GFH018

Clinical Trial Protocol GFH018X1101

A Phase I Study with Single/Multiple Dose Administered to Explore the Safety/Tolerability and Pharmacokinetics of GFH018 in the Treatment of Subjects with Advanced Solid Tumors

Type:	Clinical trial protocol
Version number:	1.6
Study phase:	Phase I
Status	Finalized
Release Date:	2021-03-02

Signature page—Investigator

Protocol Title: A Phase I Study with Single/Multiple Dose Administered to Explore the Safety/Tolerability and Pharmacokinetics of GFH018 in the Treatment of Subjects with Advanced Solid Tumors

Study ID: GFH018X1101

This protocol is a confidential document of Zhejiang Genfleet Therapeutics Co., Ltd and Genfleet Therapeutics (Shanghai) Inc., and is only disseminated under the premise of confidentiality. I confirm that I have read this protocol, I understand and agree with the content of the protocol, and I will carry out clinical trial work in accordance with this protocol. In addition, I will work in accordance with the ethical principles in the Declaration of Helsinki, as well as in accordance with the Good Clinical Trial Practice for Drugs and applicable laws and regulations. By signing this document, I agree that the undisclosed information contained herein is prohibited without the prior written permission of Zhejiang Genfleet Therapeutics Co., Ltd and Genfleet Therapeutics (Shanghai) Inc.

Signature of the Investigator: _____

Date:_____

Name: _____

Title: _____

Site Name/Address: _____

Signature page—Sponsor

Protocol Title: A Phase I Study with Single/Multiple Dose Administered to Explore the Safety/Tolerability and Pharmacokinetics of GFH018 in the Treatment of Subjects with Advanced Solid Tumors

Study ID: GFH018X1101

This study will be conducted in accordance with the requirements of this clinical research protocol and GCP and relevant national laws and regulations.

This study will comply with the Declaration of Helsinki and treat subjects with the highest respect. Necessary measures will be taken to safeguard the safety and interests of the subject.

Sponsor's signature: _____

Date:_____

Name: _____

Title: _____

Abbreviations

Abbreviation	Full name
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate transaminase
ANC	absolute neutrophil count
AUC	Area under the curve
BID, bid	up to the
BNP	Brain Natriuretic Peptide
BOR	Best of Response
C_{max}	Maximal concentration
C_{min}	Trough concentration
CI	Confidence Interval
CL	Clearance
CLr	Renal clearance
CR	Complete response
CRO	Contract Research Organization
CT	Computed Tomography
CRR	Complete Radiological Response
CV	Coefficient of Variance
DLT	Dose Limiting Toxicities
DCR	Disease Control Rate
DOR	Duration of Response
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GLP	Good Laboratory Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
LLOQ	Lower Limit of Quantitation
M1/M2	Type 1/2 tumor associated macrophage
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NOAEL	No Observed Adverse Effect Level
OR	Objective Response
ORR	Objective Response Rate
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
PFS	Progression Free Survival
PI	Primary Investigator

PO, po, p.o.	Oral administration
PS	Physical performance
PR	Partial Response
Racc	Accumulation ratio
RDE	Recommended dose for expansion
RP2D	Recommended phase 2 dose
SAE	Serious Adverse Event
SD	Stable Disease
TTP	Time to Progression
ULN	Upper Limit of Normal
TEAE	Treatment-emergent Adverse Event
Vd,ss	Volume of distribution at stead state

Synopsis

<table>
<tr><td>Protocol ID</td><td>GFH018X1101</td></tr>
<tr><td>Protocol Title</td><td>A Phase I Study with Single/Multiple Dose Administered to Explore the Safety/Tolerability and Pharmacokinetics of GFH018 in the Treatment of Subjects with Advanced Solid Tumors</td></tr>
<tr><td>Version number</td><td>Version 1.6</td></tr>
<tr><td>Sponsor</td><td>Zhejiang Genfleet Therapeutics Co., Ltd
Genfleet Therapeutics (Shanghai) Inc.</td></tr>
<tr><td>Clinical stage</td><td>Phase I</td></tr>
<tr><td>Investigational drugs</td><td>Drug code: GFH018
Dosage form: tablets
Specifications: 5 mg and 50 mg</td></tr>
<tr><td>Study Objectives and endpoints</td><td>
<table>
<tr><th>Study Objective</th><th>Endpoints</th></tr>
<tr><td>Primary
1) To evaluate the safety and tolerability of single/multiple administration of GFH018 in subjects with advanced solid tumors.
2） Determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of GFH018.</td><td>• Safety: DLT, incidence and severity of AE, SAEs, laboratory tests, vital signs, ECG, ECHO
• Tolerability: dose reduction, dose interruption, permanent discontinuation</td></tr>
<tr><td>Secondary
1) To evaluate the pharmacokinetic characteristics of GFH018 after single/multiple administration in subjects with advanced solid tumors.
2) To evaluate the preliminary efficacy of GFH018 in subjects with advanced solid tumors.
3) To evaluate blood TGF-β levels and correlate with the clinical responses.</td><td>• Pharmacokinetics: PK parameters (PK parameters after single dose administration include $C_{max,}$ $T_{max,}$ $AUC_{0-12h,}$ $AUC_{0-24h,}$ $AUC_{0-inf,}$ $T_{1/2,}$ CL/F, V_d/F; Steady-state PK parameters include $C_{max,ss,}$ $C_{min,ss,}$ $T_{max,ss,}$ $AUC_{tau,}$ $T_{1/2,}$ CL/F, V_d/F, $CL_{r,}$ R_{acc}）
• Efficacy: BOR, ORR, DCR, PFS, TTP evaluated according to RECIST version 1.1
• Pharmacodynamic marker: TGF-β levels in peripheral blood at baseline and during</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td></td><td>treatment</td></tr>
<tr><td>Exploratory
To evaluate possible pharmacodynamic marker in the blood</td><td>• Changes of pSMAD2/3 in PBMC (peripheral blood single cells).</td></tr>
</table>
</td></tr>
<tr><td>Study Design</td><td>
This is the first-in-human trial of GFH018, using an open-label, non-randomized, single/multi-dose dosing design to evaluate the safety, tolerability, pharmacokinetics, and preliminary anti-tumor efficacy of GFH018 in subjects with advanced solid tumors.
This study is divided into two parts: a dose-escalation part aimed at determining MTD and/or RDE followed by a dose expansion part to confirm the safety of RDE and RP2D and explore the preliminary efficacy of GFH018 in the potentially benefited population. The RDE will be determined for exploration in expansion. Different dosing regimens will be explored, RDE dose and optimal dosing regimen will be further confirmed, and RP2D will be obtained. Both parts were divided into three periods: screening, treatment, and follow-up.
Part 1: Dose escalation study
This part is a safety, tolerability, and pharmacokinetic study with a modified 3+3 design to determine MTD and/or RDE. According to preclinical data, the starting dose is selected as 10 mg/day (5 mg administered twice daily). In the first cycle, each group of subjects is given a single dose (5 mg as the starting dose) on day 1 and taken serial PK sampling. After the first dose on day 1, serial PK blood samples will be collected up to 72 h post-dose to obtain the complete PK profile of a single dose (the collection point design may be modified based on preliminary PK results). Subjects will be administered with GFH018 BID, 14d-on/14d-off from day 4. Four to six dose levels are planned (refer to Table 3-1). The first cycle is defined as 31 days, and subsequent cycles are all defined as 28 days. After the last dose of cycle 1 (day 17), serial PK blood samples will be collected to obtain PK characteristics at steady state. Starting from the third dose level, urine samples from steady state will also be collected for PK studies to fully understand GFH018 PK characteristics.
Table 1-1 Dose escalation regimen (provisional dose level)
<table>
<tr><th>Dose level</th><th>Regimen</th><th>Incremental percentage (%)</th></tr>
</table>
</td></tr>
</table>

1	5 mg bid, 14-d on/14-d off	-
2	10 mg bid, 14-d on/14-d off	100
3	20 mg bid, 14-d on/14-d off	100
4	30 mg bid, 14-d on/14-d off	50
5	40 mg bid, 14-d on/14-d off	33
6	50 mg bid, 14-d on/14-d off	25

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

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

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

	part. At the end of the dose escalation, at least six evaluable subjects in the MTD/RDE group should be ensured. **Part II Dose Expansion** The primary objective of this part is to confirm the safety of RDE dose and explore different dose regimens to ultimately determine RP2D. The secondary objective is to initially explore the efficacy in potentially benefited populations. The 14d-on/14d-off and 7d-on/7d-off dose regimens under RDE dose will be explored based on the data from the dose escalation part, while the SMC will review the safety, PK, and biomarker data then decide whether to also explore other dose regimens at RDE, such as daily dosing. This part will further confirm the safety of RDE dose and optimal dose regimen and obtain RP2D. At least 12 subjects (including subjects receiving the same dose during the dose escalation part) are required to be enrolled to determine the final RP2D. Potential benefited tumor types will be selected for dose expansion part based on the mechanism of action of the drug and preliminary efficacy data in dose escalation part, including hepatocellular carcinoma, cholangiocarcinoma/gallbladder cancer, colorectal cancer, urothelial cancer, pancreatic, cervical, head and neck squamous cell or esophageal cancer, and nasopharyngeal carcinoma.
Definition of DLT	DLT is defined as an adverse event or abnormal laboratory test related to the study drug that occurred during the first cycle (31 days) and meet the following criteria. All toxicities will be graded according to CTCAE version 5.0. **a) Non-hematologic toxicity** Grade 3 and above toxicity. Except for diarrhea, nausea, vomiting, and rash recovering to grade 2 or less within 3 days of supportive care. **Specific cardiotoxicity** ■ Cardiac structure/function related: • Grade 2 and above heart valve dysfunction. • Grade 2 or above left ventricular ejection fraction

	decreased. • Radiographic evidence of damage to any heart and great vessels. ■ Biomarkers of cardiac injury related: • Troponin T or troponin I (hs-cTnT or hs-cTnI) twice the baseline and above the upper limit of normal ≥ 2 consecutive times (the interval ≥3 days). If hypersensitivity troponin is not available in the site, troponin can be substituted for evaluation according to the criteria listed above. **b) Hematological toxicity** ■ Grade 3 neutropenia with infection. ■ Grade 4 neutropenia, lasting more than 5 days. ■ Grade 3 febrile neutropenia (neutrophil count < 1.0×109/L with a single temperature > 38.3 °C (101°F) or a sustained temperature of ≥ 38 °C (100.4°F) for more than one hour); or neutropenic infection requiring clinical intervention. ■ Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia requiring clinical intervention. ■ Grade 4 anemia. **c) Investigator and sponsor need to discuss whether to decide whether to be any other clinically significant abnormalities of DLT.**
Sample size	Enroll about 40~60 subjects
Study population	**Subjects eligible to participate in this study must meet all of the following inclusion criteria:** 1. Voluntary participation in the study and sign the informed consent form. 2. Male or female aged 18–75 years (inclusive). 3. Histologically or cytologically confirmed diagnosis of advanced or metastatic solid tumors with progression on, intolerance to standard therapy, or no suitable standard anticancer therapy available. 4. At least one non-measurable lesion per RECIST 1.1. For subjects enrolled in the expansion part, at least one measurable

	lesion per RECIST 1.1 5. Eastern Cooperative Oncology Group Performance Status (ECOG P.S.) ≤ 1. For subjects with liver metastases, Child–Pugh score of 0–7. 6. Life expectancy ≥ 12 weeks. 7. With sufficient organ functions, including: 1) Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, hemoglobin ≥ 9 g/dL, without blood transfusion or granulocyte colony-stimulating factor, thrombopoietin, erythropoietin, or other therapies within 14 days prior to hematology tests. 2) Total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN, alkaline phosphatase (ALP) ≤ 2.5 × ULN; for subjects with tumor involvement of the liver, TBIL ≤ 3.0 × ULN, AST and ALT ≤ 5.0 × ULN. 3) Creatinine (Cr) ≤ 1.5 × ULN, or calculated creatinine clearance (CrCl) ≥ 50 mL/min (Cockcroft-Gault formula) if Cr > 1.5 × ULN. 4) International normalized ratio (INR) ≤ 1.5 × ULN. 8. Toxicities left from prior anti-tumor therapy resolved to baseline or CTCAE v5.0 Grade 1 (neurotoxicity or alopecia ≤ Grade 2). 9. For women of childbearing potential (WOCBP) and male subjects with WOCBP partners, agreement to use an effective contraception method from the signing of the informed consent to 90 days after the last administration of the study drug. For WOCBP, negative pregnancy test results within 7 days (inclusive) prior to initiation of the study treatment. 10. Subjects or their legal representatives are able to communicate well with the investigators and willing to comply with the protocol and complete the study. **Exclusion Criteria:** Subjects who meet any of the following exclusion criteria are not

	allowed to enter this clinical study: 1. With significant cardiovascular diseases: a. Baseline QT/QTc prolongation (QTcF > 450 ms). b. Baseline ECG abnormalities of clinical significance c. Clinically significant cardiovascular diseases within 6 months, eg: myocardial infarction, angina, congestive heart failure, angioplasty, stent implantation, and coronary artery bypass grafting, etc. d. Abnormal doppler echocardiography confirmed by cardiologist such as left ventricular ejection fraction (LVEF) < 50%,heart valve stenosis, and ≥G2 valve regurgitation. e. Ascending aorta aneurysm or major artery aneurysm history, or predisposing conditions consistent with the development of aneurysms (for example, family history of aneurysm, Marfan syndrome, evidence of damage to the large vessels of the heart documented by computerized tomography [CT] scan with contrast). f. Troponin T or I increase of clinical significance. 2. Clinically significant gastrointestinal diseases, such as: ・ Intractable hiccup, nausea, and vomiting ・ Chronic gastrointestinal disorders: untreated peptic ulcer, Crohn's Disease, ulcerative colitis, et al. ・ Unable to swallow. ・ Severe cirrhosis and gastric varicose veins, hepatic encephalopathy ・ Active gastrointestinal bleeding. 3. With other severe disease, such as: a. With definitive neurological or mental disorders, including epilepsy or dementia. b. Known positive human immunodeficiency virus antibody (HIV-Ab). c. Active hepatitis B virus infection (positive HBsAg and positive HBV-DNA), or active hepatitis C virus infection (positive HCV-Ab and positive HCV-RNA. d. With current or history of interstitial pneumonia. Other uncontrolled systemic diseases, such as hypertension and diabetes. e. Other active infections. 4. Uncontrolled ascites, or pleural effusion clinically. 5. Known active autoimmune diseases or with history of autoimmune diseases that may recur (such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel

	disease, autoimmune thyroid disease, vasculitis, psoriasis, etc.) or subjects at risk (eg, those who have undergone organ transplantation and require immunosuppressive treatment). However, subjects with well-controlled diabetes mellitus, hypothyroidism requiring only hormone replacement therapy, skin disorders that do not require systemic therapy (such as vitiligo, psoriasis, or alopecia), or who are not expected to relapse in the absence of external triggers. 6. Subjects who need to receive glucocorticoids (prednisone >10 mg/day or equivalent doses of other similar drugs) or other immunosuppressants due to certain conditions within 14 days before treatment initiation. Note: in the absence of active autoimmune disease, the use of prednisone or equivalent adrenal drugs at a dose of ≤10 mg/day is allowed; subjects are allowed to use topical, ocular, intraarticular, intranasal, and inhaled type of glucocorticoid therapy (extremely low systemic absorption); short-term (≤ 7 days) use of glucocorticoids is permitted for prophylaxis (e.g., contrast media allergy) or for treatment of non-autoimmune conditions (e.g., due to contact allergens) delayed-type hypersensitivity). 7. Unstable brain metastasis. For subjects with brain metastases unintentionally detected during the screening, if they do not cause clinical symptoms and do not require therapeutic intervention, they can be discussed with the sponsor's medical director to decide whether to be enrolled. 8. Pregnant or lactating women. 9. Treatment with chemotherapy, radiotherapy, targeted therapy, endocrine therapy, immunotherapy, or other anti-tumor therapies, or other investigational drugs within 28 days prior to starting the study drug (For mitomycins and nitrosoureas: within 6 weeks. For oral fluorouracils and small molecule targeted drugs: within 2 weeks or 5 half-lives of the drug, whichever is longer). 10. Major surgery (needle biopsy not included) within 4 weeks prior to treatment initiation. 11. Administration of a strong inhibitor or inducer of CYP3A4 within 5 half-life periods or within 2 weeks (whichever is longer), or traditional Chinese medicines within 2 weeks prior to treatment initiation. 12. For subjects enrolled in the expansion part, diagnosis of other malignant tumors within 3 years prior to starting the study drug, except for cured in situ cervical carcinoma and skin basal cell carcinoma.

	13. Other conditions judged by the investigator as inappropriate for participation in the study.
Statistical analysis	**Sample size determination** In the dose-escalation part, 3 to 6 subjects were enrolled in each dose group, and a total of about 20 to 40 subjects are expected to be enrolled. If other dose levels need to be explored in addition to the predetermined dose level or other dosing regimens need to be explored, additional subjects may be enrolled for treatment. The second part of the dose expansion phase is planned to enroll 6 to 12 subjects in each treatment group, with at least 12 subjects (including those receiving the same treatment during the dose escalation phase) guaranteed in the RP2D dose group for the optimal dosing regimen. For an adverse event with an incidence of 10%, the probability of observing at least 1 of this adverse event in 12 subjects is approximately 72%. **Statistical Analysis Sett** • Full analysis set (FAS) consists of all subjects who have received at least one dose of study treatment. • Safety Set (SS) consists of all subjects who have received at least one dose of study treatment and had at least one valid post-baseline safety assessment. • Pharmacokinetic analysis set (PKAS) consists of all subjects who take at least one dose of study treatment and have at least one blood sample providing evaluable concentration data. • Dose determining set (DDS) consists of all subjects who have received at least 80% of the total planned dose of GFH018, are considered to have sufficient safety evaluation during the 31-day-observation period or developed DLT during the first cycle. **Statistical methods** Because the primary objective of this study is to evaluate the safety, tolerability, and pharmacokinetic profile of GFH018, no hypothesis

	testing is performed. The statistical analysis software SAS v9.4 was used for statistical analysis, mainly using descriptive statistical analysis, and using data lists and summaries and graphs to analyze and present data such as safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy. **Safety evaluation** All AEs will be graded according to CTCAE version 5.0 and be coded using MedDRA. All post-treatment AEs/SAEs, grade≥3 AEs, treatment-related AEs/SAEs, AEs leading to study drug discontinuation, AEs leading to study drug interruption, DLT, and AESIs will be summarized by system organ class, preferred term, and dose levels. Vital signs, physical examination, laboratory tests, and 12-lead ECG values will be analyzed descriptively and statistically for changes in observed values and relative baselines. **Efficacy evaluation** The disease assessments will be evaluated according to RECIST 1.1. Best overall response (BOR), ORR, and DCR will be summarized with corresponding 90% confidence intervals for each dose level. A waterfall plot will be used to show the best change from baseline in tumor size. A by-subject listing of DOR, PFS, and TTP will be provided. **Pharmacokinetic evaluation** Pharmacokinetic analysis will be based on the PKAS. Concentration-time data will be summarized by dose group, while descriptive statistical analysis will be performed at each planned time point. Individual and average concentration-time curves will be provided for each dose group. The calculation method of PK parameters is described in Section 6.2.4. Summary statistics of pharmacokinetic parameters for each GFH018 dose group are presented in tabular form. Provides geometric mean and coefficient of variation, maximum, median, minimum, and arithmetic mean and standard deviation for each PK parameter (except T_{max}). For T_{max}, the median, maximum, and minimum values are provided.

	Evaluation of pharmacodynamic markers To assess the changes of TGF-β in the peripheral blood and pSMAD2/3 in PBMCs before and after GFH018 treatment.

Contents

Contents of Tables

Contents of Figures

1. Introduction

1.1 TGF-β as a target for anti-tumor drug development

TGF-β (Transforming growth factor-β, transforming growth factor-β) is a multifunctional cytokine that binds to and activates TGF-β receptor II (TGF-βRII) on the cell membrane, and then phosphorylates TGF-β receptor I (TGF-βRI). And activate it, and then phosphorylate downstream Smad 2/3, conduct signals, regulate gene expression, and play a variety of biological functions.

A large number of studies have shown that in subjects with advanced tumors, the activation of TGF-β signaling pathway could promote epithelial-mesenchymal transformation (EMT) and metastasis of tumor cells, inhibit the anti-tumor immune response within the tumor microenvironment, and increase angiogenesis in the tumor microenvironment, increase tissue fibrosis, thereby promoting tumor progression [1-2]. Moreover, in subjects with a variety of solid tumors, such as hepatocellular carcinoma, glioma, colorectal cancer, lung cancer, pancreatic cancer, urothelial cancer, etc., high expression of TGF-β signaling pathway genes in blood and tumors were found, and their expression level were positively correlated with the low differentiation and high grade of tumors, and positively correlated with the poor prognosis of subjects [3-6]。 In addition, a retrospective analysis of IMvigor211, a phase III study of the PD-L1 immune checkpoint inhibitor atezolizumab against urothelial carcinoma, found that TGFB1 gene expression level was inversely correlated with subjects' response to atezolizumab therapy. Moreover, TGF-β signaling pathway inhibitors and immune checkpoint inhibitors can improve the efficacy of immune checkpoint inhibitors in animal models [7]. Therefore, inhibition of TGF-β signaling pathway can inhibit tumor growth and progression through a variety of ways, including inhibition of tumor metastasis, enhancement of anti-tumor immune response in tumor microenvironment, inhibition of tumor angiogenesis, etc., and has great potential to increase synergy in combination with PD-1/L1 immune checkpoint inhibitors.

At present, there are a number of clinical candidates targeting the TGF-β signaling pathway, all of which are in the phase I or II clinical stage. According to the mechanism of action, it can be divided into: 1) small molecule TGF-βRI inhibitors, including galunisertib (LY2157299), LY3200882, TEW-7197; 2) antisense oligonucleotides, which inhibit TGF-β expression, such

as trabedersen; 3) anti-TGF-β antibodies, such as SAR439459; 4) immune checkpoint inhibitors and TGF-β inhibitors bifunctional (simultaneously targeting PD-L1 and TGF-β pathways) fusion proteins, such as M7824.

Among small molecule TGF-βRI inhibitors, galunisertib developed by Eli Lilly is currently the most comprehensively studied clinically, and a number of single-agent and combination (in combination with chemotherapy and immunotherapy) clinical trials have been carried out for different tumor indications. In a phase II clinical trial of subjects with hepatocellular carcinoma for whom sorafenib was not indicated (resistant or intolerant), the median survival was 16.8 months. and a 20% decrease in plasma TGF-β levels after galunisertib treatment > greater benefit from a 20% reduction than ≤ 20% (median survival 21.8 versus 7.9 months). These studies demonstrate that blocking the TGF-β signaling pathway through TGF-βRI small molecule inhibitors is effective in associated tumors.

The above data shows that small molecule TGF-βRI inhibitors targeting the TGF-β signaling pathway are expected to become an effective, safe and controllable treatment for advanced solid tumors.

1.2 GFH018 Introduction

GFH018 is a novel TGF-βRI inhibitor that inhibits TGF-β signaling by inhibiting the function of TGF-βRI and thereby inhibits tumor growth. GFH018 has been studied in detail in terms of pharmacology, preclinical pharmacokinetics and toxicology, and the specific sub-items are briefly summarized below.

1.2.1 Overview of pharmacological research

[redacted]

[redacted]

[redacted]

1.2.3 Overview of toxicological studies

[redacted]

[redacted]

2. Study objectives and endpoints

The objectives and the corresponding endpoints are summarized in Table 2-1.

Table 2-1 Study objectives and endpoints

Study Objective	Endpoints
Primary	
1) To evaluate the safety and tolerability of single/multiple administration of GFH018 in subjects with advanced solid tumors. 2） Determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of GFH018.	• Safety: DLT, incidence and severity of AE, SAEs, laboratory tests, vital signs, ECG, ECHO • Tolerability: dose reduction, dose interruption, permanent discontinuation
Secondary	
1) To evaluate the pharmacokinetic characteristics of GFH018 after single/multiple administration in subjects with advanced solid tumors. 2) To evaluate the preliminary efficacy of GFH018 in subjects with advanced solid tumors. 3) To evaluate blood TGF-β levels and correlate with the clinical responses.	• Pharmacokinetics: PK parameters (PK parameters after single dose administration include $C_{max,}$ $T_{max,}$ $AUC_{0-12h,}$ $AUC_{0-24h,}$ $AUC_{0-inf,}$ $T_{1/2,}$ CL/F, V_d/F; Steady-state PK parameters include $C_{max,ss,}$ $C_{min,ss,}$ $T_{max,ss,}$ $AUC_{tau,}$ $T_{1/2,}$ CL/F, V_d/F, $CL_{r,}$ R_{acc}） • Efficacy: BOR, ORR, DCR, PFS, TTP evaluated according to RECIST version 1.1 • Pharmacodynamic marker: TGF-β levels in peripheral blood at baseline and during treatment
Exploratory	
To evaluate possible pharmacodynamic	• Changes of pSMAD2/3 in PBMC

marker in the blood	(peripheral blood single cells).

3. Study design

3.1 Overview of study design

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

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

Part I Dose Escalation

The study schema is shown in Figure 3-1 **(14-day on/14-day off regimen).**

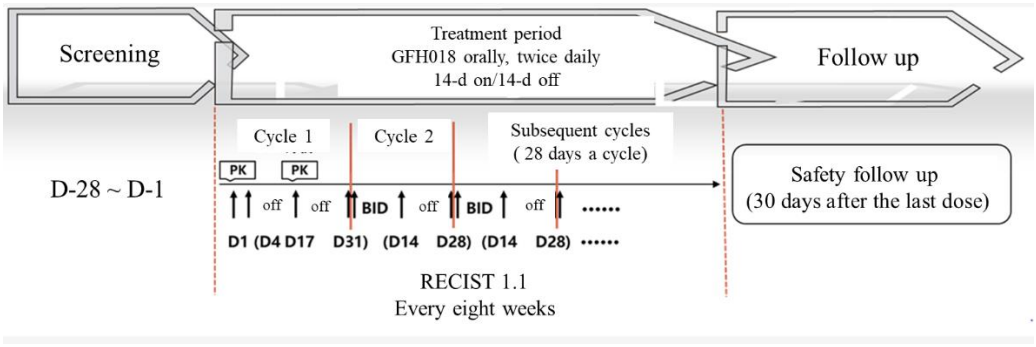

Fig 3-1 Study Schema (Dose Escalation Part)

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

serial PK blood samples will be collected to obtain PK characteristics at steady state. Starting from the third dose level, urine samples from steady state will also be collected for PK studies to fully understand GFH018 PK characteristics.

Table 3-1 Dose escalation regimen (provisional dose level)

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

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

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

85 mg BID, etc.

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

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

Part II Dose Expansion

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

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

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

3.2 Rationale of study design

Subjects with advanced solid tumors will be enrolled in the study. The study adopts an open-label, non-randomized, modified 3+3 design, which is the classical design of the first human trial of anti-tumor drugs. And the starting dose selection is reasonable, which meets the guidelines of drug regulatory authorities.

3.3 Rationale for dose and regimen selection

3.3.1 Rationale of starting dose selection

To support the clinical development of GFH018, adequate preclinical toxicology studies were

conducted. [redacted]

3.3.2 Planned incremental dose group

The planned dose group is shown in Table 3-1 and consists of 5, 10, 20, 30, 40, 50 mg BID, 14d-on/14d-off. The increasing amplitudes between the dose groups were 100%, 100%, 50%, 33%, and 25%, respectively.

Drug concentration measurements will be performed in a timely manner after each dose group is completed to obtain pharmacokinetic parameters in the human body as an important consideration in the dose escalation part. If the subject's drug exposure level is higher than the exposure level under the dose of cardiac NOEL in rat toxicology studies, the safety monitoring committee will carefully decide whether to escalate to the next dose based on a comprehensive assessment of all obtained safety information and et al.

3.3.3 Rationale of dosing regimen selection

To ensure patient safety to the greatest extent, dosing regimens are initially designed to be given twice daily for 14d-on/14d-off. This regimen is based on the research and development experience of similar drugs [8], which can avoid the occurrence of cardiotoxicity to the greatest extent. When the safety of the 14d-on/14d-off regimen has been fully assessed, other regimens such as 7d-on/7d-off or daily or other dose regimens will be explored to optimize dose levels and regimens.

3.3.4 Risk/benefit assessment

GFH018 is a small molecule TGF-βRI inhibitor developed by the sponsor, and based on its preclinical pharmacological and toxicity characteristics, it is expected that its risks and benefits are similar to the same class.

Based on preclinical toxicological findings, cardiac safety is an event of special interest for small molecule TGF-βRI inhibitors [9]. Currently no clinically significant drug-related cardiac adverse events have been reported in many clinical studies of the same class [10-12]. [redacted]

[redacted] Considering that this study is the first-in-human trial of GFH018, and cardiotoxicity has also been observed in rats at high doses in previous toxicological studies, a series of cardiac safety risk control measures are adopted in the study: in addition to the routine exams of electrocardiogram and blood pressure monitoring, a number of cardiac safety parameters are added, including imaging (cardiac Doppler ultrasound), blood markers (BNP, hypertroponin T, hs-CRP and cysteine protease inhibitor C）； defined heart related DLT. The cardiology experts from the study sites will be involved in the interpretation and processing of the abnormal cardiac test results.

According to the results of preclinical toxicological studies, other possible toxicities in addition to cardiovascular system toxicity include:

- [redacted] Gastrointestinal system: [redacted]
- Immune system: [redacted]
- Skeletal lesions: [redacted]

- Endocrine system:
- Reproductive system:

As the first human trial, other unanticipated adverse effects may also occur.

The study is designed to minimize these risks as much as possible: set strict inclusion criteria, strict and specific definitions of DLT, detailed dose adjustments and procedures for termination of GFH018, and close clinical safety monitoring. Any adverse events will be treated accordingly per protocol and clinical guidelines.

4. Study population

Subjects with advanced solid tumors will be enrolled in this study, with the first part of the dose escalation phase regardless of tumor type, and the second part of the dose extension phase will select specific tumors that may benefit from GFH018 treatment, including hepatocellular carcinoma, cholangiocarcinoma/gallbladder cancer, colorectal cancer, urothelial cancer, pancreatic cancer, cervical cancer, head and neck squamous cell carcinoma or esophageal cancer, and nasopharyngeal carcinoma.

Investigators must ensure that only subjects who meet all of the inclusion criteria and do not meet any of the exclusion criteria are enrolled in this study.

4.1 Inclusion Criteria

Subjects eligible to participate in this study must meet all of the following inclusion criteria:

1. Voluntary participation in the study and sign the informed consent form.
2. Male or female aged 18–75 years (inclusive).
3. Histologically or cytologically confirmed diagnosis of advanced or metastatic solid tumors with progression on, intolerance to standard therapy, or no suitable standard anticancer therapy available.
4. At least one non-measurable lesion per RECIST 1.1. For subjects enrolled in the expansion part, at least one measurable lesion per RECIST 1.1
5. Eastern Cooperative Oncology Group Performance Status (ECOG P.S.) ≤ 1. For subjects with liver metastases, Child–Pugh score of 0–7.
6. Life expectancy ≥ 12 weeks.
7. With sufficient organ functions, including:
    5) Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, hemoglobin ≥ 9 g/dL, without blood transfusion or granulocyte colony-stimulating factor, thrombopoietin, erythropoietin, or other therapies within 14 days prior to hematology tests.
    6) Total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), aspartate

aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN, alkaline phosphatase (ALP) ≤ 2.5 × ULN; for subjects with tumor involvement of the liver, TBIL ≤ 3.0 × ULN, AST and ALT ≤ 5.0 × ULN.

7) Creatinine (Cr) ≤ 1.5 × ULN, or calculated creatinine clearance (CrCl) ≥ 50 mL/min (Cockcroft-Gault formula) if Cr > 1.5 × ULN.

8) International normalized ratio (INR) ≤ 1.5 × ULN.

8. Toxicities left from prior anti-tumor therapy resolved to baseline or CTCAE v5.0 Grade 1 (neurotoxicity or alopecia ≤ Grade 2).

9. For women of childbearing potential (WOCBP) and male subjects with WOCBP partners, agreement to use an effective contraception method from the signing of the informed consent to 90 days after the last administration of the study drug. For WOCBP, negative pregnancy test results within 7 days (inclusive) prior to initiation of the study treatment.

10. Subjects or their legal representatives are able to communicate well with the investigators and willing to comply with the protocol and complete the study.

4.2 Exclusion criteria

Subjects who meet any of the following exclusion criteria are not allowed to enter this clinical study:

1. With significant cardiovascular diseases:
   a. Baseline QT/QTc prolongation (QTcF > 450 ms)
   b. Baseline ECG abnormalities of clinical significance
   c. Clinically significant cardiovascular diseases within 6 months, eg: myocardial infarction, angina, congestive heart failure, angioplasty, stent implantation, and coronary artery bypass grafting, etc.
   d. Abnormal doppler echocardiography confirmed by cardiologist such as left ventricular ejection fraction (LVEF) < 50%,heart valve stenosis, and ≥G2 valve regurgitation.
   e. Ascending aorta aneurysm or major artery aneurysm history, or predisposing conditions consistent with the development of aneurysms (for example, family history of aneurysm, Marfan syndrome, evidence of damage to the large vessels of the heart documented by computerized tomography [CT] scan with contrast).

f. Troponin T or I increase of clinical significance.

2. Clinically significant gastrointestinal diseases, such as:
   - Intractable hiccup, nausea, and vomiting
   - Chronic gastrointestinal disorders: untreated peptic ulcer, Crohn's Disease, ulcerative colitis, et al.
   - Unable to swallow.
   - Severe cirrhosis and gastric varicose veins, hepatic encephalopathy
   - Active gastrointestinal bleeding.
3. With other severe disease, such as:
   f. With definitive neurological or mental disorders, including epilepsy or dementia.
   g. Known positive human immunodeficiency virus antibody (HIV-Ab).
   h. Active hepatitis B virus infection (positive HBsAg and positive HBV-DNA), or active hepatitis C virus infection (positive HCV-Ab and positive HCV-RNA.
   i. With current or history of interstitial pneumonia. Other uncontrolled systemic diseases, such as hypertension and diabetes.
   j. Other active infections.
4. Uncontrolled ascites, or pleural effusion clinically.
5. Known active autoimmune diseases or with history of autoimmune diseases that may recur (such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, autoimmune thyroid disease, vasculitis, psoriasis, etc.) or subjects at risk (eg, those who have undergone organ transplantation and require immunosuppressive treatment). However, subjects with well-controlled diabetes mellitus, hypothyroidism requiring only hormone replacement therapy, skin disorders that do not require systemic therapy (such as vitiligo, psoriasis, or alopecia), or who are not expected to relapse in the absence of external triggers.
6. Subjects who need to receive glucocorticoids (prednisone >10 mg/day or equivalent doses of other similar drugs) or other immunosuppressants due to certain conditions within 14 days before treatment initiation.

   Note: in the absence of active autoimmune disease, the use of prednisone or equivalent adrenal drugs at a dose of ≤10 mg/day is allowed; subjects are allowed to use topical, ocular, intraarticular, intranasal, and inhaled type of glucocorticoid therapy (extremely low systemic absorption); short-term (≤ 7 days) use of glucocorticoids is permitted for prophylaxis (e.g., contrast media allergy) or for treatment of non-autoimmune conditions (e.g., due to contact allergens) delayed-type hypersensitivity).

7. Unstable brain metastasis. For subjects with brain metastases unintentionally detected during the screening, if they do not cause clinical symptoms and do not require therapeutic intervention, they can be discussed with the sponsor's medical director to decide whether to be enrolled.
8. Pregnant or lactating women.
9. Treatment with chemotherapy, radiotherapy, targeted therapy, endocrine therapy, immunotherapy, or other anti-tumor therapies, or other investigational drugs within 28 days prior to starting the study drug (For mitomycins and nitrosoureas: within 6 weeks. For oral fluorouracils and small molecule targeted drugs: within 2 weeks or 5 half-lives of the drug, whichever is longer).
10. Major surgery (needle biopsy not included) within 4 weeks prior to treatment initiation.
11. Administration of a strong inhibitor or inducer of CYP3A4 within 5 half-life periods or within 2 weeks (whichever is longer), or traditional Chinese medicines within 2 weeks prior to treatment initiation.
12. For subjects enrolled in the expansion part, diagnosis of other malignant tumors within 3 years prior to starting the study drug, except for cured in situ cervical carcinoma and skin basal cell carcinoma.
13. Other conditions judged by the investigator as inappropriate for participation in the study.

For abnormal laboratory tests, if the investigator deems it necessary, one retest is allowed to rule out detection errors.

5. Study treatment

5.1 Study drugs

The investigational drug in this study is GFH018 tablets, which will be provided by the sponsor.

5.1.1 Drug dosage forms and strength

Dosage form: tablets.

[redacted]

5.1.2 Package and label of study drugs

All investigational drugs will be labeled in accordance with the requirements of the Good Clinical Practice (GCP). All drugs are shipped as primary materials for research.

Unified format of drug labels, including clinical trial approval number, protocol number, subject identification code, clinical trial drug name (indicating clinical trial specific), dosage, strength, storage, batch number, expiration date, sponsor, etc.

Complete records of all study lot numbers and expiration dates, as well as drug labels, will be kept in the sponsor study folder.

5.1.3 Storage, management and distribution of study drugs

Study drugs shall be stored, managed and distributed by special personnel of the research center.

It must be stored in a safe place in accordance with national regulations, in a locked medicine cabinet and in accordance with the storage conditions specified in the programme. The storage temperature of the study drug needs to be recorded and kept in the corresponding file.

The person in charge of the research center will confirm in writing that the investigational drug has been received and will use the investigational drug within the framework of the clinical study in accordance with the protocol requirements. The receipt, distribution and return of investigational drugs will be documented in accordance with the detailed procedures of the sponsor agreement.

Dispensing will be carried out by a member of the research team who will ensure and record that subjects receive the dispensing as planned, and that the quantity and date of the drug issued and recovered are recorded in the original medical record. At the end of the study, the packaging of the study drug was processed uniformly and centrally.

5.1.4 Return and destruction of study drugs

The remaining investigational drugs and packaging are collected and destroyed by the sponsor or a research center authorized by the sponsor. All recycling and destruction shall be carried out in accordance with the corresponding regulations, guidelines and rules and regulations, and relevant inspection, verification, signature and recording shall be done.

5.2 GFH018 administration

GFH018 is administered orally with approximately 200 mL of warm water. Subjects should be advised that the tablet must be swallowed whole, not chewed or broken apart.

Cycle 1 (14d-on/14d-off):

- Day 1: Eligible subjects will receive their first dose at the study site around 8:00. After 20:00 at the evening prior to Day 1, subjects are not allowed to consume food and can drink water freely. Fasting and water for half an hour before and half an hour after administration in the morning, and drinking water freely after half an hour. Subjects are required to be fasted for 1 hour and 3-4 hours after administration for breakfast and lunch respectively.
- Day 2-3: No medication administration.
- Days 4-16: Subjects should take the medication twice daily, if possible, around 8:00 and 20:00, and should take the medication on an empty stomach.

  Day 10: Take the corresponding pre-administration PK blood sample and laboratory blood sample before taking the medicine in the morning, and take the study drug at the site. After half an hour of observation, subject can leave the site if no abnormalities occur. The second dose of GFH018 is taken around 20:00.
- Day 17: After 20:00 on D16, the subjects should be fasted and only can drink water. At about 8:00 on D17, the study drug will be administered at the site. Subjects are

required to be fasted for half an hour respectively prior to and after medication administration (water is not allowed as well). Water is allowed after the periods mentioned above. Subjects are required to be fasted for 1 hour and 3-4 hours after administration for breakfast and lunch respectively. After taking a 12-h PK blood sample in the evening, take the second dose of the day.

- Days 18-31: No medication administration.

Cycle 2 and subsequent cycles (14d-on/14d-off):

- Days 1-13: Take the drug twice a day around 8:00 am and 20:00. And take the medicine on an empty stomach.
- Day 14: Complete PK sampling and lab tests before taking the medication in the morning. After administration, the subjects should be observed for half an hour, and then can leave the site. The second dose should be taken at about 20:00.
- Days 15-28: No medication administration.

Vomiting and missed doses:

It is recommended to keep the daily medication time to be consistent as possible. If a missing dose occurs, it can be made up within 4 hours after the scheduled timepoints. In this case, the actual dosing time should be recorded, and the subsequent dosing timepoints will remain on schedule. If it has been more than 4 hours, the exact dose should be skipped, and the patient should continue the subsequent dose treatment at the scheduled timepoints. If vomiting occurs after administration, re-dosing is not allowed before the next scheduled dose. All actual dosing timepoints are recorded in the subject diary or recorded as ‘missing doses’.

5.3 Duration of Treatment

The subjects will continue to receive GFH018 until disease progression, or intolerance to toxicity, informed consent withdrawal, or study ends, or death.

5.4 Dose escalation methods

5.4.1 DLT definition

DLT is defined as an adverse event or abnormal laboratory test related to the study drug that occurred during the first cycle (31 days) and meet the following criteria. All toxicities will be

graded according to CTCAE version 5.0.

d) Non-hematologic toxicity

Grade 3 and above toxicity. Except for diarrhea, nausea, vomiting, and rash recovering to grade 2 or less within 3 days of supportive care.

Specific cardiotoxicity

- Cardiac structure/function related:
  - Grade 2 and above heart valve dysfunction.
  - Grade 2 or above left ventricular ejection fraction decreased.
  - Radiographic evidence of damage to any heart and great vessels.
- Biomarkers of cardiac injury related:
  - Troponin T or troponin I (hs-cTnT or hs-cTnI) twice the baseline and above the upper limit of normal ≥ 2 consecutive times (the interval ≥3 days). If hypersensitivity troponin is not available in the site, troponin can be substituted for evaluation according to the criteria listed above.

e) Hematological toxicity

- Grade 3 neutropenia with infection.
- Grade 4 neutropenia, lasting more than 5 days.
- Grade 3 febrile neutropenia (neutrophil count < 1.0×109/L with a single temperature > 38.3 ° C (101° F) or a sustained temperature of ≥ 38 ° C (100.4° F) for more than one hour); or neutropenic infection requiring clinical intervention.
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia requiring clinical intervention.
- Grade 4 anemia.

f) Investigator and sponsor need to discuss whether to decide whether to be any other clinically significant abnormalities of DLT.

5.4.2 MTD/RDE/RP2D definitions

The MTD referred to in this study is defined as the highest dose with a DLT incidence ≤1/3. If

the MTD has been obtained in the dose escalation part, it can be used as an RDE for further research. If MTD is not obtained, the RDE used in the dose expansion part will be determined by the SMC based on comprehensive data such as safety and tolerability, PK, pharmacodynamics, and preliminary antitumor efficacy during the dose escalation part. The RP2D will be determined based on the data obtained in the dose expansion part.

5.4.3 Dose escalation method

The starting dose is 5 mg. The single dose PK sampling will be performed after the first dose. Multi-dose will be initiated on day 4 with a regimen of 14d-on/14d-off. The first cycle consists of 31 days.

At least three subjects (but generally no more than six subjects) will be enrolled in each dose group. Simultaneous increments of 2 or more dose levels are not permitted to be carried out.

"Subjects" in the dose escalation part described below are eligible for inclusion in the Dose Determination Set, defined as subjects who have completed the first cycle of the study, achieved a minimum drug exposure (defined as 80% of the total planned dose received in the first cycle), have not undergone dose reduction, and have completed a 31-day safety assessment, or have developed DLT within the first cycle.

1. If none of the three subjects in a dose group developed DLT within the first cycle (31 days), three new subjects will be enrolled in the next ascending dose group. At the same time, subjects in this dose group can continue to receive the current dose of therapy.
2. If two or more of three subjects in a dose group develop DLTs in the first cycle (31 days), the dose escalation will be stopped (i.e., the next high-dose group study is not conducted). And the next lower dose group will be further tested for safety/tolerability.

   If one of three subjects in a dose group develops DLT in the first cycle (31 days), three additional subjects should be added to the dose group: if none of the three additional subjects develop DLT, three new subjects will be enrolled in the next ascending dose group; If one or more of the three additional subjects develop DLTs, the dose escalation will be stopped. And the next lower dose group will be further tested for safety/tolerability.
3. When the next lower dose group is further tested for safety/tolerability, if there are only three subjects in this dose group, three additional subjects will be added. If there are already

six subjects in this dose group, the dose is the MTD.

4. If the dose reaches the planned highest dose group (50 mg twice daily) and the MTD is still not reached, the Safety Monitoring Committee (SMC) will jointly decide whether to continue the dose escalation and which is the specific dose based on the safety, efficacy and PK data already obtained.
5. At the time of the first enrollment of the dose group, if multiple subjects participate in the screening at the same time, the modified 3+3 dose escalation protocol allows enrollment of ≥ 3 subjects, but no more than 6 subjects. If no DLT occurs in the enrolled evaluable subjects (≥ 3 subjects), it will be escalated to the next dose; If one DLT occurs, new subjects will be added to the total of 6 in this dose group, and if more than or equal to two DLT occur in 3-6 subjects, the escalation will be stopped. The dose will be reduced to the previous dose group.

5.4.4 Dose escalation decision

During the study, an SMC composed of principal investigators, representatives of contract research organizations (CROs) and sponsor representatives will be established to review the safety data generated in the study, mainly for DLTs and all other grade 2 and above adverse events per CTCAE v5.0, as well as pharmacokinetic and pharmacodynamic data, and carefully evaluate whether to escalate to the next dose level.

The decision to increment to the next dose will be notified to investigators in writing, confirming that the data from the previous dose group has been reviewed and that the SMC agrees to proceed with the next higher dose.

5.4.5 Intra-patient dose escalation

This study does not allow for intra-patient dose escalation.

5.5 Study drug interruption, dose reduction, and discontinuation

5.5.1 GFH018 interruption and dose reduction

Dose adjustments are not permitted during the first cycle of the dose escalation part. If DLT occurs, subject will discontinue from the study drug.

In cycle 2 and subsequent cycles:

- When grade 3 hematologic toxicity or grade 2 non-hematologic toxicity occurs, GFH018 will be interrupted until the adverse event returns to grade ≤ 1. Subjects will restore the former dose level if the adverse event is a return to grade 0-1 within 7 days of the last dose. If AE recovers to grade 0-1 for more than 7 days, subjects may restart GFH018 treatment at a lower dose level if it is judged by the investigator and deemed necessary after consulting with the sponsor. If AE recovers to grade 0-1 for more than 14 days, GFH018 will be permanently discontinued.
- Special interest of adverse events – cardiac toxicity
  - Clinically significant elevation of BNP or NT-proBNP.
  - Clinically significant elevation of troponin T (or troponin I).
  - Cardiac ultrasound abnormalities, such as heart valve stenosis or worsening of regurgitation, or a significant decrease in LVEF that the investigator judged to be clinically significant compared to baseline.

If BNP/NT-proBNP or hs-TnI/hs-TnI clinically increases, repeated testing is warranted. If necessary, cardiology consultation is preferred for further evaluation.

During the trial, only one dose reduction of the drug is allowed. Two dose interruption is allowed. If a third occurrence of toxicity requiring dose interruption occurs, the study treatment will be permanently discontinued after consultation with the sponsor.

5.5.2 Study drug discontinuation

Study drug administration should be permanently discontinued after consultation with the sponsor if any of the following applies:

- Grade 4 non-hematologic toxicity.
- Grade 4 neutropenia last for > 7 days.
- AST or ALT ≥ 5 times the upper limit of normal; If subjects with liver metastases have a grade 2 AST/ALT increased at the time of enrollment, study drug will be permanently discontinued when AST/ALT is ≥ 50% increase compared to baseline last for ≥ 1 week；
- Total bilirubin > 3 times the upper limit of the normal range; If subjects have Gilbert syndrome, permanently discontinue the study drug if TBIL increases ≥ 50% compared to the

baseline lasting for ≥ 1 week.

5.6 Medication and dietary restrictions

5.6.1 Permitted concomitant medications

In general, treatment that is necessary to ensure the safety of the subject is permitted. Concomitant medications used throughout the study should be documented. All drugs used from 28 days prior to screening to the end of treatment period should be documented in the relevant eCRF with justification for use and details of treatment.

When treatment-related adverse events occur, subjects should be closely monitored and treated adequately. The corresponding drug used should be documented in the eCRF.

5.6.2 Prohibited concomitant medications

Subjects may receive other drugs deemed medically necessary by the investigator, but may not accept the prohibitions listed as below. If, based on the investigator's assessment, subjects need to be treated using any of the treatments described below, please discuss with the sponsor whether these subjects need to be excluded from the study.

- Antineoplastic drugs: Do not use any antineoplastic drugs other than study drugs, including but not limited to chemotherapy, immunotherapy, targeted therapy, hormone therapy (subjects taking hormones that antagonize GnRH for prostate cancer, oral contraceptives, subjects with hormone replacement therapy can continue to take GFH018), and traditional Chinese medicines approved with anti-tumor indications.
- Any other drugs under clinical investigation other than the treatment in this study.
- Palliative care therapies (e.g., local radiotherapy for pain, or thoracentesis and drainage to relieve subjects' symptoms) can be used at any time after completion of the second dosing cycle, if necessary, after discussion between the investigator and the sponsor.
- Live vaccines are prohibited during the study. However, inactivated influenza or attenuated vaccines may be permitted, and the washout period is not required. The use of other inactivated or attenuated vaccines for the prevention of infectious diseases must be discussed on a case-by-case basis and discussed with the investigator and sponsor prior to administration. Any vaccine used during the study must be documented in the subject's

medical records and eCRF.

- According to preclinical pharmacokinetic studies, GFH018 is mainly metabolized by CYP3A4 in vivo. In order to avoid drug-drug interactions, the use of strong inducers and strong inhibitors of the drug metabolizing enzyme CYP3A4/5 are prohibited, as detailed in Table 5-1. If investigators suspect that the drug may have a strong inducing or strong inhibitory effect on CYP3A4/5, but it is not listed in Table 5-1, the sponsor can be contacted for specific discussion.
- The use of Chinese herbal medicines is prohibited in the first cycle.
    - Other treatments prohibited per the inclusion and exclusion criteria.

Table 5-1 Inducers and inhibitors of CYP3A4/5 (partial)

Interaction mechanisms	Drug name
Strong inducer	Carbamazepine, phenytoin, rifampicin, St. John's wort
Strong inhibitors	Clarithromycin, ritonavir, indinavir, ketoconazole, itraconazole
Moderate inducer	Bosentan, modafinil, nafcillin, thioridazine hydrochloride
Moderate inhibitors	Cimetidine, ciprofloxacin, grapefruit, verapamil, imatinib

5.6.3 Permitted medications with caution

- Moderate inhibitors and inducers of CYP3A4/5 (see Table 5-1).
- Colony-stimulating factor: subjects should not have been used within 14 days before participating in screening; Prophylactic use is not possible in the first cycle, and application is allowed when serious adverse reactions occur; The use of subsequent cycles can be determined by the investigator in conjunction with clinical practice in accordance with the ASCO 2015 guidelines.
- If the dose of warfarin or low molecular weight heparin has been stable for 2 weeks in the pre-enrollment patient, >continued use of the anticoagulant is allowed, subject to continuous monitoring of INR at the discretion of the investigator. The investigator may decide to suspend the use of anticoagulants according to the clinical norms of the research center, such as when tumor tissue samples need to be taken.

5.6.4 Dietary restrictions

Subjects must abstain from taking grapefruit fruits and beverages for at least 7 days prior to the first dose, and from grapefruit fruits and beverages throughout the study period.

5.7 Participant number and treatment assignment

5.7.1 Subject number

Subjects are assigned a screening number after signing the informed consent form, entering the screening period, which is determined by a two-digit site code (01, 02, ...). Plus a three-digit serial subject number (001,002,...).) composition. Screening numbers cannot be reused and are

unique for each subject.

Subjects who are eligible for admission will be assigned enrollment numbers in order of enrollment, 5001, 5002, 5003, 5004, ...。 Enrollment numbers cannot be reused.

5.7.2 Treatment assignment

All enrolled subjects in this study will be treated with GFH018.

6. Study Procedure

6.1 Schedule of Activities

Table 6-1 and Table 6-2 are the flowcharts for the dose escalation part and the dose expansion part, respectively.

Screening should be performed within ≤ 28 days before day 1 of the first cycle (excluding pregnancy tests, which are required within 72 hours prior to the first dose).

All visits and operations during the study should be carried out as long as possible according to the schedule of the study. The corresponding accepted window is shown in the test flow chart. The specific time points and allowable time windows for PK sample collection are shown in Table 6-4.

Table 6-1 Schedule of Activities in Dose Escalation

Cycle	**Screening[1]**	**Treatment period**											**Follow up**	
		Cycle 1								**Cycle 2 and subsequent cycles**			**EoT Follow-up[12]**	**Safety Follow-up[13]**
Days	**-28 to -1**	**1**	**2**	**3**	**4**	**10**	**17 (7/7 regimen * only).**	**24 (14/14 regimen only*)**	**31**	**1**	**14 (D21 for 7/7 regimen)**	**28 (±2)**	**0-7 days after EoT**	**30 ± 3 days after the last dose**
Informed consent form[2]	X													
Eligibility criteria	X													
Demographics	X													
Medical history[3]	X													
ECOG PS	X								X			X	X	X
Serum pregnancy	X													X
Vital Signs[4]*	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PE	X	X				X				X			X	X
Hematology	X	X	X			X	X	X	X			X	X	X
Chemistry	X	X	X			X	X	X	X			X	X	X

Cycle	**Screening[1]**	**Treatment period**											**Follow up**	
		Cycle 1								**Cycle 2 and subsequent cycles**			**EoT Follow-up[12]**	**Safety Follow-up[13]**
Days	**-28 to -1**	**1**	**2**	**3**	**4**	**10**	**17 (7/7 regimen * only).**	**24 (14/14 regimen only*)**	**31**	**1**	**14 (D21 for 7/7 regimen)**	**28 (±2)**	**0-7 days after EoT**	**30 ± 3 days after the last dose**
Urinalysis	X	X	X			X	X	X	X			X	X	X
Coagulation[5]	X								X			X		X
Thyroid function (FT3, FT4, TSH)	X								X			X		X
12-lead ECG[6]*	X	X			X	X	X	X	X	X	X	X	X	X
ECHO	X								X			X		
BNP + troponin	X						X	X	X			X		
hsCRP	X						X	X	X			X		
Cystatin C	X						X	X	X			X		
Adverse events[7]	X													
Blood PK sample[8]		X												
Urinary PK sample[8]		X												

Cycle	**Screening[1]**	**Treatment period**											**Follow up**	
		Cycle 1								**Cycle 2 and subsequent cycles**			**EoT Follow-up[12]**	**Safety Follow-up[13]**
Days	**-28 to -1**	**1**	**2**	**3**	**4**	**10**	**17 (7/7 regimen * only).**	**24 (14/14 regimen only*)**	**31**	**1**	**14 (D21 for 7/7 regimen)**	**28 (±2)**	**0-7 days after EoT**	**30 ± 3 days after the last dose**
Biomarker sample collection[9]		X												
Tumor imaging [10]	X	X												
GFH018 administration[11]		X												

Footnote:

1. Laboratory assessments results within 3 days prior to C1D1 are not required to be repeated on C1D1. Rescreening is allowed under limited conditions in consultation with the sponsor. Only one rescreening is allowed.

2. Written informed consent should be obtained prior to the implementation of any particular procedure in the protocol. These tests may be used in lieu of screening tests if they are performed as part of routine clinical care within a specific time frame (eg, within 28 days prior to day 1 of cycle 1).

3. Including diagnosis and extent of tumor, history of treatment for the primary diagnosis, etc. The date of the most recent oncology treatment must be recorded. Medical history is requested to be collected within 30 days prior to the signing of ICF.

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

5. Determination of PT/INR and APTT. In addition to the planned time point, coagulation should be measured throughout the study when relevant clinical indications are present. PT/INR and APTT analysis is performed by local laboratories.

6. Three ECGs (12-lead ECG) will be performed, each at least 5 minutes apart, and the subject should rest for at least 10 minutes before the examination. If clinically indicated, the frequency of ECG may be increased. If the drug is planned to be given at the same time on the same day, the specific time point of ECG examination: 2 hours (±30 minutes)

after the morning administration. If the drug is not administered on the same day, it can be done between 8:00 and 11:00 am.

7. Adverse events will be graded according to NCI-CTCAE version 5.0. The severity of all adverse event will be assessed.

8. Blood and urine samples will be collected for PK analysis of GFH018. The specific time points are shown in Table 6-4. Collection of urine samples is limited to the first cycle of the dose escalation, starting with the third dose group.

9. For blood sampling scheme of pharmacodynamic markers, please refer to 6.2.5.

10. Tumor imaging (CT or MRI, preferably CT) will be performed within 28 days prior to enrollment and checked approximately every 8 weeks (± 7 days) for the duration of the study. The same imaging technique should be used for one subject throughout the duration of the study.

11. The first cycle dose regimen is, single dose on day 1, no dose on days 2 and 3, starting BID from D4 for 14 days and then stopping the drug for 14d-on/14d-off, 7d-on/7d-off, daily, or other regimens, a total of 31 days. The dosing regimen for cycle 2 and all subsequent cycles is BID for 14d-on/14d-off, 7d-on/7d-off, or daily for 28 days per cycle.

12. The EOT date will be the date on which the decision is made to permanently discontinue the study treatment and is not necessarily the actual last dosing date. EOT visits should take place within 0-7 days of the EOT date. If the EOT visit occurs within the time window of the safety follow-up, there is no need to repeat the same procedure.

13. The safety follow-up should be performed 30 (±3 days) after the last dose of study treatment. Subjects who discontinue the study treatment due to intolerable toxicity will be followed until toxicities are ≤ grade 1 or stable.

Table 6-2 Schedule of Activities in Dose Expansion

	Screening[1]	Treatment period						Follow	
		Cycle 1			Cycle 2 and subsequent cycles			End of treatment follow-up[12]	Safety follow-up[13]
Days	**-28 to -1**	**1**	**14 (D21 for the 7/7 regimen).**	**28 (±2)**	**1**	**14 (D21 for the 7/7 regimen).**	**28 (±2)**	**0-7 days after EoT**	**30 ± 3 days after the last dose**
Informed consent form[2]	X								
Eligibility criteria	X								
Demographic information	X								
Medical history3	X								
ECOG PS	X			X			X	X	X
Serum pregnancy	X								X
Vital signs [4]	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X
Hematology	X	X		X			X	X	X
Chemistry	X	X		X			X	X	X

	Screening[1]	Treatment period						Follow	
		Cycle 1			Cycle 2 and subsequent cycles			End of treatment follow-up[12]	Safety follow-up[13]
Days	**-28 to -1**	**1**	**14 (D21 for the 7/7 regimen).**	**28 （±2）**	**1**	**14 (D21 for the 7/7 regimen).**	**28 （±2）**	**0-7 days after EoT**	**30 ± 3 days after the last dose**
Urinalysis	X	X		X			X	X	X
Coagulation [5]	X			X			X		X
Thyroid function (FT3, FT4, TSH).	X			X			X		X
12-lead ECG [6]	X	X	X	X	X	X	X	X	X
ECHO	X			X			X		
BNP+ troponin	X		X	X			X		
hsCRP	X		X	X			X		
Cystatin C	X		X	X			X		
Adverse events[7]	X								
PK blood sample[8]		X							
Blood collection		X							
Tumor imaging[10]	X								

	Screening[1]	Treatment period						Follow	
		Cycle 1			Cycle 2 and subsequent cycles			End of treatment follow-up[12]	Safety follow-up[13]
Days	**-28 to -1**	**1**	**14 (D21 for the 7/7 regimen).**	**28 (±2)**	**1**	**14 (D21 for the 7/7 regimen).**	**28 (±2)**	**0-7 days after EoT**	**30 ± 3 days after the last dose**
Study drug administration[11]		X							

Footnote:

1. Laboratory assessments results within 3 days prior to C1D1 are not required to be repeated on C1D1. Rescreening is allowed under limited conditions in consultation with the sponsor. Only one rescreening is allowed.
2. Written informed consent should be obtained prior to the implementation of any particular procedure in the protocol. These tests may be used in lieu of screening tests if they are performed as part of routine clinical care within a specific time frame (eg, within 28 days prior to day 1 of cycle 1).
3. Including diagnosis and extent of tumor, history of treatment for the primary diagnosis, etc. The date of the most recent oncology treatment must be recorded. Medical history is requested to be collected within 30 days prior to the signing of ICF.
4. Vital signs include temperature, blood pressure, heart rate, and respiratory rate.
5. Determination of PT/INR and APTT. In addition to the planned time point, coagulation should be measured throughout the study when relevant clinical indications are present. PT/INR and APTT analysis is performed by local laboratories.
6. Three ECGs (12-lead ECG) will be performed, each at least 5 minutes apart, and the subject should rest for at least 10 minutes before the examination. If clinically indicated, the frequency of ECG may be increased. If the drug is planned to be given at the same time on the same day, the specific time point of ECG examination: 2 hours (±30 minutes) after the morning administration. If the drug is not administered on the same day, it can be done between 8:00 and 11:00 am.
7. Adverse events will be graded according to NCI-CTCAE version 5.0. The severity of all adverse event will be assessed.
8. Blood and urine samples will be collected for PK analysis of GFH018. The specific time points are shown in Table 6-4. Collection of urine samples is limited to the first cycle of the dose escalation, starting with the third dose group.
9. For blood sampling scheme of pharmacodynamic markers, please refer to 6.2.5.

10. Tumor imaging (CT or MRI, preferably CT) will be performed within 28 days prior to enrollment and checked approximately every 8 weeks (± 7 days) for the duration of the study. The same imaging technique should be used for one subject throughout the duration of the study.
11. The first cycle dose regimen is, single dose on day 1, no dose on days 2 and 3, starting BID from D4 for 14 days and then stopping the drug for 14d-on/14d-off, 7d-on/7d-off, daily, or other regimens, a total of 31 days. The dosing regimen for cycle 2 and all subsequent cycles is BID for 14d-on/14d-off, 7d-on/7d-off, or daily for 28 days per cycle.
12. The EOT date will be the date on which the decision is made to permanently discontinue the study treatment and is not necessarily the actual last dosing date. EOT visits should take place within 0-7 days of the EOT date. If the EOT visit occurs within the time window of the safety follow-up, there is no need to repeat the same procedure.
13. The safety follow-up should be performed 30 (±3 days) after the last dose of study treatment. Subjects who discontinue the study treatment due to intolerable toxicity will be followed until toxicities are ≤ grade 1 or stable.

6.1.1 Screening period

Once a subject has been considered for entry into the study, the nature and content of the study must be explained, and an informed consent signed by the subject must be obtained prior to any study-related process.

The screening period is from day -28 to day -1, and the items to be completed during the screening period are shown in the research flow chart. The details of each item are shown in **Table 6-3**.

Table 6-3 Specific requirements for the observation indicators of subjects during the screening period

Parameter	
Demographic	Age, gender, ethnicity, smoking history and alcohol history; Height, weight, body mass index
physical examination	General condition, skin condition, head/neck, lungs, cardiovascular, liver, kidneys, gastrointestinal, lymphatic system, musculoskeletal system, limbs, larynx; Weight (no need to repeat measurements when already measured in the demographic data item)
Eligibility criteria	Verification of inclusion and exclusion criteria
Medical history	Previous and present medical history
Tumor diagnosis and confirmation	Histopathological and/or cytology diagnosis, including clinical staging; tumor-related symptoms, pain score, ECOG score; Bone scan and brain CT (if applicable)
History of oncology treatment	Previous topical or systemic antineoplastic therapy, start and end time, optimal response, reason for discontinuation of treatment
Imaging of tumors (CT/MRI of chest, abdomen, pelvis, and any other suspected tumor lesion)	The imaging modalities used were consistent throughout the study. Tumor imaging at baseline and after study entry should be performed in the same site/facility.
Biopsy of tumor or other tissue (optional)	Biopsy is performed only when no other history is available to confirm the diagnosis. Biopsy of tumors or other tissues (eg, inflammatory tissue obtained without general anesthesia) may be performed during the screening period and when other clinically indicated. Biopsy requires informed consent from the subject.
Vital signs	Temperature, heart rate, respiratory rate, systolic and diastolic blood pressure
Electrocardiogram	Standard 12-lead ECG
Echocardiography	Left ventricular ejection fraction, heart valve function, etc
Concomitant medications	Previous and current medications

Parameter	
Adverse events	
Laboratory tests	
Hematology	Red blood cell count (RBC), hemoglobin concentration (HGB), hematocrit (HCT), mean red blood cell volume (MCV), mean red blood cell hemoglobin content (MCH), mean red blood cell hemoglobin concentration (MCHC), white blood cell count (WBC), platelet count (PLT), neutrophil count (ANC), lymphocyte (LY) count, monocytes (MO) count, eosinophil (EO) count, Basophil (BA) count, percentage neutrophils, percentage lymphocytes, percentage monocytes, percentage eosinophils, percentage basophils
Urinalysis	Urine leukocytes (LEU), urine nitrite (NIT), urine pH, urine specific gravity (SG), urine protein (PRO), urine glucose (GLU), urine ketone bodies (KET), urine bilinogen (UBG), urine bilirubin (BIL), urine occult blood (BLD), 24-hour protein1
Coagulation function	Prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR)
Chemistry	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), glutamyl transpeptidase (GGT), urea (UREA)/urea nitrogen, blood creatinine (CREA), total protein (TP), albumin (ALB), white globular ratio (A/G ratio), total bilirubin (TBIL), direct bilirubin (DBIL), creatine kinase (CK), pancreatic amylase (AMY), fasting blood glucose (FPG), total cholesterol (TCHO), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), bicarbonate, phosphate, calcium, sodium, chloride, potassium
Virus testing	Hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV), HIV antibody, treponemal antibody
Thyroid function tests	Free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH).
Cardiac markers	Hypertroponin T (or Hypertroponin I), brain natriuretic peptide (BNP), hs-CRP, cysteine protease inhibitor (Cystatin C)
Pregnancy test	Serum β-HCG pregnancy test (blood pregnancy test in women of childbearing age)

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

6.1.2 Treatment period

During the treatment period of this study, various examinations will be performed at the specified time points in each dosing cycle (see **Table 6-1 and Table 6-2** for details). Subjects who meet the inclusion criteria could start treatment with GFH018 up to 28 days after the screening visit.

The first cycle dose regimen is, single dose on day 1, no dose on days 2 and 3, starting BID

from D4 for 14 days and then stopping the drug for 14d-on/14d-off, 7d-on/7d-off, daily, or other regimens, a total of 31 days. The dosing regimen for cycle 2 and all subsequent cycles is BID for 14d-on/14d-off, 7d-on/7d-off, or daily for 28 days per cycle.

For daily or other dosing regimens, subjects will follow the 14d-on/14d-off visits and SoA.

Subjects will continue to receive GFH018 until disease progression, or intolerance, withdrawal of knowledge, or study end, or death.

All scheduled visits should be completed within the time window specified in the protocol.

6.1.2.1 Subject substitution

No subject substitution will be performed in this study.

6.1.3 Follow-up period

6.1.3.1 End-of-treatment (EoT) follow-up

For subjects who discontinue the study drug early, follow up with the EoT within -7 days (as soon as possible) after the decision to permanently discontinue the study drug, and the following procedures are required to be performed during the follow-up period and the results of the assessment are required to be recorded in the eCRF.

- Vital signs
- physical examination
- ECOG
- Hematology, chemistry, urinalysis (see section 6.1.1 for specific items).
- Concomitant medications
- AE

6.1.3.2 Safety follow-up

After the EOT visit, the patient enters into the follow-up period. The safety follow-up visit should occur 30 (± 3) days after the last study treatment, and patients will return to the study center for a safety follow-up visit. The following procedures will be performed:

- Pregnancy test (serum or urine)
- Vital signs

- physical examination
- ECOG
- Tumor imaging
- Hematology, chemistry, urinalysis (see section 6.1.1 for specific items).
- Thyroid function
- Coagulation
- Combined medications
- AE

6.1.3.3 Disease progression follow-up

For subjects who discontinue GFH018 for reasons other than disease progression, tumor evaluation should continue at a frequency of every 8 weeks (± 7 days) until disease progression or until the end of the study.

6.1.4 Loss to follow-up

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

6.2 Evaluation

6.2.1 Safety evaluation

Safety assessment is performed based on medical review of AE and laboratory abnormality. Evaluate the toxicity according to CTCAE v5.0.

The following assessments will be performed throughout the study to confirm the safety and tolerability of GFH018: vital signs, clinical laboratory tests, pregnancy tests (if required), ECOG PS, tumor imaging, physical examination, ECG, ECHO, frequency and severity of AEs.

Adverse event of special interest (AESI)

According to the toxicological results of GFH018, ASEIs include elevated cardiac biomarkers BNP or troponin, and abnormal cardiac ultrasound. Therefore, in this study, additional monitoring of cardiac safety is required to be performed. In addition to routine blood pressure

and electrocardiogram monitoring, a series of cardiac Doppler ultrasonography and heart-related biomarkers laboratory tests have been added.

6.2.1.1 Physical examination

Physical examination will be performed during the screening period, before the first dose on day 1 of each cycle, and at safety follow-up.

A complete PE will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

6.2.1.2 Vital signs

Vital signs include blood pressure (BP), respiratory rate, pulse rate and body temperature. They will be obtained in the same position, either sitting or supine, as appropriate prior to any blood collection.

6.2.1.3 Electrocardiogram

An electrocardiogram (ECG) will be completed according to the date and time requirements specified in the Schedule of Activities.

Patients need to rest comfortably on their back for at least 10 minutes prior to the first ECG. Recording of specific ECG parameters, including but may not be limited to heart rate, QT, QTcF, and PR. It will be performed three times at approximately 5 minutes apart at baseline and when the results are of clinical significance. Otherwise, ECG will be only performed once at each time point.

The average of the triplicate QTcFs will be used as the baseline QTcF. During the study period, the investigator will compare the ECG results with baseline, if there is an increase of ≥30 msec from baseline, or a QTcF ≥450 msec in any specified ECG measurement, then another 2 ECG measurements are required to be performed to obtain the average value.

Blood samples scheduled at the same time point should be taken after the ECGs are completed. Each ECG tracing should be labeled with the study number, patient number, date, and kept in the source documents at the study site.

6.2.1.4 Cardiac ultrasound

A cardiac Doppler ultrasound will be performed during the screening period and on the last day of each cycle to assess the structure and function of the heart, including left ventricular ejection fraction, valve function, etc. Cardiac ultrasound reports judged by investigators to be abnormal and clinically significant will be interpreted by cardiologists if necessary.

6.2.1.5 Laboratory tests

Blood and urine samples evaluated by clinical laboratories will be collected in accordance with the protocol (see study flow chart for details).

The following parameters will be measured in this study, the specific test items are shown in Table 6-3, and the blood sample collection volume for laboratory tests is shown in Appendix **I**.

- Chemistry
- Hematology
- Urinalysis
- Coagulation function
- Thyroid function
- Blood tests for cardiac biomarkers
- Pregnancy test

6.2.2 Tolerance evaluation

Tolerability will be assessed based on the proportion of subjects who experience dose reduction, interruption, and permanent discontinuation.

6.2.3 Efficacy evaluation

The evaluation of tumor response will include all known or suspected sites by radiologic techniques. Imaging includes computed tomography (CT) or magnetic resonance imaging (MRI) scanning; brain CT or MRI is used for the known or suspected brain metastasis of the patients; bone scanning and/or bone X-ray are/is used for the known or suspected bone metastasis of the patients. CT/MRI scans (with preference for CT) should be performed with contrast agent enhancement, unless the patient has contraindications. CT/MRI scans of brain, chest, abdomen,

and pelvis cavity are acceptable within 28 days prior to the first treatment, and bone scanning is acceptable within 42 days prior to the first treatment.

All subsequent scans will be performed in the same manner as at screening, with the same contrast, preferably on the same scanner. Other metastatic disease sites (e.g., bone or brain metastases) should be followed at scheduled visits using appropriate imaging, as clinically indicated.

The first tumor assessment will be performed every 8 (±1) weeks thereafter in the first 48 weeks, and every 12 (±1) weeks later during the whole study treatment. The tumor assessments will be performed at screening and the subsequent visits according to Schedule of Activities. Tumor assessment should also be performed when progression of disease is suspected (e.g., worsening of symptoms) and when the patient withdraws from treatment (imaging scans performed within 4 weeks do not need to be repeated).

For the phase II study, best response confirmation must be performed at least 4 weeks after the initial evaluation of complete response (CR) or partial response (PR).

The tumor response will be assessed based on the RECIST 1.1 (see Appendix 1 Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1)). Tumor responses according to RECIST 1.1 will be determined according to the local investigator interpretations. All data shall be properly preserved and can be verified by source and peer review.

If a patient discontinues due to reasons other than disease progression and does not start subsequent antitumor therapy, the radiological tests will be performed on the scheduled visit till disease progression, start of new anticancer treatment, withdrew consent, lost to FU or study termination for other reasons.

6.2.4 Pharmacokinetic evaluation

6.2.4.1 Sample collection

Dose escalation

After the first dose on day 1 of cycle 1, serial PK blood samples will be collected up to 72 h after administration, the complete PK characteristics of a single dose will be obtained, and

multiple doses will be started from day 4. The first cycle is 31 days, and subsequent cycles are all 28 days. After the last dose of cycle 1 (day 17 or 24), serial PK blood samples will be collected to obtain PK characteristics at steady state. In cycles 2 and subsequent cycles, a trough sample will be taken prior to administration in the morning on the last dosing day of each cycle (day 14 or 21), primarily for the purpose of determining the compliance.

Unscheduled PK blood sample collection: When an unexpected adverse event occurs, if possible, a blood sample at that time is required to be collected for PK as soon as the investigator get the information of the event.

The specific timing of pharmacokinetic blood sample collection for the first and second cycles is shown in Table 6-4.

Table 6-4 Pharmacokinetics Sampling Schema in Dose Escalation Part

Cycle	Days	Volume of blood taken (mL).	Planned point in time (h)
1	1	3	Prior to administration
1	1	3	0.5 h (± 10 min) after administration
1	1	3	1 h (± 10 min) after administration
1	1	3	2 h (± 10 min) after administration
1	1	3	4 h (± 15 min) after administration
1	1	3	8 h (± 30 min) after administration
1	1	3	12 h (± 30 min) after administration
1	2	3	24 h (± 1 h) after administration
1	3	3	48 h (±1 h) after administration
1	4	3	72 h (± 1 h) after dosing / D4 before administration
1	10	3	In the morning, before administration
1	17 (for 14d-on/14d-off) or 24 (for 7d-on/7d-off)	3	In the morning, before administration
1	17 (for 14d-on/14d-off) or 24 (for 7d-on/7d-off)	3	0.5 h (± 10 min) after morning administration
1	17 (for 14d-on/14d-off) or 24 (for 7d-on/7d-off)	3	1 h (± 10 min) after morning administration
1	17 (for 14d-on/14d-off) or 24 (for 7d-on/7d-off)	3	2 h (± 10 min) after morning administration

1	17 (for 14d-on/14d-off) or 24 (for 7d-on/7d-off)	3	4 h (± 15 min) after morning administration
1	17 (for 14d-on/14d-off) or 24 (for 7d-on/7d-off)	3	8 h (± 30 min) after morning administration
1	17 (for 14d-on/14d-off) or 24 (for 7d-on/7d-off)	3	12 h (± 30 min) after morning administration
2	17 (for 14d-on/14d-off) or 24 (for 7d-on/7d-off)	3	In the morning, before administration

Starting from the third dose group, urine samples at steady state will also be collected for PK studies to fully understand. Urine samples are collected during the morning of the last dosing day of the first cycle (D17 or D24), 0-4 hours after administration, and 4-12 hours after administration.

Dose expansion

On the last dosing day of the first cycle (D14 for 14d-on/14d-off regimen, or D21 for 7d-on/7d-off regimen), serial PK blood samples will be collected to obtain the PK characteristics at steady state, and the specific time points are shown in Table 6-5.

Table 6-5. Dose extension period pharmacokinetics blood sample collection schedule

Cycle	Days	Volume of blood taken (mL).	Planned point in time (h)
1	Last dosing day	3	Before administration
1	Last dosing day	3	0.5 h (± 10 min) after administration
1	Last dosing day	3	1 h (± 10 min) after administration
1	Last dosing day	3	2 h (± 10 min) after administration
1	Last dosing day	3	4 h (± 15 min) after administration
1	Last dosing day	3	8 h (± 30 min) after administration
1	Last dosing day	3	12 h (± 30 min) after administration

In subsequent cycles, a trough sample is required to be taken before administration in the morning of the last dosing day of each cycle (D14 for 14d-on/14d-off regimen, or D21 for 7d-on/7d-off regimen), primarily for the purpose of determining compliance.

For daily or other dosing regimens, subjects will follow a 14-day discontinuation of dosing and 14-day visits and study activities.

Unscheduled PK blood sample collection: When an unexpected adverse event occurs, if possible, a blood sample at that time should be collected for PK as soon as possible.

6.2.4.2 Sample analysis methods

The PK sample of GFH925 will be analyzed with the validated bioanalytical method. Any results below the lower limit of quantification and any missing samples will be labeled accordingly. For details of sample preparation and processing, refer to the Laboratory Manual.

6.2.4.3 Calculation of pharmacokinetic parameters

The pharmacokinetic parameters of GFH018 after steady-state administration with single dose and multiple doses will be calculated using a NCA model. The PK parameters for single-dose administration include $C_{max,}$ $T_{max,}$ $AUC_{0\text{-}12h,}$ $AUC_{0\text{-}24h,}$ $AUC_{0\text{-}inf,}$ $T_{1/2,}$ CL/F, V_d/F. Steady-state PK parameters include $C_{max,ss,}$ $C_{min,ss,}$ $T_{max,ss,}$ $AUC_{tau,}$ $T_{1/2,}$ CL/F, V_d/F, $CL_{r,}$ $R_{acc.}$

6.2.5 Pharmacodynamic evaluation

In this study, blood samples will be collected for evaluation of pharmacodynamic markers. The pharmacodynamic markers involved in this study are TGF-β in peripheral blood and pSMAD2/3 in PBMC.

Blood samples for analysis of TGF-β will be collected before treatment and 1 h after the 1st dose in cycle 1, and 1 h after the dose in the morning of the last dosing day (D17 or D24) in cycle 1; from cycle 2 and within 1year, it will be measured every 3 cycles during the treatment of GFH018, i.e. 1 h (±10 minutes) after the dose on the last day of the 4th, 7th, 10th cycle. For daily dosing or other dosing regimens, subjects will follow a 14-day on and 14-day off schedule.

PBMC for pSMAD2/3 evaluation will be collected before treatment and 1 h after the 1st dose in cycle 1, and before drug administration in the morning of the last day each week (every 7 days, i.e., days 10, 17, 24, 31) since day 4. From cycle 2, please follow the TGF-β blood sampling arrangement.

7 End of Study and End of Treatment

7.1 Definition of End of Study (EoS)

Defined as the time when the last enrolled subject has been under the study treatment for at least 1 year or discontinued for any reason (whichever is earlier).

7.2 End of Treatment and withdrawal from the study

End of Treatment Criteria:

- Disease progression.
- Intolerable toxicity.

Withdrawal criteria:

- ICF withdraw.
- Major protocol deviation.
- Investigator's decision.

The investigator must fill in the reason for withdrawal in the eCRF and, if possible, contact the subject to complete the end-of-treatment assessment, and complete the end-of-treatment follow-up record form, recording the last medication as much as possible.

All study-related AEs and SAEs present at the time of study discontinuation must be followed up until they are recovered or stable.

After the subject has completed all the tests at the last visit, the investigator must be informed by the subject as soon as possible if a new SAE or pregnancy is detected within 30 days of the study drug.

7.3 Early Study Termination

This study may also be discontinued early or interrupted. This may be due to decision of the authority, opinion of the Ethics Committee (EC) and et al. Additionally, the sponsor reserves the right to stop the research and development of GFH925.

The party that decides to discontinue/interrupt the study will give a written notice to record the reasons for the discontinuation or interruption to the investigator, sponsor, and regulator. If the study is early discontinued or interrupted, the investigator should immediately notify the EC.

8 Adverse event reporting

8.1 Adverse Events

8.1.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject that has developed since signing of informed consent, which does not necessarily have to have a causal relationship with the medicinal product. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pretreatment or post-treatment complications resulting from protocol-specified procedures, overdose, drug abuse/misuse, or occupational exposure. Any pre-existing event that worsens or changes in nature during or as a result of participation in a clinical study is also considered an AE. AEs should be reported on the Adverse Event eCRF page.

Severity of all AEs will be graded according to CTCAE v5.0. For those events not listed by CTCAE, the following criteria may be used.

Table 1 Criteria for judging the severity of adverse events not listed in CTCAE

Grade	Clinical descriptions of severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
4	Life-threatening consequences; urgent intervention indicated.

5	Death related to AE.

It is important to distinguish between serious and severe AEs. Severe is a measure of intensity and standard definition of serious adverse events is listed in Section 8.2.1 Definition of Serious Adverse Events. Severe AEs are not necessarily SAEs. For example, nausea lasting several hours is considered severe nausea, but not an SAE. For another example, a stroke causing only mild disability is considered a minor stroke but is an SAE.

Adverse events of signs and symptoms

All AEs spontaneously reported by the subject or caregiver or answered by the subject after the investigator asked "Have you had any new health problems since the last follow-up/visit?" or detected by the subject 's voluntary report should be recorded in the eCRF. When collecting AEs, the diagnosis record (where possible) should preferably list the signs and symptoms of the subject.

Adverse events based on physical examination and tests

Results of laboratory tests, cardiac ultrasound, vital signs, ECGs, and other safety assessments should be reported as AEs if these parameters worsen from baseline values and meet the criteria for AEs. If associated with appropriate clinical signs and symptoms, the sign or symptom should be reported as an AE, and relevant laboratory or other results should be provided as additional information. Reported investigators should use clinical rather than laboratory terms whenever possible (eg, use anemia rather than hemoglobin decreased). Abnormal laboratory findings without clinical significance will not be recorded as AEs or SAEs.

AEs do not include:

- pre-existing diseases, conditions, or laboratory abnormalities that were present or detected prior to the Screening Visit that did not worsen further;
- absence of an untoward medical occurrence (eg, hospitalization for elective surgery, social reasons, and/or self-convenience reasons);
- any medical condition or clinically significant laboratory abnormality that occurred prior to signing of informed consent and is not associated with a protocol-related procedure is not considered an AE. This condition is considered pre-existing and should be recorded as medical history in the eCRF.

8.1.2 Adverse events collection and documentation

Any AEs (clinical symptoms, signs, or diseases) occurring during the administration of the study drug will be recorded in the eCRF, whether or not related to the study drug.

Time period for collecting adverse events

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

After a subject discontinues study drug, investigators are required to collect SAEs related to study procedures, and patients who discontinue study drug for reasons other than disease progression should be followed for disease progression until disease progression or the end of the study as shown in **Table *2***.

Table 2 Time period for collecting adverse events

	Treatment period	**Follow-up period**	**After follow-up period**
Collect all new AEs in the eCRF	Yes	Yes	No
Collect all ongoing AEs in the eCRF	Yes	Yes	No
Collect all treatment-related SAEs in the eCRF	Yes	Yes	Yes

Information required for adverse events

AEs will be documented by investigators and the following information should be collected for each AE:

- Diagnosis/description of AEs
- AEs onset date and end date

- Severity (CTCAE grade)
- Investigator's judgment of causal relationship to study drug
- Action taken with study drug (none, dose reduction, dose interruption, permanent discontinuation, etc.)
- Medication administered for AEs (if yes, corresponding treatment medication information should be recorded)
- Whether it is a serious adverse event (SAE) (see Section 8.2 Serious Adverse Events)
- Outcome (recovered, recovering, not recovered)

8.1.3 Handling of adverse events

All subjects experiencing AEs, whether considered treatment-related or not, must be monitored regularly (if feasible) and medically judged and appropriately managed by investigators until the symptoms subside, any abnormal laboratory values return to normal or return to baseline or are considered irreversible, or until the changes observed can be explained appropriately.

Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing, if feasible, and preferably within 3 calendar days of receipt of the initial test result the subject should be returned for review and then processed accordingly.

Cardiac adverse events of special interest

- Clinically significant elevations in cardiac biomarkers BNP or NT-proBNP;
- Clinically significant elevations in high-sensitivity troponin T (or high-sensitivity troponin I);
- Abnormal cardiac ultrasound, such as worsening of valvular stenosis or regurgitation from baseline, or a clinically significant decrease in LVEF from baseline as judged by the investigator.

If the subject presents clinically significant elevation of cardiac biomarkers BNP or NT-proBNP, or clinically significant elevation of high-sensitivity troponin T (or high-sensitivity troponin I), reexamination is required and consultation with the cardiology department is requested for further evaluation if necessary.

Follow-up of unrecovered adverse events

The investigator should continue to follow up AEs that were not resolved at the last study visit, but do not need to be documented in the eCRF. The sponsor had the right to request information on subjects who had an AE ongoing at the end of the study, if deemed necessary.

8.2 Serious Adverse Events

8.2.1 Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that occurs from the time the patient signs the informed consent through the end of the safety follow-up visit and meets one or more of the following criteria:

- results in death,
- is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Important medical events: such events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in such situations. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm.

8.2.1.1 Hospitalization

An AE resulting in hospitalization (even if less than 24 hours) or prolonged hospitalization in a clinical study should be considered an SAE. Hospitalization did not include the following:

- a visit to an emergency department, outpatient clinic, or other hospital department for < 24 hours and no hospitalization (unless considered an "important medical event" or a life-threatening event),

- elective surgery planned prior to signing informed consent,
- planned medical/surgical treatment or monitoring based on the protocol,
- routine health assessments requiring hospitalization, such as routine colonoscopy,
- hospitalization for Grade 1 AEs, including overnight hospitalization for nonmedical reasons after study drug administration,
- hospitalization for medical insurance reimbursement,
- hospitalization that had no impact on health status and did not require medical/surgical intervention (eg, no residence, financial difficulties, family reasons, management needs, etc.).

8.2.1.2 Malignant neoplasm progression

Clinical symptoms of malignant neoplasm progression may be reported as adverse events if the symptoms cannot be determined as exclusively due to the progression of the underlying malignant neoplasm or do not fit the expected pattern of progression for the disease under study. If it is clearly consistent with the suspected progression of the underlying malignant neoplasm, it will not be reported as adverse events. Progression of malignant neoplasm itself will not be reported as an AE.

Clinical symptoms of malignant neoplasm progression that meet SAE criteria may be reported as SAEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignant neoplasm or does not fit the expected pattern of progression for the disease under study. An event should not be reported as an SAE if it met the criteria for an SAE (except for a death event) but is clearly consistent with suspected progression of the disease under study.

Death events that occur during the safety follow-up period must be reported as SAEs, whether or not the investigator assesses them as possibly related to disease progression. The term “death” should not be reported as an SAE term, but rather as an outcome of an event. The cause of death, medical conditions/disease (including exacerbation of symptoms, signs) should be used as SAE terms and reported as SAEs; if the cause of death is unknown at the time of report, it should be

recorded as ‘unknown cause of death’.

8.2.2 SAE reporting requirements

In case of any SAE occurring from the signing of informed consent form by the subject to 30 days (± 3 days) after the last dose, no matter whether or not it is related to the study drug, the investigator shall:

- immediately take appropriate treatment measures for the subject, and report to the sponsor within 24 hours after being informed of its occurrence, and timely report to relevant units according to regulatory requirements.
- complete the SAE Report Form and complete all applicable sections of the form. The investigator should evaluate and record the relationship between SAE and each specific study treatment, and send the completed and signed form to the drug safety department of the sponsor and the drug safety department of CRO [redacted] as entrusted by the sponsor by fax or email within 24 hours:
- Genfleet Drug Safety Public Mailbox: [redacted]
- [redacted] Drug Safety Public Mailbox: [redacted]
- [redacted] Drug Safety Fax: [redacted]

Follow-up information will use a new SAE Report Form and will be identified as follow-up information for previously reported SAEs.

At the end of the trial or early withdrawal of a subject, unresolved SAEs must be followed up until any of the following occurs:

- event resolved;
- event stable;
- event returns to baseline (if available at baseline);
- event is attributable to a drug other than study drug or to factors unrelated to study procedures;
- subject lost to follow-up (loss to follow-up is defined in Section 6.1.6).

If the investigator learns that a subject experienced an SAE, including death, after completing the study, and considers the event to be possibly related to the study drug, the investigator

should report it to the sponsor.

8.3 Causality assessment

The investigator should determine the relationship of AE/SAE to the study drug according to the following criteria:

- Definitely related: there was a reasonable temporal sequence between the onset of the AE (including laboratory abnormalities), and the administration of the study drug; the study drug more reasonably explains the AE than other causes (e.g., the subject 's pre-existing disease, environmental or toxic factors, or other treatments the subject received, etc.); and the reaction after study drug discontinuation is clinically reasonable.
- Possibly related: there was a reasonable temporal sequence between the onset of the AE (including laboratory abnormalities), and the administration of the study drug; the AE is equally plausible to be explained by the study drug as for other reasons (e.g., the subject 's preexisting disease, environmental or toxic factors, or other treatments the subject received, etc.); information of the event is lacking or unknown after study drug discontinuation.
- Unlikely related: the temporal relationship between the onset of AE (including laboratory abnormalities) and the administration of the study drug is unclear; the event may also be caused by the clinical state or other treatments (e.g., the subject 's preexisting disease, environmental or toxic factors, or other treatments the subject received.
- Definitely unrelated: the AE does not occur in a reasonable temporal sequence from administration of the study drug; the AE has other obvious causes (e.g., the subject 's preexisting disease, environmental or toxic factors, or other treatments the subject received, etc.).
- Unable to judge: the above information was unknown, causal relationship was difficult to determine, and the data could not be supplemented.

The causality relationship will be considered related if the investigator judged the relationship to study drug as "definitely related" or "possibly related". And it will be considered related if the investigator judged it as " unable to judge" and the investigator will be required to collect as much information as possible and make a causality relationship assessment again. The

causality relationship will be considered unrelated if judged by the investigator as "definitely unrelated" or " unlikely related ".

8.4 Pregnancy

Pregnancy reports are used to report any case of pregnancy following maternal or paternal exposure to study drug.

The investigator should report all pregnancy cases identified after the subject first agreed to participate in the study (ie, signed informed consent) and throughout the study (including the follow-up period after study drug treatment until 30 days [± 3 days] after the last dose of study drug) to the sponsor in the form of a pregnancy report within 24 hours of learning of the pregnancy report.

Refer to SAE reporting guidelines for a complete description of the pregnancy reporting procedure.

Pregnancy itself is not considered an AE and artificial elective abortion without medical reasons is not required to terminate the pregnancy. Any premature termination of pregnancy (eg, spontaneous abortion due to complications or other medical reasons, artificial therapeutic abortion) must be reported within 24 hours as an SAE. Medical reasons emerging during this process should be recorded as AE terms. Spontaneous abortion is always considered an SAE and should be reported as an SAE. Subjects should receive appropriate monitoring and care until the end of pregnancy.

For male study subjects, pregnancy of their female partners must also be reported and reported as an SAE. Monitoring of the partner should continue until the end of pregnancy.

8.5 Other special situation reports

Other special situation reports include reports of medication errors, abuse, misuse, and overdose. In addition, reports of adverse reactions in infants following breastfeeding exposure are included.

Medication error refers to any unintentional error in the prescribing, dispensing, or administration of a drug.

Abuse was defined as persistent or sporadic intentional excessive use of the drug by the subject.

Misuse was defined as deliberate and inappropriate use of the drug not in accordance with the protocol instructions and prescribing information.

Overdose was defined as accidental or intentional overdose of study drug. An overdose was defined as a dose (accidental or intentional) taken by a subject that exceeded 20% of the protocol-specified dose. All other special situation reports must be faithfully recorded within 24 hours after the investigator learns of the situation. If the special situation leads to AE or SAE, the report should be made in the form of AE or SAE. These reports must include cases involving the study drug, but do not apply to concomitant medications. Special situations involving concomitant medications will not be reported except for those causing AEs. Any inappropriate use of medication prohibited by this protocol should not be reported as "misuse", but may be more appropriately documented as a protocol deviation. All clinical sequelae associated with these special situation reports should be reported as AEs simultaneously in the form of AE reports. If it leads to an SAE, it will be reported in the form of an SAE report. Details of symptoms and signs, clinical management, and results will be reported.

8.6 Expedited reporting of adverse events of special interest

As described in Section 6.2.1 Safety evaluation, cardiotoxicity is an adverse event of special interest in this study. Cardiac related adverse events of Grade 2 or higher should be reported to the sponsor within 24 hours of awareness (refer to Section 8.2.2 SAE reporting requirements).

In addition, during the first cycle (DLT observation period), AEs meeting the criteria for DLT should also be reported to the sponsor within 24 hours of awareness of their occurrence (see Section 8.2.2 SAE reporting requirements for reporting methods).

9 Data Management

9.1 CRF Data Collection

This study will use Electronic Data Capture (EDC) for data collection. The investigator or the designated staff will enter the data required by the protocol into the electronic case report forms (eCRF). Site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the staff.

Concomitant treatments and prior medications entered into the database will be coded using the WHODD, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the MedDRA terminology.

The Principal Investigator is responsible for assuring that the data entered eCRF is

9.2 Data Security

The investigator or the designated staff will have an unique account ID in EDC. The Investigator need to electronically sign the data to assure that the data entered ineCRF is complete, accurate. E-signature will require investigator to provide account ID and password, after successfully signed, system will record the date and time of signature. Investigator is not allowed to share their account and password with others. For all data modification, EDC will have a specific process and requirement to tracking all audit trail.

9.3 Site Monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, sponsor personnel (or designated CRO) will review the protocol and study procedures with the investigators and other site staff. During the study, the monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, prepared and accounted according to the instructions. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinical medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or

assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs are required. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.4 Data Quality Management

To ensure the data quality, sponsor or designated CRO may take below actions during the study:

- Provide protocol related information if needed
- Provide training to site personnel including but not limited to protocol, EDC entering guidance.etc
- Perform site monitoring regularly
- Keep close contact with site personnel via emal or phone to solve protocol problems
- Perform data review to ensure there is no data discrepancy

The investigator enters the information required by the protocol into the CRF, and the supervisor verifies that it is completed completely and accurately and directs the study center staff to make any necessary revisions and additions.

Drug regulatory authorities, Ethics Committees, sponsors' monitors and/or auditors may conduct systematic inspections of clinical study-related activities and documents to evaluate whether the study is conducted in accordance with the study protocol, SOPs, and relevant regulatory requirements, and whether study data are recorded in a timely, truthful, accurate, and complete manner. The audit shall be performed by staff who are not directly involved in the clinical study.

10 Statistical analysis

10.1 Analysis sets

- Full analysis set (FAS) consists of all subjects who have received at least one dose of study treatment.
- Safety Set (SS) consists of all subjects who have received at least one dose of study treatment and had at least one valid post-baseline safety assessment.
- Pharmacokinetic analysis set (PKAS) consists of all subjects who take at least one dose of study treatment and have at least one blood sample providing evaluable concentration data.
- Dose determining set (DDS) consists of all subjects who have received at least 80% of the total planned dose of GFH018, are considered to have sufficient safety evaluation during the 31-day-observation period or developed DLT during the first cycle.

10.2 Analysis method

10.2.1 Demographic and baseline characteristics

Descriptive statistical analysis will be used to summarize demographic and baseline characteristics, including age, sex, height, weight, and ECOG performance status scores based on FAS.

10.2.2 Primary endpoints

The primary objective of this study is to evaluate the safety and tolerability of GFH018, no hypothesis testing will be performed.

10.2.2.1 Safety analysis

Safety analysis will be based on the SS.

- DLT

DLT will be summarized for each dose group and a by-subject listing of DLT will be provided.

- AEs

All AEs will be graded according to CTCAE version 5.0 and be coded using MedDRA. All post-treatment AEs/SAEs, grade≥3 AEs, treatment-related AEs/SAEs, AEs leading to study drug discontinuation, AEs leading to study drug interruption, DLT, and AESIs will be summarized by system organ class, preferred term, and dose levels.

- Laboratory tests

Vital signs, physical examination, laboratory tests, and 12-lead ECG will be summarized by time point.

10.2.2.2 Tolerability

The proportion of subjects who experienced dose reduction, dose interruption, and dose discontinuation will be summarized.

10.2.3 Secondary endpoints

10.2.3.1 Pharmacokinetic analysis

Pharmacokinetic analysis will be based on the PKAS.

Concentration-time data will be summarized by dose group, while descriptive statistical analysis will be performed at each planned time point. Individual and average concentration-time curves will be provided for each dose group.

The calculation method of PK parameters is described in Section 6.2.4.

Summary statistics of pharmacokinetic parameters for each GFH018 dose group are presented in tabular form. Provides geometric mean and coefficient of variation, maximum, median, minimum, and arithmetic mean and standard deviation for each PK parameter (except Tmax). For$_{Tmax}$, the median, maximum, and minimum values are provided.

The power function model was used to test whether PK changed proportionally between doses.

10.2.3.2 Efficacy analysis

The disease assessments will be evaluated according to RECIST 1.1.

Best overall response (BOR), ORR, and DCR will be summarized with corresponding 90% confidence intervals for each dose level. A waterfall plot will be used to show the best change from baseline in tumor size. A by-subject listing of DOR, PFS, and TTP will be provided.

The efficacy analysis will be based on the FAS.

10.2.3.3 Pharmacodynamic markers

For pharmacodynamic markers, changes (or percentage changes) from baseline will be summarized by time points.

10.3 Sample size

For dose-escalation part, 3 to 6 subjects are planned to be enrolled in each dose level, a total of 20 to 40 subjects are planned. Additional subjects may be enrolled if more dose levels or alternative dosing regimens are to be explored.

For dose expansion part, 6 to 12 subjects are planned to be enrolled in each group. A minimum of 12 subjects are required for RP2D group (subjects who received RP2D treatment from dose escalation part are counted). For an adverse event with an incidence of 10%, the probability of observing at least 1 adverse event in 12 subjects is 72%.

11 Ethics

11.1 Institutional Review Board/ Independent Ethics Committee

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/IEC before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor or designated CRO monitors, auditors, the sponsor or designated CRO clinical quality assurance representatives, IRBs/IECs/REBs and regulatory authorities as required.

11.2 Ethical Conduct of the Study

This clinical study was designed, shall be implemented, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

The protocol and the proposed informed consent form must be reviewed and approved by IRB/IEC before study start. The study can only be conducted after it has been approved by related regulatory authorities and IRB/IEC. The sponsors and investigator must not amend this study protocol unilaterally without mutual agreement. The amended protocol cannot be conducted until being approved by the IRB/IEC. When investigator must change or deviate from the study protocol to eliminate the direct and immediate hazards to subjects, they must notify the IRB/IEC and sponsors in writing to explain and record all the deviations as soon as possible.

During the clinical study, any amendment made to the study protocol should be submitted to the IRB/IEC and Regulatory Authorities, and corresponding amendment to other documents can also be made when necessary, then be submitted and/or approved as required by the ethics committee and Regulatory Authorities. Investigators are responsible for periodic submission of the interim report to the IRB/EC in accordance with relevant requirements and should inform the ethics committee when the trial is completed.

11.3 Patient Information and Consent

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e., all the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's Informed Consent was obtained will be captured in eCRFs.

The sponsor will provide to the investigator, in a separate document, a proposed ICF that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by the sponsor before submission to the IRB/IEC, and a copy of the approved version must be provided to the sponsor monitor after IRB/IEC approval.

WOCBP should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Confidentiality of Patient's Information

The investigator must ensure anonymity of the subjects; subjects must not be identified by names in any documents submitted to the sponsor or the designated CRO. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.5 Inspection

The sponsor or regulatory authority may inspect and inspect the study during or after the study.

12 Publication of Study Results

The sponsor assures that the key design elements of this protocol will be posted in publicly accessible databases such as https://euclinicaltrials.eu. In addition, upon study completion and

finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

If the investigator intends to publish any study-related data and information, they should obtain the approval of the sponsor, and provide the manuscript, abstract or full text of all planned publications (poster, speech, or lecture) to the sponsor at least 30 days prior to the submission of the documents or materials in other forms.

References

1. Neuzillet C, Tijeras-Raballand A, Cohen R, et al. Targeting the TGF-β pathway for cancer therapy. Pharmacol Ther 2015; 147:22-31.
2. Gramont A, Faivre S, Raymond E. Novel TGF-β inhibitors ready for prime time in onco-immunology. OncoImmunology 2017; 6: e1257453.
3. An Y, Gao S, Zhao WC, et al. Transforming growth factor-β and peripheral regulatory cells are negatively correlated with the overall survival of hepatocellular carcinoma. World J Gastroenterol 2018; 25: 2733-2740.
4. Peng L, Yuan XQ, Zhang CY, et al. High TGF-β1 expression predicts poor disease prognosis in hepatocellular carcinoma subjects. Oncotarget 2017; 8: 34387-34397.
5. Calon A, Lonardo E, Berenguer-Llergo A, et al. Stromal gene expression defines poor-prognosis subtypes in colorectal cancer. Nat Genet 2015; 47:320-329.
6. Xia X, Wu WD, Huang C, et al. SMAD4 and its role in pancreatic cancer. Tumor Biol 2015; 36:111-119.
7. Sanjeev M, Shannon JT, Dorothee N, et al. TGF-β attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature 2018; 554: 544–548.
8. Gueorguieva I, Cleverly AL, Stauber A, et al. Defining a therapeutic window for the novel TGF-β inhibitor LY2157299 monohydrate based on a pharmacokinetic/pharmacodynamic model. Br J Clin Pharmacol 2014;77:796-807.
9. Anderton MJ, Mellor HR, Bell A, et al. Induction of heart valve lesions by small-molecule ALK5 inhibitors. Toxicol Pathol 2011; 39:916-924.
10. Rodon J, Carducci MA, Sepulveda-Sánchez JM, et al. First-in-human dose study of the novel transforming growth factor-β receptor I kinase inhibitor LY2157299 monohydrate in subjects with advanced cancer and glioma. Clin Cancer Res 2015; 21: 553-60.
11. Herbertz S, Sawyer JS, Stauber AJ, et al. Clinical development of galunisertib (LY2157299 monohydrate), a small molecule inhibitor of transforming growth

factor-beta signaling pathway. Drug Des Devel Ther 2015; 9:4479-4499.

12. Kovacs RJ, Maldonado G, Azaro A, et al. Cardiac Safety of TGF-β Receptor I Kinase Inhibitor LY2157299 Monohydrate in Cancer Subjects in a First-in-Human Dose Study. Cardiovasc Toxicol 2015;15:309-323.

Appendix 1 Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1)

(E.A. Eisenhauer, P. Therasse, J. Bogaerts, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1), European Journal of Cancer,2009;228-247.)

1 Measurability of tumor at baseline

1.1 Definition

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

Measurable lesions

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

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

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

Non-measurable lesions

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

Special considerations regarding lesion measurement

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

Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- A lesion located at a site that has been radiated or otherwise treated regionally is generally treated as a non-measurable lesion unless the lesion shows definite progression. The study protocol shall describe in detail the conditions under which these lesions are measurable.

1.2 Specifications by methods of measurements

Measurement of lesions

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

Method of assessment

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

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

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

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

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is ad- vised. If there is concern about radiation

exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published.16–18 In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

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

2. Tumor response evaluation

2.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis 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 (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or

more new lesions is also considered progression).

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

2.2 Special notes on the assessment of target lesions

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

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

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

2.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to deter- mine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

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

The concept of progression of non-target disease requires additional explanation as follows:

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

When the patient has only non-measurable disease. This circum- stance arises in some

phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable dis- ease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy

and follow-up evaluation will clarify if it represents truly new disease. If repeat scans con- firm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.6 Missing assessments and inevaluable designation

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

2.7 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to

overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of ‘zero’ on the case report form (CRF).

In trials where confirmation of response is required, re-peated ‘NE’ time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as ‘symptomatic deterioration’. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in Tab 1.

Conditions that define ‘early progression, early death and in evaluability’ are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by dis-ease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Tab 1 Time point response: subjects with target (+/-non-target) disease

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

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

Tab 2 Time point response: subjects with non-target disease only

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

Note: CR = complete response, PD = progressive disease, and NE = inevaluable. a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Tab 3 Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable. a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have

reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.8 Confirmatory measurement/duration of response Confirmation

In non-randomized trials where response is the primary end- point, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. However, in all other circumstances, i.e., in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive dis- ease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of subjects achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: the duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should consider many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be considered if comparisons between trials are to be made.

2.9 PFS/TTP

PFS or TTP is the main endpoint in many studies of advanced cancer. If the protocol requires all subjects to have measurable lesions, the evaluation of progression is relatively simple. More and more studies allow subjects with measurable lesions and non- measurable lesions to enter the study. In this situation, the clinical findings of disease progression in subjects without measurable lesions must be described in detail. Because the progression date often has definite deviation, the observation time arrangement of each study group shall be the same.

Appendix 2 ECOG Performance Status

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