event. The medical condition/disease (including worsening of signs and symptoms) that caused or led to death should be recorded as the SAE term in the eCRF and reported as an SAE. If the cause of death cannot be determined at the time of reporting, the SAE term should be recorded as 'death of unknown cause'. The collection period for reporting SAEs with a fatal outcome is from the time the participant signs the ICF until 30 days after the last dose.

8.2.3 New Anti-tumor Therapy

If a participant starts new anti-tumor therapy during the safety follow-up period, unrelated AEs and SAEs will no longer be collected thereafter. If a death event occurs during the safety follow-up period, it must be reported as an SAE, regardless of any interventional treatment and regardless of the causal relationship of the event to the study treatment.

8.2.4 Reporting of SAEs

SAE collection will begin at the time of ICF signing, regardless of whether the participant is a screening failure. Follow-up of SAEs will continue until symptoms resolve or there is clinical improvement or stabilization.

To ensure participant safety, any SAE that occurs after the participant signs the ICF and within 30 days after the participant stops study treatment, regardless of the suspected causal relationship, must be reported to the sponsor within 24 hours of awareness of its occurrence. After 30 days following the participant's last treatment, only SAEs suspected to be related to the study treatment will be reported. Any additional information for an SAE, including complications, progression of the initial SAE, and recurrent episodes, must be reported as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. SAEs that occur at different time intervals or are considered completely unrelated to a previously reported SAE should be reported separately as new events.

Any SAE occurring after the safety follow-up period should only be reported to the sponsor if the investigator suspects a causal relationship with the study treatment.

Information for all SAEs will be collected and recorded on the SAE report form; to provide a complete clinical report, all applicable sections of the form must be completed. The investigator must assess and record the relationship of each SAE to the study treatment, complete the SAE report form signed by the investigator, and send the report form to the sponsor and the designated CRO pharmacovigilance department within 24 hours, and report to the relevant authorities in a timely manner according to local requirements.

- **Sponsor Pharmacovigilance Email**: drugsafety@genfleet.com
- **Tigermed Pharmacovigilance Email:** PV@TigermedGrp.com

Follow-up information should be submitted in the same manner as the original SAE report form, using a new SAE report form, indicating that it is a follow-up report to a previously reported SAE, and providing the date of the original report. The follow-up information should describe whether the event has resolved or is ongoing, how it was treated, and whether the participant continued in the study or withdrew.

8.3 Causality Assessment of Adverse Events

Causality assessment of an AE with the study treatment refers to a comprehensive evaluation to determine whether there is a reasonable possibility that the study treatment caused or contributed to the AE. Factors the investigator should consider include whether the occurrence of the AE has a

reasonable temporal relationship with the administration of the study treatment, the characteristics of the study treatment, the toxicological and pharmacological effects of the study treatment, the use of concomitant medications, the participant's pre-existing disease, medical history, family history, dechallenge (whether signs/symptoms lessen or improve after study drug discontinuation or dose reduction), and rechallenge (whether signs/symptoms reappear or worsen after re-administration of the drug), etc. The facts and rationale for determining causality should generally be provided.

The investigator should assess the relationship of the AE/SAE to the study drug according to the criteria listed below:

Table 8 Classification and Criteria for Adverse Event Relationship Assessment

Relationship	Assessment Criteria
Related	• Reasonable temporal relationship • Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug • Positive dechallenge • No other reasonable cause to explain it • Positive rechallenge
Probably related	• Reasonable temporal relationship • Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug • Positive dechallenge • No other reasonable cause to explain it • Lack of positive rechallenge evidence
Possibly related	• Reasonable temporal relationship • Lack of positive rechallenge evidence • Manifests as any of the following situations: 1) Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug, with a positive dechallenge, but can also be explained by other reasonable causes; 2) Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug, with a lack of positive dechallenge evidence, and no other reasonable cause to explain it; 3) Inconsistent with the known mechanism of action, characteristics, or known adverse reactions of the drug, with a positive dechallenge, and no other reasonable cause to explain it; 4) Inconsistent with the known mechanism of action, characteristics, or known adverse reactions, with a lack of positive dechallenge evidence, and no other reasonable cause to explain it.
Unlikely related	• Temporal relationship cannot be excluded • Lack of positive dechallenge evidence • Lack of positive rechallenge evidence • Manifests as any of the following situations: 1) Inconsistent with the known mechanism of action, characteristics, or known adverse reactions, and can be explained by other reasonable causes; 2) Consistent with the known mechanism of action, characteristics, or known adverse reactions, but can be explained by other more reasonable causes;
Not related	• No reasonable temporal relationship • Inconsistent with the known mechanism of action, characteristics, or known adverse reactions of the drug • Lack of positive dechallenge evidence • Lack of positive rechallenge evidence • Can be explained by other reasonable causes

Note: When assessing an AE, if it does not completely correspond to the criteria in the table, please refer to the professional judgment logic for the relationship between AEs and the drug in this table to make the most reasonable assessment possible.

Table 9 Summary for Adverse Event Relationship Assessment

Assessment Result / Assessment Criteria	Related	Probably related	Possibly related				Unlikely related		Not related
Reasonable temporal relationship?	+	+	+				±		-
Consistent with known drug mechanism, characteristics, or adverse reactions?	+	+	+		-		+	-	-
Dechallenge result	+	+	+	-/?	+	-/?	-/?		-/?
Rechallenge result	+	-/?	-/?				-/?		-/?
Can it be explained by other reasonable causes?	-	-	+	-	-	-	++	+	+

Note: + indicates affirmative, or positive result; - indicates negative, or negative result, or a situation where the result is not yet available; ± indicates that a temporal relationship cannot be excluded; ++ indicates that it can be explained by other 'more' reasonable causes; -/? indicates that the dechallenge/rechallenge result is negative, or dechallenge/rechallenge has not yet been performed, or dechallenge/rechallenge is not applicable.

Events assessed as related, probably related, or possibly related will be considered 'related'; events assessed as not related or unlikely related will be considered 'unrelated'. If the investigator's causality assessment is 'unknown', or if a relationship assessment cannot be made, the event should be considered related to the drug. The investigator should collect further information on the AE and provide a causality assessment based on the subsequent information.

8.4 Pregnancy Reporting

If a female participant becomes pregnant during the clinical study, the participant must discontinue study treatment and withdraw from the study; if the partner of a male participant becomes pregnant during the clinical study, the participant may continue in the clinical study. The investigator should complete the "Clinical Study Pregnancy Report/Follow-up Form" and report it to the sponsor and the designated CRO pharmacovigilance department within 24 hours of awareness of the pregnancy event. The investigator must follow up on the pregnancy event until the final outcome (including any premature termination of pregnancy or delivery), with delivery follow-up extending to 1 month after the mother gives birth. The pregnancy outcome must be reported to the sponsor. If the pregnancy outcome meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal death, death neonatal, or congenital anomaly, etc.), it must be reported following the SAE

procedure.

If a participant experiences a concurrent SAE during pregnancy, it must also be reported following the SAE reporting procedure.

8.5 Reporting of Events Meeting Hy's Law

If abnormal AST and/or ALT levels are concurrent with an abnormal elevation in total bilirubin levels, and conditions (1), (2), and (3) below are met simultaneously with no other cause for the abnormalities, such cases should always be reported as an SAE, following the SAE reporting procedure.

Table 10 Criteria for Determining Events Meeting Hy's Law

Condition Met	Assessment Criteria
(1) Abnormal ALT or AST	1) Normal baseline: ALT or AST > 3×ULN during treatment period Abnormal baseline: ALT or AST > 3× baseline level during treatment period
(2) Abnormal TBIL	2) Normal baseline: TBIL > 2×ULN during treatment period Abnormal baseline: TBIL > 2× baseline level during treatment period
(3) Alkaline phosphatase < 2×ULN (or information not available)	

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, TBIL=total bilirubin, ULN=upper limit of normal.

If a participant has abnormal AST and/or ALT levels concurrent with an abnormal elevation in total bilirubin levels during the treatment or follow-up period, they should return to the study site for examination and assessment as soon as possible after the abnormal results are known. This should include relevant liver function laboratory tests, a detailed medical history inquiry, and a physical examination, and the possibility of liver tumors (primary or secondary) should be considered.

If a liver injury event meeting the above criteria occurs, corresponding dose adjustments or treatment discontinuation should be made according to Sections 5.3.1 and 5.3.2.

8.6 Reporting of Overdose

An overdose is defined as any accidental or intentional administration of a dose that exceeds the planned dose. If an overdose results in an AE, the AE must be recorded in the eCRF. If an overdose is associated with any SAE, please refer to Section **8.2.4 Reporting of SAEs**.

8.7 Reporting Timelines for AE/SAE/Pregnancy

Table 11 Reporting Timelines for AE/SAE/Pregnancy Events

Period	Collection Requirement
From the time the participant signs the ICF until 30±3 days after the last dose of treatment, or until the start of new anti-tumor therapy	All AE/SAE/pregnancy events Pregnancy events: Collection begins after the first dose of study treatment
After the above period	SAEs related to the study treatment

Abbreviations: AE=adverse event, SAE=serious adverse event.

9. Statistical Analysis

Detailed statistical analysis methods will be described in the Statistical Analysis Plan (SAP), and the final version of the SAP will be completed before the clinical database is locked.

9.1. Sample Size

9.1.1. Phase I Part: Dose Escalation

According to the BOIN design, 3-6 participants will be enrolled in each dose cohort (except during accelerated titration) for 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 part).

If more dose cohorts or alternative dosing regimens need to be explored, additional participants may be enrolled.

9.1.2. Phase II Part

A total of approximately 317 participants are planned for enrollment, including approximately 73 patients with advanced NSCLC, 94 patients with advanced PDAC, 50 patients with advanced CRC, and 100 patients with other advanced solid tumors.

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% 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/PR cases, 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 α = 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 α = 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 Rsoftware. Among them, the sample size was calculated using the “nBinomial1Sample” function in the “gsDesign” package (option: conservative = TRUE); the ORR and its 95% exact CI were calculated using the “binom.exact” function in the “epitools” package (with default options).

9.2. 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 have received undiminished doses of GFH375 for at least 15 cumulative days during the DLT observation period and had adequate safety assessments, or who have 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.

9.3. Statistical Analysis Methods

Data from Phase I and Phase II will be analyzed and summarized separately. Data from the Phase I stage will be analyzed and summarized by different dose levels and dosing regimens; data from the Phase II stage will be analyzed and summarized separately by tumor type.

9.4. Safety Analysis

The incidence of AEs, treatment-related AEs, and SAEs will be summarized by System Organ Class (SOC), Preferred Term (PT), and severity. For the Phase I part, the incidence of various types of DLTs will be summarized based on the DDS, and the DLTs will be listed. Descriptive summaries will be provided for laboratory tests, vital signs, and ECGs.

9.5. Efficacy Analysis

The proportion of the respective population for BOR, ORR, and DCR will be calculated, and the two-sided 95% CI for ORR and DCR will be estimated using the Clopper-Pearson method. The median DoR, PFS, and OS and their 95% Brookmeyer-Crowley CIs will be estimated using the Kaplan-Meier method. TTR will be summarized descriptively.

For the Phase I stage, when the sample size of an analysis group is less than 10, DoR, TTR, PFS, and OS will be listed individually by participant, and the Kaplan-Meier method will not be used for analysis.

For the Phase II stage, the **primary estimand** is set as follows:

Study Population	Participants with advanced solid tumors with KRAS G12D mutation (by tumor type)
Treatment	GFH375
Endpoint	Percentage of participants who achieve CR or PR as assessed by RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant is considered a non-responder. **Note:** For NSCLC and PDAC, this will be the percentage of participants with confirmed CR or PR based on Blinded Independent Central Review (BICR) assessment.
Intercurrent Event	Start of new anti-tumor therapy (Handling strategy: Treatment policy strategy, assessment results after the start of new anti-tumor therapy are not included in the analysis.)
Population-level Summary	ORR

9.6. PK Analysis

Plasma concentration data of GFH375 will be listed and summarized descriptively according to the sampling times specified in the protocol. The summaries will be presented by study phase, dose group, and dosing regimen. Individual participant plasma concentration-time curves of GFH375 and

corresponding summary curves (mean + standard deviation) will be plotted using linear and semi-logarithmic coordinates, by study phase, dose group, and dosing regimen. Planned PK sampling times will be used to calculate summary statistics and plot summary curves (mean + standard deviation); actual PK sampling times will be used to plot individual participant curves.

Phoenix WinNonlin software (version v8.2 or later, Certara USA, Inc., New Jersey, US) will be used to perform non-compartmental analysis (NCA) to calculate the PK parameters of GFH375 based on actual blood sampling time points. The PK parameters of GFH375 after single and multiple doses in participants in the Phase I dose escalation part will be summarized descriptively, with summaries presented by dose group and dosing regimen.

9.7 Biomarker Assessment

In Phase I and II, blood samples will be collected at baseline and at the end of treatment to isolate ctDNA for NGS testing, to explore tumor gene variations associated with treatment sensitivity or drug resistance.

Phase II PDAC participants will have CA19-9 tested at baseline, during the treatment period, and at the end of treatment to explore the correlation of its changes with treatment response.

9.8 Interim Analysis

A futility interim analysis will be performed separately for NSCLC, PDAC, and CRC. For a single tumor type, the analysis is planned 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 for the ORR of 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 Phase II 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

Tumor Type	Number of Participants*	Recommended to terminate the cohort when the number of responders is ≤
	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: The sum 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 these must be met).

The planned interim analysis 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.

10. Safety Monitoring

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 parts, SMC members will review safety data, PK data, etc., to decide on enrollment for the next dose or to explore potential other dose cohorts, and to recommend a suitable 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.

11 Study Quality Assurance and Quality Control

According to the guiding principles of Good Clinical Practice (GCP), the sponsor is responsible for implementing and maintaining a quality assurance and quality control system according to the corresponding standard operating procedures to ensure that the clinical study is conducted and that the data is authentic, and that collection, recording, and reporting follow the protocol, GCP, and corresponding regulatory requirements.

11.1 Clinical Monitoring

The sponsor or a contract research organization (CRO) authorized by the sponsor will conduct clinical monitoring for this study. Clinical monitors should conduct monitoring according to the standard operating procedures of the sponsor or CRO and have the same rights and responsibilities as the sponsor's monitors. The monitor should maintain regular communication with the investigator, authorized study personnel, and the sponsor.

Before the start of the study, the monitor will assess the competence of each study site and report any issues related to facilities, technical equipment, or medical personnel to the sponsor. During the study, the monitor will be responsible for monitoring whether the investigator has obtained written informed consent from all participants and whether the data records are correct and complete. At the same time, the monitor will also compare the data entered into the eCRF with the source data and inform the investigator of any errors or omissions. The monitor will also control the study site's compliance with the protocol and trial procedures, arrange for the supply of the investigational drug, and ensure that the drug is stored under appropriate conditions.

Monitoring visits will be conducted in accordance with the requirements of relevant laws and regulations. From the start of participant enrollment, each site will receive regular monitoring visits. After each visit to the investigator, the monitor should submit a written report to the sponsor.

11.2 Quality Assurance Audit

During the study, the sponsor or a representative authorized by the sponsor may conduct quality assurance audits of the study site, study database, and related study documents. At the same time, the corresponding regulatory authorities may also inspect the study site, study database, and related study documents at their own discretion. When the investigator receives a notice of inspection from a regulatory authority, they must immediately inform the sponsor.

The sponsor's quality assurance department will audit the clinical study site. The audit includes: supply of the drug, required trial documents, records of the informed consent process, and the consistency of the case report forms with the source documents, etc. The content and scope of the audit may also be

increased depending on the situation. After reasonable notification, the investigator should allow auditors commissioned by the sponsor to conduct study-related audits and inspections by regulatory authorities. The main purpose of an audit or inspection is to confirm that the rights and health of the participants participating in the study are protected, that the signing of informed consent and the implementation of the trial process are conducted correctly, and that all data processing and reporting related to the evaluation of the investigational drug are consistent with the pre-planned arrangements, protocol, facilities, ethical standard operating procedures, GCP, and applicable regulatory requirements. The investigator should provide direct access to all study documents, source records, and source data.

12 Ethics

12.1 Ethics Committee

The sponsor or its authorized representative will prepare the relevant documents to be submitted to the study site's EC, including the study protocol, ICF, investigator's brochure, participant recruitment materials or advertisements, and other documents required by regulations, all of which must be submitted to the corresponding EC for approval. Before starting this study, written approval from the study site's EC must be obtained and provided to the sponsor. The EC's approval letter must specify the name, number, and version number of the study protocol, as well as the version numbers (e.g., for the ICF) and approval dates of other documents. The investigator must notify the sponsor of the EC's written opinions regarding delays, suspensions, or re-approvals.

The study site must follow the requirements of its EC. This may include submitting protocol amendments, ICF amendments, and participant recruitment material amendments to the EC for approval, local safety reporting requirements, periodic reporting and updates according to EC regulations, and submission of the final report. All the above documents and EC approval letters must be provided to the sponsor or their designee.

12.2 Ethical Conduct

The study process and the acquisition of informed consent should comply with the Declaration of Helsinki, relevant GCP requirements, and Chinese laws and regulations related to drugs and data protection.

GCP provides an ethical and scientific global quality standard for the design, conduct, recording, and reporting of clinical studies involving human participants. This study will be conducted in accordance with GCP and relevant national regulations, and will adhere to the relevant ethical principles of the Declaration of Helsinki to protect the rights, safety, and health of the participants.

The investigator must follow the procedures specified in this study protocol and may not make changes without the sponsor's permission. Any protocol deviations will be reported to the EC, the sponsor, or regulatory authorities.

12.3 Participant Information and Informed Consent

Before any study procedures begin, the potential risks and benefits of this study will be explained to potential participants using the ICF, and the language of the informed consent should be simple and easy to understand. The ICF statement should clarify that signing the informed consent is voluntary, specify the potential risks and benefits of participating in this study, and state that the participant may

withdraw from the study at any time. The investigator may only enroll a participant after fully explaining the details of the study, satisfactorily answering the participant's questions, allowing sufficient time for consideration, and obtaining written consent from the participant or their legal guardian. All signed ICFs must be kept in the investigator's files or the participant's folder.

The investigator is responsible for explaining the content of the informed consent to the participant and obtaining a signed and dated ICF from the participant or their legal guardian before the study begins. After signing, the investigator should give the participant a copy of the signed ICF. The investigator must document the informed consent process in the study source documents.

The initial ICF, any subsequent revised written ICFs, and any written information provided to participants should be reviewed by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) before use. If new information becomes available that may be relevant to the participant's willingness to continue participating in the study, the participant or their legal guardian should be informed in a timely manner. The communication of this information will be provided and documented through a revised ICF or an addendum to the original ICF (obtaining a dated signature from the participant or the participant's legal guardian).

12.4 Data Protection

The ICF will contain (or in some cases, be accompanied by a separate document with) information regarding data protection and privacy protection.

Precautions will be taken to ensure the confidentiality of documents and to prevent the identification of participants. However, in special circumstances, certain personnel may see a participant's genetic data and personal identification code. For example, in the event of a medical emergency, the sponsor, their representative physician, or the investigator will be aware of the participant's identification code and have access to that participant's genetic data. In addition, relevant regulatory authorities may require access to related documents.

12.5 Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH GCP), or the operations manual. Non-compliance may originate from the participant, investigator, or study site staff. Corrective actions should be taken and completed in a timely manner for any violations.

13 Study Administration

13.1 Data Handling and Record Keeping

Documents in the clinical study (protocol and protocol amendments, completed eCRFs, signed ICFs, etc.) must be stored and managed in accordance with GCP requirements. The study site should retain these documents for 5 years after the end of the study.

Study documents should be properly stored for future access or data traceability. Safety and environmental risks should be considered when storing documents.

No study documents may be destroyed without the written permission of the sponsor and the investigator. Only after notifying the sponsor and obtaining their written consent may the investigator/study site transfer study documents to another party that complies with document retention requirements or move them to another location that meets the requirements for storage.

13.2 Access to Source Data/Documents

The investigator agrees to allow the sponsor, CRO, and relevant authorized regulatory authorities direct access to all study-related documents, including participant medical records.

13.3 Protocol Amendments

All amendments to the protocol during the course of the study must be communicated between the sponsor and the investigator and agreed upon. The sponsor should ensure that protocol amendments are submitted to the regulatory authorities in a timely manner.

All amendments to the protocol should be kept as protocol addenda. Any modification to the protocol must be submitted to the EC for approval or filing according to the EC's regulations. If necessary, it should also be submitted to the regulatory authorities for approval, and can only be implemented after approval by the EC and regulatory authorities (if required) (except for changes to the protocol made to eliminate an immediate hazard to study participants).

13.4 Investigator Responsibilities

The investigator will conduct this study in accordance with the protocol, the ethical principles of the Declaration of Helsinki, ICH GCP, and corresponding regulatory requirements.

The detailed responsibilities of the relevant investigators are listed in Chapter 5 of the China GCP (No. 57, 2020).

13.5 Publication Policy

All data generated from this study are confidential information of the sponsor, and the sponsor has the right to publish the study results. Information regarding the publication policy between the sponsor and the investigator will be described in the clinical study agreement.

All information related to this study (not limited to the following documents: protocol and investigator's brochure) must be kept strictly confidential. The investigator must recognize that the scientific or medical conclusions drawn from this study may have commercial value to the sponsor. The investigator should keep the information and data related to this trial confidential. If they wish to publicly publish data related to this study or conclusions drawn from the study, they must consult with the sponsor in advance and obtain the sponsor's written consent. To protect its own rights and interests, the sponsor may require the investigator not to publish relevant trial data before the study product obtains marketing approval.

The sponsor has the right to publish or release information or data related to this study, or to submit it to the drug regulatory authorities. If the sponsor needs to use the investigator's name in publications, releases, or advertising content, they should obtain the investigator's consent.

13.6 Finance and Insurance

The sponsor will purchase insurance for participants participating in this study in accordance with local regulations and minimum requirements. The relevant insurance terms will be kept in the study folder.

14 Data Management

14.1 Data Confidentiality

Information related to study participants will be kept confidential and managed in accordance with applicable laws and regulations.

Access to the data collection system will be controlled through a series of individually assigned usernames and passwords, which will only be provided to authorized personnel who have completed the necessary training.

14.2 Data Collection

Data collection for this study will be completed using an Electronic Data Capture (EDC) system.

The investigator or designated study personnel will enter data into the eCRF according to the protocol. Study site staff may only access the EDC system after receiving training. The system will use an automated check process to inspect data inconsistencies in the eCRF, allowing for modification or verification of the data entered by site staff.

When modifying data in the EDC, the reason for the modification must be entered as prompted by the system. The modification history and reasons for modification will be recorded in the audit trail of the EDC system. The investigator or their authorized personnel need to confirm the authenticity, completeness, and timeliness of the eCRF data and provide an electronic signature in the EDC system.

14.3 Data Management

The sponsor or designated CRO personnel will review the completeness and accuracy of the data entered by the study personnel. For any inconsistent or missing data, a data query will be sent to the study site. Designated study site personnel are required to answer queries in a timely manner and make necessary changes to the data.

This project will use the World Health Organization Drug Dictionary (WHODrug) to code concomitant therapies and prior medications entered into the database. MedDRA terminology will be used to code medical history/current diseases and AEs.

Before the database is locked, the study team needs to complete data cleaning, summarize all protocol deviation events that occurred during the study, and hold a data review meeting to determine the analysis sets. All decisions made during the data review meeting must be documented. After the data review meeting is passed, the study database in the EDC system will be locked upon confirmation by the study team. If any changes need to be made to the locked data, the database must be unlocked with authorization after discussion by the project team.

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16 Appendices

Appendix 1: Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

Note: This translated version is for reference only. The final version shall be the English version.

1. Measurability of Tumors at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be classified as either measurable or non-measurable according to the following definitions:

Measurable Lesions

Tumor lesions: At least one accurately measurable dimension (recorded as the longest diameter), with a minimum length as follows:

- CT scan 10 mm (CT scan slice thickness no greater than 5 mm)
- Conventional clinical examination instruments 10 mm (tumor lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- Chest X-ray 20 mm
- Malignant lymph nodes: Pathologically enlarged and measurable, with a short axis of a single lymph node ≥15 mm on CT scan (recommended CT scan slice thickness not to exceed 5 mm). Only the short axis is measured and followed up at baseline and during follow-up.

Non-measurable Lesions

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph node short axis ≥10 mm to <15 mm) and unmeasurable lesions. Unmeasurable lesions include: meningeal disorder, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangiosis carcinomatosa of the skin/lung, abdominal masses that cannot be confirmed and followed up by imaging, and cystic lesions.

Special Considerations for Lesion Measurement

Bone lesions, cystic lesions, and lesions that have previously received local treatment require special notation:

Bone lesions:

- Bone scans, Positron Emission Tomography (PET) scans, or plain films are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;
- Lytic or mixed lytic/blastic bone lesions with an identifiable soft tissue component that meets the

definition of measurability described above can be considered measurable lesions if they can be evaluated by tomographic imaging techniques such as CT or MRI;

- Blastic bone lesions are non-measurable.
- Cystic lesions:
- Lesions that meet the radiological criteria for a simple cyst should not be considered malignant lesions simply because they are defined as simple cysts, and are neither measurable nor non-measurable lesions;
- If they are cystic metastatic lesions and meet the definition of measurability described above, they can be considered measurable lesions. However, if non-cystic lesions exist in the same patient, non-cystic lesions should be preferentially selected as target lesions.

Locally treated lesions;

- Lesions in a previously irradiated area or an area that has undergone other local regional treatment are generally considered non-measurable, unless there is definite progression of the lesion. The study protocol should detail the conditions under which these lesions are considered measurable.

1.2 Description of Measurement Methods

Lesion Measurement

For clinical evaluation, all tumor measurements must be recorded in metric units. All baseline assessments of tumor lesion size should be completed as close as possible to the start of treatment and must be completed within 28 days (4 weeks) before the start of treatment.

Evaluation Methods

The same technique and method should be used for baseline assessment and subsequent measurements of lesions. All lesions must be evaluated using imaging examinations, except for those that cannot be evaluated by imaging and can only be evaluated by clinical investigation.

Clinical lesions: Clinical lesions can only be considered measurable if they are superficial and have a diameter ≥10 mm at the time of measurement (e.g., skin nodules). For patients with skin lesions, it is recommended to use color photographs with a ruler to measure the lesion size for archival purposes. When lesions are evaluated using both imaging and clinical investigation, imaging evaluation should be used whenever possible, as it is more objective and can be reviewed repeatedly at the end of the study.

Chest X-ray: When tumor progression is an important study endpoint, chest CT should be prioritized, as CT is more sensitive than X-ray, especially for new lesions. Chest X-ray is only applicable when the measured lesion has clear borders and the lungs are well-aerated.

CT, MRI: CT is currently the best available and repeatable method for efficacy evaluation. The definition of measurability in these guidelines is based on a CT scan slice thickness of ≤5 mm. If the CT slice thickness is greater than 5 mm, the minimum measurable lesion should be twice the slice thickness. It is recommended to use contrast-enhanced CT for efficacy assessment (unless there is a contraindication to contrast agents). MRI is also acceptable in some cases (e.g., whole body scan).

Ultrasound: Ultrasound should not be used as a method for measuring lesion size. Due to its operator dependence, ultrasound investigation is not repeatable after the measurement is completed and cannot guarantee consistency of technique and measurement between different measurements. If a new lesion is discovered using ultrasound during the study, it should be confirmed with CT or MRI. If radiation exposure from CT is a concern, MRI can be used instead.

Endoscopy, laparoscopy: The use of these techniques for objective tumor evaluation is not recommended, but they can be used to confirm CR when obtaining biopsy specimens, and also to confirm recurrence in studies where the endpoint is recurrence after CR or surgical resection.

Tumor markers: Tumor markers cannot be used alone to evaluate objective tumor response. However, if the marker level is above the upper limit of normal at baseline, it must return to the normal range for the evaluation of complete response. Because tumor markers vary by disease, this factor must be considered when writing the measurement criteria into the protocol. Specific criteria for CA-125 response (ovarian cancer recurrent) and prostate-specific antigen (PSA) response (prostate cancer recurrent) have been published. Furthermore, the Gynecologic Cancer InterGroup has developed CA-125 progression criteria, which will be incorporated into the objective tumor evaluation criteria for first-line treatment of ovarian cancer.

Cytology/Histology techniques: In specific situations defined by the protocol, these techniques can be used to identify PR and CR (e.g., residual benign tumor tissue is often present in lesions of germ cell tumors). When effusion may be a potential side effect of a certain therapy (e.g., treatment with taxane compounds or angiogenesis inhibitors), and the measurable tumor meets the criteria for response or stable disease, the appearance or worsening of tumor-related effusion during treatment can be confirmed by cytology to distinguish between response (or stable disease) and PD.

2. Assessment of Tumor Response

2.1 Target Lesion Assessment

Complete Response (CR): Disappearance of all target lesions, and all pathological lymph nodes (including target and non-target nodes) must have their short axis reduced to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as

reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest); in addition to the relative increase, the sum must also demonstrate an absolute increase of at least 5 mm (the appearance of one or more new lesions is also considered PD).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.2 Notes on Target Lesion Assessment

Lymph nodes: Even if a lymph node identified as a target lesion shrinks to within 10 mm, the actual short axis value corresponding to the baseline must still be recorded at each measurement (consistent with the anatomical plane of the baseline measurement). This means that if a lymph node is a target lesion, even if it meets the criteria for complete response, it cannot be said that the lesion has completely disappeared, because the short axis of a normal lymph node is defined as <10 mm. In the CRF or other recording methods, target lymph node lesions must be specifically recorded in a designated location: for CR, all lymph node short axes must be <10 mm; for PR, SD, and PD, the actual measured value of the target lymph node short axis will be included in the sum of diameters of target lesions.

Target lesions that are too small to measure: In clinical studies, all lesions (nodular or non-nodular) recorded at baseline should have their actual measured values recorded again in subsequent assessments, even if the lesion is very small (e.g., 2 mm). However, sometimes they may be too small, resulting in a very blurry image on the CT scan, making it difficult for the radiologist to define an exact value, and it may be reported as "too small to measure". When this occurs, it is very important to record the previous value on the CRF. If the radiologist believes the lesion may have disappeared, it should be recorded as 0 mm. If the lesion is indeed present but is blurry and an exact measurement cannot be given, a default value of 5 mm can be used. (Note: This situation is unlikely to occur with lymph nodes, as they normally have a measurable size or are often surrounded by fatty tissue, as in the retroperitoneal space; however, if a measurement cannot be given, a default of 5 mm is also used). The default value of 5 mm is derived from the slice thickness of the CT scan (this value does not change with different CT slice thicknesses). Since the chance of the same measurement value recurring is low, providing this default value will reduce the risk of incorrect assessment. However, it must be reiterated that if the radiologist can provide an exact value for the lesion size, the actual value must be recorded, even if the lesion diameter is less than 5 mm.

Fragmented or coalescent lesions: When a non-nodular lesion fragments, the longest diameters of each separate part are added together to calculate the sum of diameters of the lesion. Similarly, for coalescent lesions, they can be distinguished by the plane between each coalesced part, and then their respective longest diameters are calculated. However, if they are inseparably coalesced, the longest diameter should be the longest diameter of the entire fused lesion.

2.3 Non-target Lesion Assessment

This section defines the response criteria for non-target tumor lesions. Although some non-target lesions are actually measurable, they do not need to be measured; only a qualitative assessment at the time points specified in the protocol is required.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes are non-pathological in size (short axis <10 mm).

Non-CR/Non-PD: Presence of one or more non-target lesions and/or persistence of tumor marker levels above the normal range.

PD: Unequivocal PD of existing non-target lesions. Note: The appearance of one or more new lesions is also considered PD.

2.4 Special Notes on the Assessment of Non-target Lesion Progression

The definition of non-target lesion progression is further explained as follows: When a patient has measurable non-target lesions, even if the target lesion assessment is stable or partial response, to define unequivocal PD based on non-target lesions, the overall deterioration of the non-target lesions must have reached a degree that requires termination of treatment. A general increase in the size of one or more non-target lesions is often insufficient to meet the PD criteria. Therefore, when target lesions are stable or in partial response, it is very rare to define overall tumor PD based solely on changes in non-target lesions.

When all of a patient's non-target lesions are non-measurable: This situation occurs in some Phase III parts where the inclusion criteria do not require the presence of measurable lesions. The overall assessment still refers to the above criteria, but in this case, there is no measurable data for the lesions. Deterioration of non-target lesions is not easy to assess (by definition: all non-target lesions must be truly unmeasurable). Therefore, when changes in non-target lesions lead to an increase in overall disease burden equivalent to PD in target lesions, an effective detection method needs to be established to assess and define unequivocal PD based on non-target lesions. For example, an increase in tumor burden described as an additional 73% increase in volume (equivalent to a 20% increase in the diameter of a measurable lesion). Another example is peritoneal effusion changing from "trace" to

"massive"; lymphangiopathy from "local" to "widespread dissemination"; or described in the protocol as "sufficient to alter treatment". Examples include pleural effusion changing from trace to massive, lymphatic involvement spreading from the primary site to distant sites, or what might be described in the protocol as "necessitating a change in treatment". If unequivocal progression is found, the patient should be considered to have overall PD at that time point. It is best to have objective criteria applicable to the assessment of non-measurable lesions; note that the added criteria must be reliable.

2.5 New Lesions

The appearance of a new malignant lesion indicates PD; therefore, some evaluation of new lesions is very important. Currently, there are no specific criteria for detecting lesions by imaging; however, the discovery of a new lesion should be unequivocal. For example, progression cannot be attributed to differences in imaging techniques, changes in imaging modality, or other lesions besides the tumor (e.g., some so-called new bone lesions are merely the healing of the original lesion, or recurrence of the original lesion). This is very important when a patient's baseline lesions show a PR or CR. For example, necrosis of a liver lesion may be identified as a new cystic lesion on a CT report, when in fact it is not.

Lesions detected during follow-up that were not found at baseline will be considered new lesions and indicate PD. For example, if a patient with visceral lesions found at baseline undergoes a head CT or MRI and is found to have metastases, the patient's intracranial metastatic lesions will be considered evidence of PD, even if they did not have a head examination at baseline.

If a new lesion is equivocal, for example, due to its small size, further treatment and follow-up evaluation are needed to confirm whether it is a new lesion. If repeated examinations confirm it is a new lesion, the time of PD should be calculated from the time of its initial discovery.

Lesion assessment by Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) generally requires additional tests for supplementary confirmation. It is reasonable to combine FDG-PET examination and supplementary CT examination results to evaluate PD (especially for new suspicious disease). New lesions can be clarified by FDG-PET examination, according to the following procedure:

A negative baseline FDG-PET examination followed by a positive follow-up FDG-PET examination indicates PD.

No baseline FDG-PET examination was performed, and a subsequent FDG-PET examination is positive:

If the new lesion found on the follow-up positive FDG-PET examination is consistent with the CT examination results, it proves PD.

If the new lesion found on the follow-up positive FDG-PET examination is not confirmed by CT examination results, another CT examination is required for confirmation (if confirmed, the time of PD is calculated from the discovery of the abnormality on the previous FDG-PET examination).

If the follow-up positive FDG-PET examination result is consistent with an existing lesion on CT examination, and that lesion shows no PD on imaging, then there is no PD.

2.6 Missing Assessments and Unevaluable Descriptions

If lesion imaging or measurement cannot be performed at a specific time point, the patient is unevaluable at that time point. If only some lesions can be evaluated in an assessment, this is usually considered unevaluable at that time point, unless there is evidence that the missing lesions do not affect the efficacy response evaluation at the specified time point.

2.7 Special Notes on Efficacy Assessment

When nodular lesions are included in the overall target lesion assessment, and their size shrinks to 'normal' size (<10 mm), they will still have a lesion size scan report. To avoid over-assessing the situation reflected by an increase in nodule size, the measurement results will be recorded even if the nodule is normal. As mentioned earlier, this means that for participants with a complete response, the CRF will not record a value of 0.

If efficacy confirmation is required during the study, repeated "non-measurable" time points will complicate the assessment of BOR. The study's analysis plan must state that these missing data/assessments can be clearly explained when determining efficacy. For example, in most studies, a participant's response of PR-NE-PR can be considered as confirmed efficacy.

When a participant's overall health deteriorates, requiring discontinuation of treatment, but there is no objective evidence, it should be reported as symptomatic progression. Even after treatment discontinuation, an effort should be made to assess objective progression. Symptomatic deterioration is not a description of objective response; it is the reason for stopping treatment. The objective response of such participants will be assessed based on the status of target and non-target lesions as shown in Appendix Tables 1-3.

Cases defined as early progression, early death, and unevaluable are study-specific and should be clearly described in each protocol (depending on the treatment interval and treatment cycle).

In some cases, it is difficult to distinguish local lesions from normal tissue. When the assessment of complete response is based on such a definition, we recommend performing a biopsy before assessing the efficacy of complete response of the local lesion. When abnormal imaging results of a participant's local lesion are considered to represent lesion fibrosis or scar formation, FDG-PET is used as an

assessment standard similar to biopsy to confirm the efficacy of complete response. In this case, the use of FDG-PET should be prospectively described in the protocol, supported by reports from specialized medical literature on this situation. However, it must be recognized that the limitations of FDG-PET and biopsy themselves (including their resolution and sensitivity) will lead to false-positive results in the assessment of complete response.

Appendix Table 1. Time Point Response - Participants with Target Lesions (with or without Non-target Lesions)

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or not fully evaluable	No	PR
SD	Non-PD or not fully evaluable	No	SD
Not fully evaluable	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not Evaluable.

Appendix Table 2. Time Point Response - Participants with Non-target Lesions Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR or Non-PD	No	Non-CR or Non-PD
Not fully evaluable	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: For non-target lesions, "Non-CR/Non-PD" refers to a response better than SD. Since SD is increasingly used as an endpoint for efficacy evaluation, the Non-CR/Non-PD response is established to address situations where no measurable lesions are specified.

For equivocal findings of progression (e.g., a very small, uncertain new lesion; cystic change or necrosis of an existing lesion), treatment may be continued until the next assessment. If PD is confirmed at the next assessment, the date of PD should be the date when suspected PD was first observed.

Appendix Table 3. Best Overall Response for Confirmed CR and PR

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	If SD persists for a sufficient duration, it is SD; otherwise, it should be PD
CR	PD	If SD persists for a sufficient duration, it is SD; otherwise, it should be PD
CR	NE	If SD persists for a sufficient duration, it is SD; otherwise, it should be NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD persists for a sufficient duration, it is SD; otherwise, it should be PD
PR	NE	If SD persists for a sufficient duration, it is SD; otherwise, it should be NE
NE	NE	NE

Note: CR is Complete Response, PR is Partial Response, SD is Stable Disease, PD is Progressive Disease, NE is Not Evaluable. Superscript "a": If a true CR occurs at the first time point, any disease appearing at a subsequent time point will be evaluated as PD at that later time point (because the disease has reappeared after CR), even if the participant's response meets the PR criteria relative to baseline. Best response depends on whether SD occurs within the shortest treatment interval. However, sometimes the first assessment is CR, but a subsequent scan suggests that a small lesion still seems to be present; therefore, the participant's response at the first time point should actually be PR, not CR. In this case, the initial CR judgment should be revised to PR, and the best response is PR.

2.8 Confirmation of Efficacy Assessment/Duration of Response

Confirmation of Response

For non-randomized clinical studies where tumor response is the primary endpoint, the efficacy of PR and CR must be confirmed to ensure that the response is not the result of measurement error. In studies where SD or PD is the primary endpoint, confirmation of response is no longer necessary, as it has no value in the interpretation of the study results. In the case of SD, at least one measurement meeting the protocol-specified criteria for SD must be made within the shortest time interval after the start of the study (generally not less than 6-8 weeks).

Duration of Overall Response

The duration of overall response is from the time of the first measurement that meets the criteria for CR or PR (whichever is measured first) to the time of the first true record of disease recurrence or PD (using the smallest measurement recorded in the study as the reference for PD). The duration of CR

is from the time of the first measurement that meets the CR criteria to the time of the first true record of disease recurrence or PD.

Duration of Stable Disease

The time from the start of treatment to PD (in randomized studies, from the time of randomization), using the smallest sum on study as the reference (if the baseline sum is the smallest, it is used as the reference for calculating PD). The clinical relevance of the duration of SD varies between different studies and different diseases. If, in a particular study, the proportion of patients who maintain SD for a minimum duration is the study endpoint, the protocol should specify the minimum time interval between two measurements in the definition of SD.

Note: The duration of response, duration of SD, and PFS are affected by the frequency of follow-up after the baseline assessment. Defining a standard follow-up frequency is beyond the scope of these guidelines. The follow-up frequency should consider many factors, such as disease type and stage, treatment cycle, and standard practices. However, if comparisons between studies are to be made, the limitations on the accuracy of these measurement endpoints should be considered.

2.9 PFS/TTP

Many studies of advanced tumors use PFS or TTP as the primary endpoint. If the protocol requires all patients to have measurable lesions, the assessment of progression is relatively simple. An increasing number of studies allow patients with both measurable and non-measurable lesions to be enrolled. In this case, the clinical findings of PD in patients with non-measurable lesions must be described in detail and clearly. Because the date of PD often has ascertainment bias, the observation time points should be scheduled the same for all study groups.

Appendix 2: Performance Status Scoring Criteria (ECOG PS)

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

Appendix 3: Cockcroft-Gault Formula

Formula for serum creatinine concentration in (mg/dL):

$$\text{Male creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight})^{a}}{72 \times \text{serum creatinine}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{weight})^{a}}{72 \times \text{serum creatinine}}$$

Formula for serum creatinine concentration in (μmol/L):

$$\text{Male creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight})^{a}}{0.818 \times \text{serum creatinine}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{weight})^{a}}{0.818 \times \text{serum creatinine}}$$

a: Age in years, weight in kg.

Appendix 4: List of Prohibited Medications

Interaction Mechanism	Drug Name
Strong Inducers of CYP3A and P-gp	Apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor/ivacaftor, mitotane, phenytoin, rifampin, St. John's wort
Strong Inhibitors of CYP3A and P-gp	Ceritinib, clarithromycin, cobicistat, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir tablets, nefazodone, amiodarone, cyclosporine, dronedarone, erythromycin, lapatinib, propafenone, quinidine, ranolazine, verapamil
Sensitive Substrates of CYP3A4	Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, isavuconazonium, ivabradine, lemborexant, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, mobocertinib, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, venetoclax
Sensitive Substrates of OAT1	Adefovir, ciprofloxacin, furosemide, tenofovir

The table lists common strong inhibitors and inducers of CYP3A4 and P-gp, and sensitive substrates of OAT1 and CYP3A4. If there are questions about other possible concomitant medications, the investigator can communicate with the sponsor. Drug interactions can be queried on the FDA's official website at the following URL: https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems.

Appendix 5: Detailed Parameters and Simulation Performance of the BOIN Design

Using the Shiny app 'BOIN' obtained from http://www.trialdesign.org, and considering the following two scenarios:

1. Accelerated titration is used for the first two dose levels

The specific parameters of the BOIN design are as follows:

Parameter	Value
Number of dose groups	5
Starting dose	1
Number of participants per cohort	3
Number of cohorts	10
If the number of participants assigned to a dose group reaches m and the next participant is still to be assigned to that dose group, the study is terminated. m =	6
Target toxicity probability	0.3
Use default dose escalation/de-escalation boundaries (recommended)	True
Use accelerated titration	Yes
Maximum dose for accelerated titration	2
When 1 DLT is observed in 3 participants, change the decision from de-escalate to stay at the current dose	Yes
Dose elimination threshold p_K	0.95
Number of repetitions for each scenario	1000
Random number generator seed	12345

Note: Maximum sample size = Number of participants per cohort * Number of cohorts = 3 * 10 = 30.

The simulation performance of this BOIN design is as follows:

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Number of patients	Early termination %
Scenario 1							
True DLT rate	0.3	0.46	0.5	0.54	0.58		
Selection %	56.6	22.4	11.7	1.6	0		7.7
Patients treated %	44.1	35.1	17.6	2.9	0.3	12.1	
Scenario 2							
True DLT rate	0.16	0.3	0.47	0.54	0.6		
Selection %	24.8	47.5	23.8	2.9	0.1		0.9
Patients treated %	26.7	39.7	28.1	5.1	0.4	14.4	
Scenario 3							
True DLT rate	0.04	0.15	0.3	0.48	0.68		
Selection %	1.6	22.9	56.7	18	0.8		0
Patients treated %	9.8	23.3	43.4	20.7	2.8	15.3	
Scenario 4							
True DLT rate	0.02	0.07	0.12	0.3	0.45		

Selection %	0.2	3.3	23.8	51.2	21.4		0.1
Patients treated %	6.8	9.7	31.8	35.7	15.9	17	
Scenario 5							
True DLT rate	0.02	0.06	0.1	0.13	0.3		
Selection %	0.3	2.2	11.1	22.7	63.7		0
Patients treated %	7	9.2	24.3	29.5	30	16.4	

2. BOIN design considering only the last three dose levels

The specific parameters of the BOIN design are as follows:

Parameter	**Value**
Number of dose groups	5
Starting dose	1
Number of participants per cohort	3
Number of cohorts	10
If the number of participants assigned to a dose group reaches m and the next participant is still to be assigned to that dose group, the study is terminated. m =	6
Target toxicity probability	0.3
Use default dose escalation/de-escalation boundaries (recommended)	True
Use accelerated titration	No
When 1 DLT is observed in 3 participants, change the decision from de-escalate to stay at the current dose	Yes
Dose elimination threshold p_K	0.95
Number of repetitions for each scenario	1000
Random number generator seed	12345

The simulation performance of this BOIN design is as follows:

	Dose 1	Dose 2	Dose 3	Number of patients	Early termination %
Scenario 1					
True DLT rate	0.3	0.48	0.67		
Selection %	70.6	20.4	0.9		8.1
Patients treated %	63.7	32	4.3	10.4	
Scenario 2					
True DLT rate	0.13	0.3	0.44		
Selection %	27.7	50.1	21.7		0.5
Patients treated %	39.3	41.7	19	13.9	
Scenario 3					
True DLT rate	0.05	0.13	0.3		
Selection %	3.6	26.2	70.1		0.1
Patients treated %	25.1	37.4	37.5	14.7	

Based on the above simulation performance results, this design can select the correct MTD with a high probability (if an MTD exists) and will assign more patients to the dose level with a DLT rate

closest to the target probability of 0.3.

Appendix 6: Statistical Methods for Interim Analysis

The interim analysis uses the Bayesian predictive probability (PP) method to calculate the probability of success, providing a rationale for early futility assessment. Based on the efficacy data observed at the interim analysis, the probability of success (i.e., concluding that the study drug is effective) at the maximum planned sample size is calculated. Based on the observed data, a high PP indicates a high likelihood of concluding that the study treatment is effective at the end of the study, whereas a low PP suggests that the study treatment may not have sufficient efficacy.

The table below shows the relevant parameter values and calculation results set via the online software (https://www.trialdesign.org/one-page-shell.html#BEMPR):

Input Parameter	Input Value		
	NSCLC	CRC	PDAC
Reference response rate (θ_0)	0.23	0.10	0.15
Threshold for declaring efficacy at the end of the trial (p_T)	0.7		
Early Stopping for Futility	TRUE		
Probability confidence threshold for futility stopping (p_L)	0.2		
Early Stopping for Efficacy	FALSE		
Prior distribution for θ: Beta(a_0,b_0) a_0	0.5		
Prior distribution for θ: Beta(a_0,b_0) b_0	0.5		
Input Cohort Manually	FALSE		
Maximum number of patients in the trial	73	50	94
Minimum number of patients before early stopping rule applies	20		
Cohort size	1		

Appendix 7: Central Laboratory Information and Sample Destruction Company Information

Central Laboratory 1: PK Testing

Name: Teddy Clinical Research Laboratory (Shanghai) Limited

Unified Social Credit Code: 91310110MA1G83F27K

Address: Room 101-110, Block C, 3rd Floor, Building 12, No. 128 Xiangyin Road, Yangpu District, Shanghai

Central Laboratory 2: ctDNA Sequencing

Name: Guangzhou Burning Rock Biotech Co., Ltd.

Unified Social Credit Code: 91440116094098415C

Address: No. 5 Xingdao Huanbei Road, Guangzhou International Bio Island, Huangpu District, Guangzhou

Sample Destruction Company 1: PK Sample Destruction Unit

Name: Shanghai Solid Waste Disposal Co., Ltd.

Unified Social Credit Code: 913101147294906145

Address: No. 2491 Jiazhu Highway, Jiading District, Shanghai

Sample Destruction Company 2: ctDNA Sequencing Sample Destruction Unit

Name: Guangzhou GRANDTOP Group Co., Ltd.

Unified Social Credit Code: 91440101671815024A

Address: Room 1218, No. 121 Liuhua Road (South Tower), Yuexiu District, Guangzhou