Clinical Trial Protocol

A Phase I Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetic Profiles and Efficacy of Oral BB102 Tablets in Patients with Advanced Solid Tumors

Protocol No.: BB102-ST-I-02

Version: Version 1.0

Date: Jul 14, 2022

Sponsor: BroadenBio Co., Ltd.

Contract Research Organization: To be determined

Protocol Signature Page

I agree to:

- Conduct this study in strict accordance with the protocol, *Good Clinical Practice* (GCP) and applicable laws and regulations.
- Keep all materials provided by the sponsor according to the confidentiality requirements. It must be indicated that these materials are confidential when they are required to be submitted to the Institutional Review Board (IRB) or Ethics Committee (EC).

I have read and understood the entire clinical trial protocol, and agree on all of its contents.

Responsible Person of the Sponsor		Position	
Signature		Date	
Company Name	BroadenBio Co., Ltd.		
Contact Address		Postal Code	
Telephone			

Statistician		Position	
Signature		Date	
Company Name			
Contact Address		Postal Code	
Telephone			

Principal Investigator		Title and Position	
Signature		Date	
Clinical Trial Institution			
Contact Address		Postal Code	
Telephone			

Sponsor

Company Name	BroadenBio Co., Ltd.		
Project Leader		Position	
Contact Address	Room 602, 6th Floor, Unit 1, Building 7, Yard 88, Kechuang 6th Street, Beijing Economic and Technological Development Zone, Beijing	Postal Code	100176
Telephone		Mobile	
Fax	None	E-mail	

Company Name			
Medical Expert		Position	
Contact Address		Postal Code	
Telephone		Mobile	
Fax		E-mail	

Contract Research Organization

Company Name			
Project Leader		Position	
Contact Address		Postal Code	
Telephone		Mobile	
Fax		E-mail	

Data Management

Company Name			
Project Leader		Position	
Contact Address		Postal Code	
Telephone		Mobile	
Fax		E-mail	

Statistical Analysis Institution

Company Name			
Project Leader		Position	
Contact Address		Postal Code	
Telephone		Mobile	
Fax		E-mail	

PK Sample Testing Facility

Company Name			
Project Leader		Position	
Contact Address		Postal Code	
Telephone		Mobile	
Fax		E-mail	

Biomarker Sample Testing Facility

Company Name			
Project Leader		Position	
Contact Address		Postal Code	
Telephone		Mobile	
Fax		E-mail	

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Abbreviations

Abbreviations and terms	Interpretation
ABEOS	Absolute eosinophil count
ABLYMP	Absolute lymphocyte count
ABMONO	Absolute monocyte count
ABRETIC	Absolute reticulocyte count
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AFP	Alphafetoprotein
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{ss}	Area under the plasma concentration-time curve during a dosing interval at steady state
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time 0 to infinity
$AUC_{0\text{-}t}$ or AUC_{last}	Area under the drug concentration-time curve from 0 to the time point of quantifiable concentration
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
BS	Biomarker analysis set
CA125	Carbohydrate antigen 125
CA15-3	Carcinoma antigen 15-3
CA242	Carbohydrate antigen 242
CEA	Carcinoembryonic antigen
c-Fos	Immediate-early gene
CK	Creatine kinase
CKI	Creatine kinase isozyme
CL_z/F	Apparent clearance
C_{max}	Peak concentration
CR	Complete response
CRO	Contract Research Organization
$C_{ss,\ av}$	Mean plasma concentration at steady state
$C_{ss,\ max}$	Peak concentration at steady state
$C_{ss,\ min}$	Trough concentration at steady state
CT	Computed tomography

Abbreviations and terms	Interpretation
CTCAE	Common terminology criteria for adverse event
CTGF	Connective tissue growth factor
CYFRA21-1	Cytokeratin 19
DCR	Disease control rate
DF	Fluctuation coefficient at steady state
DLT	Dose-limiting toxicity
DM	Data Manager
DOR	Duration of response
DS	DLT set
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
Egr-1	Early growth response gene-1
EMT	Epithelial-mesenchymal transition
EOT	End of treatment visit
FGFR	Fibroblast growth factor receptor
FGFR1	Fibroblast growth factor receptor 1
FGFR2	Fibroblast growth factor receptor 2
FGFR3	Fibroblast growth factor receptor 3
FGFR4	Fibroblast growth factor receptor 4
FGF19	Fibroblast growth factor 19
GCP	Good Clinical Practice
GGT	γ-glutamyltransferase
GLO	Globulin
GLU	Fasting plasma glucose
GSK3β	Glycogen synthase kinase-3β
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCG	Human chorionic gonadotropin
HCT	Haematocrit
HCV	Hepatitis C virus
HCV-Ab	Hepatitis C virus antibody
HDL	High density lipoprotein cholesterol
HIV-Ab	Human immunodeficiency virus antibody
HNSTD	Highest non-severely toxic dose
ICC	Intrahepatic cholangiocarcinoma
ICF	Informed Consent Form

Abbreviations and terms	Interpretation
ICH	International Conference on Harmonization
IC_{50}	Half maximal inhibitory concentration
IHC+	Immunohistochemistry positive
IL-6	Interleukin-6
Kel	Elimination rate constant
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein cholesterol
LVEF	Left ventricular ejection fraction
MCHC	Mean corpuscular hemoglobin concentration
mDOR	Median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
MEK-ERK	Mitogen extracellular kinase/extracellular signal-regulated kinase
mPFS	Median progression-free survival
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MRT	Mean residence time
MTD	Maximum tolerated dose
NOAEL	No observed adverse effect level
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
P-gp	P-glycoprotein
PI3K/AKT	Phosphatidylinositol 3 kinase/protein kinase B
PK	Pharmacokinetics
PKS	PK set
PLT	Platelet
PR	Partial response
PSA	Prostatic specific antigen
QD	Once daily
QTcF	QT interval corrected by Fridericia
Rac	Accumulation ratio
RBC	Red blood cell
RP2D	Recommended phase II dose
SAE	Serious adverse event
SD	Stable disease
SMC	Safety Monitoring Committee
SOP	Standard operating procedure
SS	Safety set
STD_{10}	Severely toxic dose to 10% of animals

Abbreviations and terms	Interpretation
SUSAR	Suspected unexpected serious adverse reaction
TBIL	Total bilirubin
T/C	Treatment/control ratio
TG	Triglyceride
TGF-β	Transforming growth factor beta
TGI	Tumor growth inhibition
TKI	Tyrosine kinase inhibitor
t_{lag}	Lag time
T_{max}	Time to maximum plasma concentration
$T_{1/2}$	Half-life
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization
95% CI	95% confidence interval

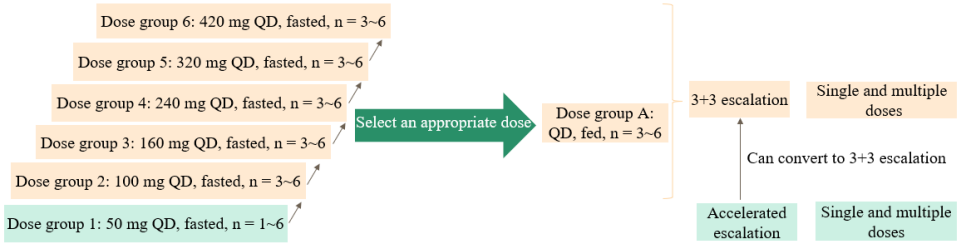
Protocol Synopsis

Protocol No.	BB102-ST-I-02
Protocol Title	A Phase I Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetic Profiles and Efficacy of Oral BB102 Tablets in Patients with Advanced Solid Tumors
Version No.	Version 1.0
Date	Jul 14, 2022
Sponsor	BroadenBio Co., Ltd.
Trial Phase	Phase I
Study Background	Fibroblast growth factor receptor 4 (FGFR4) is a tyrosine kinase receptor that selectively binds to fibroblast growth factor 19 (FGF19) for dimerization and autophosphorylation. By activating the signaling pathways such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), mitogen-activated extracellular signal-regulated kinase/extracellular signal-regulated kinase (MEK-ERK), and glycogen synthase kinase-3β/β-catenin (GSK3β/β-catenin), FGFR4 promotes tumor cell proliferation, promotes epithelial-mesenchymal transition (EMT), and inhibits tumor cell apoptosis. Studies have found that, overexpression of FGF19 and its receptor FGFR4 may upregulate early growth response gene-1 (Egr-1), immediate early gene (c-Fos), interleukin-6 (IL-6), and connective tissue growth factor (CTGF) to induce proliferation of liver cancer cells. Meanwhile, it promotes EMT of liver cancer by activating GSK3β/β-catenin signaling pathway and promotes the invasion and metastasis of liver cancer by activating transforming growth factor β (TGF-β). The abnormal signaling pathway of FGF19-FGFR4 complex has been confirmed to be an oncogenic driver of hepatocellular carcinoma (HCC). Besides, FGF19 overexpression is one of the mechanisms for sorafenib resistance. Therefore, FGFR4 is considered as a new potential treatment target for liver cancer. A variety of small molecule FGFR4 inhibitors (e.g., BLU-554, FGF401) with different selectivity and binding patterns have been developed, and the related clinical trials have been started (all ongoing) for the treatment of HCC and other solid tumors with abnormal FGFR4 signal transduction. BB102 is a small molecule FGFR4 inhibitor independently discovered and developed by the sponsor. It is an innovative drug/molecular, characterized by an explicit mechanism of action, a high selectivity, high activities *in vitro* and *in vivo* (a variety of liver cancer, rhabdomyosarcoma, and breast cancer xenograft models), and good safety.
Indications	**Dose escalation trial:** advanced solid tumors **Expansion trial:** FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors
Trial Objectives	**Dose escalation trial** **<u>Primary objectives:</u>** ● To evaluate the safety and tolerability of different doses of BB102 tablets monotherapy (fasted or fed) in patients with advanced solid tumors. ● To explore the maximum tolerated dose (MTD) by observing the dose-limiting toxicity (DLT) of BB102 tablets monotherapy (fasted or fed) within the specified dose range, so as to provide rationale for determining the recommended phase II dose (RP2D). **<u>Secondary objectives:</u>**

	● To investigate the pharmacokinetic (PK) profiles of BB102 tablets monotherapy (fasted) administered as single and multiple oral doses in patients with advanced solid tumors. ● To preliminarily investigate the effect of food on the PK profiles of BB102 tablets monotherapy administered as single and multiple oral doses in patients with advanced solid tumors. ● To preliminarily investigate the efficacy of BB102 tablets monotherapy (fasted or fed) in patients with advanced solid tumors. ● To investigate the relationship between biomarker and efficacy and to preliminarily infer the correlation. ● To explore the correlation between plasma concentration of study drug and Fridericia method corrected QT interval (QTcF) (C-QTcF analysis). ● To identify the metabolites of BB102 in patients with advanced solid tumors. **Expansion trial** **<u>Primary objective:</u>** ● To evaluate the efficacy of BB102 tablets monotherapy (fasted) in patients with FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors. **<u>Secondary objectives:</u>** ● To investigate the PK profiles of BB102 tablets monotherapy (fasted) in patients with FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors. ● To investigate the safety of BB102 tablets monotherapy (fasted) in patients with FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors. ● To investigate the relationship between biomarker and efficacy and to preliminarily infer the correlation.
Study Design	This study consists of a dose escalation trial and an expansion trial, both of which are designed as multi-center and open-label trials. This study aims to investigate the safety, tolerability, PK profiles and efficacy of BB102 tablets monotherapy (fasted or fed) orally administered at different doses in patients with advanced solid tumors and to evaluate the effect of food on the PK profiles. **1. Dose escalation trial (6 fasted dose escalation groups and 1 fed dose escalation group)** **<u>1.1 Selection of starting dose and escalation doses</u>** According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-S9 "*Guideline on Nonclinical Evaluation for Anticancer Pharmaceuticals*", a common approach for many small molecules anticancer drugs is to set a starting dose at 1/10 the severely toxic dose to 10% of the animals (STD_{10}) in rodents of repeat-dose toxicity study; if the non-rodent is the most appropriate species, then 1/6 the highest non-severely toxic dose (HNSTD) is considered an appropriate starting dose. According to the CDE "*Technical Guidelines for Clinical Trials of Anticancer Drugs*" and "*Considerations for Starting Dose Calculation for Phase I Clinical Trial of New Anticancer Pharmaceuticals*", in view of the ethical factors in tumor patients, 1/3 to 1/5 the no observed adverse effect level (NOAEL) is most commonly adopted for small molecule targeted anticancer pharmaceuticals. The

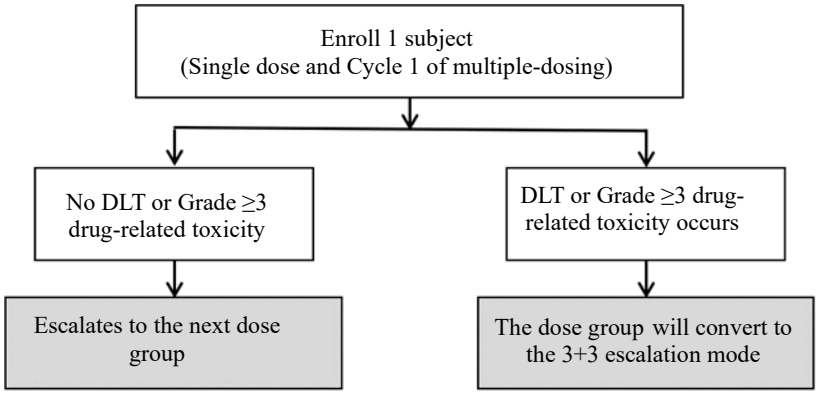
	corresponding human doses are calculated using the body surface area method based on the above parameters and nonclinical effective starting dose. The female rat is the most sensitive species, and the corresponding maximum recommended starting dose (MRSD) is 107.4 mg/day based on the above parameters of nonclinical toxicology; the human equivalent dose calculated based on the nonclinical effective starting dose is 53.6 mg/day. With comprehensive consideration of the starting doses, escalation doses and RP2D of similar drugs as well as the strengths (10 mg, 50 mg) of BB102 tablets, this study plans to adopt 50 mg as the starting dose. With a reference to the MTD of repeat-dose toxicity study, MTD and RP2D in the first-in-human study of similar drugs as well as the strengths (10 mg, 50 mg) of BB102 tablets, this study plans to adopt 420 mg as the maximum dose. Based on the modified Fibonacci method, the proposed fasted escalation doses are 50 mg once daily (QD), 100 mg QD, 160 mg QD, 240 mg QD, 320 mg QD and 420 mg QD. Taking into account the human dose corresponding to the nonclinical effective starting dose (53.6 mg/day), the accelerated escalation (enrolling 1 subject only) of 50 mg enables quick escalation to the effective dose under the premise of guaranteeing the safety of subjects and subsequently avoids excessive exposure of subjects to ineffective doses. In addition, according to the action mechanism of FGFR4 inhibitors, inhibition of FGF19/FGFR4 signaling pathway will upregulate CYP7A1 expression (CYP7A1 is associated with metabolism of bile acid) and subsequently cause an increase in bile acid secretion; bile acid secretion also increases after meal. Dose escalation trial of the similar drug FGF401 (NCT02325739) set up separate fed dose escalation groups. Therefore, in order to investigate the effect of food on the safety and tolerability (primary), PK profiles (secondary) of BB102 tablets monotherapy, in this study, an appropriate dose will be selected as the fed dose escalation group according to the previously obtained clinical trial data of BB102 tablets. Rationale for the selection of starting dose and escalation doses is detailed in Sections 4.1.1.1 and 4.1.1.2 of the main text. **1.2 Escalation method** This study adopts a modified 3+3 escalation design, including accelerated escalation and 3+3 escalation, with 6 fasted dose groups (50 mg QD, 100 mg QD, 160 mg QD, 240 mg QD, 320 mg QD and 420 mg QD) and 1 fed dose group. Note: Before the start of the dose escalation trial, the dosage of the fed dose group cannot be determined temporarily, and an appropriate dose will be selected subsequently by the safety monitoring committee (SMC) according to the previously obtained clinical trial data of BB102 tablets; the trial of the fed dose group can be synchronized with the dose escalation process of the fasted dose groups, and the trial of the fed dose group can also be started after the dose escalation of the fasted dose groups is completed, but the trial of the fed dose group must only be initiated after the equivalent dose is demonstrated to be safe under the fasted condition. The starting dose group (50 mg QD group) is the accelerated escalation group; other dose groups are 3+3 escalation groups. See the figure below. All subjects enrolled will firstly receive a single dose for safety observation and PK study, and then undergo a 5-day washout period. Later, subjects will receive multiple-dosing to continue the safety observation and PK study. Multiple-dosing is tentatively scheduled as: once daily in 21-

day cycles. After Cycle 1 is finished, a subject can continue to receive the next cycle of treatment if the investigator believes that the subject may benefit from the study treatment.



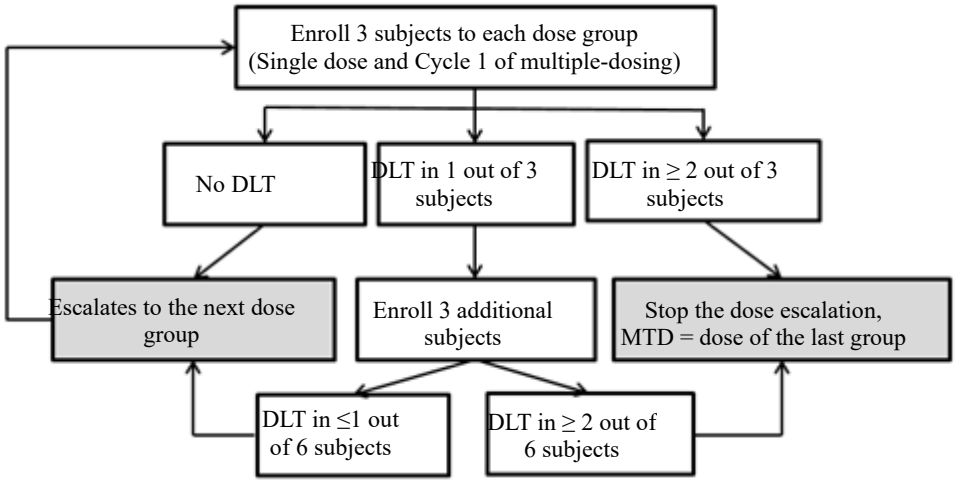
The modified 3+3 escalation design in dose escalation trial

In order to avoid excessive exposure of subjects to ineffective doses, the accelerated escalation group (50 mg QD group) is planned to enroll 1 subject. The method for judging dose escalation is shown in the figure below. During the DLT observation period (defined as the period from a single dose to the end of Cycle 1 of multiple-dosing), if there is no DLT or grade ≥3 drug-related toxicity [defined as an adverse event (AE) definitely/possibly related to the study drug], the enrollment of the next dose group will be started; if any DLT or grade ≥3 drug-related toxicity occurs, the group will be converted to the 3+3 escalation mode.



The accelerated escalation diagram in dose escalation trial

It is planned to enroll 3 subjects to other groups, and the specific dose escalation method is shown in the figure below. For each dose group, if none of the 3 subjects experiences DLT, the trial will proceed to the next dose group. If ≥2 out of the 3 subjects experience DLT, the dose escalation will be discontinued. If 1 of the 3 subjects experiences DLT, 3 additional subjects should be enrolled into this dose group (if none of the 3 newly enrolled subjects experiences DLT, the trial will proceed to the next dose group; If ≥1 of the 3 newly enrolled subjects experience DLT, dose escalation will be discontinued).



The 3+3 escalation diagram in dose escalation trial

The second and third subjects in the 3+3 escalation groups should only be enrolled after the first subject is observed for at least 5 days after dosing (enrolled on or after C1D1 of the first subject). If the previous subject experiences DLT, the sponsor and the investigator need to cautiously judge whether to enroll the next subject based on the safety data; if subsequent subjects have already been enrolled, the enrolled subjects should continue the study treatment (unless these subjects meet the criteria for study treatment discontinuation), with his/her safety data closely monitored.

SMC will decide whether to perform dose escalation or reduction and determine whether to and how to adjust the escalation doses based on the safety, tolerability and/or PK data obtained during the DLT observation period of a certain dose group. Based on the safety, tolerability, PK and efficacy data of a certain group, if the investigator believes that it is necessary to expand the number of subjects of this dose group to further observe the safety and efficacy and obtain PK data, the number of subjects of this dose group may be increased to 4-12 after reaching a consensus with the sponsor through discussion.

To ensure the safety of subjects, the washout time after single-dosing, dosing frequency, cycle setting, and time points of PK sample collection in the subsequent study as well as the design of subsequent escalation doses (e.g., adding dose groups of 520 mg QD and 600 mg QD) may be timely adjusted based on the previously obtained safety, tolerability, PK parameters [e.g., half-life ($T_{1/2}$), drug accumulation after multiple-dosing] and other previously obtained clinical trial data of BB102 tablets.

MTD is defined as the highest dose level in which DLT occurs in ≤1/6 of the total subjects during the DLT observation period. If MTD is not reached after administration of the maximum dose level shown above, the SMC will decide whether to increase dose groups based on the nonclinical data and the efficacy doses and PK parameters of domestic and foreign similar drugs observed in human.

1.3 Definition of a DLT

DLT observation period is defined as the period from a single dose to the end of Cycle 1 of multiple-dosing.

	DLT is defined as an AE definitely/possibly related to the study drug occurring in the DLT observation period [AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0] which meets any of the following criteria: **(1) Hematologic toxicity** 1) Grade 4 neutrophil count decreased for >3 days. 2) Grade 3 febrile neutropenia: absolute neutrophil count (ANC) $<1.0\times10^9$/L with single temperature ≥38.3°C (101°F) or persistent temperature ≥38°C (100.4°F) for more than 1 hour. 3) Grade 4 Platelet (PLT) count decreased. 4) Grade 3 PLT count decreased with bleeding. 5) Grade 4 anemia. 6) Other grade 3 hematologic toxicities which do not recover to grade ≤2 after 7 days of symptomatic supportive treatment. **(2) Non-hematologic toxicity** 1) Grade ≥4 non-hematologic toxicity. Note: Toxicities with no safety risk at the discretion of the investigator are excepted, such as grade 4 γ-glutamyltransferase (GGT) increased and alkaline phosphatase (ALP) increased. 2) Grade 3 non-hematologic toxicity (including but not limited to hepatobiliary disorders). Note: Toxicities with no safety risk at the discretion of the investigator (such as grade 3 nausea, vomiting, diarrhea, asthenia, constipation, loss of appetite, mucositis, GGT increased, ALP increased) are not defined as DLT, but they will be defined as DLT when the toxicities do not recover to grade ≤2 within 7 days under the circumstance of symptomatic supportive treatment are permitted. **(3) Other conditions** 1) The grade is elevated from baseline with clinically significant and/or unacceptable toxicity, which is judged as a DLT by the SMC. 2) Drug discontinuation lasting 7 days or more due to drug-related toxicity. 3) The dose received by the subject during the DLT observation period is less than 75% of the scheduled dose due to toxicities attributable to study drug, and the investigator believes that it should be considered as a DLT. **1.4 DLT evaluable subjects** If the dose received by a subject during the DLT observation period is less than 75% of the scheduled dose for reasons other than toxicities attributable to study drug, this subject should not be included into the final DLT analysis of this dose group or the overall groups. If the above situation occurs in any subject, the corresponding dose group needs to enroll one more subject for replacement to ensure the minimum required number of DLT evaluable subjects. **2. Expansion trial (expansion groups)** Based on the safety, tolerability, PK and efficacy data obtained in previous trials, 1 to 3 appropriate doses (e.g., 100 mg QD, 160 mg QD, and 240 mg QD) will be selected for the expansion trial. The expansion trial can be initiated when the above doses are demonstrated to have a favorable safety in the dose escalation trial (i.e., the number of subjects experiencing DLT

	in the group is ≤1/6 of total subjects of the group), without waiting for the completion of the entire dose escalation trial. Each expansion group will enroll 12 subjects to investigate the efficacy, safety and PK profiles of BB102 tablets. During the expansion trial, AEs meeting the definition of DLT will be regarded as AEs of special interest for safety assessment, thereby enriching the safety assessment data. **3. Collection and analysis of PK samples** **During the single-dosing period of the dose escalation trial, the PK blood sampling time points are as follows:** within 0.5 h (0 h) before single-dosing on D1 and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min), 24 h (±1 h; D2), 48 h (±1 h; D3), 72 h (±2 h; D4) and 96 h (±2 h; D5) after dosing. **During the multiple-dosing period of the dose escalation trial, the PK blood sampling time points are as follows:** within 0.5 h pre-dose on C1D1, within 0.5 h pre-dose on C1D8, within 0.5 h pre-dose on C1D15, within 0.5 h pre-dose and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min) and 24 h (±30 min; collected before dosing on C2D1) post-dose on C1D21. **During the expansion trial, the PK blood sampling time points are as follows:** within 0.5 h pre-dose on C1D1, within 0.5 h pre-dose on C1D8, within 0.5 h pre-dose on C1D15, within 0.5 h pre-dose and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min), and 24 h (±30 min; collected before dosing on C2D1) post-dose on C1D21. The PK blood sampling time points of the subsequent study may be adjusted based on the previously obtained clinical trial data of BB102 tablets. If there is dose interruption or missed dose(s) of BB102 tablets within 3 days before a PK sample collection time point, the investigator should discuss its impact on the PK sampling schedule with the sponsor and clinical pharmacologist as soon as possible within 24 hours of awareness, thereby determining whether to continue PK blood sampling as planned and how to adjust the PK blood sampling time points. The date and time of each dosing and each blood sampling should be recorded. Concentration of BB102 (and its main metabolites, if applicable) in the PK samples will be quantitatively measured using the methodologically validated high-performance liquid chromatography- mass spectrometry/ mass spectrometry (HPLC-MS/MS) method. **4. Identification of metabolites** Blood samples will be collected for identification of metabolites only at a high dose group (e.g., 160 mg QD, 240 mg QD, 320 mg QD or 420 mg) during the single-dosing period of the dose escalation trial. **Blood sampling time points:** within 0.5 h (0 h) before single-dosing on D1 and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min), 24 h (±1 h; D2), 48 h (±1 h; D3), 72 h (±2 h; D4) and 96 h (±2 h; D5) after dosing. **5. Interim analysis** No interim analysis will be performed in this study.
Total Number of Subjects	This trial plans to enroll 31-78 subjects in total. It is expected that the dose escalation trial will enroll 19-42 subjects. It is expected that the expansion trial will enroll 12-36 subjects.

Number of Study Sites	3-6 study sites in the United States of America
Study Duration	Approximately 24 months
Selection Criteria of Subjects	**Inclusion criteria:** Patients must meet all of the following criteria before being enrolled in the study: (1) 18-78 years of age (inclusive) in dose escalation trial and ≥18 years of age in expansion trial at the time of signing the informed consent form (ICF), male or female. (2) For the dose escalation trial, histologically, cytologically confirmed or clinically confirmed advanced solid tumors patients who without available standard treatment, failed in standard treatment or cannot tolerate standard treatment (primary HCC patients are preferred; primary HCC patients should have a liver function score of ≤9 points as assessed according to the Child-Pugh classification criteria). Note: Only primary liver cancer can be clinically diagnosed, and other tumors need to be confirmed by histology or cytology. For the expansion trial, histologically or cytologically confirmed FGF19 or FGFR4 positive advanced primary HCC (primary HCC patients should have a liver function score of ≤9 points as assessed according to the Child-Pugh classification criteria) or other advanced solid tumors patients who without available standard treatment, failed in standard treatment or cannot tolerate standard treatment. Note: FGF19 or FGFR4 positivity includes but is not limited to FGF19 amplification, FGF19 overexpression, elevation of serum FGF19 protein level, FGFR4 amplification, FGFR4 overexpression and FGFR4 activating mutation. At the discretion of the investigator, the patient's previous positive test results for FGF19 or FGFR4 can be accepted (patients must agree to provide previous positive test results for FGF19 or FGFR4). Newly reported FGF19 or FGFR4 positive test results from a central laboratory based on tumor tissue and/or blood samples are also acceptable (patients must agree to provide tumor tissue samples and/or blood samples for FGF19 or FGFR4 positive testing. If there are special circumstances such as the tissue is difficult to obtain or the risk of obtaining biopsy is high, etc., the investigator can communicate with the sponsor to discuss whether it can be exempted. Tumor tissue: During screening period, tumor tissue samples from patients in the past 2 years or fresh tumor tissue samples can be collected; the samples can be collected from the primary lesion or metastatic lesions. Blood: A fresh blood sample 5 mL can be collected during the screening period). (3) For the dose escalation trial, at least one evaluable tumor lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix I). For the expansion trial, at least one measurable tumor lesion according to RECIST v1.1. (4) Eastern Cooperative Oncology Group (ECOG) performance status score of ≤1 (Appendix II). (5) Life expectancy of ≥3 months. (6) With good organ function, including: ➢ Liver function: total bilirubin (TBIL) ≤1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) ≤3×ULN, and aspartate aminotransferase (AST) ≤3×ULN (for patients with liver cancer or liver metastases, the criteria will be TBIL ≤3×ULN, ALT ≤5×ULN, and AST ≤5×ULN);

	➢ Renal function: blood creatinine ≤1.5×ULN and creatinine clearance rate ≥50 mL/min (calculated based on Cockcroft-Gault formula); ➢ Hematology (no blood transfusion or hematopoietic stimulating factor therapy within 14 days of blood sampling for hematology): PLT ≥100×10^9/L (for patients with liver cancer, the criteria will be PLT ≥85×10^9/L), ANC ≥1.5×10^9/L, and hemoglobin (Hb) ≥90 g/L (90 mg/mL); ➢ Coagulation function: activated partial thromboplastin time ≤1.5×ULN and international normalized ratio ≤1.5×ULN. (7) For female patients of childbearing potential, the pregnancy test result within 7 days before the first dose is negative and promise to use adequate and effective methods of contraception or abstinence from the start of screening period to 6 months after the last dose of study treatment; male patients who promise to use adequate and effective methods of contraception or abstinence from the start of screening period to 6 months after the last dose of study treatment. The definition of female with childbearing potential and contraceptive requirements are detailed in Appendix III. (8) Voluntarily participate in this clinical study, understand the content of the ICF and sign it voluntarily, with good compliance. **Exclusion criteria:** Patients who meet any of the criteria cannot be enrolled in this study: (1) Use of systemic immunosuppressive or systemic cortisol (≥10 mg prednisone or other equivalent hormone) within 4 weeks prior to the first dose. (2) Prior use of selective FGFR4 inhibitor and/or pan-FGFR inhibitor therapy. (3) Use of cytotoxic chemotherapeutics within 4 weeks prior to the first dose, OR use of state-approved Chinese traditional patent drugs/Chinese traditional drugs with an anti-tumor effect within 2 weeks prior to the first dose. Note: For mitomycin C or nitrosoureas, 6-week washout is required; for small molecule targeted drugs and oral fluorouracil drugs, a washout period of 2 weeks or five $T_{1/2}$ of the drug (whichever is longer) is required. (4) Anti-tumor endocrine therapy, radiotherapy, interventional embolization, radiofrequency, proton therapy, radioimmunotherapy, immunotherapy or other biotherapies within 4 weeks prior to the first dose (if five $T_{1/2}$ of the drug/therapy used by the patient is confirmed to be <4 weeks, five $T_{1/2}$ shall prevail). (5) Use of other clinical investigational drug or therapy that not marketed within 4 weeks prior to the first dose. (6) Patient is receiving drugs or therapies prohibited in the protocol (e.g., strong CYP3A4 inhibitors, strong CYP3A4 inducers, strong CYP3A5 inhibitors, strong CYP3A5 inducers, sensitive CYP3A4 substrates with a narrow therapeutic index, sensitive CYP2B6 substrates with a narrow therapeutic range, etc., see Section 6.2 of the main text for details) and cannot discontinue such use at least 2 weeks prior to the first dose or throughout the study. (7) Pregnant or lactating females. (8) Patient with known hypersensitivity to any ingredient of BB102 tablets, or patient who have a history of drug allergy and is judged as not suitable for participating in this study by the investigator.

	(9) Presence of clinically significant gastrointestinal disorder that may affect the intake, transport or absorption of the study drug (e.g., dysphagia, uncontrollable nausea and vomiting, active gastric ulcer, ulcerative colitis, Crohn's disease, chronic diarrhea, intestinal obstruction, and other conditions determined by the investigator that may cause gastrointestinal bleeding, perforation, etc.) at screening. (10) Patient with concurrent cancer (adequately treated non-melanoma skin cancer or lentigo maligna with no evidence of disease recurrence, except carcinoma in situ) within 5 years prior to the first dose. (11) Adverse reaction of the prior anti-tumor therapy not yet recovered to grade ≤1 as assessed by CTCAE v5.0 at screening (except the toxicities that are judged as having no safety risk by the investigator, such as alopecia, asthenia, GGT increased, ALP increased, grade 2 peripheral neurotoxicity, thyroid function decreased stabilized by hormone replacement therapy, etc.). (12) Clinically uncontrollable third space effusion at screening, which, at the investigator's discretion, is not suitable for enrollment. Note: For patients with third space effusion (pleural ascites, pericardial effusion) who are stable after local drainage and drug infusion, and drug-eluted for at least five $T_{1/2}$ or 14 days (whichever is shorter), they can be considered for enrollment. (13) Presence of clinically symptomatic metastases to central nervous system or meninges or other evidence showing that metastatic lesions in central nervous system or meninges have not yet been controlled at screening, which, at the investigator's discretion, is not suitable for enrollment. Note: Patients with central nervous system metastases or meningeal metastases who are asymptomatic or in a stable state after treatment before the first dose can be considered for enrollment. (14) History of severe neurological or psychiatric disorders, including epilepsy, dementia, or moderate to severe depression, etc. (15) History of drug abuse or dependence. (16) Clinically significant and uncontrolled cardiovascular diseases, including: ➢ Serious cardiac rhythm or conduction abnormality at screening, such as ventricular arrhythmia that requires clinical intervention, second/third-degree AV block, etc.; ➢ Myocardial infarction within 12 months prior to the first dose; ➢ Acute coronary syndrome, congestive cardiac failure, aortic dissection, cerebral stroke or other grade ≥3 cardiovascular and cerebrovascular events within 6 months prior to the first dose; ➢ Arterial or deep venous thrombosis within 6 months prior to the first dose, or those who need to monitor international normalized ratios or use anticoagulants at screening. Note: Patients with superficial venous thrombosis which do not need treatment can be considered for enrollment; patients who can stop anticoagulant within 2 weeks before the first dose and during the administration period can be considered for enrollment; ➢ Mean resting QTcF >480 ms at screening, which are obtained from three 12-lead electrocardiograms (ECGs) [Note: QTcF is calculated based on Fridericia formula, QTcF = QT/(RR^0.33)]; ➢ Heart failure of New York Heart Association Class ≥II at screening;

	➢ Left ventricular ejection fraction (LVEF) <50% at screening; ➢ Hypertension (defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg) that medication fails to control stably at screening; ➢ Hyperglycemia that medication fails to control stably at screening. (17) Pulmonary embolism within 6 months prior to the first dose, or interstitial pneumonia at screening. (18) Prior allogeneic stem cell transplantation, bone marrow transplantation or vital organ transplantation. (19) Surgical operation (excluding aspiration biopsy) of vital organs or significant trauma within 8 weeks prior to the first dose, or unrecovered surgical effect at screening, or planned elective major surgery during the study period. (20) Presence of uncontrollable infectious disease, congenital immunodeficiency disease, acquired immunodeficiency syndrome [positive for human immunodeficiency virus antibody (HIV-Ab)], syphilis (positive for syphilis antibody), active hepatitis B [for non-HCC patients, hepatitis B virus (HBV)-DNA >500 IU/mL; for HCC patients, HBV-DNA >10^4 copies/mL or 2000 IU/mL; hepatitis B patients need to take oral anti-HBV drugs regularly during the administration of BB102 tablets], hepatitis C virus (HCV) infection (positive for HCV antibody, and positive for quantitative detection of HCV ribonucleic acid amplification). (21) Severe active infection, including but not limited to bacteremia, severe pneumonia, etc., occurred within 2 weeks before the first dose; active infection that received therapeutic intravenous antibiotics within 2 weeks before the first dose. (22) Patient with active autoimmune disease, such as rheumatism, rheumatoid, etc. (23) The investigator considers that the patient is not suitable for participating in this study (e.g., study treatment is not in the best interest of patient, patients with mental disorder, patients with poor compliance, etc.).
Investigational Drug	**Generic name:** BB102 tablets **Dosage form:** Tablet **Active ingredient:** BB102 **Strength:** 10 mg, 50 mg **Storage condition:** store in a sealed condition at room temperature **Shelf life:** 24 months tentatively **Drug source:** provided by the sponsor **Dose levels:** possibly 50 mg QD, 100 mg QD, 160 mg QD, 240 mg QD, 320 mg QD and 420 mg QD (for the dose escalation groups, the escalation doses may be adjusted according to the previously obtained clinical trial data of BB102 tablets, e.g., adding dose groups of 520 mg QD and 600 mg QD) **Administration route:** Oral **Administration method:** ➢ For dose groups 1, 2, 3, 4, 5 and 6 in the dose escalation trial, subjects will be fasted overnight for at least 10 hours before dosing on D1 and C1D21 and take BB102 tablets with about 240 mL of water; no drinking is allowed from 1 h pre-dose to 1 h post-dose; and no food is allowed within 2 h post-dose. Subjects will be on a normal diet.

- For dose groups 1, 2, 3, 4, 5 and 6 in the dose escalation trial, subjects will be fasted at least 2 hours before dosing on the other dosing days, and take BB102 tablets with water; no food is allowed within 1 h post-dose. Subjects will be on a normal diet.
- For dose groups A in the dose escalation trial, subjects will be fasted overnight for at least 10 hours before dosing on D1 and C1D21, start eating a low-fat meal at 30 min before dosing on D1 and C1D21 (breakfast), finish the meal within 30 min and take BB102 tablets with about 240 mL of water at 30 min from the start of meal (if the meal takes more than 30 minutes, BB102 tablets should be administered immediately after the meal); no drinking is allowed from 1 h pre-dose to 1 h post-dose; no food is allowed within 4 h post-dose. Except for the low-fat meal (breakfast) on the specified days, subjects will be on a normal diet.

  Composition of the low-fat meal:

Total calories (kcal)	400-500
Fat (g)	11-14
Calories from fat (%)	25
An example of a low-fat breakfast*	● Eight ounces milk (1 percent fat) ● One boiled egg ● One packet flavored instant oatmeal made with water

  *Note: 25% of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained. A registered dietician at the study site should determine the appropriate meal to be consumed, based on the fat and calorie requirements assigned to the patient for that treatment day. The start/stop time of meal consumption, and estimated % of test meal consumed (based on fat and caloric content), must be listed in the meal record electronic case report form (eCRF) for patients allocated in exploratory food effect group.
- For dose group A in the dose escalation trial, subjects will take BB102 tablets with water within 30 minutes following the meal on the other dosing days; no food is allowed within 1 h post-dose. Subjects will be on a normal diet.
- In the expansion trial, subjects will be fasted for at least 2 hours before dosing and take BB102 tablets with water; no food is allowed within 1 h post-dose. Subjects will be on a normal diet. Note: The administration method of the expansion trial may be adjusted according to the previously obtained food effect evaluation results of BB102 tablets.

Dosing frequency and cycles: once daily in 21-day cycles (the dosing frequency and cycle setting may be adjusted according to the previously obtained clinical trial data of BB102 tablets).

In the dose escalation trial, dose interruption, resumption and permanent discontinuation during the DLT observation period:

- No dose adjustment is allowed in the DLT observation period, but the doses may be interrupted, resumed and permanently discontinued.
- If several toxicities occur at the same time, dose interruption, resumption and permanent discontinuation should be carried out according to the most serious toxicity.

(1) During the DLT observation period, if the subject develops DLT, the doses should be interrupted, and supportive treatment should be given as needed. The doses can be continued when the dosage has been administered before dose interruption is more than 75% of the scheduled dose, and the subject recovers to grade ≤1 or baseline (or, recovers to grade ≤2 and the investigator believes that there is no safety risk).

(2) If the subject develops DLT again, the doses should be permanently discontinued, and unscheduled safety follow-up should be arranged until the toxicity is resolved or stabilized.

(3) If the subject has other non-DLT toxicities, dose interruption needs to be determined according to the investigator's medical assessment, and supportive treatment will be provided as needed.

Dose interruption, resumption, adjustment and permanent discontinuation in post-DLT observation period of dose escalation trial and during the dosing period in the expansion trial:

- If the AE is attributable to BB102 tablets according to the investigator's judgment, dose interruption, resumption, adjustment and permanent discontinuation will be performed according to the following table. If there is any other situation not described in the table below, the sponsor and investigator will decide whether to interrupt, resume, adjust, or permanently discontinue the dose after a comprehensive assessment of the benefits and risks.
- Subjects can be given appropriate supportive treatment to relieve symptoms and signs of toxic reactions.
- Dose interruption, resumption, adjustment and permanent discontinuation should be perfomed according to the most serious toxic reaction when several toxic reactions occur simultaneously.
- Once the dose is decreased, up-titration to the previous level is not allowed.
- A maximum of 2 dose interruptions is allowed for each subject, and each interruption shall not exceed 14 days. If a 3rd dose interruption is required, or a dose interruption is required for >14 days, permanent discontinuation is required for the subject unless it is considered that the continuation of BB102 tablets treatment at an appropriate dose is in the best interest of the patient after the sponsor and the investigator comprehensively evaluate the benefits and risks.
- Rules for dose interruption, resumption, adjustment and permanent discontinuation are shown in the table below.

Hematologic toxicity [a]	**Rules for dose interruption, resumption, adjustment and permanent discontinuation [b]**
Neutrophil count decreased	
Grade 1-2	Continue the study treatment at the original dose level.
Grade 3	Administration interruption until the toxicity is resolved to grade ≤2. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days.

		➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within 7-14 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
	Grade 4	Administration interruption until the toxicity is resolved to grade ≤2. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within ≤7 days. ➢ Discontinue permanently if the toxicity is resolved within >7 days.
	Febrile neutropenia	
	Grade 3	Administration interruption until the toxicity is resolved. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within ≤14 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
	Grade 4	Discontinue permanently.
	Platelet count decreased	
	Grade 1-2	Continue the study treatment at the original dose level.
	Grade 3	Administration interruption until the toxicity is resolved to grade ≤1. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within 7-14 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
	Grade 4	Administration interruption until the toxicity is resolved to grade ≤1. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within ≤7 days. ➢ Discontinue permanently if the toxicity is resolved within >7 days.
	Anemia	
	Grade 1-2	Continue the study treatment at the original dose level.
	Grade 3	Administration interruption until the toxicity is resolved to grade ≤2.

		➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within 7-14 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
	Grade 4	Administration interruption until the toxicity is resolved to grade ≤2. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within ≤7 days. ➢ Discontinue permanently if the toxicity is resolved within >7 days.
	Other hematologic toxicity	
	Grade 1-2	Continue the study treatment at the original dose level.
	Grade 3	Administration interruption until the toxicity is resolved to grade ≤2. Resume the study treatment at the original dose level after the toxicity is resolved to grade ≤2.
	Abnormal grade 4 laboratory test results that are not life-threatening judged by the investigator	Administration interruption until the toxicity is resolved to grade ≤2. Resume the study treatment at the original dose level after the toxicity is resolved to grade ≤2 (the sponsor and investigator will decide whether to continue the administration after a comprehensive assessment of the benefits and risks).
	Grade 4	Administration interruption until the toxicity is resolved to grade ≤2. Continue the study treatment at the dose reduced by one level [c] after the toxicity is resolved to grade ≤2.
	Nonhematologic toxicity [a]	**Rules for dose interruption, resumptionadjustment and permanent discontinuation [b]**
	Creatinine increased	
	Grade 1	Continue the study treatment at the original dose level.
	Grade 2	Administration interruption until the toxicity is resolved to baseline. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within >7 days.

	Grade 3-4	Discontinue permanently.
	Blood bilirubin increased	
	Grade 1	Continue the study treatment at the original dose level.
	Grade 2	Administration interruption until the toxicity is resolved to baseline. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within >7 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
	Grade 3	Administration interruption until the toxicity is resolved to baseline. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within ≤7 days. ➢ Discontinue permanently if the toxicity is resolved within >7 days. Note: Continue the study treatment at the dose reduced by one level [c] at the discretion of the investigator if the grade 3 increase in blood bilirubin is only due to the increase in indirect bilirubin (unconjugated bilirubin), and hemolytic factors (e.g., peripheral blood smear examination and haptoglobin assay) have been excluded according to the guidelines of each study center.
	Grade 4	Discontinue permanently. Note: Continue the study treatment at the dose reduced by one level [c] at the discretion of the investigator if the grade 4 increase in blood bilirubin is only due to the increase in indirect bilirubin (unconjugated bilirubin), and hemolytic factors (e.g., peripheral blood smear examination and haptoglobin assay) have been excluded according to the guidelines of each study center.
	AST or ALT increased	
	Grade 1-2	Continue the study treatment at the original dose level.
	Grade 3	Administration interruption until the toxicity is resolved to grade ≤2 (liver cancer or liver metastases) or grade ≤1. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days.

	➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within 7-14 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
Grade 4	Discontinue permanently.
Other nonhematologic toxicity	
Grade 1-2	Continue the study treatment at the original dose level.
Grade 3 toxicities with no safety risk at the discretion of the investigator, such as grade 3 nausea, vomiting, diarrhea, asthenia, constipation, loss of appetite, mucositis, GGT increased and ALP increased.	Administration interruption until the toxicity is resolved to grade ≤2. Resume the study treatment at the original dose level after the toxicity is resolved to grade ≤2.
Grade 3 Note: Toxicities with no safety risk at the discretion of the investigator are excepted, such as grade 3 nausea, vomiting, diarrhea, asthenia, constipation, loss of appetite, mucositis, GGT increased and ALP increased.	Administration interruption until the toxicity is resolved to grade ≤2 or grade ≤1. Resume the study treatment at the dose reduced by one level [c] after the toxicity is resolved to grade 2 (only when the investigator believes resuming the study treatment poses no safety risk to the subject) or grade ≤1.
Abnormal grade 4 laboratory test results that are not life-threatening judged by the investigator (such as grade 4 GGT increased and ALP increased).	Administration interruption until the toxicity is resolved to grade ≤2 or grade ≤1. Resume the study treatment at the dose reduced by one level [c] after the toxicity is resolved to grade 2 (only when the investigator believes resuming the study treatment poses no safety risk to the subject) or grade ≤1 (the sponsor and investigator will decide whether to continue the administration after a comprehensive assessment of the benefits and risks).
Grade 4 Toxicities with no safety risk at the discretion of the investigator are excepted, such as grade 4 GGT increased and ALP increased.	Discontinue permanently.

Abbreviations: ALP = alkaline phosphatase; DLT = dose-limiting toxicity; GGT = γ-glutamyltransferase.

	Note: a. Applicable to all hematologic toxicities (if a hematologic toxicity is related to other non-hematologic clinical events, refer to the rules for dose interruption, resumption and adjustment of non-hematologic toxicities). B: The rules may be modified based on the previously obtained clinical trial data of BB102 tablets. C: Available dose levels of BB102 tablets include 50 mg QD, 100 mg QD, 160 mg QD, 240 mg QD, 320 mg QD and 420 mg QD. If dose reduction is required at the starting dose level, the subject should discontinue the treatment permanently. **Criteria for study treatment discontinuation (whichever occurs first):** ● Subject has disease progression, unless the investigator believes the subject can still benefit from the study treatment clinically. ● The investigator determines that the subject cannot clinically benefit from the study treatment and continued study treatment may pose an unacceptable risk to the subject. ● There is major protocol deviation. After enrollment, the subject is found to be non-compliant with enrollment criteria in the study protocol or does not follow requirements in the study protocol, and the investigator believes that continued study treatment may pose an unacceptable risk to the subject. ● The subject has a poor compliance, uses prohibited concomitant medications without permission or fails to attend visits on schedule, which affects the evaluation of efficacy and/or safety, and the subject is considered inappropriate to continue the study at the discretion of the investigator. ● The subject experiences a particular comorbidity or complication, which, in the discretion of the investigator, makes it inappropriate to continue the study treatment. ● The subject experiences an intolerable toxicity. ● Subject pregnancy. ● Subject is lost to follow-up for more than 8 weeks. ● Subject death. ● Any other conditions in which the investigator believes that the study should be terminated. ● The subject refuses to continue the study treatment. ● The study site is closed prematurely, the study is prematurely terminated or the study ends. **Notes: After study treatment discontinuation, subjects will enter into the follow-up period (unless follow-up is not applicable).**
Comparators	None.
Concomitant Medications	Concomitant medications include any medications other than the study drug (including prescription drugs, over-the-counter drugs, natural extracts, nutritional supplements and traditional Chinese medicines) used by subjects from the start of first dose to 28 days after the last dose of study treatment. Note: Medications used by subjects at screening will be recorded as medication history. (1) **For the dose escalation trial and expansion trial, the following drugs/therapies will be allowed during the treatment period:**

	➢ Bisphosphonates for treating bone metastasis. Note: Bisphosphonate therapy should be administered according to the local medical practice. ➢ Palliative radiotherapy for relieving pain caused by bone lesion, on the condition that this lesion has existed at the time of enrollment and the investigator clarifies the requirement of palliative radiotherapy does not represent disease progression. Note: As there is currently a lack of data on the interaction between BB102 tablets and radiotherapy, BB102 tablets therapy should be interrupted at 1 day before palliative radiotherapy and throughout the radiotherapy period and be resumed after the acute radiotoxicity recovers to baseline level. Note: Palliative radiotherapy is not allowed during the DLT observation period; if the study drug dose received by a subject during the DLT observation period is less than 75% of the scheduled dose due to use of palli'tive therapy and no DLT occurs, the corresponding dose group needs one more subject for replacement. ➢ Therapeutic drugs used for AE (dose escalation trial), such as choleretics, but only the non-prohibited medications can be used. ➢ Preventive drugs and therapeutic drugs used for AE (expansion trial), such as choleretics, but only the non-prohibited medications can be used. (2) **In the dose escalation trial and expansion trial, the following drugs/therapies will be prohibited during the treatment period:** ➢ Anti-tumor therapies rather than the study drug (including but not limited to chemotherapy, radiotherapy, immunotherapy, anti-tumor biotherapy, etc.), including state-approved Chinese traditional patent drugs with an anti-tumor effect. ➢ Adjuvants (e.g., preventive leukocyte increasing drugs, antiemetics, etc.) related to anti-tumor therapy (for dose escalation trial only). ➢ Strong CYP3A4 inhibitors, strong CYP3A4 inducers, strong CYP3A5 inhibitors, strong CYP3A5 inducers, sensitive CYP3A4 substrates with a narrow therapeutic index, and sensitive CYP2B6 substrates with a narrow therapeutic index (Appendix IV). (3) **In the dose escalation trial and expansion trial, the following drugs/therapies can be used with cautious during the treatment period:** ➢ Moderate or weak CYP3A4/5 inhibitors and inducers. ➢ Breast cancer resistance protein (BCRP) substrates, P-glycoprotein (P-gp) substrates, OAT1 substrates, OAT3 substrates, OATP1B3 substrates, MATE1 substrates, and MATE2-K substrates with a narrow therapeutic index (Appendix V). ➢ Strong BCRP inhibitors and strong P-gp inhibitors (Appendix V). ➢ Drugs which are known to or may prolong QT interval or induce tip torsion ventricular tachycardia (Appendix VI). ➢ Given that FGFR4 inhibitor can increase CYP7A1 expression, try not to use drugs that can increase CYP7A1 expression or enzyme activity (e.g., atorvastatin, troglitazone); try not to use cholesterol (CYP7A1 substrates)-containing drugs. (4) **Prevention and management of expected adverse drug reactions (ADRs):** The actual ADR treatment measures will be taken by the investigator according to the actual situation of the subjects in combination with clinical practice and relevant

	guidelines. The following suggestions are only for reference. For common ADRs in the dose escalation trial, prophylaxis can be given in advance during the expansion trial. ➢ Diarrhea: Among the adverse effects of FGFR inhibitor, diarrhea's incidence is 15%-60%, which may be related to preventing the binding of FGF19 and FGFR4. The homeostasis of bile acids will be regulated after FGF19 binding with FGFR4, while bile acids have effects on colonic mucosal permeability. It is recommended to continue the study treatment at the original dose level, and loperamide, probiotics, and smecta (montmorillonite powder) should be given to treat ADR at the same time when drug-related grade 1-2 diarrhea occurs during the clinical trial. If grade 3 diarrhea occurs, it is recommended to interrupt the study treatment, and loperamide, probiotics, and smecta (montmorillonite powder) should be given to treat ADR at the same time (codeine and prophylactic antibiotics may be used if necessary), the addition of somatostatin may be considered in severe conditions. If grade 4 diarrhea occurs, it is recommended to discontinue the study treatment permanently, at the same time, the above symptomatic treatment should be given. ➢ Asthenia: FGFR4 has the function of regulating the differentiation of muscle cells and tissue repair. If asthenia occurs in the trial, it is considered to be related to the inhibition of the physiological function of FGFR4. It is recommended to continue the study treatment at the original dose level, and have more rest at the same time when drug-related grade 1-2 asthenia occurs during the clinical trial. If grade 3 asthenia occurs, it is recommended to discontinue the study treatment permanently and have more rest at the same time. ➢ Nausea/vomiting: They are not caused by FGFR4 physiological mechanism and can be considered as the gastrointestinal irritation of the investigational drug. It is recommended to continue the study treatment at the original dose level, and metoclopramide and so on should be given to treat ADR at the same time when drug-related grade 1-2 nausea/vomiting occurs during the clinical trial. If grade 3 nausea/vomiting occurs, it is recommended to interrupt the study treatment, and metoclopramide and so on should be given to treat ADR at the same time. If grade 4 nausea/vomiting occurs, it is recommended to discontinue the study treatment permanently, and the above symptomatic treatment should be given at the same time. ➢ Fever: Generally, it may be the non-inflammatory fever caused by the death or rupture of cancer cells. It is recommended to continue the study treatment at the original dose level, at the same time, strengthen body temperature monitoring, and perform physical cooling, ice compress and drink warm water if necessary when drug-related grade 1 fever occurs during the clinical trial. If grade 2 fever occurs, it is recommended to continue the study treatment at the original dose level, and cooling medications (e.g., dexamethasone, loratadine, etc.) should be given to treat ADR at the same time. If grade 3 fever occurs, it is recommended to interrupt the study treatment and the above symptomatic treatment should be given at the same time. If grade 4 fever occurs, it is recommended to discontinue the study treatment permanently, and the above symptomatic treatment should be given at the same time. ➢ Hepatotoxicity: It is considered to be caused by damage to liver cells or functional overload. It is recommended to continue the study treatment at the original dose level, and hepatoprotective medications [e.g., Chinese traditional patent drug, polyene

	phosphatidylcholine, reduced glutathione, magnesium isoglycyrrhizinate, simetai (adenosylmethionine butanedisulfonate enteric-coated tablet)] should be given for symptomatic treatment at the same time when drug-related grade 1-2 hepatotoxicity occurs during the clinical trial. If grade 3 hepatotoxicity occurs, it is recommended to interrupt the study treatment and the above symptomatic treatment should be given at the same time. If grade 4 hepatotoxicity occurs, it is recommended to discontinue the study treatment permanently, and the above symptomatic treatment should be given at the same time. Any prescription drugs, over-the-counter drugs, natural extracts, nutritional supplements, traditional Chinese medicines, herbal medicines and vitamins should be reviewed and approved by the investigator. All information on concomitant medications should be recorded in the subjects' medical records and reported on the electronic eCRF. For the specifications on concomitant medications, see Section 6.2 of the main text.
Study Procedures	Throughout the Phase I study, all subjects need to receive study treatment, safety assessment, PK blood sampling and efficacy evaluation according to the visit schedule. See Study Flow Chart for details. The tumor tissue specimens will be collected and preserved. For the specific collection, handling and storage methods, refer to the related standard operation procedure (SOP) of each study site. Computed tomography (CT) and other electronic documents should be saved on disc. The cut-off time for data collection of this Phase I study is 8 weeks after the last subject starts the study treatment, unless the entire study is prematurely terminated. At the time of study data collection cutoff, if a subject can tolerate the study drug and remains complete response (CR)/partial response (PR)/stable disease (SD) and is willing to continue the study drug treatment, the investigator believes that the subject will still clinically benefit from the continued treatment and the investigator confirms that there is no problem in drug supply after discussion with the sponsor, the subject can continue the study drug treatment (i.e., compassionate use), until he/she meets the criteria for study treatment discontinuation or there is a drug supply problem (whichever occurs first). During the compassionate use, drug-related AEs and serious adverse events (SAEs) will be recorded according to the relevant national regulations, and the SAEs will be reported to the sponsor/CRO safety department. Routine safety monitoring should be continued as needed. The investigator will select and schedule test items at his/her own discretion and should preserve relevant documents in the source files. The sponsor will not routinely collect relative results of these tests. Data collected during compassionate use will not be included in statistical analysis of the study.
Study Endpoints	**Dose escalation trial** **Primary endpoints:** ● **Safety and tolerability of BB102 tablets (fasted or fed):** Incidences of AEs and SAEs; abnormalities or changes in laboratory tests, vital signs, ECG, physical examination and ECOG score. ● **DLT of BB102 tablets (fasted or fed):** Classification, severity and frequency of DLT. **Secondary endpoints:**

	● **PK parameters of BB102 tablets (fasted):** Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), lag time (t_{lag}), elimination rate constant (Kel), $T_{1/2}$, area under the concentration-time curve from 0 to the time point of last quantifiable concentration (AUC_{0-t}), area under the concentration-time curve from time 0 to infinity (AUC_{0-inf}), apparent clearance (CL_z/F), apparent volume of distribution (V_z/F), mean residence time (MRT), steady-state minimum plasma concentration ($C_{ss,\ min}$), steady-state maximum plasma concentration ($C_{ss,\ max}$), average steady-state plasma concentration ($C_{ss,\ av}$), area under the concentration-time curve during a dosing interval at steady state (AUC_{ss}), steady-state degree of fluctuation (DF) and accumulation ratio (Rac) of BB102 (and its main metabolites, if applicable). ● **PK parameters of BB102 tablets (fed):** C_{max}, T_{max}, t_{lag}, Kel, $T_{1/2}$, AUC_{0-t}, AUC_{0-inf}, CL_z/F, V_z/F, MRT, $C_{ss,\ min}$, $C_{ss,\ max}$, $C_{ss,\ av}$, AUC_{ss}, DF and Rac of BB102 (and its main metabolites, if applicable); **whether food has an effect on the exposure parameters (AUC_{0-inf}, AUC_{0-t} and C_{max}) and the extent of effect.** ● **Efficacy of BB102 tablets (fasted or fed):** objective response rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS). ● **Relationship between biomarker and efficacy.** Biomarkers include but are not limited to protein expression level, amplification, mRNA level and activating mutation profiles of FGF19 or FGFR4 in tumor tissues; bile acid precursors (e.g., 7-α-hydroxy-4-cholestene-3-one), total bile acids, total cholesterol, triglycerides (TG) and serum FGF19 protein level in blood. ● **Correlation between plasma concentration of study drug and QTcF (C-QTcF analysis).** ● **Metabolites of BB102.** **Expansion trial** **Primary endpoints:** ● **Efficacy of BB102 tablets (fasted):** ORR, DCR, DOR, PFS and OS. **Secondary endpoints:** ● **PK parameters of BB102 tablets (fasted):** $T_{1/2}$, AUC_{0-t}, AUC_{0-inf}, $C_{ss,\ min}$, $C_{ss,\ max}$, $C_{ss,\ av}$, AUC_{ss} and DF of BB102 (and its main metabolites, if applicable). ● **Safety of BB102 tablets (fasted):** Incidences of all AEs and SAEs; abnormalities or changes in laboratory tests, vital signs, ECG, physical examination and ECOG score. ● **Relationship between biomarker and efficacy.** Biomarkers include but are not limited to protein expression level, amplification, mRNA level and activating mutation profiles of FGF19 or FGFR4 in tumor tissues; bile acid precursors (e.g., 7-α-hydroxy-4-cholestene-3-one), total bile acids, total cholesterol, TG and serum FGF19 protein level in blood.
Statistical Analysis	**Statistical analysis sets:** ① **Screening set:** All subjects who signed the ICF. The screening set is used to analyze the number of subjects screened, number of subjects enrolled and number of screening failures.

	② **Safety set (SS):** All subjects who are enrolled and have taken the study drug. SS is used for the description of demographic data, description of baseline characteristics, safety analysis and efficacy analysis. ③ **DLT analysis set (DS):** All subjects who are enrolled and have taken the study drug, but excluding subjects who receive study drug at a dose less than 75% of the scheduled dose for reasons other than toxicities attributable to study drug during the DLT observation period. DS is used for the analysis and summary of DLT. ④ **PK analysis set (PKS):** All subjects who are enrolled, have taken the study drug, have at least one PK data for statistical analysis and have no any protocol deviation (e.g., missed dosing of BB102 tablets) that significantly affects the PK parameters [e.g., area under the concentration-time curve (AUC), C_{max}, etc.] during the treatment cycle or dosing period containing blood sampling time point. Whether a subject is included into PKS will be determined case by case on the data review meeting. PKS is used for the analysis of PK parameters. ⑤ **Biomarker analysis set (BS):** All subjects who have at least one biological sample for biomarker analysis in the SS. BS is used for the analysis of relationship between biomarker and efficacy. **General principles for statistics:** SAS® 9.4 or updated version (SAS Institute, Inc., Cary, North Carolina) will be used for statistical analysis. Quantitative data will be described with the number of subjects of non-missing, mean, standard deviation, median, lower quartile, upper quartile, maximum and minimum. Qualitative data will be statistically described using the number, frequency and percentage of non-missing subjects. If necessary, the two-sided 95% confidence interval (95% CI) for the percentage will be calculated. Baseline of safety endpoints is the most recent data prior to the first dose (data at screening are acceptable), including laboratory tests, vital signs, ECG, physical examination and ECOG score. Prior medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (current or updated version). Previous medications and concurrent/concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary (current or updated version). Since this study is a Phase I trial, only descriptive statistics will be provided, and no hypothesis test will be performed. Safety, PK and efficacy analyses will be performed for the dose escalation trial and expansion trial separately. In the dose escalation trial, it will be summarized overall and by dose group. In addition, it should also be summarized by gender. The statistical analysis methods will be described in detail in the Statistical Analysis Plan. **Statistical method:** **(1) Subject disposition analysis** Information of screening failures will be tabulated and summarized. Subjects included in each analysis set will be summarized.

	For the enrolled subjects, the number of subjects with treatment discontinuation, number of subjects who terminate the study and percentage of reasons will be summarized. **(2) Analysis of demographics and baseline characteristics** The demographic data and baseline characteristics will be descriptively summarized, including gender, age, race, ethnicity, body height, body weight, body mass index (BMI), prior medical history, medication history, history of all neoplastic diseases, history of all anti-tumor therapies, family history, surgical history, allergic history, smoking history and history of drug abuse/dependence. **(3) Analysis of compliance and concomitant medication** Descriptive statistical analysis will be performed for the planned dose and actual dose by the following formula: Compliance (%) = actual dose/planned dose × 100%. The frequency and percentage of concomitant medications occurring during the dosing period will be summarized. The concomitant medication of subjects will be tabulated in detail. **(4) Safety analysis** Drug safety will be evaluated by analyzing the incidences of AEs, ADRs, grade ≥3 AEs and SAEs, as well as abnormalities or changes in laboratory tests, vital signs, ECG, physical examination and ECOG score. AEs, ADRs, grade ≥3 AEs and SAEs will be coded according to MedDRA (current or updated version), and their incidences will be summarized according to system organ class, preferred term and the severity (CTCAE, Grades 1-5), respectively. The number of subjects with different AEs will be summarized, regardless of the number of times each subject actually reported the event. Laboratory test parameters of subjects will be summarized before and after dosing. For vital signs, ECG and physical examination, subjects with abnormal changes during the study will be described. For ECOG score, patients' score and change in the score will be described. If applicable, the data listings before and after dosing will be provided, and the mean ± standard deviation will be calculated. Patients with parameters being normal pre-dose but abnormal post-dose (regardless of the clinically significance) will be listed. **(5) DLT analysis** Number of subjects with DLT as well as the category, severity and incidence of DLT will be summarized. **(6) PK parameters analysis** Individual concentration-time curve of BB102 (and its main metabolites, if applicable) of each subject. Moreover, mean (Mean ±SD) concentration-time curve of BB102 (and its main metabolites, if applicable) will be plotted by dose group. The PK parameters of BB102 (and its main metabolites, if applicable) will be analyzed using the non-compartment analysis method of the Phoenix WinNonlin 8.3.1 or updated version (Pharsight Corp., Mountain View, CA, USA) software. For the plasma PK parameters of BB102 (and its main metabolites, if applicable), descriptive statistical analysis will be performed by dose group, with the descriptive statistics including the number of samples, mean, standard deviation, coefficient of

variation, minimum and maximum. If considered necessary by the investigator and the sponsor, the linear relationship between the AUC and C_{max} of BB102 (and its main metabolites, if applicable) and dose can be analyzed.

(7) Analysis of food effect

Data analysis will be performed by the average bioequivalence method with fasted condition as the reference, and the exposure parameters (AUC_{0-inf}, AUC_{0-t} and C_{max}) will be log transformed using natural logarithm to calculate the geometric mean ratio of fed group to fasted group and its 90%CI. If the 90%CI of the geometric mean ratios (fed group/fasted group) of AUC_{0-inf} (or AUC_{0-t}) and C_{max} all fall within the range of 80%-125%, it can be preliminarily concluded that food has no significant effect on the bioavailability of the drug.

(8) Efficacy analyses

- **ORR:** The proportion of patients with a best overall response of CR and PR as assessed per RECIST v1.1 in all patients.
- **DCR:** The proportion of patients with a best overall response of CR, PR and SD (duration of SD ≥12 weeks) as assessed per RECIST v1.1 in all patients.
- **DOR:** The duration from the firstly documented CR or PR to the date of confirmed objective tumor progression (based on RECIST v1.1) or death for the subjects with a best overall response of CR or PR. For the patients who have no objective tumor progression or death at the end of trial, the date of the last objective tumor assessment will be taken as the censored date of DOR.
- **PFS:** The duration from the first dose of study drug to objective tumor progression (based on RECIST v1.1) or death. For the patients who have no objective tumor progression or death at the end of trial, the date of the last objective tumor assessment will be taken as the censored date of PFS.
- **OS:** The duration from the first dose of study drug to death. For patients who are alive at the end of trial, their last date known to be alive will be used as the censored date of OS.

Point estimates of ORR and DCR and their two-sided 95%CI will be calculated. The two-sided 95% CI of ORR and DCR are calculated based on the Clopper-Pearson method. Meanwhile, the number and percentage of subjects with CR, PR, SD and disease progression will be presented.

For DOR (for subjects experiencing CR and/or PR only), PFS and OS, Kaplan-Meier method will be adopted to calculate the median, lower quartile, upper quartile and two-sided 95% CI, and survival curves will be drawn.

For ORR, the estimated objective is shown in the table below.

Estimated objective:	
Population:	FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors
Treatment:	See Section 6 of the main body for details
Endpoint:	ORR
Intercurrent events and handling strategies:	● Discontinuation of study treatment or initiation of new anticancer therapy prior to CR or PR will be handled according to the while-on-treatment strategy.

Summary at the population level:	ORR and corresponding two-sided 95%CI (estimated by Clopper-Pearson method) will be calculated

For DOR, the estimated objective is shown in the table below.

Estimated objective:	
Population:	FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors
Treatment:	See Section 6 of the main body for details
Endpoint:	DOR
Intercurrent events and handling strategies:	● Discontinuation of study treatment or initiation of new anticancer therapy prior to objective tumor progression or death will be handled according to the hypothetical strategy.
Summary at the population level:	The variables of event time will be descriptively summarized, and KM curves will be plotted

For other efficacy measures (DCR, PFS and OS), an estimation method like that of ORR or DOR will be used.

(9) Biomarker analysis

The relationship between biomarker and efficacy will be analyzed, and the correlation will be inferred preliminarily.

(10) C-QTcF analysis

If considered necessary by the investigator and the sponsor, C-QTcF modeling analysis will be performed based on the data features and appropriate models to explore C-QTcF and investigate the possibility of QTC interval prolongation induced by BB102.

(11) Analysis of metabolites

Metabolites of BB102 will be identified. The metabolites and subjects will be tabulated.

(12) Subgroup analysis

Subgroup analysis will be performed by gender.

(13) Interim analysis

Not applicable.

Study Flow Chart

Period	Screening period/ baseline	Single-dosing period*					Multiple-dosing period						End of treatment visit (EOT)	Follow-up period	
Time (days)	D-28 to D-1	D1	D2	D3	D4	D5	The 1st cycle				The 2nd cycle	From the 2nd cycle	Within 7 days after the last dose	Safety visit	Subsequent follow-up
Per multiple-dosing time (days)							C1D1	C1D8 (±1 day)	C1D15 (±1 day)	C1D21 (±1 day)	C2D1 (±1 day)	CnD21 (±3 days)		28 days (±7 days) after the last dose	Follow-up once every 8 weeks (±7 days) after the last dose
Informed consent [1]	X														
Reviewing inclusion/exclusion criteria	X														
Demographics [2]	X														
Medical history and medication history [3]	X														
Hematology [4]	X					X		X[a]	X[a]	X[a]		X[b]	X[d]	X[d]	
Urinalysis [5]	X					X		X[a]	X[a]	X[a]		X[c]	X[d]	X[d]	
Stool routine [6]	X					X (±1 day)		X[a]	X[a]	X[a]		X[c]	X[d]	X[d]	

Period	**Screening period/ baseline**	**Single-dosing period***					**Multiple-dosing period**						**End of treatment visit (EOT)**	**Follow-up period**	
Time (days)	**D-28 to D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**The 1st cycle**				**The 2nd cycle**	**From the 2nd cycle**	**Within 7 days after the last dose**	**Safety visit**	**Subsequent follow-up**
Per multiple-dosing time (days)							**C1D1**	**C1D8 (±1 day)**	**C1D15 (±1 day)**	**C1D21 (±1 day)**	**C2D1 (±1 day)**	**CnD21 (±3 days)**		**28 days (±7 days) after the last dose**	**Follow-up once every 8 weeks (±7 days) after the last dose**
Blood biochemistry [7]	X					X		X[a]	X[a]	X[a]		X[b]	X[d]	X[d]	
Coagulation [8]	X					X		X[a]	X[a]	X[a]		X[b]	X[d]	X[d]	
Vital signs [9]	X	X		X		X	X	X	X	X		X[b]	X		
12-lead ECG [10]	X	X		X		X	X	X	X	X		X[b]	X		
Physical examination [11]	X					X		X	X	X		X[b]	X		
ECOG assessment	X					X				X		X[c]	X		
Pregnancy-related test [12]	X									X		X[c]	X		
Echocardiography [13]	X									X		X	X		
Serum etiological test [14]	X														

Period	**Screening period/ baseline**	**Single-dosing period***					**Multiple-dosing period**						**End of treatment visit (EOT)**	**Follow-up period**	
Time (days)	**D-28 to D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**The 1st cycle**				**The 2nd cycle**	**From the 2nd cycle**	**Within 7 days after the last dose**	**Safety visit**	**Subsequent follow-up**
Per multiple-dosing time (days)							**C1D1**	**C1D8 (±1 day)**	**C1D15 (±1 day)**	**C1D21 (±1 day)**	**C2D1 (±1 day)**	**CnD21 (±3 days)**		**28 days (±7 days) after the last dose**	**Follow-up once every 8 weeks (±7 days) after the last dose**
Study drug administration		X					Administration of BB102 tablets is tentatively scheduled as: oral, once daily in 21-day cycles								
Dispensing/collecting diary cards and drugs							X			X		X	X		
Tumor assessment [15]	X									X		X	X		X
Detection of biomarkers [16]	X								X			X	X		X
PK blood sampling [17]		X	X	X	X	X	X	X	X	X	X				
Blood sampling for identification of metabolites [18]		X	X	X	X	X									

Period	**Screening period/ baseline**	**Single-dosing period***					**Multiple-dosing period**						**End of treatment visit (EOT)**	**Follow-up period**	
Time (days)	**D-28 to D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**The 1st cycle**				**The 2nd cycle**	**From the 2nd cycle**	**Within 7 days after the last dose**	**Safety visit**	**Subsequent follow-up**
Per multiple-dosing time (days)							**C1D1**	**C1D8 (±1 day)**	**C1D15 (±1 day)**	**C1D21 (±1 day)**	**C2D1 (±1 day)**	**CnD21 (±3 days)**		**28 days (±7 days) after the last dose**	**Follow-up once every 8 weeks (±7 days) after the last dose**
Anti-tumor treatment and survival information after the end of study treatment [19]														X	X
Adverse event [20]	X	X----------X													
DLT evaluation *		X----------X													
Concomitant medication [21]		X----------X													
Inpatient nutrition assessment (NRS-2002)	Assessed as needed														

Note:

1. **Informed consent:** Subjects should sign an informed consent form (ICF) before starting any study-related procedure.

2. **Demographics:** Age, gender, race and ethnicity.
3. **Medical history and medication history:** History of all neoplastic diseases, history of all anti-tumor therapies, history of other diseases (within 6 months before enrollment and at present), history of other medications (within 6 weeks before enrollment and at present), family history, surgical history, allergic history, smoking history, history of drug abuse/dependence and history of menstruation and childbearing.
4. **Hematology:** Red blood cell (RBC) count, white blood cell (WBC) count, absolute monocyte count (ABMONO), platelet (PLT) count, absolute neutrophil count (ANC), absolute lymphocyte count (ABLYMP), basophil count, absolute eosinophil count (ABEOS), absolute reticulocyte count (ABRETIC), neutrophil percentage, hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume and mean corpuscular hemoglobin concentration (MCHC). Hematology test at screening visit should be completed within 7 days prior to the first dose, and abnormal test parameters with clinical significance can be re-tested once within 7 days as needed.
5. **Urinalysis:** Potential of hydrogen (pH), specific gravity, urine RBC, urine WBC, urine glucose, urine bilirubin, urine protein, urobilinogen, urine ketone bodies and urine occult blood. Urinalysis at screening visit should be completed within 7 days prior to the first dose, and abnormal test parameters with clinical significance can be re-tested once within 7 days as needed.
6. **Stool routine**: Color, shape, fecal RBC, fecal WBC, fecal occult blood, fecal choline and fecal bilirubin. Stool routine test at screening visit should be completed within 7 days prior to the first dose, and abnormal test parameters with clinical significance can be re-tested once within 7 days as needed.
7. **Blood biochemistry**:
    1) **Liver function**: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyltransferase (GGT), total bilirubin (TBIL), direct bilirubin, total bile acids, albumin (ALB), total protein and globulin (GLO).
    2) **Renal function:** Urea/urea nitrogen, creatinine, creatinine clearance and uric acid.
    3) **Blood lipids:** Total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) and triglycerides (TG).
    4) **Electrolytes:** Potassium, sodium, chloride, phosphorus, magnesium and calcium.
    5) **Cardiac function:** Creatine kinase (CK) and creatine kinase isozyme (CKI).
    6) **Blood glucose:** Fasting blood glucose (GLU).

    Blood biochemistry test at screening visit should be completed within 7 days prior to the first dose, and abnormal test parameters with clinical significance can be re-tested once within 7 days as needed.
8. **Coagulation**: Prothrombin time, activated partial thromboplastin time, fibrinogen quantification and international normalized ratio. Coagulation test at screening visit should be completed within 7 days prior to the first dose, and abnormal test parameters with clinical significance can be re-tested once within 7 days as needed.
9. **Vital signs**: Body temperature, blood pressure, heart rate and respiration. For D1 and C1D1, vital signs will be measured within 1 h pre-dose and at 10 h (±1 h) post-dose on D1 and C1D1; at other visits, vital signs will be measured according to the visit time window. If there are corresponding clinical symptoms at other time, vital signs should also be measured, and the data should be recorded.

10. **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. For D1 and C1D1, ECG will be performed within 1 h pre-dose and at 10 h (±1 h) post -dose on D1 and C1D1; for C1D21, ECG will be performed within 0.5 h pre-dose and at 2 h (±15 min), 4 h (±15 min), 6 h (±20 min), 8 h (±30 min) and 24 h (±1 h, pre -dose on C2D1) post-dose on C1D21; at other visits, ECG will be performed according to the visit time window. If there are corresponding clinical symptoms at other time, ECG should also be performed, the data should be recorded, and the ECG results should be kept.
11. **Physical examination:** Assessments will be performed per organ and system. At screening, a comprehensive physical examination will be performed, including body height, body weight, body mass index (BMI), general condition, nervous system, head and neck, lymph nodes, skin, mucosa, chest, abdomen, four limbs and spine; at other visits, only a simple physical examination will be performed, which includes but is not limited to body weight, BMI, general condition, skin and any abnormal signs of concern at the investigator's discretion.
12. **Pregnancy-related tests:**
    1) For women of childbearing potential, human chorionic gonadotropin (HCG) will be tested. Blood HCG pregnancy test at screening visit should be completed within 7 days prior to the first dose.
    2) For women ≥40 to <60 years of age and at least 12 months post-menopausal, follicle stimulating hormone, estradiol and luteinizing hormone will be tested; if necessary, anti-Mullerian hormone can be tested additionally. This test will be performed at screening only.
    3) For men and women ≥60 years of age, a pregnancy-related test is not required.
13. **Echocardiography**: Left ventricular ejection fraction (LVEF). During treatment, echocardiography will be performed at the same frequency with tumor assessment, i.e., echocardiography will be performed at the end of the 1st cycle, and the time window is ±1 day after the end of t he cycle. After that, echocardiography will be performed every 2 cycles with a time window of ±7 days from the end of every 2 cycles.
14. **Serum etiology test:** Human immunodeficiency virus antibody (HIV-Ab), hepatitis B surface antigen (HbsAg), hepatitis B virus (HBV)-DNA (as needed), hepatitis C virus antibody (HCV-Ab) and hepatitis C virus (HCV)-RNA (as needed). Serum etiology test at screening visit should be completed within 14 days prior to the first dose.
15. **Tumor assessment:**
    1) Imaging tests like computed tomography/magnetic resonance imaging (CT/MRI) and other radiological examinations of chest, upper abdomen, lower abdomen, pelvic cavity and other positions will be performed. For patients with suspected or known brain metastasis, a radiological examination must be performed at screening/baseline, and contrast-enhanced MRI is preferred (for those allergic to contrast medium, CT/MRI plain scan is acceptable). If brain metastasis is confirmed at screening, the frequency of brain CT/MRI in the subsequent cycles should be kept consistent with the tumor assessment frequency specified in the study; if it is confirmed that there is no brain metastasis by brain CT/MRI at screening, brain CT/MRI will be performed for confirmation if brain metastasis is suspected by the investigator later. For patients with bone metastasis symptoms, a bone scan must be performed at screening/baseline, and those with a positive result should receive contrast-enhanced MRI scan at the corresponding position for further confirmation. If bone metastasis is confirmed at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if progression of the pre-existing bone metastasis or new bone metastasis is suspected by the investigator later; if it is confirmed that there is no bone metastasis at screening, a

bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if bone metastasis is suspected by the investigator later. Tumor assessments will be performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Tumor markers: During the corresponding visits for imaging tests, 4 mL of peripheral blood will be collected for the detection of tumor biomarkers, such as liver cancer [alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA)], breast cancer [cancer antigen 15-3 (CA15-3)], ovarian cancer and endometrial cancer [carbohydrate antigen 125 (CA125)], prostate cancer [prostate specific antigen (PSA)], lung cancer [cytokeratin 19 fragment (CYFRA21-1)] and pancreatic cancer [carbohydrate antigen 242 (CA242)], which serve as auxiliary efficacy indicators.

2) If a subject received a CT/MRI or other radiological examinations within 4 weeks prior to the first dose and has not received any anti-tumor therapy since this tumor assessment, and at the investigator's discretion, the tumor assessment can be performed according to RECIST v1.1, this examination result can be used as baseline tumor assessment result (repeated examination is not necessary).
3) A tumor assessment will be performed at the end of Cycle 1, for which the time window is the end of the cycle ±1 day. Therea fter, tumor assessments will be performed once every 2 cycles, for which the time window is the end of every 2 cycles ±7 days [if a subj ect's assessment result is complete response (CR), partial response (PR) or stable disease (SD), the subject can continue the treatment and continue to receive tumor assessments once every 2 cycles].
4) The radiological confirmation examination of CR or PR should be completed 4-8 weeks after the first evaluation of CR or PR.
5) For the end of treatment visit (EOT), the investigator will determine whether a tumor assessment is required according to the actual condition. If a tumor assessment has been performed within 2 months prior to EOT, it is not necessary to repeat the tumor assessment at EOT visit.
6) During the subsequent follow-up visits once every 8 weeks (±7 days) after the last dose, a tumor assessment will be performed for the subjects who are assessed as having no tumor progression in the previous assessment.

16. Detection of biomarkers:

1) Detection of biomarkers in tumor tissues: Subjects' tumor tissue specimens within the past 2 years or fresh tumor tissue specimens can be collected at screening; the specimens can be collected from the primary lesion or metastatic lesions.

   After enrollment, fresh tumor tissue specimens will be collected as much as possible at EOT visit or disease progression; the specimens can be collected from the primary lesion or metastatic lesions (keeping consistent with the lesion source at screening as much as possible).
2) Detection of biomarkers in blood: fresh blood samples can be collected at screening, during the treatment period (C1D15 visit, C3D21 visit and C5D21 visit) and at EOT visit, 5 mL at each time points, with no more than 5 sampling time points.

17. PK blood sampling:

During the single-dosing period of the dose escalation trial, the PK blood sampling time points are as follows: within 0.5 h (0 h) before single-dosing on D1 and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min), 24 h (±1 h; D2), 48 h (±1 h; D3), 72 h (±2 h; D4) and 96 h (±2 h; D5) after dosing.

During the multiple-dosing period of the dose escalation trial, the PK blood sampling time points are as follows: within 0.5 h pre-dose on C1D1, within 0.5 h pre-dose on C1D8, within 0.5 h pre-dose on C1D15, within 0.5 h pre-dose and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min) and 24 h (±30 min; collected before dosing on C2D1) post -dose on C1D21.

During the expansion trial, the PK blood sampling time points are as follows: within 0.5 h pre-dose on C1D1, within 0.5 h pre-dose on C1D8, within 0.5 h pre-dose on C1D15, within 0.5 h pre-dose and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min) and 24 h (±30 min; collected before dosing on C2D1) post-dose on C1D21.

The PK blood sampling time points of the subsequent study may be adjusted based on the previously obtained clinical trial data of BB102 tablets.

18. **Blood sampling for the identification of metabolites:** Blood samples will be collected for identification of metabolites only at a high dose group (e.g., 160 mg QD, 240 mg QD, 320 mg QD or 420 mg) during the single-dosing period of the dose escalation trial. **Blood sampling time points:** within 0.5 h (0 h) before single-dosing on D1 and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min) , 6 h (±10 min) , 8 h (±10 min), 10 h (±10 min), 24 h (±1 h; D2), 48 h (±1 h; D3), 72 h (±2 h; D4) and 96 h (±2 h; D5) after dosing.
19. **Anti-cancer therapy and survival information after study treatment discontinuation:** During the follow-up period following study treatment discontinuation, the anti-cancer therapy and survival information of all subjects will be recorded.
20. **Adverse event:** Adverse event are defined as all untoward adverse medical events following the use of the investigational product in subjects of a clinical trial. It is manifested as symptoms, signs, diseases or abnormal laboratory findings, but it does not necessarily have a causal relationship with the investigational product. See Section 8.1.1 of the main text for details.

All adverse medical events that occur during the period from subject's signing of the ICF to the first dose of the investigational product will be recorded as medical history instead of being recorded as AEs, unless they meet one of the following conditions:

- Any adverse medical event related to procedures specified in the clinical study protocol (e.g., bruising caused by blood sampling for laboratory test, etc.);
- Adverse medical events caused by treatment discontinuation related to clinical study protocol (e.g., change or discontinuation of prior concomitant medications). See Section 8.1.2 of the main text for details.

21. **Concomitant medication:** Concomitant medications include any medications other than the study drug (including prescription drugs, over-the-counter drugs, natural extracts, nutritional supplements and traditional Chinese medicines) used by subjects from the start of first dose to 28 days after the last dose of study treatment. Medications used by subjects at screening will be recorded as medication history.

DLT evaluation and single-dosing period *: For the dose escalation trial only.

X[a]: Existing laboratory test results within 48 h are acceptable.

X[b]: Twice in Cycle 2, e.g., D14 and D21 of the cycle, with a time window of ±3 days; for Cycles 3 to 5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days.

X[c]: For Cycle 2-5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end o f every 2 cycles, with a time window of ±3 days.

X[d]: Existing laboratory test results within the visit time window are acceptable.

In addition to the safety test items specified in the protocol, additional safety test items may be measured as necessary.

1. Study Background

1.1 Disease Introduction

Malignant tumor is one of the diseases seriously threatening human health in current society. According to the latest *World Cancer Report* released by the World Health Organization (WHO) in February 2020, the number of annual new cancer cases worldwide is expected to increase from 18 million in 2018 to 27 million in 2040, an increase of 50%. Among them, the growth rate of new cancer cases in developing countries is higher than that in developed countries [1]. China, in particular, as a developing country, is faced with an increasingly serious situation of malignant tumors due to the acceleration of industrialization, urbanization and population aging, and the existence of unhealthy lifestyles, environmental pollution and other problems, and the incidence of cancer is on the rise, increasing at an average annual rate of 3% to 5%. The data released by the National Cancer Center in February 2018 showed that there were 3.804 million new cases of malignant tumors in China each year, with an average of more than 10,000 people diagnosed with cancer every day, and 7 diagnosed every minute. Each year, the American Cancer Society estimates the numbers of newcancer cases and deaths in the United States. In 2022, there will be approximately 1,918,030 cancer cases and 609,360 cancer deaths in the United States, the equivalent of about 5250 new cancer cases and 1700 cancer deaths each day [2].

Malignant tumor is a worldwide problem, and its therapies mainly include surgical resection, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, etc. Traditional anti-tumor drugs are mainly cytotoxic drugs, which lack selectivity in killing cells and are toxic and cause adverse effects. Target-based drugs can effectively inhibit tumor growth while reducing toxicity and adverse effects, and thus are increasingly and extensively applied in clinical practice, and also a hotspot in the current research and development of new drugs [3-5].

Fibroblast growth factor receptor (FGFR), as a member of the receptor tyrosine kinase family, is involved in the regulation of various biological processes (such as cell proliferation, migration, anti-apoptosis and angiogenesis, etc.) by binding to ligand fibroblast growth factor and activating downstream signaling pathways, and has become an important target in cancer therapy. Currently, most of these studies have focused on fibroblast growth factor receptor 1 (FGFR1), fibroblast growth factor receptor 2 (FGFR2), and fibroblast growth factor receptor 3 (FGFR3). However, many evidences suggest that fibroblast growth factor receptor 4 (FGFR4) plays an important role in the occurrence of various tumors and resistance to treatment of anti-tumor drugs. Among them, abnormal fibroblast growth factor 19 (FGF19)-FGFR4 signaling pathway has been confirmed to be an oncogenic factor for liver cancer, and multiple FGFR4 inhibitors have entered clinical trials.

1.2 Mechanism of Action of FGFR4 Inhibitors

FGFR4 is a tyrosine kinase receptor that selectively binds to FGF19 for dimerization and

autophosphorylation. By activating the signaling pathways such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), mitogen-activated extracellular signal-regulated kinase/extracellular signal-regulated kinase (MEK-ERK), and glycogen synthase kinase-3β/β-catenin (GSK3β/β-catenin), FGFR4 promotes tumor cell proliferation, promotes epithelial-mesenchymal transition (EMT), and inhibits tumor cell apoptosis [6]. Studies have found that, overexpression of FGF19 and its receptor FGFR4 may upregulate early growth response gene-1 (Egr-1), immediate early gene (c-Fos), interleukin-6 (IL-6), and connective tissue growth factor (CTGF) to induce proliferation of liver cancer cells [7-9]. Meanwhile, it promotes EMT of liver cancer by activating GSK3β/β-catenin signaling pathway and promotes the invasion and metastasis of liver cancer by activating transforming growth factor β (TGF-β) [10]. The abnormal signaling pathway of FGF19-FGFR4 complex has been confirmed to be an oncogenic driver of hepatocellular carcinoma (HCC) [11]. In addition, overexpression of FGF19 can inhibit the generation of sorafenib-induced reactive oxygen species (ROS) in liver cancer cells, downregulate ROS signaling, promote cell survival, and inhibit cell apoptosis, which is one of the mechanisms for sorafenib resistance [12]. Therefore, FGFR4 is considered as a new potential treatment target for liver cancer. A variety of small molecule FGFR4 inhibitors (e.g., BLU-554, FGF401) with different selectivity and binding patterns have been developed, and the related clinical trials have been started (all ongoing) for the treatment of HCC and other solid tumors with abnormal FGFR4 signal transduction [13].

1.3 Overview of Clinical Trials of Similar Drugs

Currently, FGFR4 inhibitors are under research at home and abroad, including BLU-554 (Fisogatinib) and FGF401 (Roblitinib; EVER4010001) undergoing phase I/II clinical trials, BPI-43487, SY-4798, HS236, HS-10340, ZSP1241, H3B-6527, ABSK011 and ICP105 undergoing phase I clinical trials, and INCB062079 whose phase I trial has been terminated. See Table 1.

Table 1 Study status of FGFR4 inhibitors

Product Name	Company Name	Indications	Research and development phase
BPI-43487 Capsules	Betta Pharmaceuticals	Dose escalation: subjects with advanced solid tumors who have had disease progression after standard therapy, or are intolerable to or cannot accept standard therapy, or have no standard therapy available Dose expansion: subjects with FGF19-amplified, FGF19-overexpressed, or FGFR4-overexpressed advanced solid tumors who are no longer suitable for local therapy with curative intent, have had disease progression after standard therapy, or that	Phase I

Product Name	Company Name	Indications	Research and development phase
		are intolerable to or cannot accept standard therapy, or have no standard therapy available	
SY-4798 tablets	Shouyao Holdings	Dose escalation: subjects with advanced solid tumors who have failed to respond to standard therapy or have no standard therapy regimen available, or are currently not suitable for standard therapy Dose expansion: subjects with FGF19 IHC+ advanced solid tumors who have failed to respond to standard therapy or have no standard therapy regimen available, or are currently not suitable for standard therapy	Phase I
HS236 capsules	Zhejiang Hisun	Advanced solid tumors that have failed to respond to standard therapy or have no standard therapy regimen available, or are currently not suitable for standard therapy	Phase I
HS-10340 capsules	Hansoh/Hengbang	Advanced solid tumors that have no standard therapy available, or are intolerable to standard therapy	Phase I
ZSP1241 tablets	Guangdong Zhongsheng	Liver cancer, gastric cancer, bile duct cancer, esophageal cancer, colorectal cancer and other advanced solid tumors that do not respond to, are intolerable to, are not suitable for, or have no standard treatment regimen available	Phase I
H3B-6527	H3 Biomedicine	HCC subjects who have previously been treated with standard therapy at least once (unless contraindicated)	Phase I
ABSK011	Abbisko Therapeutics	Dose escalation: advanced solid tumors that have progressed or are intolerable to standard therapy, or have no standard therapy available Dose expansion: FGF19 expression-positive advanced HCC subjects who have disease progression or are intolerable to or refuse to or cannot accept first-line systemic therapy and are not suitable for other standard therapy	Phase I
ICP-105	Beijing InnoCare	Solid tumors that have progressed after standard	Phase I

Product Name	Company Name	Indications	Research and development phase
		therapy, are intolerable to standard therapy, or have no standard therapy available	
INCB062079	Incyte	• Part 1: HCC, cholangiocarcinoma, esophageal cancer, nasopharyngeal cancer, and serous ovarian cancer regardless of FGF19/FGFR4 status; or other solid malignant tumors with FGF19/FGFR4 alterations based on local detection (FGF19/FGFR4 pathway activation alterations include but are not limited to FGFR4 amplification, FGFR4 activation mutation and FGF19 amplification). • Part 2: Subjects will be enrolled in one of the following 3 cohorts: Cohort A: HCC with FGF19 amplification. Cohort B: HCC without FGF19 amplification. Cohort C: Cholangiocarcinoma, esophagus, nasopharyngeal, or serous ovarian cancer (regardless of FGF19/FGFR4 status), or other solid malignancies with confirmed FGF19/FGFR4 alterations. • Progression after prior therapy and either a) no further effective standard anticancer therapy is available (including subject refusal) or b) intolerance to standard anticancer therapy.	Phase I
FGF401 (Roblitinib; EVER4010001)	Novartis	Phase I monotherapy group: FGFR4 and KLB expression-positive HCC or other advanced malignant solid tumors that have progressed after standard therapy, are intolerable to standard therapy, or do not have standard therapy available; Phase I combination group: FGFR4 and KLB expression-positive advanced HCC subjects who have been previously treated with first- or second-line systemic therapy (one of which must include sorafenib therapy), and is diagnosed to have disease progression during sorafenib treatment or treatment discontinuation, or	Phase I/II

Product Name	Company Name	Indications	Research and development phase
		intolerant to sorafenib treatment; Group 1 in phase II: FGFR4 and KLB expression-positive advanced HCC patients from Asian countries who have previously received sorafenib therapy due to advanced HCC, are diagnosed with disease progression or intolerant to sorafenib treatment during sorafenib treatment or treatment discontinuation. Group 2 in phase II: FGFR4 and KLB expression-positive advanced HCC patients from non-Asian countries who have previously received sorafenib therapy due to advanced HCC, are diagnosed with disease progression or intolerant to sorafenib treatment during sorafenib treatment or after treatment discontinuation, non-Asians. Group 3 in phase II: FGFR4 and KLB expression-positive patients with other advanced malignant tumors who have progressed after standard therapy, are intolerant to standard therapy, or do not have standard therapy available (regardless of their geographic location).	
	EverNov Medicines	Phase I: Metastatic locally advanced solid tumors that do not have effective standard therapy available or have failed to respond to standard therapy; Phase II: FGF19-positive metastatic or locally advanced somatic tumors.	
BLU-554 (Fisogatinib)	Cstone/Blueprint Medicines	Part 1 dose escalation: HCC; Part 2 dose expansion study 1: HCC; Part 3 dose expansion study 2: FGF19 IHC+ HCC without prior TKI treatment; Phase Ib: Unresectable locally advanced or metastatic HCC that has failed standard systemic therapy or is not suitable for standard therapy; Phase II: Locally advanced or metastatic HCC without prior systemic therapy	Phase Ib/II

Abbreviations: FGFR4 = fibroblast growth factor receptor 4; FGF19 = fibroblast growth factor 19; HCC = hepatocellular carcinoma; IHC+ = immunohistochemistry positive; TKI = tyrosine kinase inhibitor.

So far, no FGFR4 inhibitor has been approved for marketing at home and abroad. The highest development stage of FGFR4 inhibitors is clinical phase II trials. Only FGF401, BLU-554 and H3B-6527 have clinical trial results published. The relevant research results are summarized as follows:

Roblitinib (FGF401)

The NCT02325739 study [14] was the first-in-human clinical trial of FGF401, a multicenter, non-randomized, open-label, monotherapy/combination therapy (PD-1 checkpoint inhibitor PDR001) phase I/II study. According to the information publicized at https://clinicaltrials.gov, the trial enrolled a total of 172 subjects and aimed to assess the safety, pharmacokinetics (PK), pharmacodynamics and preliminary antitumor activity of FGF401 in patients with both FGFR4- and KLB-positive advanced cancer patients. **The phase I part** explored the safety and tolerability of FGF401 in fasted and fed states based on the effect of FGF19 signaling pathway on bile acid synthesis. Dose escalation was performed based on a Bayesian hierarchical model, and a total of 8 dose escalation groups were set up (50 mg fasted, 80 mg fasted, 80 mg fed, 120 mg fasted, 120 mg fed, 150 mg fasted, FGF401 80 mg fasted + PDR001 300 mg, FGF401 120 mg fasted + PDR001 300 mg). The dose-toxicity relationship at each dose was assessed, and the primary objective was to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D). The phase I part enrolled a total of 86 subjects, and the finally determined RP2D of FGF401 monotherapy in fasted state was 120 mg, the RP2D of FGF401 monotherapy in fed state was 120 mg, and the RP2D of FGF401 + PDR001 combination therapy was FGF401 120 mg and PDR001 300 mg. The phase II part explored the safety and preliminary efficacy of FGF401 in 3 groups of subjects (Group 1: HCC patients from Asian countries; Group 2: HCC patients from non-Asian countries; Group 3: patients with other malignant solid tumors, regardless of their geographic location). All subjects received FGF401 treatment 120 mg once daily (QD). The phase II part enrolled a total of 86 subjects. The median time to disease progression was 2.6 months in Group 1 and 3.9 months in Group 2, and the objective response rate (ORR) was 0.0% in Group 3. The ORR in the 50 mg fasted, 80 mg fasted, 80 mg fed, 120 mg fasted, 120 mg fed, 150 mg fasted, FGF401 80 mg fasted + PDR001 300 mg, FGF401 120 mg fasted + PDR001 300 mg, Group 1, Group 2 and Group 3 was 0.0%, 16.7%, 20%, 3.8%, 0.0%, 14.3%, 16.7%, 16.7%, 6.7%, 5.6%, and 0.0%, respectively; the disease control rate (DCR) was 18.2 %, 33.3%, 60.0%, 50.0%, 47.4%, 71.4%, 50.0%, 50.0%, 43.3%, 61.1%, and 30.0%, respectively; the incidence of serious adverse events (SAE) was 27.27%, 83.33%, 60.00% 57.69%, 47.37%, 42.86%, 0.00%, 33.33%, 50.00%, 25.00%, and 40.00%, respectively. The incidence of SAEs with FGF401 monotherapy was 43.75%, and the incidence of SAEs with combination therapy was 16.67%. Among them, diarrhea, asthenia, pyrexia, vomiting and nausea were the main adverse events (AEs).

Fisogatinib (BLU-554)

The NCT02508467 study [15] was the first-in-human clinical trial of BLU-554, a multicenter, non-randomized, open-label, single-agent, single-arm, phase I study that planned to enroll 150 subjects (115 subjects had been enrolled as of Oct. 2019) and aimed to assess the safety, tolerability, PK, pharmacodynamics and preliminary antitumor activity of BLU-554 in FGF19 immunohistochemically positive (IHC+) HCC patients. This trial consisted of three parts: (1) Part 1 dose escalation (classical 3+3 design), 140 mg-900 mg; (2) Part 2 dose expansion, RP2D administration; (3) Part 3 dose expansion, patients who had not previously received tyrosine kinase inhibitors (TKIs), RP2D administration. The preliminary phase I results showed that the 600 mg group well tolerated the treatment, and 2 subjects in the 900 mg group experiencing dose-limiting toxicity (DLT). The RP2D was 600 mg QD. The collected safety data showed that most AEs were grade 1 or 2 with manageable adverse effects, with the main AEs being diarrhea, nausea and vomiting. As of Oct. 2019, a total of 98 of the 106 subjects who received the QD dose had undergone efficacy assessment; among the 66 FGF19 IHC+ subjects, 11 (17%) were assessed to have objective response, including 1 (2%) subject with complete response (CR) and 10 (15%) subjects with partial response (PR); the median duration of response (mDOR) was 5.3 months; the median progression-free survival (mPFS) was 3.3 months (2.1-3.7 months). Among 34 subjects with FGF19 IHC-negative or unknown FGF19 status, the ORR was 0.0%. The above efficacy further confirmed the oncogenic driving role of FGF19-FGFR4 signaling pathway in HCC, and further confirmed that FGF19 is a predictive biomarker for precise treatment of HCC.

H3B-6527

The NCT02834780 study [16] was the first-in-human clinical trial of H3B-6527, a multicenter, non-randomized, open-label, single-agent, single-arm, phase I study that planned to enroll 128 subjects (128 subjects were enrolled actually) and aimed to assess the safety, tolerability, PK, pharmacodynamics, and preliminary antitumor activity of H3B-6527 in subjects with HCC or intrahepatic cholangiocarcinoma (ICC). The trial used a 3+3 design with dose escalation ranging from 300 to 2000 mg QD or 500 to 700 mg twice daily (BID). So far, 128 subjects have been enrolled in the study, of whom 90 FGF19-positive HCC subjects were treated (48 QD, 42 BID), and ICC subjects (38 subjects have been enrolled actually) were suspended due to limited efficacy. No DLT was observed, and no treatment-related grade 4-5 AEs were observed. Based on the safety, efficacy and PK data, the RP2D of H3B-6527 was 1000 mg QD. In the QD administration group, 12.5% subjects experienced grade 3 AEs, and 62.5% subjects experienced treatment-related AEs, the most common of which were diarrhea (45.8%), asthenia (12.5%), and nausea (12.5%). The incidence of discontinuation due to AEs in the QD administration group was 8.3%. The interim data analysis showed that for HCC subjects who had previously received >2 lines of therapy, the overall survival (OS) of QD administration was 10.6 months, the progression-free survival (PFS)

was 4.1 months, the overall response rate was 16.7 % (both PR), and the clinical benefit rate was 45.8% (response + stable disease for >17 weeks). The existing results have shown that H3B-6527 has good tolerability and anti-HCC activity.

1.4 BB102 Introduction

Generic name: BB102 tablets

Other code: None

English chemical name: N-(5-cyano-4-((2-methoxyethyl) amino) 56yridine-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-2,4-methano-1,8-naphthyridine-1(2H)-carboxamide 2-hydroxypropane-1,2,3-tricarboxylate

Molecular formula: $C_{26}H_{30}N_8O_4 \cdot C_6H_8O_7$

Molecular weight: 710.70

Stereochemistry: None

BB102 is a small molecule FGFR4 inhibitor independently developed by the sponsor. It has the same mechanism of action as BLU-554 and FGF401, and belongs to the innovative drug/molecular.

The dosage, route of administration, method of administration and treatment schedule of the investigational product (BB102 tablets) are detailed in Sections 5.2 and 6.2.

1.5 Summary of Nonclinical Studies of BB102

Nonclinical studies have shown that BB102, as a novel FGFR4 inhibitor with completely independent intellectual property rights, has a clear mechanism of action, high pharmacodynamic target selectivity, and high activity *in vitro* and *in vivo*, can significantly inhibit the growth of various liver cancer, rhabdomyosarcoma, and breast cancer xenograft models, and has good safety. BB102 is expected to be characterized by few adverse effects, low effective dose, and long duration of drug effect in clinical applications.

The results of nonclinical studies are detailed in the Investigator's Brochure. This protocol only provides a brief description.

1.5.1 Pharmacology

Primary Pharmacodynamics

The study of compounds effects on FGFR4 kinase detected the inhibitory activity of BLU-554 and BB102 on FGFR4, and the half maximal inhibitory concentration (IC_{50}) of BLU-554 and BB102 were 13.94 nM and 2.522 nM, respectively, showing strong inhibitory effects. Compared with BLU-554, BB102 has higher inhibitory activity on FGFR4. **The study of inhibitory effect of BB102 on the FGF19/FGFR4-mediated signal pathway in human hepatocellular**

carcinoma Hep 3B cells showed that BB102 completely inhibited ERK and AKT protein phosphorylation which is downstream of FGF19/FGFR4 in human hepatocellular carcinoma cell Hep 3B even at 16.7 nM, and its inhibitory potency was similar to FGF401 and stronger than BLU-554. It was demonstrated that BB102 inhibited the growth of hepatocellular carcinoma Hep 3B cells by selectively inhibiting the kinase activity of FGFR4, thereby inhibiting its downstream ERK/AKT signal pathway.

The study of inhibitory activity on cell proliferation showed that BB102 had a strong inhibitory effect on the proliferation of FGF19/FGFR4 high-expressing tumor cells, such as human hepatocellular carcinoma cells Hep 3B, HuH-7 and JHH-7, human breast cancer cell MDA-MB-453, and human rhabdomyosarcoma cell SJCRH30. The inhibitory effect of BB102 on Hep 3B, HuH-7 and JHH-7 was IC_{50} = 5.8 nM, 8.7 nM and 21.760 nM, respectively, which was better than the positive control BLU-554 (IC_{50} = 23.7 nM, 30.7 nM and 87.980 nM), and slightly worse than the positive control FGF401 (IC_{50} = 2.3 nM, 3.2 nM and 10.810 nM). The IC_{50} of BB102 on SJCRH30 was 1.9 nM, which was better than that of positive control BLU-554 (IC_{50} = 5.2 nM) and slightly worse than that of positive control FGF401 (IC_{50} = 0.6 nM). The IC_{50} of BB102 on MDA-MB-453 was 24.7 nM, which was slightly worse than that of positive control FGF401 and BLU-554 (IC_{50} = 9.5 nM and 6.6 nM). **In addition,** BB102 also had a strong inhibitory effect on the proliferation of Ba/F3 cell lines with $FGFR4^{V550L}$ or $FGFR4^{N535K}$ mutation (IC_{50} = 0.045 μM and 0.023 μM, respectively), which was better than the positive control BLU-554 (IC_{50} = 0.572 μM and 0.206 μM, respectively).

In the *in vivo* pharmacodynamic study, five FGF19/FGFR4 high-expressing xenograft models were selected: human hepatocellular carcinoma cells Hep 3B, HuH-7 and JHH-7, human breast cancer cell MDA-MB-453, and human rhabdomyosarcoma cell SJCRH30. **The study of "Inhibitory Effect of BB102 on the Growth of Subcutaneous Xenografts of Human Hepatocellular Carcinoma HuH-7 cells in Balb/c nude Mice"** consisted of 7 groups, including the vehicle control group (BID, 21 days), the positive control sorafenib 60 mg/kg group (QD, 21 days), the positive control BLU-554 30 mg/kg group (BID, 21 days), positive control BB181 (FGF401 citrate) 30 mg/kg group (BID, 21 days), BB102-citrate 30 mg/kg group (BID, 21 days), BB102-citrate 60 mg/kg group (BID, 21 days), BB102-citrate 90 mg/kg group (BID, 7 days; QD, 14 days). On Day 20 after treatment, compared with the vehicle control group, BB102-citrate had a significant antitumor effect at doses of 30 mg/kg, 60 mg/kg and 90 mg/kg, with the treatment/control ratio (T/C) value of 19.35%, 14.52% and 13.55%, respectively; tumor growth inhibition (TGI) values of 96.21%, 101.97% and 103.12%, respectively. The positive control FGF401 at 30 mg/kg had significant antitumor effect compared with the vehicle control group, with the T/C value of 15.31% and TGI value of 101.04%, measured on Day 20 after treatment; Sorafenib at 60 mg/kg had moderate antitumor effect with the T/C value of 32.75% and TGI value of 80.10%, measured on Day 20 after treatment. BLU-554 at 30 mg/kg had slight antitumor effect

with the T/C value of 68.59% and TGI value of 37.49%, measured on Day 20 after treatment. The antitumor effect of BB102 in this model was similar to that of positive control FGF401, and was significantly better than that of positive control sorafenib and BLU-554. **The study 1 of "Inhibitory Effect of BB102 on the Growth of Subcutaneous Xenografts of Human Hepatocellular Carcinoma JHH-7 cells in Balb/c nude Mice"** consisted of 5 groups, including the vehicle control group, positive control BB181 (FGF401-citrate) 10 mg/kg group, BB102-citrate 10 mg/kg group, BB102-citrate 30 mg/kg group, and BB102-citrate 60 mg/kg group; BID, administered orally for 18 days. Compared with the vehicle control group, BB102-citrate had no significant antitumor effect at dose of 10 mg/kg; BB102-citrate had a certain antitumor effect at dose of 30 mg/kg; BB102-citrate showed significant antitumor effect at dose of 60 mg/kg. The T/C value on Day 17 of these 3 dosing groups was 94.07%, 69.75% and 46.51%, respectively; TGI value was 6.17%, 31.51% and 55.69%, respectively. Compared with the vehicle control group, positive control FGF401-citrate at 10 mg/kg had no significant antitumor effect with the T/C value of 86.61% and TGI value of 13.95% on Day 17 after treatment. **The study 2** consisted of 4 groups, including the vehicle control group, positive control BLU-554 60 mg/kg group, BB102-citrate 60 mg/kg group, and BB102-citrate 80 mg/kg group; BID, administered orally for 3 weeks. Compared with the vehicle control group, BB102-citrate had a significant antitumor effect at doses of 60 mg/kg and 80 mg/kg, with T/C value of 36.07% and 20.04%, respectively, measured on Day 20 after treatment; TGI value was 66.44% and 83.10%, respectively. Compared with the vehicle control group, the positive control BLU-554 had a significant antitumor effect at a dose of 60 mg/kg with the T/C value of 43.22% and TGI value of 59.02%, measured on Day 20 after treatment. Considering the results of the two studys, BB102-citrate significantly inhibited the growth of human hepatocellular carcinoma JHH-7 cell mouse xenografts with dose dependent manner, the high dose group had the best antitumor effect, and the effect decreased along with the decrease of dose. The antitumor effect of BB102 in this model was slightly better than that of positive control BLU-554. **The study of** "**Inhibitory Effect of BB102 on the Growth of Subcutaneous Xenografts of Human Breast Cancer MDA-MB-453 cells in B-NDG Mice**" consisted of 3 groups, including the vehicle control group (BID, 22 days), BB102-citrate 80 mg/kg group (BID, 22 days), and positive control BLU-554 80 mg/kg group (BID, 22 days). The results showed that BB102-citrate 80 mg/kg had a significant antitumor effect compared with the vehicle control group with the T/C value of 28.01% and TGI value of 120.94%, measured on Day 21 after treatment. The positive control BLU-554 80 mg/kg had a significant antitumor effect compared with the vehicle control group with the T/C value of 23.01% and TGI value of 129.35%, measured on Day 21 after treatment. The antitumor effect of BB102 in this model was similar to that of positive control BLU-554. **The study of "Inhibitory Effect of BB102 on the Growth of Subcutaneous Xenografts of Human Rhabdomyosarcoma SJCRH30 cells in Balb/c nude Mice**" consisted of 3 groups, including the vehicle control group (BID, 22 days), BB102-citrate 60 mg/kg group (BID,

22 days), and positive control BLU-554 60 mg/kg group (BID, 22 days). The results showed that BB102-citrate had a significant antitumor effect at a dose of 60 mg/kg compared with the vehicle control group, with T/C value of 28.97% and TGI value of 76.10%, measured on day 21 after treatment. The positive control BLU-554 had a significant antitumor effect at a dose of 60 mg/kg compared with the vehicle control group, with T/C value of 28.65% and TGI value of 77.11%, measured on day 21 after treatment. The antitumor effect of BB102 in this model was similar to that of positive control BLU-554. **The study of "Inhibitory Effect of BB102 on the Growth of Subcutaneous Xenograft Tumor of Human Hepatocellular Carcinoma Hep 3B cells in CB17.SCID Mice**" consisted of 5 groups, including the vehicle control group, positive control BB181 (FGF401-citrate) 5 mg/kg group, BB102-citrate 5 mg/kg group, BB102-citrate 10 mg/kg group, and BB102-citrate 30 mg/kg group; BID, administered orally for 3 weeks. The results showed that BB102-citrate had a significant antitumor effect compared with the vehicle control group at doses of 5 mg/kg, 10 mg/kg and 30 mg/kg, with T/C values of 54.19%, 43.26% and 8.36%, respectively; TGI values of 48.51%, 60.09% and 97.04%, respectively. Positive control FGF401-citrate at 5 mg/kg had a significant antitumor effect compared with the vehicle control group with the T/C value of 38.52% and TGI value of 65.11%, measured on Day 20 after treatment. The BB102-citrate significantly inhibited the growth of human hepatocellular carcinoma Hep 3B cell mouse xenografts in a dose-dependent manner: the high-dose group had the best effect, and the effect decreased with the decrease of dose. The antitumor effect of BB102 in this model was similar to that of positive control FGF401.

Secondary Pharmacodynamics

In the *in vitro* kinase selectivity study, for 207 kinases (such as FGFR4, HCK, PAK3, NEK2, MET, PIM3, FGFR1, ZAP70, AurA, etc.), 1 μM BB102 had an inhibitory effect on FGFR4 only and the inhibition rate was up to 102.03%. However, BB102 had no inhibitory effect on the other kinases (%Inh <40%). The above results showed that BB102 has extremely high kinase selectivity, and its inhibitory activity on FGFR4 kinase is more than 400 times higher than that of other 206 kinases.

The inhibitory effect of BB102 on the proliferation of tumor cells with different expression levels of FGF19/FGFR4 was evaluated by the cell proliferation inhibition experiment. The results showed that BB102 showed a strong inhibitory effect on the proliferation of FGF19/FGFR4 high-expressing tumor cells, such as human hepatocellular carcinoma cells Hep 3B and HuH-7, human breast cancer cell MDA-MB-453, and human rhabdomyosarcoma cell SJCRH30 (IC_{50} was 5.8, 8.7, 24.7 and 1.9 nM, respectively). However, BB102 showed little or no inhibitory effect on FGF19/FGFR4 low-expressing tumor cells such as human hepatocellular carcinoma cells SNU-387 and SNU-878, human rhabdomyosarcoma cell RD and human colon adenocarcinoma cell HT-29 (IC_{50} of RD cell >10 μM, and IC_{50} of other cells >20 μM).

Meanwhile, BB102 had no inhibitory effect on the proliferation of normal cells, such as mouse embryonic fibroblast NIH3T3, human umbilical vein vessel endothelial cell HUVEC, and human normal lung epithelial cell BEAS-2B (IC_{50} >20 μM).

Safety Pharmacology

The results of the safety pharmacology showed that BB102 was expected to have no adverse effects on the cardiovascular system, respiratory system, or central nervous system in humans. The IC_{50} of BB102 inhibiting the hERG current was >12 μM (maximum solubility of BB102 under test conditions) in the human embryonic kidney cell lines (hERG-HEK293) with stable expression of hERG channels. A single oral administration of BB102-citrate in Beagle dogs at doses of 40, 100 and 250 mg/kg had no significant test article-related changes in any of the evaluated cardiovascular parameters including blood pressure (systolic blood pressure, diastolic blood pressure, mean arterial blood pressure), heart rate, ECG (RR interval, PR interval, QRS duration, QT and corrected QT intervals) and body temperature. Single oral dosing with BB102-citrate up to 300 mg/kg in SD rats had no test article-related notable effects on respiratory parameters, including tidal volume, minute volume and respiratory rate. Single oral dosing of BB102-citrate to SD rats up to 300 mg/kg had no effect on the evaluated neurobehavioral parameters.

1.5.2 (Nonclinical) PK

Absorption

Caco-2 cells permeability study: BB102-citrate was a moderate permeability compound, and it is a substrate of efflux transporters.

Single-dose and 7-day repeat-dose PK studies in SD rats: Following intravenous (2 mg/kg) and oral administration at 3 dose levels (30 mg/kg, 90 mg/kg and 270 mg/kg) of BB102-citrate in SD rats, there was no significant gender differences in drug exposure (AUC_{last}) of BB102 in both intravenous group (the male/female ratio was 0.663) and single-dose oral groups (the male/female ratios were 0.537-0.750), while the exposure (AUC_{last}) in males was slightly lower than that in females in repeat-dose oral groups (the male/female ratios were 0.437-0.647). Following intravenous administration of BB102-citrate at 2 mg/kg in SD rats, the AUC_{last} of BB102 in males and females was 2194 h*ng/mL and 3308 h*ng/mL, respectively; BB102 was a low clearance compound in SD rats, and it was widely distributed in rat body. Following single oral administration of BB102-citrate at three dose levels (i.e., 30 mg/kg, 90 mg/kg and 270 mg/kg) in SD rats, in males, the AUC_{last} were 27209 h*ng/mL, 50642 h*ng/mL and 160093 h*ng/mL, respectively; the C_{max} were 5927 ng/mL, 8460 ng/mL and 10253 ng/mL, respectively; the half-life ($T_{1/2}$) were 5.18 h, 4.51 h and 6.00 h, respectively; in females, the AUC_{last} were 36269 h*ng/mL, 92869 h*ng/mL and 297985 h*ng/mL, respectively; the C_{max} were 8733 ng/mL, 12067 ng/mL and 15700 ng/mL, respectively; the $T_{1/2}$ were 6.47 h, 6.80 h and 5.13 h, respectively. In the dose range

of 30-270 mg/kg, in both female and male rats, the increase of C_{max} was lower than dose-proportional, while the increase of AUC_{last} was close to dose-proportional. Following 7-day repeat oral administration of BB102-citrate at 90 mg/kg in SD rats, in males and females, the C_{max} ratios between Day 7 and Day 1 were 0.905 and 1.23, respectively; the AUC_{last} ratios were 0.858 and 1.27, respectively, indicating that there was no obvious drug accumulation of BB102 in rats. When it was calculated using AUC_{last}, following single oral administration of BB102-citrate at 30 mg/kg in SD rats, the absolute bioavailability of BB102 in males and females were 82.7% and 73.1%, respectively. Following oral administration of BB102-citrate at 90 mg/kg in SD rats at fasted and fed conditions, in males and females, the C_{max} ratios between fasted and fed group were 1.11 and 0.919, respectively; the AUC_{last} ratios were 1.21 and 1.02, respectively, indicating that food had no significant effect on BB102 exposure in rats.

Single-dose and 7-day repeat-dose PK studies in Beagle Dogs: Following intravenous and oral administration of BB102-citrate in Beagle dog, the AUC_{last} ratio between males and females was 1.00-1.34, and the C_{max} ratio between males and females was 0.983-1.38, indicating that there was no obvious gender difference for the exposure. Following intravenous administration of BB102-citrate at 1 mg/kg in Beagle dogs, the AUC_{last} of BB102 in Beagle dogs was 2040 h*ng/mL; BB102 was a low clearance compound in Beagle dog, and it was extensively distributed in Beagle dogs. Following single oral administration of BB102-citrate at three dose levels (i.e., 10 mg/kg, 30 mg/kg and 90 mg/kg) in Beagle dog, the AUC_{last} were 14562 h*ng/mL, 27598 h*ng/mL and 27415 h*ng/mL, respectively; the C_{max} were 4492 ng/mL, 8687 ng/mL and 8292 ng/mL, respectively; the $T_{1/2}$ were 6.54 h，6.30 h and 7.26 h, respectively. The increase of C_{max} and AUC_{last} were slightly lower than dose-proportional in the dose range of 10-30 mg/kg; however, C_{max} and AUC_{last} did not increase in the dose range of 30-90 mg/kg. It was speculated that there might be saturated absorption in the animals (Beagle dogs) in the dose range of 30-90 mg/kg. Following 7-day repeat oral administration of BB102-citrate at 30 mg/kg, the C_{max} and AUC_{last} ratios between Day 7 and Day 1 in Beagle dog were 1.07 and 1.22, respectively, indicating there was no obvious accumulation of BB102 in Beagle dog following 7-day repeat-dose at 30 mg/kg. When it was calculated using AUC_{last}, following single oral administration of BB102-citrate at 10 mg/kg in Beagle dog, the absolute bioavailability in Beagle dog was 71.1%.

Distribution

Plasma protein binding: The plasma protein binding of BB102-citrate was not concentration dependent over the range of 0.5-50 μM in the dog, monkey, or human plasma. The mean bound fraction was 0.704, 0.748 and 0.834, respectively. In the mouse and rat plasma, there was a trend for higher unbound fraction at higher BB102-citrate concentrations over the range of 0.5-50 μM. At the test concentrations of 0.5, 5 and 50 μM, the bound fraction was 0.880, 0.881 and 0.815, respectively in mouse plasma; 0.891, 0.830 and 0.725, respectively in rat plasma. The percentage

remaining for BB102-citrate was 69.8%-98.2%, 63.6%-79.8%, 69.7%-74.7%, 50.2%-63.6% and 62.8%-73.3%, respectively, in mouse, rat, dog, monkey and human plasma following 18-hour incubation, indicating that BB102-citrate may be unstable in mouse, rat, dog, monkey and human plasma.

Tissue distribution in SD rats: Following a single oral administration of BB102-citrate at 90 mg/kg in SD rats, BB102 was distributed rapidly in rat, the concentration of BB102 in all tissues reached a maximum at 30 min post-dose, except kidney and lung in males and ovary, spleen and small intestine in females reached a maximum at 2 h post-dose. BB102 was mainly distributed in gastrointestinal tract and liver; the exposures of BB102 in liver, small intestine and stomach in both sexes were higher than that in plasma; the exposures of BB102 in brain in both sexes, skeletal muscle and ovary in females, and epididymis in males were lower than that in plasma; the exposures of BB102 in other tissues were close to that in plasma. The obvious elimination trend of BB102 concentration in all tissues was observed at 24 h post-dose, and the concentration of BB102 in other tissues was lower than 15% of C_{max}, except kidney (16.5%) and overy (17.5%) in female rats. Meanwhile, except for the three reproductive tissues (i.e., testis, epididymis and ovaries) evaluating the exposure in single sex only, the exposure of BB102 in all tissues of males was lower than that in females (the ratio between males and females was 0.209-0.886).

Metabolism

Metabolic stability in hepatocytes: BB102-citrate showed low intrinsic clearance in rat and human hepatocytes and moderate intrinsic clearance in mouse, dog and monkey hepatocytes.

Identification of BB102 metabolite in hepatocytes: Eleven metabolites of BB102 citrate were detected in mouse, rat, dog, monkey and human incubation samples in total. Nine metabolites of BB102 citrate were detected in mouse and rat incubation samples. Six metabolites of BB102 citrate were detected in dog incubation samples. Ten metabolites of BB102 citrate were detected in monkey and human incubation samples. BB102 citrate was incubated with mouse, rat, dog, monkey and human hepatocytes for 4 hours, the percentage remaining of parent drug was 94.97%, 94.24%, 96.14%, 92.49% and 96.13%, respectively, and there was no metabolite with percentage of peak area ≥3.00%.

Excretion

Following oral administration of BB102-citrate in SD rats, the mean recovery of BB102 in urine and feces within 120 h post-dose were 0.212% and 8.81%, respectively; the recovery of BB102 in bile within 32 h post-dose was 2.47%; the total recovery of BB102 in urine and feces was 9.03%. Combined the results of metabolite identification in excretion samples to make a preliminary analysis of the mass balance, 18 and 20 metabolites were detected in urine and feces samples, respectively, calculated by the peak area normalization method of mass spectrum, the peak area

percentage of metabolites were 37.24% and 41.69%, respectively (the peak area percentage of parent drug were 62.76% and 58.31%, respectively), and the total recovery of parent drug and metabolites of BB102 in urine and feces was 15.45%. However, the above area normalization method could only preliminarily evaluate the excretion ratio of parent drug and metabolites in biological samples because of the response differences of parent drug and metabolites in mass spectrum. It was speculated that BB102 had extensive metabolic transformation in rats, and that BB102 was eliminated from the body in various metabolic pathways besides the parent drug, of which De-methylation and Hydrogenation were the main metabolic pathways. Most of BB102 was excreted within 48 h post-dose, and the urine and feces excretion amount within 48 h post-dose were 98.4% and 99.4%, respectively, of the total excretion within 120 h post-dose. The bile excretion amount of BB102 in rats with bile drainage operation within 24 h post-dose was 86.3% of the total bile excretion amount within 32 h post-dose, indicating that most of BB102 excreted through bile was excreted within 24 h post-dose. The results of excretion study showed that BB102 and its metabolites were mainly excreted through feces following oral administration of BB102, and there was no gender difference in the excretion pathway.

PK interactions

CYP phenotyping: CYP3A4 and CYP3A5 were the main CYP enzymes involved in the *in vitro* metabolism of BB102.

Inhibition potential of BB102 against CYP450 enzyme and time-dependent inhibition potential of BB102 against CYP450 enzyme: BB102 had moderate inhibition against CYP2B6 (IC_{50} = 6.84 μM), and had no time-dependent inhibition potential over the concentration range of 0.15-50 μM. BB102-citrate had inhibitory effect with inhibition rate <50% on CYP2C8, CYP2C9, CYP2C19 and CYP3A at the high concentration (15 or 50 μM), and BB102-citrate had no time-dependent inhibitory effect on CYP2C8 at 50 μM, while there may have nicotinamide adenine dinucleotide phosphate-dependent time-dependent inhibitory effect on CYP2C9, CYP2C19 and CYP3A (midazolam and testosterone used as substrates). BB102 had no inhibition against CYP1A2 and CYP2D6.

Induction potential of BB102 against CYP450 enzymes (CYP1A2, CYP2B6 and CYP3A4): BB102 had no induction potential against CYP1A2 and CYP2B6 over the concentration range of 0.3-7 μM but may have induction potential against CYP3A4 at the concentration of 7 μM. Over 24-h incubation, the data suggested that BB102 may be metabolized by human primary hepatocytes.

Substrate and inhibition potential of efflux transporter: BB102-citrate was a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and BB102-citrate had the inhibitory effect on P-gp at 7.5 μM and BCRP at >0.75 μM (Inhibition rate <50%).

Substrate and inhibition potential of solute carrier transporter: BB102-citrate was not a substrate of SLC transporters OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1 or MATE2-K; BB102-citrate was an inhibitor of OAT1, OAT3, OATP1B3, MATE1 and MATE2-K transport.

1.5.3 Toxicology

BB102 was evaluated in a series of non-GLP and GLP nonclinical toxicology studies, including single and repeated dose toxicity studies. In the two nonclinical species (rats and dogs), BB102 showed similar toxicity profiles with repeated 28-day dosing. Adverse drug reactions (ADRs) of BB102 occurred mainly in the liver.

Single-dose toxicology studies:

Single-dose toxicology study in SD rats (non-GLP): There were 18 SD rats (half males, half females), with a single dose via oral administration at 100, 300 and 1000 mg/kg of BB102-citrate [the vehicle was 0.5%MC (w/v) in citric acid solution]. All animals survived to the scheduled sacrifice day and the toxicity was obviously noted in animals given 1000 mg/kg. Abnormal clinical observations included hunched posture, decreased activity, wheeze, red staining of nose and deep breathing; decreases of body weight and body weight gain. Therefore, the MTD of SD rats was defined at 1000 mg/kg.

Single-dose toxicology study in Beagle dogs (non-GLP): There were 2 Beagle dogs (1 male, 1 female), with a single dose via oral administration at 50, 100, 300 and 1000 mg/kg of BB102-citrate [the vehicle was 0.5%MC (w/v) in citric acid solution] that the animals were well tolerated after observations for four days. Test article-related clinical observation was limited to emesis and abnormal feces (soft stool, loose feces and watery feces) and no body weight changes were noted. Therefore, the MTD of Beagle dogs was defined at 1000 mg/kg.

Repeat-dose toxicology studies:

The 14-day dose range finding toxicity study in SD rats (non-GLP): SD rats were administered with vehicle and BB102-citrate at dose levels of 50, 150 and 500 (Day 1-Day 7)/300 (Day 8-Day 14) mg/kg/day [the vehicle was 0.5%MC (w/v) in citric acid solution, pH≈2.5] via oral gavage QD for 14 days, in which the obviously toxicity was noted at dose level of 500/300 mg/kg/day. Eight animals were found dead (4 main study animals, including 2 males and 2 females and 4 toxicokinetics animals, including 1 male and 3 females) when given 500 mg/kg/day, and no animal dead was noted when dose level adjusted to 300 mg/kg/day. BB102-citrate-related alterations included: abnormal clinical observations (hunched posture, decreased activity and red staining of nose); decreases of body weight gain and food consumption; alterations of clinical chemistry [increases of alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin (TBIL), decreases of blood urea, blood urea nitrogen/creatinine and fasting plasma glucose (GLU)];

alterations of hematology [decreases of haematocrit (HCT), hemoglobin (Hb), mean erythrocyte volume and mean erythrocyte red protein content, increases of absolute reticulocyte count (ABRETIC), white blood cell (WBC), absolute neutrophilic granulocyte count and absolute lymphocyte count (ABLYMP)]; alterations of coagulation (shorten activated partial thrombin time and prothrombin time); alterations of organ weight (increase in organ weight of heart, kidney and liver, decrease in organ weight of thymus, epididymis and uterus); macroscopic findings that diffuse yellowish discoloration of all lobes of liver. Therefore, the repeat dose MTD of SD rats was defined at 300 mg/kg/day in male and female animals, which corresponded to mean C_{max} and AUC_{last} values of 14200 ng/mL and 176723 h*ng/mL in males on Day 14, respectively. No C_{max} and AUC_{last} values of BB102-citrate in females were collected on Day 14 due to all toxicokinetics animals were dead.

The 28-day oral toxicity and toxicokinetic study of BB102-citrate with a 28-day recovery period in SD rats (GLP): SD rats were administered with vehicle and BB102-citrate at dose levels of 50, 150 and 300 mg/kg/day [the vehicle was 0.5%MC (w/v) in citric acid solution, pH≈2.5] via oral gavage QD for 28 days; the reversibility, progression and/or potential delayed effects were investigated during a 28-day recovery period. One female animal at high-dose group (300 mg/kg/day) was found dead on Day 13, while other animals were well tolerated. No BB102-citrate-related findings in ophthalmology examination, coagulation parameters or urinalysis parameters were noted in the study. **BB102-citrate-related clinical symptom** was red staining of nose and right eye (female animals given 300 mg/kg/day). No abnormal findings were noted in recovery phase. **For body weight and food consumption,** in dosing phase, mean body weight and body weight gain of male animals given 300 mg/kg/day were lower than that of concurrent vehicle group, and mean body weight gain of female animals given 300 mg/kg/day was significantly lower than that of concurrent vehicle group. Minimal decrease of mean food consumption was noted in male and female animals given 300 mg/kg/day when compared with concurrent vehicle group. During recovery phase, the body weight and food consumption of male and female animals in each dose group showed recovery. **BB102-citrate-related alterations in clinical chemistry parameters included:** at terminal sacrifice, increase in ALP in females and males given 300 mg/kg/day; increase in TBIL in males given 300 mg/kg/day and females given ≥50 mg/kg/day; increases in blood urea, blood urea nitrogen/creatinine ratio and triglycerides and decrease in GLU in females given 300 mg/kg/day; decrease in cholesterol in two females given 300 mg/kg/day. The alteration of TBIL in females given ≥150 mg/kg/day was considered adverse. At recovery sacrifice, all alterations in clinical chemistry parameters at terminal sacrifice were completely reversed. **BB102-citrate-related alterations in hematology parameters included:** at terminal sacrifice, consisted of minimal decrease in red blood cell (RBC) in females and males given ≥150 mg/kg/day; minimal decreases in HCT and Hb in males given 300 mg/kg/day and in females given ≥150 mg/kg/day; decreases in WBC and ABLYMP in females given 300 mg/kg/day. At recovery sacrifice, all

alterations in hematology parameters at terminal sacrifice were completely reversed. **BB102-citrate-related alterations in organ weights included:** at terminal sacrifice, BB102-citrate-related differences in organ weights included increases in absolute and relative (to brain and body weight) weights of the liver in females and males given ≥150 mg/kg/day; decreases in absolute and relative (to brain and body weight) weights of the thymus in females given 300 mg/kg/day. At recovery sacrifice, all alterations in organ weights at terminal sacrifice were completely reversed. **BB102-citrate-related macroscopic observations** noted in the liver, kidney and adrenal gland included: at terminal sacrifice, diffuse or multifocal yellowish discoloration of all lobes of the liver in females given ≥150 mg/kg/day and males given 300 mg/kg/day; diffuse or multifocal yellowish discoloration in the cortex of kidney in females given 300 mg/kg/day; multifocal dark red discoloration in the cortex of adrenal gland in 2 females given 300 mg/kg/day. At recovery sacrifice, all macroscopic observations at terminal sacrifice were completely reversed. **BB102-citrate-related microscopic observations** noted in the liver, kidney, thymus, pancreas and mandibular salivary gland in females and males, and in the adrenal gland in females included: at terminal sacrifice, minimal to moderate periportal hepatocyte vacuolation in the liver in females and males given ≥50 mg/kg/day; minimal or mild tubular vacuolation of the cortex and outer stripe of outer medulla in the kidney in females given 150 mg/kg/day as well as in females and males given 300 mg/kg/day; minimal or mild tingible body macrophage increase in the cortex of thymus in males given ≥ 150 mg/kg/day and females given ≥ 50 mg/kg/day; minimal and/or mild acinar cell secretory depletion in the pancreas in males given 50 mg/kg/day and 300 mg/kg/day and females given ≥ 50 mg/kg/day; minimal acinar cell hypertrophy in the mandibular salivary gland in females and males given 300 mg/kg/day; and minimal or mild zona fasciculata congestion/hemorrhage/necrosis in the unilateral or bilateral adrenal gland(s) in 4 females given 300 mg/kg/day. The moderate periportal hepatocyte vacuolation in the liver in females given ≥150 mg/kg/day at terminal sacrifice were considered adverse. At recovery sacrifice, all microscopic observations except for the change in the liver in males and females given ≥ 150 mg/kg/day at terminal sacrifice had completely reversed. Both on Day 1 and Day 28, the mean values of C_{max} and AUC_{last} in male animals were slightly less than female animals (Ratio: 0.496-0.876), except that the mean values of AUC_{last} in male animals were closed to female animals (Ratio: 1.10) in 150 mg/kg/day dose group on Day 28. The male/female ratio of C_{max} and AUC_{last} decreased with the increase of dose level on Day 1. On Day 1 and Day 28, mean values of C_{max} and AUC_{last} in male and female increased in a close to or less than dose proportional manner in all dose group (ratio of 50-150 mg/kg/day: 1.53-2.91; ratio of 150-300 mg/kg/day: 1.22-2.20), except that mean values of C_{max} in male were slightly decreased in the range of 150-300 mg/kg/day on Day 1 (Ratio: 0.941) and mean values of AUC_{last} in male increased in a more than dose proportional manner in the range of 50-150 mg/kg/day on Day 28 (Ratio: 4.32). No accumulation of AUC_{last} was observed after 28 days of repeat dosing in both male and female animals at all doses (ratio: 0.662-1.26 <2-

fold). Except for increase of TBIL and moderate periportal hepatocyte vacuolation in the liver in females given ≥ 150 mg/kg/day at terminal sacrifice, none of other findings were considered adverse. Therefore, the severely toxic dose to 10% of the animals (STD_{10}) in this study was 300 mg/kg/day, which corresponded to mean C_{max} and AUC_{last} values of 15925 ng/mL and 165393 h*ng/mL in males, respectively, and 27275 ng/mL and 247610 h*ng/mL in females, respectively, on Day 28. The main toxic target organ was liver, and the liver related adverse changes exhibited signs of recovery during the recovery phase.

The 14-day dose range finding toxicity study of BB102 in Beagle dogs (non-GLP): Beagle dogs were administered with vehicle and BB102-citrate at dose levels of 40, 100 and 200 mg/kg/day [the vehicle was 0.5%MC (w/v) in citric acid solution, pH≈2.5] via oral gavage QD for 14 days in which the main toxicity was noted at 200 mg/kg/day. BB102-citrate-related abnormal findings included: abnormal clinical observations (emesis, tremor, salivation, loose feces and watery feces); body weight loss; alterations of clinical chemistry parameters (increases of ALT, ALP, blood urea, blood urea nitrogen/creatinine, creatinine and phosphorus/P, and decreases of cholesterol, TG, sodium/Na, potassium/K and chlorine/Cl); alterations of organ weight (the weight of heart, kidney, liver, spleen and thymus decreased); macroscopic findings (decreased in size of thymus and spleen, multifocal dark red discoloration of mesenteric lymph, diffuse yellowish discoloration of all lobes of liver). Therefore, the repeat dose MTD of BB102-citrate was defined at 200 mg/kg/day in male and female animals, which corresponded to mean C_{max} and AUC_{last} values of 19500 ng/mL and 73131 h*ng/mL in males, respectively, and 12800 ng/mL and 122202 h*ng/mL in females on Day 14, respectively.

The 28-day oral toxicity and toxicokinetic study of BB102-citrate with a 28-day recovery period in Beagle dogs (GLP): Beagle dogs were administered with vehicle and BB102-citrate at dose levels of 40, 100 and 250 mg/kg/day (the vehicle was 0.5%MC in citric acid solution, pH≈2.5) via oral gavage QD for 28 days; the reversibility, progression and/or potential delayed effects were investigated during a 28-day recovery period. One female given 250 mg/kg/day was sacrificed on Day 24, while other animals were well tolerated. No BB102-citrate-related changes were noted in ophthalmic examination, body temperature, blood pressure, coagulation parameters or urinalysis parameters. In dosing period, **BB102-citrate-related abnormal clinical observations included:** emesis and loose feces in both females and males given ≥40 mg/kg/day; salivation in males given ≥100 mg/kg/day and females given 250 mg/kg/day; feces with white foam in males given ≥40 mg/kg/day and females given 250 mg/kg/day; watery feces and color change of feces in mals given ≥40 mg/kg/day and females given ≥100 mg/kg/day. Above findings showed recovery during recovery phase. **For body weight**, in dosing period, the decreases of body weight and body weight gain were noted in females and males at each dose level with dose-dependency. During recovery phase, the body weight and body weight gain of females and males at each dose level showed recovery. **For food consumption**, in dosing period, the frequency of "poor" in female animals

given 250 mg/kg/day was greater than that in control group. In recovery phase, the food consumption of females and males at each dose level recovered to the same level as that in control group which showed recovery. **For electrocardiogram,** in dosing period, increase of heart rate and decrease of RR interval in males given 250 mg/kg/day were observed on Day 1 when compared with the concurrent control group. At the terminal period (day 26), decrease of PR interval was noted in males given 100 mg/kg/day and 250 mg/kg/day. BB102-citrate-related alterations were comparable to concurrent control group and were comparable to pre-dose levels at the recovery period. **BB102-citrate-related alterations of clinical chemistry parmeters included:** increases of ALT and phosphorus/P; decreases of cholesterol, TG and low density lipoprotein cholesterol (LDL) in females and males given ≥40 mg/kg/day; decrease of ALP in males given ≥40 mg/kg/day and 2 females given 100 mg/kg/day; decreases of total protein, albumin (ALB) and globulin (GLO) in males given ≥ 40 mg/kg/day and 1 female given 250 mg/kg/day; decrease of GLO in 1 female given 100 mg/kg/day; increase of TBIL in 1 female given 100 mg/kg/day and 1 male and 1 female given 250 mg/kg/day; decrease of high density lipoprotein cholesterol (HDL) in males given ≥ 40 mg/kg/day and females given ≥ 100 mg/kg/day. No BB102-citrate-related alterations of clinical chemistry parmeters were noted at recovery sacrifice. **BB102-citrate-related alterations of hematology parmeters included:** decreases of ABRETIC, absolute eosinophil count (ABEOS) in females and males given ≥40 mg/kg/day; decreases of RBC, HCT, Hb in males given ≥40 mg/kg/day and females given 250 mg/kg/day. No BB102-citrate-related alterations of hematology parmeters were noted at recovery sacrifice. **BB102-citrate-related alterations in organ weights included:** increases in absolute and relative (to brain and/or body weight) weights of the liver in females and males given ≥40 mg/kg/day; decreases in absolute and relative (to brain and body weight) weights of the thymus in males given ≥ 40 mg/kg/day, one female given 100 mg/kg/day and one female given 250 mg/kg/day. No BB102-citrate-related alterations of organ weight were noted at recovery sacrifice. **BB102-citrate-related macroscopic observations included:** decrease in size of the thymus in males given 250 mg/kg/day and females given ≥100 mg/kg/day; multifocal or diffuse yellow discoloration in all lobes of the liver in females given ≥40 mg/kg/day. No BB102-citrate-related macroscopic findings were noted at recovery sacrifice. **BB102-citrate-related microscopic observations included:** minimal multifocal hepatocellular vacuolation in the liver and minimal and/or mild mucosal atrophy in the cecum, colon and rectum in both females and males given ≥40 mg/kg/day; moderate diffuse hepatocellular vacuolation in the liver in females given ≥100 mg/kg/day; minimal mucosal hyperplasia in the gallbladder and minimal and/or mild hypertrophy of follicular cell in the thyroid in both females and males given 250 mg/kg/day; minimal atrophy of acinar cell in the lacrimal gland, minimal and/or mild cortical and medullary lymphoid depletion in the thymus in males given ≥40 mg/kg/day and females given ≥100 mg/kg/day; minimal lymphoid depletion of white pulp in the spleen and minimal secretory depletion of acinar cell in the pancreas in females given 100

mg/kg/day; mild lymphoid depletion of gut associated lymphoid tissue in the ileum in females given 250 mg/kg/day; minimal atrophy of acinar cell in the mandibular salivary gland in females given ≥40 mg/kg/day; minimal epidermal atrophy and minimal adnexal atrophy in females given ≥100 mg/kg/day. The moderate diffuse hepatocellular vacuolation in liver in females given ≥ 100 mg/kg/day was considered adverse. No BB102-citrate-related microscopic findings were noted at recovery sacrifice. In the 40 mg/kg/day dose group and 100 mg/kg/day dose group, the values of C_{max} and AUC_{last} in males were closed to females on Day 1 and Day 28 (Ratio: 0.704-1.16), indicating there was no significant sex differences between males and females. In the 250 mg/kg/day dose group, the AUC_{last} on Day 1 and Day 28 and the C_{max} on Day 28 in males were slightly lower than that in females (Ratio: 0.503-0.651). On Day 1 and Day 28, C_{max} and AUC_{last} did not increase significantly or decreased in both females and males in the dose range of 40-100 mg/kg/day (Ratio: 0.759-1.29). C_{max} and AUC_{last} increased in the dose range of 100-250 mg/kg/day on Day 1 and Day 28 in both females and males in a manner close to or below the dose ratio increases (Ratio: 1.07-2.50). Compared to AUC_{last} on Day 1, no significant accumulation of AUC_{last} was observed in females and males in the 40 mg/kg/day dose group on Day 28 (Ratio: 1.56-1.96), and accumulation was observed in females and males in the 100 mg/kg/day and 250 mg/kg/day dose groups (Ratio: 2.17-3.00). The moderate diffuse hepatocellular vacuolation in the liver in females given ≥100 mg/kg/day was considered as adverse changes. The highest non-severely toxic dose (HNSTD) for males and females was defined as 250 mg/kg/day and 100 mg/kg/day, respectively, which correnspponded to mean C_{max} and AUC_{last} values for BB102 of 12620 ng/mL and 65467 h*ng/mL in males, and 10166 ng/mL and 51999 h*ng/mL in females on Day 28, respectively. The main toxic target organ was liver, and the liver related adverse changes had completely reversed during the recovery phase.

1.6 Overview of Clinical Trials of BB102

BB102 belongs to the innovative drug/molecular, and there is no clinical trial data yet.

Its preparation BB102 tablets have not been clinically investigated around the world, and this is the first clinical trial application in the United States of America.

1.7 Risk-benefit Assessment

In order to meet the clinical treatment needs of FGF19 or FGFR4-positive advanced primary HCC or other advanced solid tumors as soon as possible and fill the gap in this treatment field, the sponsor applies for a phase I clinical trial to evaluate the safety, tolerability, PK profiles and efficacy of oral BB102 tablets in patients with advanced solid tumors on the basis of nonclinical studies.

The risks and benefits of BB102 tablets will be assessed based on the mechanism of action of BB102, the nonclinical study data of BB102, and the clinical trial data of similar drugs.

Risks

The results of the safety pharmacology showed that BB102 was expected to have no adverse effects on the cardiovascular system, respiratory system, or central nervous system in humans.

The 28-day oral toxicity study of BB102-citrate in SD rats: No BB102-citrate-related findings in ophthalmology examination, coagulation parameters or urinalysis parameters were noted in the study. Increase in TBIL and moderate periportal hepatocyte vacuolation in the liver in females given ≥150 mg/kg/day were considered adverse changes, and the main toxic target organ was liver.

The 28-day oral toxicity study of BB102-citrate in Beagle dogs: No BB102-citrate-related changes were noted in ophthalmic examination, body temperature, blood pressure, coagulation parameters or urinalysis parameters. The moderate diffuse hepatocellular vacuolation in the liver in females given ≥100 mg/kg/day was considered as adverse changes, and the main toxic target organ was liver.

In clinical trials of similar drugs (FGF401, BLU-554, H3B-6527), the most common AEs were diarrhea, asthenia, pyrexia, vomiting and nausea.

By referring to the above information, in order to minimize the risk of the subjects, this trial will include the appropriate subject population through the inclusion/exclusion criteria, and ensure the safety of subjects through various safety examinations during the trial [hematology, urinalysis, fecal analysis, blood biochemistry, coagulation function test, vital signs examination, electrocardiogram examination, echocardiography examination, physical examination, Eastern Cooperative Oncology Group (ECOG) evaluation, pregnancy-related tests, etc.], AE treatment, dose interruption, dose adjustment and other measures. In addition, this trial will pay close attention to AEs and SAEs, as well as excessive bile acid levels in the blood and hepatobiliary diseases associated with hypersecretion of bile acids that occur or worsen in the trial to detect and deal with safety issues.

Benefits

BB102 tablets are an FGFR4 inhibitor with clear mechanism of action, high target selectivity and high drug activity.

Nonclinical *in vitro* pharmacodynamic studies showed that BB102 was a strong FGFR4 inhibitor, and its inhibitory effect on FGFR4 kinase was better than BLU-554. BB102 showed its antitumor effect *in vitro* by selectively inhibiting the binding of FGF19 and FGFR4, thereby inhibiting its downstream signal pathway, and then inhibiting the proliferation of solid tumor cell lines with FGF19/FGFR4 high-expression and Ba/F3 cell lines with FGFR4 mutations.

Nonclinical *in vivo* pharmacodynamic studies showed that BB102-citrate significantly inhibited the growth of human hepatocellular carcinoma HuH-7 cell mouse xenografts at 30 mg/kg BID, 60

mg/kg BID and 90 mg/kg BID doses, and its antitumor effect was similar to that of positive control FGF401, and was significantly better than that of positive control sorafenib and BLU-554. BB102-citrate significantly inhibited the growth of human hepatocellular carcinoma JHH-7 cell mouse xenografts with dose dependent manner at 10 mg/kg BID, 30 mg/kg BID, 60 mg/kg BID doses and at 60 mg/kg BID, 80 mg/kg BID doses, which was slightly better than positive control BLU-554. BB102-citrate significantly inhibited the growth of human breast cancer MDA-MB-453 cells xenograft tumor in mice at 80 mg/kg BID dose. The antitumor effect of BB102 in this model was similar to that of positive control BLU-554. BB102-citrate significantly inhibited the growth of human rhabdomyosarcoma SJCRH30 cell mouse xenografts at 60 mg/kg BID dose. The antitumor effect of BB102 in this model was similar to that of positive control BLU-554. BB102 could inhibit the growth of subcutaneous xenograft tumor of human hepatocellular carcinoma Hep 3B cells in CB17.SCID mice with a dose-dependent manner at 5 mg/kg BID, 10 mg/kg BID and 30 mg/kg BID doses, and its inhibitory effect was close to that of positive control FGF401. At the same time, the PK study of tumor bearing mice in this model showed the plasma exposure of BB102 was positively correlated with its antitumor effect, and the drug concentration in plasma of tumor-bearing mice was basically consistent with that in tumor. In addition, BB102 inhibited the FGF19/FGFR4 signal pathway, thereby inhibiting the phosphorylation of ERK, a key protein in the downstream MAPK signal pathway, and finally showed its antitumor effect. **In general, the inhibitory effect of BB102 on tumer was better than or close to that of the positive control drugs sorafenib and BLU-554, and similar to that of the positive control drug FGF401.**

Among similar drugs, only FGF401, BLU-554, and H3B-6527 have clinical trial results published. In a phase I dose-escalation study of **FGF401 monotherapy** (N=74, FGFR4- and KLB-positive HCC or other advanced malignant solid tumors that progressed after standard therapy, were intolerable to standard therapy, or had no standard therapy available), the overall ORR was 5.4% (4/74), and the DCR was 45.9% (34/74) [14]; in phase II dose expansion cohort 1 of FGF401 monotherapy (N=30, HCC patients from Asian countries; 120 mg QD fasted), the ORR was 6.7% (2/30) and the DCR was 43.3% (13/30); in phase II dose expansion cohort 2 of FGF401 monotherapy (N=36, HCC patients from non-Asian countries; 120 mg QD fasted), the ORR was 5.6% (2/36) and the DCR was 61.1% (22/36); in phase II dose expansion cohort 3 of FGF401 monotherapy (N=20, patients with other malignant solid tumors, regardless of their geographic location; 120 mg QD fasted), the ORR was 0% and the DCR was 30% (6/20) [14]. Among 66 subjects with FGF19 IHC+ receiving **BLU-554 monotherapy**, 11 (17%) subjects were assessed to have an objective response, including 1 (2%) subject with CR and 10 (15%) subjects with PR; the mDOR was 5.3 months; the mPFS was 3.3 months (2.1-3.7 months). Among 34 subjects with FGF19 IHC-negative or unknown FGF19 status, the ORR was 0.0% [15]. After **H3B-6527 monotherapy** was given to HCC subjects who had previously received >2-line treatment receiving, the OS of QD administration (48 subjects) was 10.6 months, the PFS was 4.1 months, the total

response rate was 16.7% (all PR), and the clinical benefit rate was 45.8% (response + stable disease for >17 weeks) [16].

Therefore, it is estimated that BB102 tablets have good efficacy for FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors.

Risk-benefit assessment

Based on the above-mentioned mechanism of action of BB102, the nonclinical study data of BB102, and the clinical trial data of similar drugs, the possible clinical benefits of BB102 tablets outweigh the potential risk of toxicity. The successful development of BB102 will further meet the urgent clinical needs of tumor patients, be of great clinical significance and bring economic and social benefits. Since this trial is an early phase trial of BB102 tablets, the suitable subject population will be included based on the inclusion/exclusion criteria; potential risks suggested by nonclinical studies have all been monitored and controlled in the clinical protocol; the safety of subjects will be ensured through AE treatment, dose interruption, dose adjustment and other measures; close attention will be paid to AEs and SAEs.

2. Study Objectives

2.1 Dose Escalation Trial

Primary objectives:

- To evaluate the safety and tolerability of different doses of BB102 tablets monotherapy (fasted or fed) in patients with advanced solid tumors.
- To explore the MTD by observing the DLT of BB102 tablets monotherapy (fasted or fed) within the specified dose range, so as to provide rationale for determining the RP2D.

Secondary objectives:

- To investigate the PK profiles of BB102 tablets monotherapy (fasted) administered as single and multiple oral doses in patients with advanced solid tumors.
- To preliminarily investigate the effect of food on the PK profiles of BB102 tablets monotherapy administered as single and multiple oral doses in patients with advanced solid tumors.
- To preliminarily investigate the efficacy of BB102 tablets monotherapy (fasted or fed) in patients with advanced solid tumors.
- To investigate the relationship between biomarker and efficacy and to preliminarily infer the correlation.
- To explore the correlation between plasma concentration of study drug and Fridericia method corrected QT interval (QTcF) (C-QTcF analysis).
- To identify the metabolites of BB102 in patients with advanced solid tumors.

2.2 Expansion Trial

Primary objectives:

- To evaluate the efficacy of BB102 tablets monotherapy (fasted) in patients with FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors.

Secondary objectives:

- To investigate the PK profiles of BB102 tablets monotherapy (fasted) in patients with FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors.
- To investigate the safety of BB102 tablets monotherapy (fasted) in patients with FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors.
- To investigate the relationship between biomarker and efficacy and to preliminarily infer the correlation.

3. Selection and Withdrawal of Subjects

3.1 Inclusion Criteria

Patients must meet all of the following criteria before being enrolled in the study:

(1) 18-78 years of age (inclusive) in dose escalation trial and ≥18 years of age in expansion trial at the time of signing the informed consent form (ICF), male or female.

(2) For the dose escalation trial, histologically, cytologically confirmed or clinically confirmed advanced solid tumors patients who without available standard treatment, failed in standard treatment or cannot tolerate standard treatment (primary HCC patients are preferred; primary HCC patients should have a liver function score of ≤9 points as assessed according to the Child-Pugh classification criteria). Note: Only primary liver cancer can be clinically diagnosed, and other tumors need to be confirmed by histology or cytology.

For the expansion trial, histologically or cytologically confirmed FGF19 or FGFR4 positive advanced primary HCC (primary HCC patients should have a liver function score of ≤9 points as assessed according to the Child-Pugh classification criteria) or other advanced solid tumors patients who without available standard treatment, failed in standard treatment or cannot tolerate standard treatment. Note: FGF19 or FGFR4 positivity includes but is not limited to FGF19 amplification, FGF19 overexpression, elevation of serum FGF19 protein level, FGFR4 amplification, FGFR4 overexpression and FGFR4 activating mutation. At the discretion of the investigator, the patien's previous positive test results for FGF19 or FGFR4 can be accepted (patients must agree to provide previous positive test results for FGF19 or FGFR4). Newly reported FGF19 or FGFR4 positive test results from a central laboratory based on tumor tissue and/or blood samples are also acceptable (patients must agree to provide tumor tissue samples and/or blood samples for FGF19 or FGFR4 positive testing. If there are special circumstances such as the tissue is difficult to obtain or the risk of obtaining biopsy is high, etc., the investigator can communicate with the sponsor to discuss whether it can be exempted. Tumor tissue: During screening period, tumor tissue samples from patients in the past 2 years or fresh tumor tissue samples can be collected; the samples can be collected from the primary lesion or metastatic lesions. Blood: A fresh blood sample 5 mL can be collected during the screening period).

(3) For the dose escalation trial, at least one evaluable tumor lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix I).

For the expansion trial, at least one measurable tumor lesion according to RECIST v1.1.

(4) Eastern Cooperative Oncology Group (ECOG) performance status score of ≤1 (Appendix II).

(5) Life expectancy of ≥3 months.

(6) With good organ function, including:

- Liver function: TBIL ≤1.5 × upper limit of normal (ULN), ALT ≤3×ULN, and AST ≤3×ULN (for patients with liver cancer or liver metastases, the criteria will be TBIL ≤3×ULN, ALT ≤5×ULN, and AST ≤5×ULN);
- Renal function: blood creatinine ≤1.5×ULN and creatinine clearance rate ≥50 mL/min (calculated based on Cockcroft-Gault formula);
- Hematology (no blood transfusion or hematopoietic stimulating factor therapy within 14 days of blood sampling for hematology): blood platelet (PLT) $\geq 100\times10^9$/L (for patients with liver cancer, the criteria will be PLT $\geq 85\times10^9$/L), absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L, and Hb ≥90 g/L (90 mg/mL);
- Coagulation function: activated partial thromboplastin time ≤1.5×ULN and international normalized ratio ≤1.5×ULN.

(7) For female patients of childbearing potential, the pregnancy test result within 7 days before the first dose is negative and promise to use adequate and effective methods of contraception or abstinence from the start of screening period to 6 months after the last dose of study treatment; male patients who promise to use adequate and effective methods of contraception or abstinence from the start of screening period to 6 months after the last dose of study treatment. The definition of female with childbearing potential and contraceptive requirements are detailed in Appendix III.

(8) Voluntarily participate in this clinical study, understand the content of the ICF and sign it voluntarily, with good compliance.

3.2 Exclusion Criteria

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

(1) Use of systemic immunosuppressive or systemic cortisol (≥10 mg prednisone or other equivalent hormone) within 4 weeks prior to the first dose.

(2) Prior use of selective FGFR4 inhibitor and/or pan-FGFR inhibitor therapy.

(3) Use of cytotoxic chemotherapeutics within 4 weeks prior to the first dose, OR use of state-approved Chinese traditional patent drugs/Chinese traditional drugs with an anti-tumor effect within 2 weeks prior to the first dose. Note: For mitomycin C or nitrosoureas, 6-week washout is required; for small molecule targeted drugs and oral fluorouracil drugs, a washout period of 2 weeks or five $T_{1/2}$ of the drug (whichever is longer) is required.

(4) Anti-tumor endocrine therapy, radiotherapy, interventional embolization, radiofrequency, proton therapy, radioimmunotherapy, immunotherapy or other biotherapies within 4 weeks prior to the first dose (if five $T_{1/2}$ of the drug/therapy used by the patient is confirmed to be <4 weeks, five $T_{1/2}$ shall prevail).

(5) Use of other clinical investigational drug or therapy that not marketed within 4 weeks prior to the first dose.

(6) Patient is receiving drugs or therapies prohibited in the protocol (e.g., strong CYP3A4 inhibitors, strong CYP3A4 inducers, strong CYP3A5 inhibitors, strong CYP3A5 inducers, sensitive CYP3A4 substrates with a narrow therapeutic index, sensitive CYP2B6 substrates with a narrow therapeutic range, etc., see Section 6.2 of the main text for details) and cannot discontinue such use at least 2 weeks prior to the first dose or throughout the study.

(7) Pregnant or lactating females.

(8) Patient with known hypersensitivity to any ingredient of BB102 tablets, or patient who have a history of drug allergy and is judged as not suitable for participating in this study by the investigator.

(9) Presence of clinically significant gastrointestinal disorder that may affect the intake, transport or absorption of study drugs (e.g., dysphagia, uncontrollable nausea and vomiting, active gastric ulcer, ulcerative colitis, Crohn's disease, chronic diarrhea, intestinal obstruction, and other conditions determined by the investigator that may cause gastrointestinal bleeding, perforation, etc.) at screening.

(10) Patient with concurrent cancer (adequately treated non-melanoma skin cancer or lentigo maligna with no evidence of disease recurrence, except carcinoma in situ) within 5 years prior to the first dose.

(11) Adverse reaction of the prior anti-tumor therapy not yet recovered to grade ≤1 as assessed by CTCAE v5.0 at screening (except the toxicities that are judged as having no safety risk by the investigator, such as alopecia, asthenia, γ-glutamyltransferase (GGT) increased, ALP increased, grade 2 peripheral neurotoxicity, thyroid function decreased stabilized by hormone replacement therapy, etc.).

(12) Clinically uncontrollable third space effusion at screening, which, at the investigator's discretion, is not suitable for enrollment. Note: For patients with third space effusion (pleural ascites, pericardial effusion) who are stable after local drainage and drug infusion, and drug-eluted for at least five $T_{1/2}$ or 14 days (whichever is shorter), they can be considered for enrollment.

(13) Presence of clinically symptomatic metastases to central nervous system or meninges or other evidence showing that metastatic lesions in central nervous system or meninges have not yet been controlled at screening, which, at the investigator's discretion, is not suitable for enrollment. Note: Patients with central nervous system metastases or meningeal metastases who are asymptomatic or in a stable state after treatment before the first dose can be considered for enrollment.

(14) History of severe neurological or psychiatric disorders, including epilepsy, dementia, or moderate to severe depression, etc.

(15) History of drug abuse or dependence.

(16) Clinically significant and uncontrolled cardiovascular diseases, including:

- Serious cardiac rhythm or conduction abnormality at screening, such as ventricular arrhythmia that requires clinical intervention, second/third-degree AV block, etc.;
- Myocardial infarction within 12 months prior to the first dose;
- Acute coronary syndrome, congestive cardiac failure, aortic dissection, cerebral stroke or other grade ≥3 cardiovascular and cerebrovascular events within 6 months prior to the first dose;
- Arterial or deep venous thrombosis within 6 months prior to the first dose, or those who need to monitor international normalized ratios or use anticoagulants at screening. Note: Patients with superficial venous thrombosis which do not need treatment can be considered for enrollment; patients who can stop anticoagulant within 2 weeks before the first dose and during the administration period can be considered for enrollment;
- Mean resting QTcF >480 ms at screening, which are obtained from three 12-lead electrocardiograms (ECGs) [Note: QTcF is calculated based on Fridericia formula, QTcF = QT/(RR^0.33)];
- Heart failure of New York Heart Association Class ≥II at screening;
- Left ventricular ejection fraction (LVEF) <50% at screening;
- Hypertension (defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg) that medication fails to control stably at screening;
- Hyperglycemia that medication fails to control stably at screening.

(17) Pulmonary embolism within 6 months prior to the first dose, or interstitial pneumonia at screening.

(18) Prior allogeneic stem cell transplantation, bone marrow transplantation or vital organ transplantation.

(19) Surgical operation (excluding aspiration biopsy) of vital organs or significant trauma within 8 weeks prior to the first dose, or unrecovered surgical effect at screening, or planned elective major surgery during the study period.

(20) Presence of uncontrollable infectious disease, congenital immunodeficiency disease, acquired immunodeficiency syndrome [positive for human immunodeficiency virus antibody (HIV-Ab)],

syphilis (positive for syphilis antibody), active hepatitis B [for non-HCC patients, hepatitis B virus (HBV)-DNA >500 IU/mL; for HCC patients, HBV-DNA >10^4 copies/mL or 2000 IU/mL; hepatitis B patients need to take oral anti-HBV drugs regularly during the administration of BB102 tablets], hepatitis C virus (HCV) infection (positive for HCV antibody, and positive for quantitative detection of HCV ribonucleic acid amplification).

(21) Severe active infection, including but not limited to bacteremia, severe pneumonia, etc., occurred within 2 weeks before the first dose; active infection that received therapeutic intravenous antibiotics within 2 weeks before the first dose.

(22) Patient with active autoimmune disease, such as rheumatism, rheumatoid, etc.

(23) The investigator considers that the patient is not suitable for participating in this study (e.g., study treatment is not in the best interest of patient, patients with mental disorder, patients with poor compliance, etc.).

3.3 Withdrawal of Subjects

Subjects have the right to discontinue study treatment and/or withdraw from the trial for any reason at any time without affecting future treatment provided by the clinician or the study facility. The investigator also has the right to terminate the study treatment at any time during the study for reasons such as the subject's clinical condition, safety, compliance or management.

Criteria for study treatment discontinuation (whichever occurs first):

- Subject has disease progression, unless the investigator believes the subject can still benefit from the study treatment clinically.
- The investigator determines that the subject cannot clinically benefit from the study treatment and continued study treatment may pose an unacceptable risk to the subject.
- There is major protocol deviation. After enrollment, the subject is found to be non-compliant with enrollment criteria in the study protocol or does not follow requirements in the study protocol, and the investigator believes that continued study treatment may pose an unacceptable risk to the subject.
- The subject has a poor compliance, uses prohibited concomitant medications without permission or fails to attend visits on schedule, which affects the evaluation of efficacy and/or safety, and the subject is considered inappropriate to continue the study at the discretion of the investigator.
- The subject experiences a particular comorbidity or complication, which, in the discretion of the investigator, makes it inappropriate to continue the study treatment.
- The subject experiences an intolerable toxicity.

- Subject pregnancy.
- Subject is lost to follow-up for more than 8 weeks.
- Subject death.
- Any other conditions in which the investigator believes that the study should be terminated.
- The subject refuses to continue the study treatment.
- The study site is closed prematurely, the study is prematurely terminated or the study ends.

Notes: After study treatment discontinuation, subjects will enter into the follow-up period (unless follow-up is not applicable).

Handling of withdrawal/dropout subjects:

Determination of dropout: All subjects who sign the ICF and are screened to be eligible to enter the trial have the right to withdraw from the trial at any time, regardless of the time and reasons. As long as they do not complete the entire clinical trial observation, they are all dropout subjects. Blood samples and tumor tissue samples already obtained from dropout subjects should be retained, processed, and tested.

Subjects can withdraw from the trial without giving any reasons. While respecting the individual rights of the subjects, the investigator should try his best to understand the reasons for withdrawal, and fill in the reasons for withdrawal in the electronic Case Report Form (eCRF); make all possible efforts to contact the subject (if possible, the investigator should meet the subject in person) to complete the assessment items that can be completed, fill in the end of treatment follow-up record form, and record the time of last medication where possible. For those who withdraw due to an AE, the corresponding AE must be recorded in the eCRF. Subjects should return the remaining study drug to the study site. For subjects who withdraw from the trial due to any reason, their eCRFs should be retained; their last test results should be adopted as the final results; and all data on their efficacy and safety should be analyzed.

All study treatment-related toxicities and SAEs ongoing at the time of study termination must be followed up until relieved, unless in the opinion of the investigator, the improvement of this condition is impossible due to the subject's existing condition.

3.4 Rescreening

Subjects who have failed the first screening can be re-screened (they must re-sign the ICF and be assigned a new screening number) at the discretion of the investigator. Subjects can be enrolled in the trial if they meet all the inclusion criteria specified in the protocol and do not meet any of the exclusion criteria at re-screening. Each subject is allowed to be re-screened once.

4. Overall Study Design

4.1 Study Type/Design

This study consists of a dose escalation trial and an expansion trial, both of which are designed as multi-center and open-label trials. This study aims to investigate the safety, tolerability, PK profiles and efficacy of BB102 tablets monotherapy (fasted or fed) orally administered at different doses in patients with advanced solid tumors and to evaluate the effect of food on the PK profiles.

4.1.1 Dose escalation trial (6 fasted dose escalation groups and 1 fed dose escalation group)

4.1.1.1 Basis for selection of starting dose

According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-S9 "*Guideline on Nonclinical Evaluation for Anticancer Pharmaceuticals*", a common approach for many small molecules anticancer drugs is to set a starting dose at 1/10 the STD_{10} in rodents of repeat-dose toxicity study; if the non-rodent is the most appropriate species, then 1/6 the HNSTD is considered an appropriate starting dose. According to the CDE "*Technical Guidelines for Clinical Trials of Anticancer Drugs*" and "*Considerations for Starting Dose Calculation for Phase I Clinical Trial of New Anticancer Pharmaceuticals*", in view of the ethical factors in tumor patients, 1/3 to 1/5 the no observed adverse effect level (NOAEL) is most commonly adopted for small molecule targeted anticancer pharmaceuticals. The corresponding human doses are calculated using the body surface area method based on the above parameters and nonclinical effective starting dose (see the following table). The female rat is the most sensitive species, and the corresponding maximum recommended starting dose (MRSD) is 107.4 mg/day based on the above parameters of nonclinical toxicology; the human equivalent dose calculated based on the nonclinical effective starting dose is 53.6 mg/day.

Nonclinical Toxicology					
Animal/study	**Dosage (mg/kg/day)**	**Reference body weight of the subject (kg)**	**Safety factor**	**Calculation process**	**Alternative human MRSD (mg/day)**
Rats - 28 days QD - gavage - GLP	STD_{10}: 300	60	10	300/36.88*6.60*60/10=322.1	322.1
Beagle dogs - 28 days QD - gavage - GLP	HNSTD: Male 250;	60	6	250/36.88*21.47*60/6=1455.4; 100/36.88*21.47*60/6=582.2	Male 1455.4; Female 582.2;

	Female 100 (deaths at high dose)				
Rats - 28 days QD - gavage - GLP	NOAEL: Male 300; Female 50;	60	5	300/36.88*6.60*60/5=644.3；50/36.88*6.60*60/5=107.4	Male 644.3; **Female 107.4;**
Beagle dogs - 28 days QD - gavage - GLP	NOAEL: Male 250; Female 40;	60	5	250/36.88*21.47*60/5=1746.5；40/36.88*21.47*60/5=279.4	Male 1746.5; Female 279.4;
Animal pharmacodynamic tumor model					
Animal/study	**Effective dose (mg/kg)**	**Reference body weight of the subject (kg)**	**Safety factor**	**Calculation process**	**Human equivalent dose (mg/day)**
Nude mice - 21 days BID - oral	5	60	NA	5*2/36.88*3.29*60=53.6	**53.6**

Abbreviations: BID = twice daily; GLP = Good Laboratory Practice; HNSTD = highest non-severely toxic dose; MRSD = maximum recommended starting dose; NOAEL = noobservedadverseeffect level; QD = once daily; STD_{10} = severely toxic dose to 10% of animals.

Note: The body surface area method is used for conversion, human dose (mg) = animal dose (mg/kg) ÷(km human/km animal) * 60 kg; km human = 36.88; km dog = 21.47; km rat = 6.60 (body weight 200 g); km mice = 3.29.

With the starting doses (e.g., 50, 60, 75, 140, 200, 300 mg/day), escalation doses (e.g., 50, 60, 75, 80, 100, 120, 150, 180, 200, 240, 250, 300, 320, 400, 450, 600, 800, 900, 1000, 1200, 1400, 1600, 2000, 2400 mg/day) and RP2D (e.g., 120, 600, 1000 mg/day) of similar drugs and strengths (10 mg, 50 mg) of BB102 tablets, this trial intends to use 50 mg as the starting dose.

4.1.1.2 Rationale for selection of escalation doses

With a reference to the MTD of repeat-dose toxicity study (see the following table), MTD (e.g., 120 mg/day, 600 mg/day, MTD not reached) and RP2D (e.g., 120, 600 and 1000 mg/day) in the first-in-human study of similar drugs as well as the strengths (10 mg, 50 mg) of BB102 tablets, this study plans to adopt 420 mg as the maximum dose. Based on Fibonacci method, the proposed fasted escalation doses are: 50 mg QD, 100 mg QD, 160 mg QD, 240 mg QD, 320 mg QD and 420 mg QD.

Nonclinical Toxicology

Animal/study	MTD	Reference body weight of the subject (kg)	Calculation process	Human equivalent dose (mg/day)	1/2 human equivalent dose (mg/day)
Beagle dogs - long-term toxicity - 14 days QD - gavage - non-GLP	200 mg/kg/day	60	200/36.88*21.47 *60=6985.9	6985.9	3493.0
Rats - long-term toxicity - 14 days QD - gavage - non-GLP	300 mg/kg/day	60	300/36.88*6.60* 60=3221.3	3221.3	1610.6

Note: The body surface area method is used for conversion, human dose (mg) = animal dose (mg/kg) ÷ (km human/km animal) * 60 kg; km human = 36.88; km dog = 21.47; km rat = 6.60 (weight 200 g).

Taking into account the human dose corresponding to the nonclinical effective starting dose (53.6 mg/day), the accelerated escalation (enrolling 1 subject only) of 50 mg enables quick escalation to the effective dose under the premise of guaranteeing the safety of subjects and subsequently avoids excessive exposure of subjects to ineffective doses.

In addition, according to the action mechanism of FGFR4 inhibitors, inhibition of FGF19/FGFR4 signaling pathway will upregulate CYP7A1 expression (CYP7A1 is associated with metabolism of bile acid) and subsequently cause an increase in bile acid secretion; bile acid secretion also increases after meal. Dose escalation trial of the similar drug FGF401 (NCT02325739) set up separate fed dose escalation groups. Therefore, in order to investigate the effect of food on the safety and tolerability (primary), PK profiles (secondary) of BB102 tablets monotherapy, in this study, an appropriate dose will be selected as the fed dose escalation group according to the previously obtained clinical trial data of BB102 tablets.

4.1.1.3 Escalation method

This study adopts a modified 3+3 escalation design, including accelerated escalation and 3+3 escalation, with 6 fasted dose groups (50 mg QD, 100 mg QD, 160 mg QD, 240 mg QD, 320 mg QD and 420 mg QD) and 1 fed dose group. Note: Before the start of the dose escalation trial, the dosage of the fed dose group cannot be determined temporarily, and an appropriate dose will be selected subsequently by the safety monitoring committee (SMC) according to the previously obtained clinical trial data of BB102 tablets; the trial of the fed dose group can be synchronized with the dose escalation process of the fasted dose groups, and the trial of the fed dose group can also be started after the dose escalation of the fasted dose groups is completed, but the trial of the fed dose group must only be initiated after the equivalent dose is demonstrated to be safe under the fasted condition.

The starting dose group (50 mg QD group) is the accelerated escalation group; other dose groups are 3+3 escalation groups. See Figure 1. All subjects enrolled will firstly receive a single dose for safety observation and PK study, and then undergo a 5-day washout period. Later, subjects will receive multiple-dosing to continue the safety observation and PK study. Multiple-dosing is tentatively scheduled as: once daily in 21-day cycles. After Cycle 1 is finished, a subject can continue to receive the next cycle of treatment if the investigator believes that the subject may benefit from the study treatment.

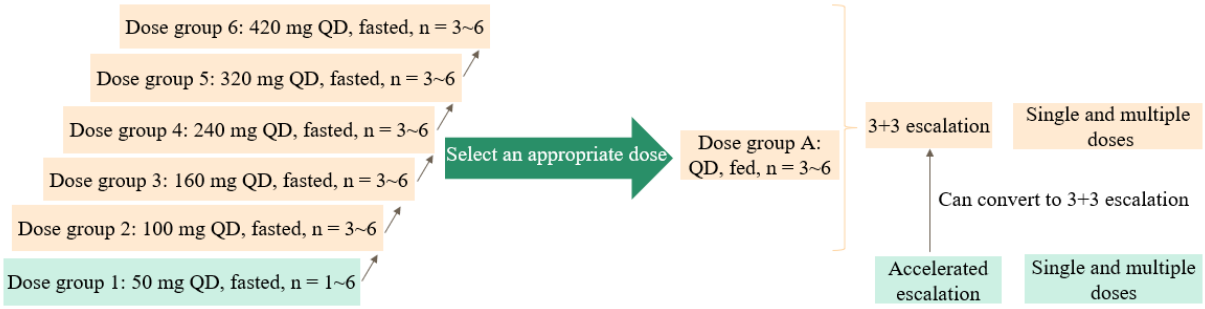


Figure 1 The modified 3+3 escalation design in dose escalation trial

In order to avoid excessive exposure of subjects to ineffective doses, the accelerated escalation group (50 mg QD group) is planned to enroll 1 subject. The method for judging dose escalation is shown in Figure 2. During the DLT observation period (defined as the period from a single dose to the end of Cycle 1 of multiple-dosing), if there is no DLT or grade ≥3 drug-related toxicity [defined as an adverse event (AE) definitely/possibly related to the study drug], the enrollment of the next dose group will be started; if any DLT or grade ≥3 drug-related toxicity occurs, the group will be converted to the 3+3 escalation mode.

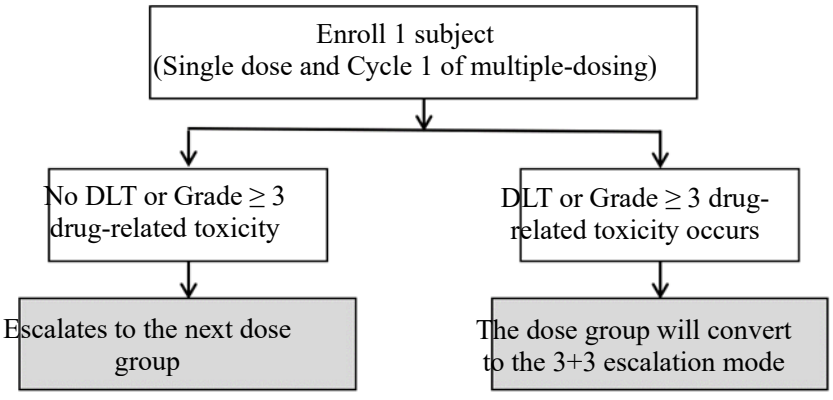


Figure 2 The accelerated escalation diagram in dose escalation trial

It is planned to enroll 3 subjects to other groups, and the specific dose escalation method is shown in Figure 3. For each dose group, if none of the 3 subjects experiences DLT, the trial will proceed

to the next dose group. If ≥2 out of the 3 subjects experience DLT, the dose escalation will be discontinued. If 1 of the 3 subjects experiences DLT, 3 additional subjects should be enrolled into this dose group (if none of the 3 newly enrolled subjects experiences DLT, the trial will proceed to the next dose group; If ≥1 of the 3 newly enrolled subjects experience DLT, dose escalation will be discontinued).

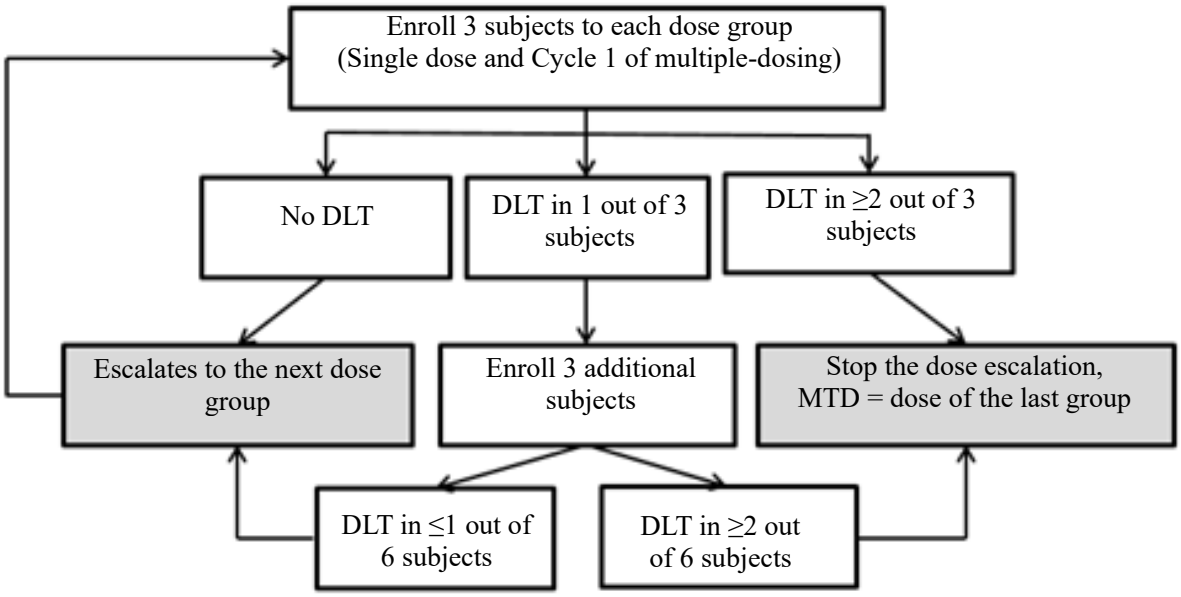


Figure 3 The 3+3 escalation diagram in dose escalation trial

The second and third subjects in the 3+3 escalation groups should only be enrolled after the first subject is observed for at least 5 days after dosing (enrolled on or after C1D1 of the first subject). If the previous subject experiences DLT, the sponsor and the investigator need to cautiously judge whether to enroll the next subject based on the safety data; if subsequent subjects have already been enrolled, the enrolled subjects should continue the study treatment (unless these subjects meet the criteria for study treatment discontinuation), with his/her safety data closely monitored.

SMC will decide whether to perform dose escalation or reduction and determine whether to and how to adjust the escalation doses based on the safety, tolerability and/or PK data obtained during the DLT observation period of a certain dose group. Based on the safety, tolerability, PK and efficacy data of a certain group, if the investigator believes that it is necessary to expand the number of subjects of this dose group to further observe the safety and efficacy and obtain PK data, the number of subjects of this dose group may be increased to 4-12 after reaching a consensus with the sponsor through discussion.

To ensure the safety of subjects, the washout time after single-dosing, dosing frequency, cycle setting, and time points of PK sample collection in the subsequent study as well as the design of subsequent escalation doses (e.g., adding dose groups of 520 mg QD and 600 mg QD) may be

timely adjusted based on the previously obtained safety, tolerability, PK parameters [e.g., $T_{1/2}$, drug accumulation after multiple-dosing] and other previously obtained clinical trial data of BB102 tablets.

MTD is defined as the highest dose level in which DLT occurs in ≤1/6 of the total subjects during the DLT observation period. If MTD is not reached after administration of the maximum dose level shown above, the SMC will decide whether to increase dose groups based on the nonclinical data and the efficacy doses and PK parameters of domestic and foreign similar drugs observed in human.

4.1.1.4 DLT Definition

DLT observation period is defined as the period from a single dose to the end of Cycle 1 of multiple-dosing.

DLT is defined as an AE definitely/possibly related to the study drug occurring in the DLT observation period (AEs will be graded according to CTCAE v5.0) which meets any of the following criteria:

(1) Hematologic toxicity

1) Grade 4 neutrophil count decreased for >3 days.

2) Grade 3 febrile neutropenia: ANC $<1.0\times10^9$/L with single temperature ≥38.3ºC (101°F) or persistent temperature ≥38ºC (100.4°F) for more than 1 hour.

3) Grade 4 PLT count decreased.

4) Grade 3 PLT count decreased with bleeding.

5) Grade 4 anemia.

6) Other grade 3 hematologic toxicities which do not recover to grade ≤2 after 7 days of symptomatic supportive treatment.

(2) Non-hematologic toxicity

1) Grade ≥4 non-hematologic toxicity. Note: Toxicities with no safety risk at the discretion of the investigator are excepted, such as grade 4 GGT increased and alkaline phosphatase (ALP) increased.

2) Grade 3 non-hematologic toxicity (including but not limited to hepatobiliary disorders). Note: Toxicities with no safety risk at the discretion of the investigator (such as grade 3 nausea, vomiting, diarrhea, asthenia, constipation, loss of appetite, mucositis, GGT increased, ALP increased) are not defined as DLT, but they will be defined as DLT when the toxicities do not recover to grade ≤2 within 7 days under the circumstance of symptomatic supportive treatment are permitted.

(3) Other conditions

1) The grade is elevated from baseline with clinically significant and/or unacceptable toxicity, which is judged as a DLT by the SMC.

2) Drug discontinuation lasting 7 days or more due to drug-related toxicity.

3) The dose received by the subject during the DLT observation period is less than 75% of the scheduled dose due to toxicities attributable to study drug, and the investigator believes that it should be considered as a DLT.

4.1.1.5 DLT evaluable subjects

If the dose received by a subject during the DLT observation period is less than 75% of the scheduled dose for reasons other than toxicities attributable to study drug, this subject should not be included into the final DLT analysis of this dose group or the overall groups. If the above situation occurs in any subject, the corresponding dose group needs to enroll one more subject for replacement to ensure the minimum required number of DLT evaluable subjects.

4.1.1.6 SMC

The SMC should be composed of the sponsor (medical monitor, etc.), the investigator, the medical monitor of the Contract Research Organization (CRO), and other relevant personnel. The SMC meetings should be held as needed in the appropriate phase of the trial, e.g., before moving to the next dose group, when significant toxicity occurs, and after escalation to the maximum dose group. The SMC should discuss the obtained data such as subject safety, tolerability, PK, food effects, and preliminary efficacy through appropriate means (such as teleconferences, online conferences or emails, and if necessary, on-site meetings), and make a decision on whether to perform dose escalation or dose de-escalation, whether and how to adjust the escalation dose, whether to add dose groups, etc.

4.1.2 Expansion trial (expansion groups)

Based on the safety, tolerability, PK and efficacy data obtained in previous trials, 1 to 3 appropriate doses (e.g., 100 mg QD, 160 mg QD, and 240 mg QD) will be selected for the expansion trial.

The expansion trial can be initiated when the above doses are demonstrated to have a favorable safety in the dose escalation trial (i.e., the number of subjects experiencing DLT in the group is ≤1/6 of total subjects of the group), without waiting for the completion of the entire dose escalation trial.

Each expansion group will enroll 12 subjects to investigate the efficacy, safety and PK profiles of BB102 tablets. During the expansion trial, AEs meeting the definition of DLT will be regarded as AEs of special interest for safety assessment, thereby enriching the safety assessment data.

4.2 Randomization and Blinding

4.2.1 Screening number

Patients must sign the ICF before they can be screened. The screening number is "XXYYY", where "XX" is the study site number, and "YYY" is the patient's serial number for signing the ICF. The first subject of site 01 is 01001, the third subject of site 02 is 02003, and so on. If a patient fails screening or withdraws from the trial, the patient's screening number can no longer be used, and patients withdrew from the study can no longer participate in the trial.

4.2.2 Randomization method

This phase I trial is a non-randomized trial and no randomization will be performed.

4.2.3 Blinding

This phase I trial is an open-label trial involving dose escalation and expansion, and does not involve blinding.

4.2.4 Blind code preservation, unblinding and unblinding procedures

Not applicable.

4.3 Study Procedures

Throughout the Phase I study, all subjects need to receive study treatment, safety assessment, PK blood sampling and efficacy evaluation according to the visit schedule.

The tumor tissue specimens will be collected and preserved. For the specific collection, handling and storage methods, refer to the related standard operation procedure (SOP) of each study site. Computed tomography (CT) and other electronic documents should be saved on disc.

All laboratory tests should be carried out in laboratories recognized by study sites. Normal ranges of all laboratory test items and the updates during the trial should be collected and preserved.

If the investigator deems it necessary, each test item can be retested within the corresponding test time window and the retest data shall prevail.

Tumor assessment:

1) Imaging tests like computed tomography (CT) /magnetic resonance imaging (MRI) and other radiological examinations of chest, upper abdomen, lower abdomen, pelvic cavity and other positions will be performed. For patients with suspected or known brain metastasis, a radiological examination must be performed at screening/baseline, and contrast-enhanced MRI is preferred (for those allergic to contrast medium, CT/MRI plain scan is acceptable). If brain metastasis is confirmed at screening, the frequency of brain CT/MRI in the subsequent cycles should be kept consistent with the tumor assessment frequency specified in the study; if it is confirmed that there is no brain metastasis by brain CT/MRI at screening, brain CT/MRI

will be performed for confirmation if brain metastasis is suspected by the investigator later. For patients with bone metastasis symptoms, a bone scan must be performed at screening/baseline, and those with a positive result should receive contrast-enhanced MRI scan at the corresponding position for further confirmation. If bone metastasis is confirmed at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if progression of the pre-existing bone metastasis or new bone metastasis is suspected by the investigator later; if it is confirmed that there is no bone metastasis at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if bone metastasis is suspected by the investigator later. Tumor assessments will be performed according to RECIST v1.1. Tumor markers: During the corresponding visits for imaging tests, 4 mL of peripheral blood will be collected for the detection of tumor biomarkers, such as liver cancer [alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA)], breast cancer [cancer antigen 15-3 (CA15-3)], ovarian cancer and endometrial cancer [carbohydrate antigen 125 (CA125)], prostate cancer [prostate specific antigen (PSA)], lung cancer [cytokeratin 19 fragment (CYFRA21-1)] and pancreatic cancer [carbohydrate antigen 242 (CA242)], which serve as auxiliary efficacy indicators.

2) If a subject received a CT/MRI or other radiological examinations within 4 weeks prior to the first dose and has not received any anti-tumor therapy since this tumor assessment, and at the investigator's discretion, the tumor assessment can be performed according to RECIST v1.1, this examination result can be used as baseline tumor assessment result (repeated examination is not necessary).

3) A tumor assessment will be performed at the end of Cycle 1, for which the time window is the end of the cycle ± 1 day. Thereafter, tumor assessments will be performed once every 2 cycles, for which the time window is the end of every 2 cycles ± 7 days [if a subject's assessment result is CR, PR or stable disease (SD), the subject can continue the treatment and continue to receive tumor assessments once every 2 cycles].

4) The radiological confirmation examination of CR or PR should be completed 4-8 weeks after the first evaluation of CR or PR.

5) For the end of treatment visit (EOT), the investigator will determine whether a tumor assessment is required according to the actual condition. If a tumor assessment has been performed within 2 months prior to EOT, it is not necessary to repeat the tumor assessment at EOT visit.

6) During the subsequent follow-up visits once every 8 weeks (±7 days) after the last dose, a tumor assessment will be performed for the subjects who are assessed as having no tumor progression in the previous assessment.

4.3.1 Screening period/baseline (D-28 to D-1)

Specific procedures and assessments are as follows:

- **Informed consent:** Subjects should sign an ICF before starting any study-related procedure.
- **Demographics:** Age, gender, race and ethnicity.
- **Medical history and medication history:** History of all neoplastic diseases, history of all anti-tumor therapies, history of other diseases (within 6 months before enrollment and at present), history of other medications (within 6 weeks before enrollment and at present), family history, surgical history, allergic history, smoking history, history of drug abuse/dependence and history of menstruation and childbearing.
- **Hematology:** RBC count, WBC count, absolute monocyte count (ABMONO), PLT count, ANC, ABLYMP, basophil count, ABEOS, ABRETIC, neutrophil ratio, Hb, HCT, mean corpuscular volume, and mean corpuscular hemoglobin concentration (MCHC). Hematology test at screening visit should be completed within 7 days prior to the first dose, and abnormal test parameters with clinical significance can be re-tested once within 7 days as needed.
- **Urinalysis:** Potential of hydrogen (pH), specific gravity, urine RBC, urine WBC, urine glucose, urine bilirubin, urine protein, urobilinogen, urine ketone bodies, and urine occult blood. Urinalysis at screening visit should be completed within 7 days prior to the first dose, and abnormal test parameters with clinical significance can be re-tested once within 7 days as needed.
- **Stool routine:** Color, shape, fecal RBC, fecal WBC, fecal occult blood, fecal choline, and fecal bilirubin. Stool routine test at screening visit should be completed within 7 days prior to the first dose, and abnormal test parameters with clinical significance can be re-tested once within 7 days as needed.
- **Blood biochemistry:**
  1) **Liver function:** AST, ALT, ALP, LDH, GGT, TBIL, direct bilirubin, total bile acids, ALB, total protein, and GLO.
  2) **Renal function:** Urea/urea nitrogen, creatinine, creatinine clearance, and uric acid.
  3) **Blood lipids:** Total cholesterol, HDL, low LDL, and TG.
  4) **Electrolytes:** Potassium, sodium, chloride, phosphorus, magnesium, and calcium.
  5) **Cardiac function:** Creatine kinase (CK) and creatine kinase isozyme (CKI).
  6) **Blood glucose**: GLU.

  Blood biochemistry test at screening visit should be completed within 7 days prior to the first

dose, and abnormal test parameters with clinical significance can be re-tested once within 7 days as needed.

- **Coagulation:** Prothrombin time, activated partial thromboplastin time, fibrinogen quantification, and international normalized ratio. Coagulation test at screening visit should be completed within 7 days prior to the first dose, and abnormal test parameters with clinical significance can be re-tested once within 7 days as needed.
- **Vital signs:** Body temperature, blood pressure, heart rate, and respiration. Follow the visit time window.
- **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. Follow the visit time window.
- **Physical examination:** Assessments will be performed by organ and system. At screening, a comprehensive physical examination will be performed, including body height, body weight, body mass index (BMI), general condition, nervous system, head and neck, lymph nodes, skin, mucosa, chest, abdomen, four limbs and spine.
- **ECOG assessment.**
- **Pregnancy-related tests:**
  1) For women of childbearing potential, human chorionic gonadotropin (HCG) will be tested. Blood HCG pregnancy test at screening visit should be completed within 7 days prior to the first dose.
  2) For women ≥40 to <60 years of age and at least 12 months post-menopausal, follicle stimulating hormone, estradiol and luteinizing hormone will be tested; if necessary, anti-Mullerian hormone can be tested additionally. This test will be performed at screening only.
  3) For men and women ≥60 years of age, a pregnancy-related test is not required.
- **Echocardiography:** LVEF.
- **Serum etiology test:** HIV-Ab, hepatitis B surface antigen (HBsAg), HBV-DNA (as needed), hepatitis C virus antibody (HCV-Ab) and HCV-RNA (as needed). Serum etiology test at screening visit should be completed within 14 days prior to the first dose.
- **Tumor assessment:**
  1) Imaging tests like CT/MRI and other radiological examinations of chest, upper abdomen, lower abdomen, pelvic cavity and other positions will be performed. For patients with suspected or known brain metastasis, a radiological examination must be performed at screening/baseline, and contrast-enhanced MRI is preferred (for those allergic to contrast

medium, CT/MRI plain scan is acceptable). If brain metastasis is confirmed at screening, the frequency of brain CT/MRI in the subsequent cycles should be kept consistent with the tumor assessment frequency specified in the study; if it is confirmed that there is no brain metastasis by brain CT/MRI at screening, brain CT/MRI will be performed for confirmation if brain metastasis is suspected by the investigator later. For patients with bone metastasis symptoms, a bone scan must be performed at screening/baseline, and those with a positive result should receive contrast-enhanced MRI scan at the corresponding position for further confirmation. If bone metastasis is confirmed at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if progression of the pre-existing bone metastasis or new bone metastasis is suspected by the investigator later; if it is confirmed that there is no bone metastasis at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if bone metastasis is suspected by the investigator later. Tumor assessments will be performed according to RECIST v1.1. Tumor markers: During the corresponding visits for imaging tests, 4 mL of peripheral blood will be collected for the detection of tumor biomarkers, such as liver cancer (AFP, CEA), breast cancer (CA15-3), ovarian cancer and endometrial cancer (CA125), prostate cancer (PSA), lung cancer (CYFRA21-1) and pancreatic cancer (CA242), which serve as auxiliary efficacy indicators.

2) If a subject received a CT/MRI or other radiological examinations within 4 weeks prior to the first dose and has not received any anti-tumor therapy since this tumor assessment, and at the investigator's discretion, the tumor assessment can be performed according to RECIST v1.1, this examination result can be used as baseline tumor assessment result (repeated examination is not necessary).

- **Biomarker detection:** See Section 4.4.3 for details.
- **AE:** See Section 8 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.
- **Reviewing inclusion/exclusion criteria.**

Subjects who have passed the screening will be enrolled into this trial.

4.3.2 Single-dose phase (for dose escalation trial only)

Day 1 (D1):

Specific procedures and assessments are as follows:

- **Vital signs:** Body temperature, blood pressure, heart rate and respiration. For D1, it will be

measured within 1 h pre-dose and at 10 h (±1 h) post-dose on D1. If there are corresponding clinical symptoms at other time, vital signs should also be measured, and the data should be recorded.

- **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. For D1, it will be measured within 1 h pre-dose and at 10 h (±1 h) post-dose on D1. If there are corresponding clinical symptoms at other time, ECG should also be performed, the data should be recorded, and the ECG results should be kept.
- **Study drug administration:** See Section 5.2 and Section 6.1 for details.
- **PK blood collection:** See Section 4.4.1 for details.
- **Blood collection for metabolite identification:** See Section 4.4.2 for details.
- **AE:** See Section 8 for details.
- **DLT evaluation.**
- **Concomitant medications**: see Section 6.2 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Day 2 (D2):

Specific procedures and assessments are as follows:

- **PK blood collection:** See Section 4.4.1 for details.
- **Blood collection for metabolite identification:** See Section 4.4.2 for details.
- **AE:** See Section 8 for details.
- **DLT evaluation.**
- **Concomitant medications**: see Section 6.2 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Day 3 (D3):

Specific procedures and assessments are as follows:

- **Vital signs:** Body temperature, blood pressure, heart rate and respiration. Follow the visit time window. If there are corresponding clinical symptoms at other time, vital signs should also be measured, and the data should be recorded.

- **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. Follow the visit time window. If there are corresponding clinical symptoms at other time, ECG should also be performed, the data should be recorded, and the ECG results should be kept.
- **PK blood collection:** See Section 4.4.1 for details.
- **Blood collection for metabolite identification:** See Section 4.4.2 for details.
- **AE:** See Section 8 for details.
- **DLT evaluation.**
- **Concomitant medications**: see Section 6.2 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Day 4 (D4):

Specific procedures and assessments are as follows:

- **PK blood collection:** See Section 4.4.1 for details.
- **Blood collection for metabolite identification:** See Section 4.4.2 for details.
- **AE:** See Section 8 for details.
- **DLT evaluation.**
- **Concomitant medications**: see Section 6.2 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Day 5 (D5):

Specific procedures and assessments are as follows:

- **Hematology:** RBC count, WBC count, ABMONO, PLT count, ANC, ABLYMP, basophil count, ABEOS, ABRETIC, neutrophil ratio, Hb, HCT, mean corpuscular volume, and MCHC.
- **Urinalysis:** Potential of hydrogen (pH), specific gravity, urine RBC, urine WBC, urine glucose, urine bilirubin, urine protein, urobilinogen, urine ketone bodies, and urine occult blood.
- **Stool routine (±1 day):** Color, shape, fecal RBC, fecal WBC, fecal occult blood, fecal choline, and fecal bilirubin.
- **Blood biochemistry:**

1) **Liver function:** AST, ALT, ALP, LDH, GGT, TBIL, direct bilirubin, total bile acids, ALB, total protein, and GLO.
2) **Renal function:** Urea/urea nitrogen, creatinine, creatinine clearance, and uric acid.
3) **Blood lipids:** Total cholesterol, HDL, LDL, and TG.
4) **Electrolytes**: Potassium, sodium, chloride, phosphorus, magnesium, and calcium.
5) **Heart function:** CK and CKI.
6) **Blood glucose**: GLU.

- **Coagulation:** Prothrombin time, activated partial thromboplastin time, fibrinogen quantification, and international normalized ratio.
- **Vital signs:** Body temperature, blood pressure, heart rate, and respiration. Follow the visit time window. If there are corresponding clinical symptoms at other time, vital signs should also be measured, and the data should be recorded.
- **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. Follow the visit time window. If there are corresponding clinical symptoms at other time, ECG should also be performed, the data should be recorded, and the ECG results should be kept.
- **Physical examination:** Assessments will be performed per organ and system, and a simple physical examination will be performed at this visit, including but not limited to weight, BMI, general condition, skin, and any abnormal signs of concern at the investigator's discretion.
- **ECOG assessment.**
- **PK blood collection:** See Section 4.4.1 for details.
- **Blood collection for metabolite identification:** See Section 4.4.2 for details.
- **AE:** See Section 8 for details.
- **DLT evaluation.**
- **Concomitant medications**: see Section 6.2 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

4.3.3 Multiple-dose phase

Day 1 of Cycle 1 (C1D1):

Specific procedures and assessments are as follows:

- **Vital signs:** Body temperature, blood pressure, heart rate and respiration. For C1D1, it will be

measured within 1 h pre-dose and at 10 h (±1 h) post-dose on C1D1. If there are corresponding clinical symptoms at other time, vital signs should also be measured, and the data should be recorded.

- **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. For C1D1, it will be measured within 1 h pre-dose and at 10 h (±1 h) post-dose on C1D1. If there are corresponding clinical symptoms at other time, ECG should also be performed, the data should be recorded, and the ECG results should be kept.
- **Study drug administration:** See Section 5.2 and Section 6.1 for details.
- **Dispensing diary cards and drugs.**
- **PK blood collection:** See Section 4.4.1 for details.
- **AE:** See Section 8 for details.
- **DLT evaluation:** For the dose escalation trial only.
- **Concomitant medications**: see Section 6.2 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Day 8 of Cycle 1 (C1D8; time window for corresponding examination: ± 1 day):

Specific procedures and assessments are as follows:

- **Hematology:** RBC count, WBC count, ABMONO, PLT count, ANC, ABLYMP, basophil count, ABEOS, ABRETIC, neutrophil ratio, Hb, HCT, mean corpuscular volume, and MCHC. Existing laboratory test results within 48 hours are acceptable.
- **Urinalysis:** Potential of hydrogen (pH), specific gravity, urine RBC, urine WBC, urine glucose, urine bilirubin, urine protein, urobilinogen, urine ketone bodies, and urine occult blood. Existing laboratory test results within 48 hours are acceptable.
- **Stool routine:** Color, shape, fecal RBC, fecal WBC, fecal occult blood, fecal choline, and fecal bilirubin. Existing laboratory test results within 48 hours are acceptable.
- **Blood biochemistry:**
  1) **Liver function:** AST, ALT, ALP, LDH, GGT, TBIL, direct bilirubin, total bile acids, ALB, total protein, and GLO.
  2) **Renal function:** Urea/urea nitrogen, creatinine, creatinine clearance, and uric acid.
  3) **Blood lipids:** Total cholesterol, HDL, LDL, and TG.

4) **Electrolytes**: Potassium, sodium, chloride, phosphorus, magnesium, and calcium.

5) **Heart function:** CK and CKI.

6) **Blood glucose**: GLU.

Existing laboratory test results within 48 hours are acceptable.

- **Coagulation:** Prothrombin time, activated partial thromboplastin time, fibrinogen quantification, and international normalized ratio. Existing laboratory test results within 48 hours are acceptable.
- **Vital signs:** Body temperature, blood pressure, heart rate, and respiration. Follow the visit time window. If there are corresponding clinical symptoms at other time, vital signs should also be measured, and the data should be recorded.
- **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. Follow the visit time window. If there are corresponding clinical symptoms at other time, ECG should also be performed, the data should be recorded, and the ECG results should be kept.
- **Physical examination:** Assessments will be performed per organ and system, and a simple physical examination will be performed at this visit, including but not limited to weight, BMI, general condition, skin, and any abnormal signs of concern at the investigator's discretion.
- **Study drug administration:** See Section 5.2 and Section 6.1 for details.
- **PK blood collection:** See Section 4.4.1 for details.
- **AE:** See Section 8 for details.
- **DLT evaluation:** For the dose escalation trial only.
- **Concomitant medications**: see Section 6.2 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Day 15 of Cycle 1 (C1D15; time window for corresponding examination: ± 1 day):

Specific procedures and assessments are as follows:

- **Hematology:** RBC count, WBC count, ABMONO, PLT count, ANC, ABLYMP, basophil count, ABEOS, ABRETIC, neutrophil ratio, Hb, HCT, mean corpuscular volume, and MCHC. Existing laboratory test results within 48 hours are acceptable.
- **Urinalysis:** Potential of hydrogen (pH), specific gravity, urine RBC, urine WBC, urine glucose, urine bilirubin, urine protein, urobilinogen, urine ketone bodies, and urine occult

blood. Existing laboratory test results within 48 hours are acceptable.

- **Stool routine:** Color, shape, fecal RBC, fecal WBC, fecal occult blood, fecal choline, and fecal bilirubin. Existing laboratory test results within 48 hours are acceptable.
- **Blood biochemistry:**
  1) **Liver function:** AST, ALT, ALP, LDH, GGT, TBIL, direct bilirubin, total bile acids, ALB, total protein, and GLO.
  2) **Renal function:** Urea/urea nitrogen, creatinine, creatinine clearance, and uric acid.
  3) **Blood lipids:** Total cholesterol, HDL, LDL, and TG.
  4) **Electrolytes**: Potassium, sodium, chloride, phosphorus, magnesium, and calcium.
  5) **Heart function:** CK and CKI.
  6) **Blood glucose**: GLU.

  Existing laboratory test results within 48 hours are acceptable.
- **Coagulation:** Prothrombin time, activated partial thromboplastin time, fibrinogen quantification, and international normalized ratio. Existing laboratory test results within 48 hours are acceptable.
- **Vital signs:** Body temperature, blood pressure, heart rate, and respiration. Follow the visit time window. If there are corresponding clinical symptoms at other time, vital signs should also be measured, and the data should be recorded.
- **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. Follow the visit time window. If there are corresponding clinical symptoms at other time, ECG should also be performed, the data should be recorded, and the ECG results should be kept.
- **Physical examination:** Assessments will be performed per organ and system, and a simple physical examination will be performed at this visit, including but not limited to weight, BMI, general condition, skin, and any abnormal signs of concern at the investigator's discretion.
- **Study drug administration:** See Section 5.2 and Section 6.1 for details.
- **Biomarker detection:** See Section 4.4.3 for details.
- **PK blood collection:** See Section 4.4.1 for details.
- **AE:** See Section 8 for details.
- **DLT evaluation:** For the dose escalation trial only.
- **Concomitant medications**: see Section 6.2 for details.

- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Day 21 of Cycle 1 (C1D21; time window for corresponding examination: ± 1 day):

Specific procedures and assessments are as follows:

- **Hematology:** RBC count, WBC count, ABMONO, PLT count, ANC, ABLYMP, basophil count, ABEOS, ABRETIC, neutrophil ratio, Hb, HCT, mean corpuscular volume, and MCHC. Existing laboratory test results within 48 hours are acceptable.
- **Urinalysis:** Potential of hydrogen (pH), specific gravity, urine RBC, urine WBC, urine glucose, urine bilirubin, urine protein, urobilinogen, urine ketone bodies, and urine occult blood. Existing laboratory test results within 48 hours are acceptable.
- **Stool routine:** Color, shape, fecal RBC, fecal WBC, fecal occult blood, fecal choline, and fecal bilirubin. Existing laboratory test results within 48 hours are acceptable.
- **Blood biochemistry:**
  1) **Liver function:** AST, ALT, ALP, LDH, GGT, TBIL, direct bilirubin, total bile acids, ALB, total protein, and GLO.
  2) **Renal function:** Urea/urea nitrogen, creatinine, creatinine clearance, and uric acid.
  3) **Blood lipids:** Total cholesterol, HDL, LDL, and TG.
  4) **Electrolytes**: Potassium, sodium, chloride, phosphorus, magnesium, and calcium.
  5) **Heart function:** CK and CKI.
  6) **Blood glucose**: GLU.

  Existing laboratory test results within 48 hours are acceptable.
- **Coagulation:** Prothrombin time, activated partial thromboplastin time, fibrinogen quantification, and international normalized ratio. Existing laboratory test results within 48 hours are acceptable.
- **Vital signs:** Body temperature, blood pressure, heart rate, and respiration. Follow the visit time window. If there are corresponding clinical symptoms at other time, vital signs should also be measured, and the data should be recorded.
- **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. For C1D21, ECG will be performed within 0.5 h pre-dose and at 2 h (±15 min), 4 h (±15 min), 6 h (±20 min), 8 h (±30 min), and 24 h (±1 h, pre-dose on C2D1) post-pose on C1D21. If there are corresponding clinical symptoms at other

time, ECG should also be performed, the data should be recorded, and the ECG results should be kept.

- **Physical examination:** Assessments will be performed per organ and system, and a simple physical examination will be performed at this visit, including but not limited to weight, BMI, general condition, skin, and any abnormal signs of concern at the investigator's discretion.
- **ECOG assessment.**
- **Pregnancy-related tests:** For women of childbearing potential, HCG will be tested. Blood HCG pregnancy test at screening visit should be completed within 7 days prior to the first dose.
- **Echocardiography:** LVEF. During treatment, echocardiography will be performed at the same frequency with tumor assessment, i.e., echocardiography will be performed at the end of the 1st cycle, and the time window is ±1 day after the end of the cycle.
- **Study drug administration:** See Section 5.2 and Section 6.1 for details.
- **Dispensing/collecting diary cards and drugs.**
- **Tumor assessment:**

1) Imaging tests like CT/MRI and other radiological examinations of chest, upper abdomen, lower abdomen, pelvic cavity and other positions will be performed. If brain metastasis is confirmed at screening, the frequency of brain CT/MRI in the subsequent cycles should be kept consistent with the tumor assessment frequency specified in the study; if it is confirmed that there is no brain metastasis by brain CT/MRI at screening, brain CT/MRI will be performed for confirmation if brain metastasis is suspected by the investigator later. If bone metastasis is confirmed at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if progression of the pre-existing bone metastasis or new bone metastasis is suspected by the investigator later; if it is confirmed that there is no bone metastasis at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if bone metastasis is suspected by the investigator later. Tumor assessments will be performed according to RECIST v1.1. Tumor markers: During the corresponding visits for imaging tests, 4 mL of peripheral blood will be collected for the detection of tumor biomarkers, such as liver cancer (AFP, CEA), breast cancer (CA15-3), ovarian cancer and endometrial cancer (CA125), prostate cancer (PSA), lung cancer (CYFRA21-1) and pancreatic cancer (CA242), which serve as auxiliary efficacy indicators.

2) A tumor assessment will be performed at the end of Cycle 1, for which the time window

is the end of the cycle ± 1 day [if a subject's assessment result is complete response (CR), partial response (PR) or stable disease (SD), the subject can continue the treatment and continue to receive tumor assessments once every 2 cycles].

3) The radiological confirmation examination of CR or PR should be completed 4-8 weeks after the first evaluation of CR or PR.

- **PK blood collection:** See Section 4.4.1 for details.
- **AE:** See Section 8 for details.
- **DLT evaluation:** For the dose escalation trial only.
- **Concomitant medications**: see Section 6.2 for detials.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Day 1 of Cycle 2 (C2D1; time window for corresponding examination: ± 1 day):

Specific procedures and assessments are as follows:

- **PK blood collection:** See Section 4.4.1 for details.
- **AE:** See Section 8 for details.
- **Concomitant medications**: see Section 6.2 for detials.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Starting from Cycle 2 treatment, on Day 21 of each cycle of treatment (CnD21; time window for corresponding examinations: ±3 days):

Specific procedures and assessments are as follows:

- **Hematology:** RBC count, WBC count, ABMONO, PLT count, ANC, ABLYMP, basophil count, ABEOS, ABRETIC, neutrophil ratio, Hb, HCT, mean corpuscular volume, and MCHC. Twice in Cycle 2, e.g., D14 and D21 of the cycle, with a time window of ±3 days; for Cycles 3 to 5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days.
- **Urinalysis:** Potential of hydrogen (pH), specific gravity, urine RBC, urine WBC, urine glucose, urine bilirubin, urine protein, urobilinogen, urine ketone bodies, and urine occult blood. For Cycle 2-5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days.
- **Stool routine:** Color, shape, fecal RBC, fecal WBC, fecal occult blood, fecal choline, and

fecal bilirubin. For Cycle 2-5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days.

- **Blood biochemistry:**

  1) **Liver function:** AST, ALT, ALP, LDH, GGT, TBIL, direct bilirubin, total bile acids, ALB, total protein, and GLO.
  2) **Renal function:** Urea/urea nitrogen, creatinine, creatinine clearance, and uric acid.
  3) **Blood lipids:** Total cholesterol, HDL, LDL, and TG.
  4) **Electrolytes**: Potassium, sodium, chloride, phosphorus, magnesium, and calcium.
  5) **Heart function:** CK and CKI.
  6) **Blood glucose**: GLU.

  Twice in Cycle 2, e.g., D14 and D21 of the cycle, with a time window of ±3 days; for Cycles 3 to 5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days.

- **Coagulation:** Prothrombin time, activated partial thromboplastin time, fibrinogen quantification, and international normalized ratio. Twice in Cycle 2, e.g., D14 and D21 of the cycle, with a time window of ±3 days; for Cycles 3 to 5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days.
- **Vital signs:** Body temperature, blood pressure, heart rate, and respiration. Performed in accordance with the visit time window (twice in Cycle 2, e.g., D14 and D21 of the cycle, with a time window of ±3 days; for Cycles 3 to 5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days). If there are corresponding clinical symptoms at other time, vital signs should also be measured, and the data should be recorded.
- **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. Performed in accordance with the visit time window (twice in Cycle 2, e.g., D14 and D21 of the cycle, with a time window of ±3 days; for Cycles 3 to 5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days). If there are corresponding clinical symptoms at other time, ECG should also be performed, the data should be recorded, and the ECG results should be kept.
- **Physical examination:** Assessments will be performed per organ and system, and a simple physical examination will be performed at this visit, including but not limited to weight, BMI,

general condition, skin, and any abnormal signs of concern at the investigator's discretion. Twice in Cycle 2, e.g., D14 and D21 of the cycle, with a time window of ±3 days; for Cycles 3 to 5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days.

- **ECOG assessment:** For Cycle 2-5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days.
- **Pregnancy-related tests:** For women of childbearing potential, HCG will be tested. Blood HCG pregnancy test at screening visit should be completed within 7 days prior to the first dose. For Cycle 2-5, once at the end of each cycle, with a time window of ±3 days; since Cycle 6, once at the end of every 2 cycles, with a time window of ±3 days.
- **Echocardiography:** LVEF. During treatment, echocardiography will be performed at the same frequency with tumor assessment, i.e., after the end of the 1st cycle, echocardiography will be performed every 2 cycles with a time window of ±7 days from the end of every 2 cycles.
- **Study drug administration:** See Section 5.2 and Section 6.1 for details.
- **Dispensing/collecting diary cards and drugs.**
- **Tumor assessment:**

  1) Imaging tests like CT/MRI and other radiological examinations of chest, upper abdomen, lower abdomen, pelvic cavity and other positions will be performed. If brain metastasis is confirmed at screening, the frequency of brain CT/MRI in the subsequent cycles should be kept consistent with the tumor assessment frequency specified in the study; if it is confirmed that there is no brain metastasis by brain CT/MRI at screening, brain CT/MRI will be performed for confirmation if brain metastasis is suspected by the investigator later. If bone metastasis is confirmed at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if progression of the pre-existing bone metastasis or new bone metastasis is suspected by the investigator later; if it is confirmed that there is no bone metastasis at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if bone metastasis is suspected by the investigator later. Tumor assessments will be performed according to RECIST v1.1. Tumor markers: During the corresponding visits for imaging tests, 4 mL of peripheral blood will be collected for the detection of tumor biomarkers, such as liver cancer (AFP, CEA), breast cancer (CA15-3), ovarian cancer and endometrial cancer (CA125), prostate cancer (PSA), lung cancer (CYFRA21-1) and

pancreatic cancer (CA242), which serve as auxiliary efficacy indicators.

2) Tumor assessments will be performed once every 2 cycles after the end of Cycle 1, for which the time window is the end of every 2 cycles ± 7 days [if a subject's assessment result is CR, PR or SD, the subject can continue the treatment and continue to receive tumor assessments once every 2 cycles].

3) The radiological confirmation examination of CR or PR should be completed 4-8 weeks after the first evaluation of CR or PR.

- **Biomarker detection:** See Section 4.4.3 for details.
- **AE:** See Section 8 for details.
- **Concomitant medications**: see Section 6.2 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

4.3.4 End of study treatment visit (EOT; within 7 days after the last dose)

Specific procedures and assessments are as follows:

- **Hematology:** RBC count, WBC count, ABMONO, PLT count, ANC, ABLYMP, basophil count, ABEOS, ABRETIC, neutrophil ratio, Hb, HCT, mean corpuscular volume, and MCHC. Existing laboratory test results within the visit time window are acceptable.
- **Urinalysis:** Potential of hydrogen (pH), specific gravity, urine RBC, urine WBC, urine glucose, urine bilirubin, urine protein, urobilinogen, urine ketone bodies, and urine occult blood. Existing laboratory test results within the visit time window are acceptable.
- **Stool routine:** Color, shape, fecal RBC, fecal WBC, fecal occult blood, fecal choline, and fecal bilirubin. Existing laboratory test results within the visit time window are acceptable.
- **Blood biochemistry:**

  1) **Liver function:** AST, ALT, ALP, LDH, GGT, TBIL, direct bilirubin, total bile acids, ALB, total protein, and GLO.

  2) **Renal function:** Urea/urea nitrogen, creatinine, creatinine clearance, and uric acid.

  3) **Blood lipids:** Total cholesterol, HDL, LDL, and TG.

  4) **Electrolytes**: Potassium, sodium, chloride, phosphorus, magnesium, and calcium.

  5) **Heart function:** CK and CKI.

  6) **Blood glucose**: GLU.

  Existing laboratory test results within the visit time window are acceptable.

- **Coagulation:** Prothrombin time, activated partial thromboplastin time, fibrinogen quantification, and international normalized ratio. Existing laboratory test results within the visit time window are acceptable.
- **Vital signs:** Body temperature, blood pressure, heart rate, and respiration. Follow the visit time window. If there are corresponding clinical symptoms at other time, vital signs should also be measured, and the data should be recorded.
- **12-lead ECG:** Measurements will be performed after resting in supine position, and the data (PR, QRS, QT and QTcF) will be recorded. Follow the visit time window. If there are corresponding clinical symptoms at other time, ECG should also be performed, the data should be recorded, and the ECG results should be kept.
- **Physical examination:** Assessments will be performed per organ and system, and a simple physical examination will be performed at this visit, including but not limited to weight, BMI, general condition, skin, and any abnormal signs of concern at the investigator's discretion.
- **ECOG assessment.**
- **Pregnancy-related tests:**
  1) For women of childbearing potential, HCG will be tested.
  2) For men and women ≥60 years of age, a pregnancy-related test is not required.
- **Echocardiography:** LVEF.
- **Collecting diary cards and drugs.**
- **Tumor assessment:**
  1) Imaging tests like CT/MRI and other radiological examinations of chest, upper abdomen, lower abdomen, pelvic cavity and other positions will be performed. If brain metastasis is confirmed at screening, the frequency of brain CT/MRI in the subsequent cycles should be kept consistent with the tumor assessment frequency specified in the study; if it is confirmed that there is no brain metastasis by brain CT/MRI at screening, brain CT/MRI will be performed for confirmation if brain metastasis is suspected by the investigator later. If bone metastasis is confirmed at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if progression of the pre-existing bone metastasis or new bone metastasis is suspected by the investigator later; if it is confirmed that there is no bone metastasis at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if bone metastasis is suspected by the investigator later. Tumor assessments will be

performed according to RECIST v1.1. Tumor markers: During the corresponding visits for imaging tests, 4 mL of peripheral blood will be collected for the detection of tumor biomarkers, such as liver cancer (AFP, CEA), breast cancer (CA15-3), ovarian cancer and endometrial cancer (CA125), prostate cancer (PSA), lung cancer (CYFRA21-1) and pancreatic cancer (CA242), which serve as auxiliary efficacy indicators.

2) For the EOT, the investigator will determine whether a tumor assessment is required according to the condition. If a tumor assessment has been performed within 2 months prior to EOT, it is not necessary to repeat the tumor assessment at EOT visit.

3) The radiological confirmation examination of CR or PR should be completed 4-8 weeks after the first evaluation of CR or PR.

- **Biomarker detection:** See Section 4.4.3 for details.
- **AE:** See Section 8 for details.
- **Concomitant medications**: see Section 6.2 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

4.3.5 Follow-up period

Safety visit [28 days (±7 days) after the last dose]:

Specific procedures and assessments are as follows:

- **Hematology:** RBC count, WBC count, ABMONO, PLT count, ANC, ABLYMP, basophil count, ABEOS, ABRETIC, neutrophil ratio, Hb, HCT, mean corpuscular volume, and MCHC. Existing laboratory test results within the visit time window are acceptable.
- **Urinalysis:** Potential of hydrogen (pH), specific gravity, urine RBC, urine WBC, urine glucose, urine bilirubin, urine protein, urobilinogen, urine ketone bodies, and urine occult blood. Existing laboratory test results within the visit time window are acceptable.
- **Stool routine:** Color, shape, fecal RBC, fecal WBC, fecal occult blood, fecal choline, and fecal bilirubin. Existing laboratory test results within the visit time window are acceptable.
- **Blood biochemistry:**

1) **Liver function:** AST, ALT, ALP, LDH, GGT, TBIL, direct bilirubin, total bile acids, ALB, total protein, and GLO.

2) **Renal function:** Urea/urea nitrogen, creatinine, creatinine clearance, and uric acid.

3) **Blood lipids:** Total cholesterol, HDL, LDL, and TG.

4) **Electrolytes**: Potassium, sodium, chloride, phosphorus, magnesium, and calcium.

5) **Heart function:** CK and CKI.

6) **Blood glucose**: GLU.

Existing laboratory test results within the visit time window are acceptable.

- **Coagulation:** Prothrombin time, activated partial thromboplastin time, fibrinogen quantification, and international normalized ratio. Existing laboratory test results within the visit time window are acceptable.
- **Anti-cancer therapy and survival information after study treatment discontinuation:** During the follow-up period following study treatment discontinuation, the anti-cancer therapy and survival information of all subjects will be recorded.
- **AE:** See Section 8 for details.
- **Concomitant medications**: see Section 6.2 for details.
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Subsequent follow-up visits [once every 8 weeks (±7 days) after the last dose]:

Specific procedures and assessments are as follows:

- **Tumor assessment:**

1) Imaging tests like CT/MRI and other radiological examinations of chest, upper abdomen, lower abdomen, pelvic cavity and other positions will be performed. If brain metastasis is confirmed at screening, the frequency of brain CT/MRI in the subsequent cycles should be kept consistent with the tumor assessment frequency specified in the study; if it is confirmed that there is no brain metastasis by brain CT/MRI at screening, brain CT/MRI will be performed for confirmation if brain metastasis is suspected by the investigator later. If bone metastasis is confirmed at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if progression of the pre-existing bone metastasis or new bone metastasis is suspected by the investigator later; if it is confirmed that there is no bone metastasis at screening, a bone scan or contrast-enhanced MRI (for those allergic to contrast medium, MRI plain scan is acceptable) will be performed for confirmation if bone metastasis is suspected by the investigator later. Tumor assessments will be performed according to RECIST v1.1. Tumor markers: During the corresponding visits for imaging tests, 4 mL of peripheral blood will be collected for the detection of tumor biomarkers, such as liver cancer (AFP, CEA), breast cancer (CA15-3), ovarian cancer and endometrial cancer (CA125), prostate cancer (PSA), lung cancer (CYFRA21-1) and

pancreatic cancer (CA242), which serve as auxiliary efficacy indicators.

2) During the subsequent follow-up visits once every 8 weeks (±7 days) after the last dose, a tumor assessment will be performed for the subjects who are assessed as having no tumor progression in the previous assessment [a].

3) The radiological confirmation examination of CR or PR should be completed 4-8 weeks after the first evaluation of CR or PR.

- **Biomarker detection:** See Section 4.4.3 for details.
- **Anti-cancer therapy and survival information after study treatment discontinuation:** During the follow-up period following study treatment discontinuation, the anti-cancer therapy and survival information of all subjects will be recorded [b].
- **Inpatient nutrition assessment (NRS-2002):** assessed as needed.

Note:

[a.] Tumor assessments will be performed on subjects whose tumor has not progressed in the last assessment until the subject is lost to follow-up, the subject dies, the subject starts new anti-tumor therapy, the subject requests to withdraw from the trial and refuses to continue follow-up, the research data collection had reached the cutoff date, the study site is early closed, the study is early terminated, or the study ends (whichever occurs first).

[b.] During the follow-up period after the end of the study treatment, all subjects will be followed up for the survival period and the tumor treatment status will be recorded until the subject is lost to follow-up, the subject dies, the subject requests to withdraw from the trial and refuses to continue follow-up, the research data collection had reached the cutoff date, the study site is early closed, the study is early terminated, or the study ends (whichever occurs first).

4.3.6 Unscheduled visit

Temporary visit may be conducted when clinically needed. Both the content and results of unscheduled visits should be recorded in the original medical record and eCRF.

In addition to the safety test items specified in the protocol, additional safety test items may be measured as necessary.

Inpatient nutrition assessment (NRS-2002): assessed as needed.

4.4 Sample Collection and Testing

4.4.1 PK samples

According to the *Technical Guidelines for Clinical Pharmacokinetic Studies of Chemical Drugs*, a blank blood sample should be collected before administration. A complete blood drug

concentration-time curve should include at least 2-3 sampling points in the absorption phase and at least 3 sampling points near the C_{max}; "for multiple administrations, to estimate the time when the drug may reach the steady state concentration, the trough concentration should be measured three times (before administration) to determine the steady state concentration", and there should be at least 3-5 sampling points in the elimination phase. Generally, there are no less than 11-12 sampling points, and there should be a time period of three to five $T_{1/2}$ or sampling should continue until the plasma concentration is 1/10-1/20 of C_{max}. The preliminarily proposed PK blood collection time points are as follows:

During the single-dosing period of the dose escalation trial, the PK blood sampling time points are as follows: within 0.5 h (0 h) before single-dosing on D1 and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min), 24 h (±1 h; D2), 48 h (±1 h; D3), 72 h (±2 h; D4) and 96 h (±2 h; D5) after dosing.

During the multiple-dosing period of the dose escalation trial, the PK blood sampling time points are as follows: within 0.5 h pre-dose on C1D1, within 0.5 h pre-dose on C1D8, within 0.5 h pre-dose on C1D15, within 0.5 h pre-dose and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min) and 24 h (±30 min; collected before dosing on C2D1) post-dose on C1D21.

During the expansion trial, the PK blood sampling time points are as follows: within 0.5 h pre-dose on C1D1, within 0.5 h pre-dose on C1D8, within 0.5 h pre-dose on C1D15, within 0.5 h pre-dose and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min) and 24 h (±30 min; collected before dosing on C2D1) post-dose on C1D21.

The PK blood sampling time points of the subsequent study may be adjusted based on the previously obtained clinical trial data of BB102 tablets.

If there is dose interruption or missed dose(s) of BB102 tablets within 3 days before a PK sample collection time point, the investigator should discuss its impact on the PK sampling schedule with the sponsor and clinical pharmacologist as soon as possible within 24 hours of awareness, thereby determining whether to continue PK blood sampling as planned and how to adjust the PK blood sampling time points. The date and time of each dosing and each blood sampling should be recorded.

Three mL of venous blood will be collected each time. The plasma will be divided into 2 tubes: 1 tube for backup and 1 tube for PK detection. The collection, preservation and transportation of PK samples should follow the corresponding national regulations as well as the SOPs and manuals of the responsible facilities (including the laboratory of each study site and the central laboratory). Note: Collected blood samples should be protected from hemolysis as far as possible.

Concentration of BB102 (and its main metabolites, if applicable) in the PK samples will be

quantitatively measured using the methodologically validated high-performance liquid chromatography- mass spectrometry/ mass spectrometry (HPLC-MS/MS) method. PK sample testing should follow the corresponding national regulations as well as the SOPs and manuals of the testing facility (central laboratory).

4.4.2 Samples for metabolite identification

Blood samples will be collected for identification of metabolites only at a high dose group (e.g., 160 mg QD, 240 mg QD, 320 mg QD or 420 mg) during the single-dosing period of the dose escalation trial.

Blood sampling time points: within 0.5 h (0 h) before single-dosing on D1 and 1 h (±3 min), 2 h (±3 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min), 24 h (±1 h; D2), 48 h (±1 h; D3), 72 h (±2 h; D4) and 96 h (±2 h; D5) after dosing.

For the blood sampling time points where PK samples and metabolite identification samples will be collected at the same time, a total of 4 mL of whole blood will be collected each time. Plasma will be divided into 3 tubes: 1 tube for backup, 1 tube for PK detection, and 1 tube for metabolite identification (the tube should contain ≥0.6 mL plasma).

The collection, preservation, transportation, and testing of these samples should follow the corresponding national regulations as well as the SOPs and manuals of the responsible facilities (including the laboratory of each study site and the central laboratory).

4.4.3 Detection of biomarkers:

1) Detection of biomarkers in tumor tissue:

The corresponding biomarkers include but are not limited to the protein expression level, amplification, mRNA level, and activating mutation of FGF19 or FGFR4 in tumor tissue.

Subjects' tumor tissue specimens within the past 2 years or fresh tumor tissue specimens can be collected at screening; the specimens can be collected from the primary lesion or metastatic lesions.

After enrollment, fresh tumor tissue specimens will be collected as much as possible at EOT visit or disease progression; the specimens can be collected from the primary lesion or metastatic lesions (keeping consistent with the lesion source at screening as much as possible).

2) **Detection of biomarkers in blood:**

The corresponding biomarkers include but are not limited to blood bile acid precursors (e.g., 7-α-hydroxy-4-cholestene-3-one), total bile acids, total cholesterol, TG, and serum FGF19 protein content.

Fresh blood samples can be collected at screening, during the treatment period (C1D15 visit, C3D21 visit and C5D21 visit) and at EOT visit, 5 mL at each time point, with no more than 5

sampling time points.

The collection, preservation, transportation (if applicable) and testing of biomarker testing samples should follow the corresponding national regulations as well as the SOPs and manuals of the responsible facilities (including the laboratory of each study site and the central laboratory).

4.4.4 Other biological samples

Other biological samples include biological samples obtained for hematology, urinalysis, fecal analysis, blood biochemistry, coagulation function, pregnancy-related tests, serum etiological examinations and other examinations. The collection, preservation, transportation (if applicable) and testing of these samples should follow the corresponding national regulations as well as the SOPs and manuals of the responsible facilities (including the laboratory of each study site).

4.5 Interim analysis

No interim analysis will be performed in this study.

4.6 Early Closure of the Study Site/Study Suspension/Early Termination of the Study

Reasons of early closure of the study site/study suspension/early termination of the study include but are not limited to:

- The study site has serious non-compliance issues or non-compliance issues that have not been corrected after dissuasion, such as non-compliance with the protocol or the relevant regulations or guidelines for trials.
- Any new drug toxicity is discovered, or the subject experiences unexpected severe impairment (including nonclinical and clinical manifestations).
- Enrollment and follow-up of subjects has been completed.
- The protocol is not followed.
- The drug study plan (e.g., if the sponsor considers continuation of this study is inappropriate for medical, ethical or commercial reason) is changed.
- The enrollment is too slow.
- The quality of clinical data is poor.

The Ethics Committee, the investigators, and the sponsor have the right to close the study site early, suspend or prematurely terminate part of the clinical trial or the entire clinical trial:

- If the Ethics Committee makes the above decision, the investigator should immediately report to the clinical trial institution and the sponsor and provide detailed written explanation.
- If the investigator makes the above decision without consultation with the sponsor, the

investigator should immediately report it to the clinical trial institution, the sponsor and Ethics Committee and provide detailed written explanation.

- If the sponsor makes the above decision, the sponsor should notify all relevant investigators, clinical trial institutions, and drug regulatory authorities; the investigator should immediately report to the clinical trial institution and the Ethics Committee and provide detailed written explanation.

All study materials (except documents that must be retained at the study site) must be returned to the sponsor upon early closure of the study site or early termination of the study. The investigator must store relevant documents until notification of destruction from the sponsor.

4.7 Definition of Study Data Collection Cut-off

The cut-off time for data collection of this Phase I study is 8 weeks after the last subject starts the study treatment, unless the entire study is prematurely terminated (see Section 4.6). At the time of study data collection cutoff, if a subject can tolerate the study drug and remains CR/PR/SD and is willing to continue the study drug treatment, the investigator believes that the subject will still clinically benefit from the continued treatment and the investigator confirms that there is no problem in drug supply after discussion with the sponsor, the subject can continue the study drug treatment (i.e., compassionate use), until he/she meets the criteria for study treatment discontinuation or there is a drug supply problem (whichever occurs first). During the compassionate use, drug-related AEs and SAEs will be recorded according to the relevant national regulations, and the SAEs will be reported to the sponsor/CRO safety department. Routine safety monitoring should be continued as needed. The investigator will select and schedule test items at his/her own discretion and should preserve relevant documents in the source files. The sponsor will not routinely collect relative results of these tests. Data collected during compassionate use will not be included in statistical analysis of the study.

4.8 Number of Study Sites

This trial is planned to be carried out at 3-6 study sites in the United States of America.

4.9 Study Duration

Approximately 24 months.

5. Study Medication

5.1 Drug Name, Dosage Form and Other Basic Information

5.1.1 Investigational product (BB102 tablets)

Table 2 Basic information of BB102 tablets

Generic name:	BB102 Tablets
Dosage form:	Tablet
Active ingredients:	BB102
Molecular formula of active ingredient:	$C_{26}H_{30}N_8O_4 \cdot C_6H_8O_7$
Appearance of active ingredients:	Off-white powder
CAS number of active ingredient:	None
Molecular weight of active ingredient:	710.70
Strength:	10 mg、50 mg
Package specification:	50 tablets/bottle
Shelf life:	24 months tentatively
Drug source:	Provided by the sponsor

5.1.2 Control drug

No control drug is designed in this trial.

5.2 Method of Administration

1. Dose levels: possibly 50 mg QD, 100 mg QD, 160 mg QD, 240 mg QD, 320 mg QD and 420 mg QD (for the dose escalation groups, the escalation doses may be adjusted according to the previously obtained clinical trial data of BB102 tablets, e.g., adding dose groups of 520 mg QD and 600 mg QD).

2. Administration route: Oral.

3. Administration method:

- For dose groups 1, 2, 3, 4, 5 and 6 in the dose escalation trial, subjects will be fasted overnight for at least 10 hours before dosing on D1 and C1D21 and take BB102 tablets with about 240

mL of water; no drinking is allowed from 1 h pre-dose to 1 h post-dose; and no food is allowed within 2 h post-dose. Subjects will be on a normal diet.

- For dose groups 1, 2, 3, 4, 5 and 6 in the dose escalation trial, subjects will be fasted at least 2 hours before dosing on the other dosing days, and take BB102 tablets with water; no food is allowed within 1 h post-dose. Subjects will be on a normal diet.
- For dose groups A in the dose escalation trial, subjects will be fasted overnight for at least 10 hours before dosing on D1 and C1D21, start eating a low-fat meal at 30 min before dosing on D1 and C1D21 (breakfast), finish the meal within 30 min and take BB102 tablets with about 240 mL of water at 30 min from the start of meal (if the meal takes more than 30 minutes, BB102 tablets should be administered immediately after the meal); no drinking is allowed from 1 h pre-dose to 1 h post-dose; no food is allowed within 4 h post-dose. Except for the low-fat meal (breakfast) on the specified days, subjects will be on a normal diet.

Composition of the low-fat meal:

Total calories (kcal)	400-500
Fat (g)	11-14
Calories from fat (%)	25
An example of a low-fat breakfast*	● Eight ounces milk (1 percent fat) ● One boiled egg ● One packet flavored instant oatmeal made with water

*Note: 25% of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained. A registered dietician at the study site should determine the appropriate meal to be consumed, based on the fat and calorie requirements assigned to the patient for that treatment day. The start/stop time of meal consumption, and estimated % of test meal consumed (based on fat and caloric content), must be listed in the meal record eCRF for patients allocated in exploratory food effect group.

- For dose group A in the dose escalation trial, subjects will take BB102 tablets with water within 30 minutes following the meal on the other dosing days; no food is allowed within 1 h post-dose. Subjects will be on a normal diet.
- In the expansion trial, subjects will be fasted for at least 2 hours before dosing and take BB102 tablets with water; no food is allowed within 1 h post-dose. Subjects will be on a normal diet. Note: The administration method of the expansion trial may be adjusted according to the previously obtained food effect evaluation results of BB102 tablets.

4. Dosing frequency and cycles: once daily in 21-day cycles (the dosing frequency and cycle setting may be adjusted according to the previously obtained clinical trial data of BB102 tablets).

Note:

- Study doctors and nurses are required to instruct subjects to administer the drug as prescribed above.
- For each subject, the time of administration every day should be basically the same.
- On the administration day with PK blood collection, the date, time and dosage of each administration of each subject must be truthfully recorded in the eCRF by the investigator or a person authorized by the investigator.
- On the day of administration without PK blood collection, the date, time and dosage of each administration of each subject must be truthfully recorded by the subject in the "Subject Diary Card" and reported to the investigator.

5.3 Storage Conditions

Store in a sealed condition at room temperature

5.4 Drug Packaging and Labeling

The sponsor and CRO will design the label for all investigational products, package and label them according to *Good Clinical Practice* (GCP) and applicable national regulations.

The label of the investigational product should contain the following information: protocol number, sponsor information, "for clinical trial use only", name, dosage form, strength, method of administration, storage conditions, product batch number, expiry date, screening number and cycle number of the investigational drugs used in the clinical trial.

Backup medicines should be prepared and used only when the original medicines supposed to be used are lost, soiled or otherwise unsuitable for use.

5.5 Drug Management

The investigator and clinical trial institution are responsible for the management of investigational products provided by the sponsor. Records of investigational product management should include date, quantity, batch number/serial number, shelf life, distribution code and signature, etc.

An investigational product management system should be established to meet the following requirements:

1) A special person (e.g., a qualified pharmacist) should be responsible for receiving the investigational products provided by the sponsor (the drug receipt form should be signed in duplicate upon receipt of the drug, one for the clinical study institution and one for the sponsor);
2) A designated person is responsible for the reasonable and safe storage of investigational

products, and should ensure that the storage conditions meet the requirements;

3) Investigational products can only be prescribed by the investigator or a study doctor authorized by the investigator;

4) The investigational products can only be distributed to the subjects or administering nurses according to the trial protocol, and the dosage and administration should follow the trial protocol;

5) If there are problems with the quality and appearance of the investigational products, they shall not be distributed. Instead, the sponsor should be promptly contacted;

6) The investigational products shall not be handed over to any non-trial participant;

7) The distribution and recovery of investigational products need to be fully recorded;

8) Subjects should return the remaining drugs of BB102 tablets and empty packages of used drugs to the investigator;

9) The investigator should keep the remaining drugs of BB102 tablets and empty packages of used drugs, and keep records of the quantity and dosage of the investigational products used by each subject for monitoring by the monitor;

10) After the drugs are counted during the visit, medication errors, overdose, and drug loss should be recorded in the source medical record and eCRF;

11) Clinical research associate should be responsible for monitoring the supply, use and storage of the investigational drugs and handling process of the remaining drug;

12) After counting by the monitor, the remaining drugs of BB102 tablets and empty packages of used drugs will be recovered by the sponsor (both parties should sign the drug recovery form);

13) At the end of the trial, the used and residual quantity of the investigational product should be consistent with the quantity provided by the sponsor. Any difference should be recorded and the cause of difference should be specified.

6. Treatment of Subjects

6.1 Investigational Treatment

6.1.1 Dosing schedule (treatment time)

All subjects in the phase I trial will receive continuous administration until they meet the criteria for discontinuation of study treatment.

6.1.2 Dose interruption, resumption, adjustment and permanent discontinuation during the dosing period

There is currently no data on BB102 tablets in humans, and its ADR is unclear. According to nonclinical toxicology data and ADRs that have been reported for similar drugs, for each single subject, the following methods of dose interruption, resumption, adjustment, and permanent discontinuation are tentatively determined.

In the dose escalation trial, dose interruption, resumption and permanent discontinuation during the DLT observation period:

- No dose adjustment is allowed in the DLT observation period, but the doses may be interrupted, resumed and permanently discontinued.
- If several toxicities occur at the same time, dose interruption, resumption and permanent discontinuation should be carried out according to the most serious toxicity.

(1) During the DLT observation period, if the subject develops DLT, the doses should be interrupted, and supportive treatment should be given as needed. The doses can be continued when the dosage has been administered before dose interruption is more than 75% of the scheduled dose, and the subject recovers to grade ≤1 or baseline (or, recovers to grade ≤2 and the investigator believes that there is no safety risk).

(2) If the subject develops DLT again, the doses should be permanently discontinued, and unscheduled safety follow-up should be arranged until the toxicity is resolved or stabilized.

(3) If the subject has other non-DLT toxicities, dose interruption needs to be determined according to the investigator's medical assessment, and supportive treatment will be provided as needed.

Dose interruption, resumption, adjustment and permanent discontinuation in post-DLT observation period of dose escalation trial and during the dosing period in the expansion trial:

- If the AE is attributable to BB102 tablets according to the investigator's judgment, dose interruption, resumption, adjustment and permanent discontinuation will be performed according to the following table. If there is any other situation not described in the table below, the sponsor and investigator will decide whether to interrupt, resume, adjust, or permanently discontinue the dose after a comprehensive assessment of the benefits and risks.

- Subjects can be given appropriate supportive treatment to relieve symptoms and signs of toxic reactions.
- Dose interruption, resumption, adjustment and permanent discontinuation should be perfomed according to the most serious toxic reaction when several toxic reactions occur simultaneously.
- Once the dose is decreased, up-titration to the previous level is not allowed.
- A maximum of 2 dose interruptions is allowed for each subject, and each interruption shall not exceed 14 days. If a 3rd dose interruption is required, or a dose interruption is required for >14 days, permanent discontinuation is required for the subject unless it is considered that the continuation of BB102 tablets treatment at an appropriate dose is in the best interest of the patient after the sponsor and the investigator comprehensively evaluate the benefits and risks.
- Rules for dose interruption, resumption, adjustment and permanent discontinuation are shown in the table below.

Hematologic toxicity [a]	**Rules for dose interruption, resumption, adjustment and permanent discontinuation [b]**
Neutrophil count decreased	
Grade 1-2	Continue the study treatment at the original dose level.
Grade 3	Administration interruption until the toxicity is resolved to grade ≤2. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within 7-14 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
Grade 4	Administration interruption until the toxicity is resolved to grade ≤2. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within ≤7 days. ➢ Discontinue permanently if the toxicity is resolved within >7 days.
Febrile neutropenia	
Grade 3	Administration interruption until the toxicity is resolved. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within ≤14 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.

Grade 4	Discontinue permanently.
Platelet count decreased	
Grade 1-2	Continue the study treatment at the original dose level.
Grade 3	Administration interruption until the toxicity is resolved to grade ≤1. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within 7-14 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
Grade 4	Administration interruption until the toxicity is resolved to grade ≤1. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within ≤7 days. ➢ Discontinue permanently if the toxicity is resolved within >7 days.
Anemia	
Grade 1-2	Continue the study treatment at the original dose level.
Grade 3	Administration interruption until the toxicity is resolved to grade ≤2. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within 7-14 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
Grade 4	Administration interruption until the toxicity is resolved to grade ≤2. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within ≤7 days. ➢ Discontinue permanently if the toxicity is resolved within >7 days.
Other hematologic toxicity	
Grade 1-2	Continue the study treatment at the original dose level.
Grade 3	Administration interruption until the toxicity is resolved to grade ≤2.

	Resume the study treatment at the original dose level after the toxicity is resolved to grade ≤2.
Abnormal grade 4 laboratory test results that are not life-threatening judged by the investigator	Administration interruption until the toxicity is resolved to grade ≤2. Resume the study treatment at the original dose level after the toxicity is resolved to grade ≤2 (the sponsor and investigator will decide whether to continue the administration after a comprehensive assessment of the benefits and risks).
Grade 4	Administration interruption until the toxicity is resolved to grade ≤2. Continue the study treatment at the dose reduced by one level [c] after the toxicity is resolved to grade ≤2.
Nonhematologic toxicity [a]	**Rules for dose interruption, resumptionadjustment and permanent discontinuation [b]**
Creatinine increased	
Grade 1	Continue the study treatment at the original dose level.
Grade 2	Administration interruption until the toxicity is resolved to baseline. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within >7 days.
Grade 3-4	Discontinue permanently.
Blood bilirubin increased	
Grade 1	Continue the study treatment at the original dose level.
Grade 2	Administration interruption until the toxicity is resolved to baseline. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within >7 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
Grade 3	Administration interruption until the toxicity is resolved to baseline. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within ≤7 days.

	➢ Discontinue permanently if the toxicity is resolved within >7 days. Note: Continue the study treatment at the dose reduced by one level [c] at the discretion of the investigator if the grade 3 increase in blood bilirubin is only due to the increase in indirect bilirubin (unconjugated bilirubin), and hemolytic factors (e.g., peripheral blood smear examination and haptoglobin assay) have been excluded according to the guidelines of each study center.
Grade 4	Discontinue permanently. Note: Continue the study treatment at the dose reduced by one level [c] at the discretion of the investigator if the grade 4 increase in blood bilirubin is only due to the increase in indirect bilirubin (unconjugated bilirubin), and hemolytic factors (e.g., peripheral blood smear examination and haptoglobin assay) have been excluded according to the guidelines of each study center.
AST or ALT increased	
Grade 1-2	Continue the study treatment at the original dose level.
Grade 3	Administration interruption until the toxicity is resolved to grade ≤2 (liver cancer or liver metastases) or grade ≤1. ➢ Resume the study treatment at the original dose level if the toxicity is resolved within ≤7 days. ➢ Continue the study treatment at the dose reduced by one level [c] if the toxicity is resolved within 7-14 days. ➢ Discontinue permanently if the toxicity is resolved within >14 days.
Grade 4	Discontinue permanently.
Other nonhematologic toxicity	
Grade 1-2	Continue the study treatment at the original dose level.
Grade 3 toxicities with no safety risk at the discretion of the investigator, such as grade 3 nausea, vomiting, diarrhea, asthenia, constipation, loss of appetite, mucositis, GGT increased and ALP increased.	Administration interruption until the toxicity is resolved to grade ≤2. Resume the study treatment at the original dose level after the toxicity is resolved to grade ≤2.

Grade 3 Note: Toxicities with no safety risk at the discretion of the investigator are excepted, such as grade 3 nausea, vomiting, diarrhea, asthenia, constipation, loss of appetite, mucositis, GGT increased and ALP increased.	Administration interruption until the toxicity is resolved to grade ≤2 or grade ≤1. Resume the study treatment at the dose reduced by one level [c] after the toxicity is resolved to grade 2 (only when the investigator believes resuming the study treatment poses no safety risk to the subject) or grade ≤1.
Abnormal grade 4 laboratory test results that are not life-threatening judged by the investigator (such as grade 4 GGT increased and ALP increased).	Administration interruption until the toxicity is resolved to grade ≤2 or grade ≤1. Resume the study treatment at the dose reduced by one level [c] after the toxicity is resolved to grade 2 (only when the investigator believes resuming the study treatment poses no safety risk to the subject) or grade ≤1 (the sponsor and investigator will decide whether to continue the administration after a comprehensive assessment of the benefits and risks).
Grade 4 Toxicities with no safety risk at the discretion of the investigator are excepted, such as grade 4 GGT increased and ALP increased.	Discontinue permanently.

Abbreviations: ALP = alkaline phosphatase; DLT = dose-limiting toxicity; GGT = γ-glutamyltransferase.

Note: a. Applicable to all hematologic toxicities (if a hematologic toxicity is related to other non-hematologic clinical events, refer to the rules for dose interruption, resumption and adjustment of non-hematologic toxicities).

b: The rules may be modified based on the previously obtained clinical trial data of BB102 tablets.

c. Available dose levels of BB102 tablets include 50 mg QD, 100 mg QD, 160 mg QD, 240 mg QD, 320 mg QD and 420 mg QD. If dose reduction is required at the starting dose level, the subject should discontinue the treatment permanently.

6.1.3 Medication error and overdose

Medication error is defined as an unexpected deviation in the administration of the investigational product, such as a wrong dose (e.g., overdose), wrong time of administration, wrong route of administration, wrong medication, and use of expired/contaminated/deteriorated study drug.

Overdose is defined as the actual dose of the investigational product administered being greater than the planned dose.

Any medication error should be recorded as a protocol deviation and recorded in detail in the source medical record and eCRF. If a medication error occurs, regardless of whether it leads to the occurrence of an AE/SAE, the investigator should fill out the “Overdose Report Form” within 24

hours, quickly report it to the sponsor/CRO safety department, and take measures as appropriate, such as delaying subsequent administration and strengthening the monitoring of subjects.

If a medication error leads to the occurrence of an AE/SAE, the investigator should give symptomatic treatment according to the situation of the AE/SAE, and report it as an AE or SAE.

6.1.4 Treatment of missed doses

On the administration day with PK blood collection, the nurse is responsible for supervision to ensure that the subjects take the medicine on time.

On the day of administration without PK blood collection, subjects can take the drug home and take it by themselves.

If any dose of BB102 tablets is missed or suspected to be missed, please refer to the following treatment methods:

1) If it is not possible to confirm whether the drug has been taken, it will be deemed that the drug has been taken, and no more additional dose will be taken this time.
2) When a missed dose is found ≥ half of the dosing interval from the next planned dose (for example, in the case of QD administration, half of 24 hours is 12 hours), the drug will be taken when the missed dose is found.
3) When a missed dose is found < half of the dosing interval from the next planned dose (for example, in the case of QD administration, half of 24 hours is 12 hours), the drug will not be taken this time, and the prescribed dose will be taken at the time of the next planned dose.
4) If vomiting occurs after administration, the drug will not be taken this time, and the prescribed dose will be taken at the time of the next planned dose.

On the day of administration without PK blood collection, the missed doses, the time of missed doses, supplementary doses, and vomiting must be truthfully recorded in the "Subject's Diary Card" and reported to the investigator.

6.2 Concomitant Medications

Concomitant medications include any medications other than the study drug (including prescription drugs, over-the-counter drugs, natural extracts, nutritional supplements and traditional Chinese medicines) used by subjects from the start of first dose to 28 days after the last dose of study treatment. Note: Medications used by subjects at screening will be recorded as medication history.

(1) For the dose escalation trial and expansion trial, the following drugs/therapies will be allowed during the treatment period:

- Bisphosphonates for treating bone metastasis. Note: Bisphosphonate therapy should be administered according to the local medical practice.
- Palliative radiotherapy for relieving pain caused by bone lesion, on the condition that this lesion has existed at the time of enrollment and the investigator clarifies the requirement of palliative radiotherapy does not represent disease progression. Note: As there is currently a lack of data on the interaction between BB102 tablets and radiotherapy, BB102 tablets therapy should be interrupted at 1 day before palliative radiotherapy and throughout the radiotherapy period and be resumed after the acute radiotoxicity recovers to baseline level. Note: Palliative radiotherapy is not allowed during the DLT observation period; if the study drug dose received by a subject during the DLT observation period is less than 75% of the scheduled dose due to use of palliative therapy and no DLT occurs, the corresponding dose group needs one more subject for replacement.
- Therapeutic drugs used for AE (dose escalation trial), such as choleretics, but only the non-prohibited medications can be used.
- Preventive drugs and therapeutic drugs used for AE (expansion trial), such as choleretics, but only the non-prohibited medications can be used.

(2) In the dose escalation trial and expansion trial, the following drugs/therapies will be prohibited during the treatment period:

- Anti-tumor therapies rather than the study drug (including but not limited to chemotherapy, radiotherapy, immunotherapy, anti-tumor biotherapy, etc.), including state-approved Chinese traditional patent drugs with an anti-tumor effect.
- Adjuvants (e.g., preventive leukocyte increasing drugs, antiemetics, etc.) related to anti-tumor therapy (for dose escalation trial only).
- Strong CYP3A4 inhibitors, strong CYP3A4 inducers, strong CYP3A5 inhibitors, strong CYP3A5 inducers, sensitive CYP3A4 substrates with a narrow therapeutic index, and sensitive CYP2B6 substrates with a narrow therapeutic index (Appendix IV).

(3) In the dose escalation trial and expansion trial, the following drugs/therapies can be used with cautious during the treatment period:

- Moderate or weak CYP3A4/5 inhibitors and inducers.
- BCRP substrates, P-gp substrates, OAT1 substrates, OAT3 substrates, OATP1B3 substrates, MATE1 substrates, and MATE2-K substrates with a narrow therapeutic index (Appendix V).
- Strong BCRP inhibitors and strong P-gp inhibitors (Appendix V).
- Drugs which are known to or may prolong QT interval or induce tip torsion ventricular

tachycardia (Appendix VI).

- Given that FGFR4 inhibitor can increase CYP7A1 expression, try not to use drugs that can increase CYP7A1 expression or enzyme activity (e.g., atorvastatin, troglitazone); try not to use cholesterol (CYP7A1 substrates)-containing drugs.

(4) Prevention and management of expected ADRs:

The actual ADR treatment measures will be taken by the investigator according to the actual situation of the subjects in combination with clinical practice and relevant guidelines. The following suggestions are only for reference. For common ADRs in the dose escalation trial, prophylaxis can be given in advance during the expansion trial.

- Diarrhea: Among the adverse effects of FGFR inhibitor, diarrhea's incidence is 15%-60%, which may be related to preventing the binding of FGF19 and FGFR4. The homeostasis of bile acids will be regulated after FGF19 binding with FGFR4, while bile acids have effects on colonic mucosal permeability. It is recommended to continue the study treatment at the original dose level, and loperamide, probiotics, and smecta (montmorillonite powder) should be given to treat ADR at the same time when drug-related grade 1-2 diarrhea occurs during the clinical trial. If grade 3 diarrhea occurs, it is recommended to interrupt the study treatment, and loperamide, probiotics, and smecta (montmorillonite powder) should be given to treat ADR at the same time (codeine and prophylactic antibiotics may be used if necessary), the addition of somatostatin may be considered in severe conditions. If grade 4 diarrhea occurs, it is recommended to discontinue the study treatment permanently, at the same time, the above symptomatic treatment should be given.
- Asthenia: FGFR4 has the function of regulating the differentiation of muscle cells and tissue repair. If asthenia occurs in the trial, it is considered to be related to the inhibition of the physiological function of FGFR4. It is recommended to continue the study treatment at the original dose level, and have more rest at the same time when drug-related grade 1-2 asthenia occurs during the clinical trial. If grade 3 asthenia occurs, it is recommended to discontinue the study treatment permanently and have more rest at the same time.
- Nausea/vomiting: They are not caused by FGFR4 physiological mechanism and can be considered as the gastrointestinal irritation of the investigational drug. It is recommended to continue the study treatment at the original dose level, and metoclopramide and so on should be given to treat ADR at the same time when drug-related grade 1-2 nausea/vomiting occurs during the clinical trial. If grade 3 nausea/vomiting occurs, it is recommended to interrupt the study treatment, and metoclopramide and so on should be given to treat ADR at the same time. If grade 4 nausea/vomiting occurs, it is recommended to discontinue the study treatment permanently, and the above symptomatic treatment should be given at the same time.

- Fever: Generally, it may be the non-inflammatory fever caused by the death or rupture of cancer cells. It is recommended to continue the study treatment at the original dose level, at the same time, strengthen body temperature monitoring, and perform physical cooling, ice compress and drink warm water if necessary when drug-related grade 1 fever occurs during the clinical trial. If grade 2 fever occurs, it is recommended to continue the study treatment at the original dose level, and cooling medications (e.g., dexamethasone, loratadine, etc.) should be given to treat ADR at the same time. If grade 3 fever occurs, it is recommended to interrupt the study treatment and the above symptomatic treatment should be given at the same time. If grade 4 fever occurs, it is recommended to discontinue the study treatment permanently, and the above symptomatic treatment should be given at the same time.
- Hepatotoxicity: It is considered to be caused by damage to liver cells or functional overload. It is recommended to continue the study treatment at the original dose level, and hepatoprotective medications [e.g., Chinese traditional patent drug, polyene phosphatidylcholine, reduced glutathione, magnesium isoglycyrrhizinate, simetai (adenosylmethionine butanedisulfonate enteric-coated tablet)] should be given for symptomatic treatment at the same time when drug-related grade 1-2 hepatotoxicity occurs during the clinical trial. If grade 3 hepatotoxicity occurs, it is recommended to interrupt the study treatment and the above symptomatic treatment should be given at the same time. If grade 4 hepatotoxicity occurs, it is recommended to discontinue the study treatment permanently, and the above symptomatic treatment should be given at the same time.

Any prescription drugs, over-the-counter drugs, natural extracts, nutritional supplements, traditional Chinese medicines, herbal medicines and vitamins should be reviewed and approved by the investigator. All information on concomitant medications should be recorded in the subjects' medical records and reported on the eCRF.

6.3 Compliance of Subjects

The investigator should emphasize the importance of compliance to the subjects during the process of informed consent. During the process of the trial, if a subject's compliance is poor, the investigator should find the cause and actively take corresponding measures (e.g., emphasizing the importance of protocol compliance to the subject), and completely record the related non-compliance, cause and measures taken.

The investigator should timely and accurately collect and record the planned dose, actual dose, and date of administration of each subject. In principle, the actual dose should be consistent with the planned dose.

The investigator should judge the study treatment compliance according to the medication details.

Compliance = actual dose/planned dose × 100%.

Subjects taking medication within the range of 80%-120% will be considered to have good treatment compliance.

7. Study Endpoints

7.1 Dose Escalation Trial

Primary endpoints:

- **Safety and tolerability of BB102 tablets (fasted or fed):** Incidences of AEs and SAEs; abnormalities or changes in laboratory tests, vital signs, ECG, physical examination and ECOG score.
- **DLT of BB102 tablets (fasted or fed):** Classification, severity and frequency of DLT.

Secondary endpoints:

- **PK parameters of BB102 tablets (fasted):** Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), lag time (t_{lag}), elimination rate constant (Kel), $T_{1/2}$, area under the concentration-time curve from 0 to the time point of last quantifiable concentration (AUC_{0-t}), area under the concentration-time curve from time 0 to infinity (AUC_{0-inf}), apparent clearance (CL_z/F), apparent volume of distribution (V_z/F), mean residence time (MRT), steady-state minimum plasma concentration ($C_{ss,\ min}$), steady-state maximum plasma concentration ($C_{ss,\ max}$), average steady-state plasma concentration ($C_{ss,\ av}$), area under the concentration-time curve during a dosing interval at steady state (AUC_{ss}), steady-state degree of fluctuation (DF) and accumulation ratio (Rac) of BB102 (and its main metabolites, if applicable).
- **PK parameters of BB102 tablets (fed):** C_{max}, T_{max}, t_{lag}, Kel, $T_{1/2}$, AUC_{0-t}, AUC_{0-inf}, CL_z/F, V_z/F, MRT, $C_{ss,\ min}$, $C_{ss,\ max}$, $C_{ss,\ av}$, AUC_{ss}, DF and Rac of BB102 (and its main metabolites, if applicable); **whether food has an effect on the exposure parameters (AUC_{0-inf}, AUC_{0-t} and C_{max}) and the extent of effect.**
- **Efficacy of BB102 tablets (fasted or fed):** ORR, DCR, duration of response (DOR), PFS, and OS.
- **Relationship between biomarker and efficacy.** Biomarkers include but are not limited to protein expression level, amplification, mRNA level and activating mutation profiles of FGF19 or FGFR4 in tumor tissues; bile acid precursors (e.g., 7-α-hydroxy-4-cholestene-3-one), total bile acids, total cholesterol, TG and serum FGF19 protein level in blood.
- **Correlation between plasma concentration of study drug and QTcF (C-QTcF analysis).**
- **Metabolites of BB102.**

7.2 Expansion Trial

Primary endpoints:

- **Efficacy of BB102 tablets (fasted):** ORR, DCR, DOR, PFS and OS.

Secondary endpoints:

- **PK parameters of BB102 tablets (fasted):** $T_{1/2}$, AUC_{0-t}, AUC_{0-inf}, $C_{ss,\ min}$, $C_{ss,\ max}$, $C_{ss,\ av}$, AUC_{ss} and DF of BB102 (and its main metabolites, if applicable).
- **Safety of BB102 tablets (fasted):** Incidences of all AEs and SAEs; abnormalities or changes in laboratory tests, vital signs, ECG, physical examination and ECOG score.
- **Relationship between biomarker and efficacy.** Biomarkers include but are not limited to protein expression level, amplification, mRNA level and activating mutation profiles of FGF19 or FGFR4 in tumor tissues; bile acid precursors (e.g., 7-α-hydroxy-4-cholestene-3-one), total bile acids, total cholesterol, TG and serum FGF19 protein level in blood.

8. Safety Evaluation

8.1 AE

8.1.1 Definition of AE

AEs refer to any untoward adverse medical events following the use of the investigational product in subjects. It is manifested as symptoms, signs, diseases or abnormal laboratory findings, but it does not necessarily have a causal relationship with the investigational product.

Other considerations for AE:

Diagnoses versus signs and symptoms:

- Each event should be recorded based on a single diagnosis. The accompanying signs (including abnormal laboratory values or ECG results) or symptoms should not be recorded as additional AEs. If the diagnosis is unknown, the signs or symptoms can be recorded as AEs accordingly.

Laboratory values and ECG results:

- Only when judged as clinically significant (i.e., some measures or interventions are required, the change is outside of normal physiological variation range as judged by the investigator), the change of laboratory values or ECG parameters can be regarded as AEs. Repeated laboratory test and/or continuous monitoring of abnormal values are not regarded as intervention. Moreover, repeated or additional non-invasive examination performed to verify, evaluate or monitor abnormality is not regarded as intervention.
- If abnormal laboratory findings or ECG findings are pathological results of an overall diagnosis (e.g., creatinine increased in renal failure), only the diagnosis should be reported as AE accordingly.

Pre-existing diseases:

- Pre-existing conditions should not be recorded as AEs. However, if these concomitant conditions worsen or have complications, such worsening or complications should be recorded as AEs (after administration of the study drug) accordingly.

Change in severity of AE:

- If the patient experiences any changes in severity of AEs: (1) when the CTCAE grade is elevated, the AEs should be recorded separately, and the start date of the grade-elevated AE should be the same as the end date of the original AE; (2) when the CTCAE grade is reduced, the AE is not recorded separately, with only the highest CTCAE grade recorded, and the actions taken with the study drug and causal relationship with the study drug all remained as the records of the highest CTCAE grade, but the relevant information should

be updated in a timely manner, especially the outcomes and the end date.

Surgeries or procedures:

- Surgeries during the study period should be considered as AEs, but operations/therapies such as abdominocentesis and thoracocentesis should not be recorded as AEs.

8.1.2 Collection and reporting process of AEs

AE collection period

AEs will be collected from the first dose of investigational product to 28 days after the last dose of investigational product or the start of new anti-tumor therapy (whichever occurs first). During the AE collection period, all AEs should be reported in the source medical record and the eCRF. After the AE collection period, only the existing AEs, newly occurred AEs definitely related/possibly related/possibly unrelated to the study drug/ucertain, and AEs leading to death will be recorded. For AEs still existing after the end of study treatment, if they are related to the study treatment, they will all be followed up until resolution, stabilization, death, loss to follow-up or it is reasonably explained.

All adverse medical events that occur during the period from subject's signing of the ICF to the first dose of the investigational product will be recorded as medical history instead of being recorded as AEs, unless they meet one of the following conditions:

➢ Any adverse medical event related to procedures specified in the clinical study protocol (e.g., bruising caused by blood sampling for laboratory test, etc.);

➢ Adverse medical events caused by treatment discontinuation related to clinical study protocol (e.g., change or discontinuation of prior concomitant medications).

AE reporting

At each study visit, the investigator will assess whether there is a subjective AE. A neutral question can be asked, such as "How do you feel since the last visit?".

All clinically significant laboratory abnormalities confirmed by repeated laboratory test will be followed-up until these abnormalities are resolved to acceptable level or satisfactory explanation is given.

For all AEs, no matter stated by the subject, asked out by the investigator or found out by physical examination, laboratory test or other methods, they should all be recorded in the source medical records and the eCRF completely no matter regardless of being related to the study drug as considered by the investigator. The following information will be recorded for AEs:

- Event term.

- Start and end date.
- Severity.
- The investigator's judgment on the causal relationship between the AE and the study drug.
- Relevant actions taken with the study drug.
- Treatment or interventional measures taken for AEs.
- Event outcome.
- SAE or not.

8.1.3 Evaluation of severity

The investigator should grade AEs according to CTCAE v5.0. Note: CTCAE v5.0 is only used for grading of AEs, and it is not used to determine whether the AE is an SAE.

Referring to CTCAE v5.0, if there are AEs not listed in the table, they can be classified into 1-5 grades according to the following criteria:

Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (instrumental ADLs refer to preparing meals, shopping for clothes, using the telephone, managing money, etc.).

Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Grade 4: life-threatening; urgent intervention indicated.

Grade 5: death related to AEs.

8.1.4 Evaluation of causal relationship

The causal relationship of AEs with the study drug is evaluated as definitely related, possibly related, possibly unrelated, definitely unrelated and uncertain (see Table 3).

Table 3 Criteria for evaluation of causal relationship between AE and study drug

Causal relationship	Temporal sequence	Known reaction type	Influence of other confounding factors
Definitely related	There is a rational temporal relationship between the AE's occurrence and	The event meets the known reaction type of study drug.	Influence of other confounding factors such as pre-existing diseases has been excluded.

Causal relationship	Temporal sequence	Known reaction type	Influence of other confounding factors
	administration. For example, the AE will disappear, be relieved or improved rapidly after drug withdrawal, which may recur even aggravate obviously after resuming the drug (that is, rechallenge positive).		
Possibly related	The event follows a temporal sequence from the drug's administration.	The event meets the known reaction type of study drug.	The patient's clinical status or other therapies may also give rise to such event.
Possibly unrelated	The event does not follow a temporal sequence from the drug's administration.	The event does not quite meet the known reaction type of study drug.	The patient's clinical status or other therapies may also give rise to such event. Relationship with administration cannot be ruled out.
Definitely unrelated	The time of the event does not follow a temporal sequence from the drug's administration.	The event meets the known reaction type of non-study drug.	The patient's clinical status or other therapies may also give rise to such event. The event disappears after the disease status improves or other treatments are stopped, but the event reoccurs after repeated use of other treatments. It is closely related to other risk factors.
Uncertain	The occurrence time of the event has no clear relationship with the temporal sequence of medication.	The event is similar to the known reaction type of the study drug.	Use of other drugs may also cause such event. There is no enough evidence for judgment.

Abbreviation: AE=adverse event.

8.1.5 Study drug-related actions

- **Drug withdrawal:** the study drug is withdrawn due to a specific AE.
- **Dose unchanged:** study drug does not need to be withdrawn for a specific AE.
- **Dose reduction:** dose reduction due to a specific AE.
- **Dose interruption:** temporary interruption/suspension of the study drug (including the subject's active interruption of the drug) due to a specific AE, and then resume the drug afterwards.
- **Unknown:** only used when the action taken cannot be determined.

- **Not applicable:** the study drug is withdrawn due to reasons other than specific AEs, e.g., the study has been terminated, the patient died, the study drug has already been stopped before the onset of the AE.

8.1.6 Outcome of AEs

Outcome of AEs can be described as follows:

- **Recovered/resolved, with no sequelae:** the event has been resolved and the patient has no sequelae. “End date of (serious) adverse events” should be indicated.
- **Recovered/resolved, with sequelae:** the event has been resolved, but the patient has long-term or lifelong sequelae, like hemiplegia caused by stroke. “End date of (serious) adverse events” should be indicated.
- **Recovering/resolving:** the event is not completely resolved, but the patient is recovering. Follow-up visits are required.
- **Unrecovered/unresolve**: the event is ongoing. Follow-up visits are required.
- **Fatal:** death date should be indicated.
- **Unknown:** the investigator cannot learn about the AE, e.g., the patient is lost to follow-up.

If outcome of an AE is determined to be "recovering/resolving" or "unrecovered/unresolved" or "unknown", the end date of the AE may not be recorded temporarily.

8.2 ADR

ADR refers to any harmful or undesirable reactions that may occur in clinical trials and be related to investigational products. There is at least a reasonable possibility of a causal relationship between the investigational product and the AE, i.e., the correlation cannot be ruled out.

In this trial, ADRs include AEs that have the causal relationship with the study drug as definitely related, possibly related, possibly unrelated, and uncertain.

8.3 SAE

8.3.1 Definition of SAE

SAEs refer to the following medical adverse events occurring after the subject receiving the investigational product:

- Death[a]
- Being life-threatening[b]
- Hospitalization or prolonged hospitalization[c]

- Persistent or serious disability or incapacity[d]
- Congenital abnormalities or birth defect[e]
- Other important medical events[f]

Further explanations for SAEs are as follows:

a. Any death occurring during the study period or within 28 days after the last dose, including those completely unrelated to the study drug. If the patient dies during the study period and an autopsy is conducted, the investigator should provide the sponsor and the Ethics Committee with other necessary information, such as autopsy report and final medical report.

b. Occurrence of AEs causes immediate risk of death for the patient. These do not include AEs that may cause death after serious progression, e.g., drug induced hepatitis without liver failure.

c. Any AEs resulting in hospitalization or prolongation of existing hospitalization (prolongation of existing hospitalization means the planned or expected discharge is delayed, usually after staying overnight in the hospital for at least one day). These do not include elective surgeries or examination before admission decided before the study, with no change of treatment course during the study.

d. Any AEs causing injury, damage or destruction of patient's function and/or physiological structure, physical activity or quality of life.

e. It is suspected that exposure of parent to the study drug may cause adverse outcome of descendants.

f. Medical and scientific judgment must be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may be considered serious if medical intervention is necessary to prevent one of the above situations. For example, intensive therapy in the emergency room or allergic bronchospasm at home, blood dyscrasia or convulsion not resulting in inpatient hospitalization, or those leading to drug dependence or drug abuse.

Death

All death events that occur during administration period or within 28 days after the last dose must be reported to the sponsor/CRO's safety department within 24 hours, and the death causes should be recorded in proper areas in the eCRF and the SAE report. If the death is jointly caused by multiple reasons, the investigator must determine the main cause of the death. The report should include information on AE condition, major or minor causes of death (if any), etc. In case of reports involving death events, the investigator should provide the sponsor/CRO and the Ethics Committee with other necessary information, such as autopsy report and final medical report.

Note: Generally, disease progression (including progressive symptoms and signs) should not be reported as an AE or SAE, but it should be reported as an SAE (with the severity as grade 5) if the patient's death is due to his/her disease progression (and the death can not be included as any of the grade 5 AEs in CTCAE).

Hospitalization

AEs requiring hospitalization for treatment are considered as SAEs. In general, hospitalization includes admission and treatment. Hospitalization does not include the followings:

- Rehabilitation facility;
- Nursing home;
- Admission to routine emergency room;
- Surgeries on the same day (e.g., outpatient/same day/ambulatory procedures);
- Unnecessary hospitalization and treatment (e.g., hospitalization for the reason of medical insurance reimbursement).

8.3.2 Collection and reporting of SAEs

Except for the SAEs unnecessary to be reported immediately as per the trial protocol or other documents (e.g., Investigator's Brochure), the investigator should report all the SAEs to the Sponsor/CRO in writing immediately, and thereafter provide a detailed and written follow-up report in a timely manner.

For any SAE in the trial, regardless of whether it is related to the study drug or not, the investigator should provide timely rescue treatment, complete the *Serious Adverse Event Reporting Form* within 24 hours of awareness, sign and date it and report it to the sponsor/CRO.

For initial SAE report, the investigator should record in detail about the report source, basic information of the subject, name of the study drug, SAE name, SAE symptoms/vital signs/examination indicators, start and end date, severity, treatment time, actions taken, causal relationship with the study drug and outcomes, etc., and ensure that the record is true, accurate, complete, timely and legal. After the initial report, the SAE should be continuously followed up and relevant new information or updated information of the previous report should be reported in the form of follow-up report timely (the follow-up report should be reported within 24 hours after obtaining the new information).

The investigator must provide causality assessment when reporting SAEs. If the investigator can not confirm whether the AE is an SAE, it will be considered as an SAE before proving its nature.

8.5 Adverse Events of Special Interest (AESIs)

In the expansion trial, AEs meet the DLT definition in Section 4.1.1.4 are considered as AESIs.

8.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs refer suspected unexpected serious ADRs whose clinical manifestations are beyond the Investigator's Brochure for the investigational drug, package inserts for marketed drugs, summary of product characteristics and other existing information in terms of their nature and severity.

After receiving safety-related information from any source, the sponsor should immediately analyze and assess, including the severity, causality with the investigational drug, and whether it is an expected event. The sponsor should report SUSARs to all participating investigators, clinical trial institutions and Ethics Committees in an expedited manner; the sponsor should report SUSARs to drug regulatory authorities and health authorities.

After receiving the relevant safety information of the clinical trial provided by the sponsor, the investigator should sign and read it in time, and consider whether to make corresponding adjustments to the treatment of the subject. If necessary, the investigator should communicate with the subject as soon as possible, and report SUSAR provided by the sponsor to the Ethics Committee.

In addition, the sponsor should make an expedited reporting of SUSARs to the center for drug evaluation (CDE) in a manner of individual case safety report (ICSR)according to *Criteria and Procedures for Expedited Reporting of Safety Data During Drug Clinical Trial* Issued by CDE on April 2018. For SUSARs, if the sponsor and the investigator can't agree on the causal relationship between the AE and the drug and any party considers that it is unable to exclude the correlation, expedited reporting should also be carried out.

The time limit for expedited reporting of SUSARs:

(I) For fatal or life-threatening SUSARs, the sponsor should report them as soon as possible and not more than 7 days after the first awareness, and should report and improve the follow-up information within the next 8 days. Note: The day of the sponsor's first awareness is Day 0.

(II) For non-fatal or life-threatening SUSARs, the sponsor should report them as soon as possible and not more than 15 days after the first awareness of the event.

After the initial report, the sponsor should continue following up the event and report relevant new information or update the previous report in the form of follow-up report timely (within 15 days after obtaining the new information).

8.7 Pregnancy

Pregnancy itself is not an AE or SAE. However, if the outcome of the pregnancy meets SAE criteria (e.g., spontaneous abortion, stillbirth, death neonatal, congenital anomaly or birth defect), the

corresponding event should be reported as an SAE.

For the contraceptive measures, definitions of child-bearing potential women, and contraceptive requirements, see Appendix III.

Female subjects become pregnant:

If female subjects are found pregnant during the study (from the start of administration to within 3 months after the last dose), the investigator should complete Pregnancy Reporting Form within 24 hours of awareness, report to the sponsor/CRO in an expedited manner, record it in the source medical records and the eCRF, and follow up the outcome of pregnancy (e.g., normal birth, preterm labour, spontaneous abortion, induced abortion, death neonatal, congenital anomaly or birth defect, etc.).

The investigator should propose advice to the subjects and discuss the risks of continuing pregnancy and the possible effects on the fetus. The subjects should terminate the study drug and withdraw from the study, and they should be monitored continuously until the end of pregnancy.

Female partners of male subjects become pregnant:

If the female partners of male subjects are found pregnant during the study (from the start of administration to within 3 months after the last dose), the investigator should complete Pregnancy Reporting Form within 24 hours of awareness, report to the sponsor/CRO in an expedited manner, record it in the source medical records and the eCRF. Under the permission of the study site, the pregnant partner should sign an authorization form of the use and release of pregnancy health information to allow the follow-up for the outcomes of their pregnancy (e.g., normal birth, preterm labour, spontaneous abortion, induced abortion, stillbirth, death neonatal, congenital anomaly or birth defect, etc.).

The investigator should propose advice to the subjects and their female partners and discuss the risks of continuing pregnancy and the possible effects on the fetus. The male subjects are not required to discontinue the study drug or withdraw from this study, however, their female partners should be monitored until the end of pregnancy.

9. Data Management

See the data management plan for detailed data management methods, e.g., collection and management procedures of trial data, system used for data collection and management, steps and tasks of data management, and quality assurance measures for data management.

9.1 Completion and Transfer of Source Data and eCRF

1) The investigator should supervise the data collection and the responsibility implementation of all trial staff at the study site.

2) The investigator should ensure that all clinical trial data are obtained from clinical trial source files and trial records, and are accurate, complete, readable and timely. Source data should be attributable, legible, contemporaneous, original, accurate, complete, consistent and enduring. In case of any amendment to source data, it should be marked, rather than being covered up, and the reasons for such amendment should be recorded. In the trial, relevant medical records should be entered into the outpatient service system or the inpatient record system. When the information-based system of the clinical trial institution manages to establish the electronic medical record of clinical trials, the investigator should give preference to such system, which should be equipped with perfect permission management and audit trail, be able to date back to the record creator or modifier, and ensure the traceability of all the source data collected.

3) The investigator should complete and modify the eCRF in accordance with the instructions provided by the sponsor and ensure that the data in various eCRFs and other reports is accurate, complete, clear and timely. The data in the eCRF should be consistent with the source documents. If there is any inconsistency, a reasonable explanation should be made. Modification of data in the eCRF should keep the initial record clear and legible and modification trail should be kept. Reasons should be given when necessary and the modifier should sign and date.

   The sponsor should have written procedures to ensure that their changes to eCRF are necessary, recorded, and approved by the investigator. The investigator should keep records of revisions and corrections.

9.2 Database Design

The Data Department of the CRO is responsible for data management of this study, and an electronic data capture (EDC) system is used to ensure the authenticity, integrity, privacy and traceability of the clinical study data.

The eCRF database is established by Data Department of CRO in the system in accordance with the requirements of Food Drug Administration 21 CFR Part 11. The database allows management of data traces such as system logins, data entry, modification and deletion, etc. The database will

be established according to the standards developed by the Clinical Data Interchange Standards Consortium as far as possible.

9.3 Data Entry

In accordance with the corresponding SOP, the investigator or personnel authorized by the investigator entered the information to the EDC system in a timely manner after the completion of visits strictly according to principle of "input what you see". After the data are entered, any correction to eCRF will be automatically recorded in the system.

9.4 Data Verification

Data manager (DM) will set logic verification program in EDC system according to the final data verification plan.

After the data are entered into EDC system, if there is any data not conforming to logic, the system verification will be initiated and trigger data queries. These inquiries have to be reviewed and responded by the investigator or the person authorized by the investigator. If updated data makes logic verification no longer valid, data inquiry will be closed immediately; if the study site confirms data and provides response, DM should review the response. If the reason is acceptable, the data inquiry will be closed; if data problem is not resolved, DM can continue adding data inquiry to communicate with the study site until final resolution.

Subject data listings/reports will be generated through programming to support manual data verification throughout the study. If data has to be clarified/verified/confirmed by the investigator, manual inquiry can be added in EDC system. DM should ensure that all queries are resolved before database lock and the investigator completes electronic signature in EDC system to ensure the integrity and accuracy of subject data in the EDC system.

9.5 Medical Coding

DM in Data Management of CRO are responsible for medical coding of this study. Coding contents include past medical history, AEs, and concomitant medications.

Prior medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (current or updated version). Previous medications and concurrent/concomitant medications will be coded according to the WHO Drug Dictionaries (current version or updated version).

During the coding process, if the data cannot be coded due to inappropriate, inaccurate, ambiguous medical terms, DM will ask the investigator to check and confirm it in the manner of data queries.

Before database lock, DM will send medical coding report to the sponsor for review.

9.6 Database Locking and Unlocking

After the review is completed and the established database is confirmed to be correct, the principal investigator, sponsor, DM, and statistician will jointly lock the data. In principle, any changes to the locked database are not allowed. If unlocking is required, the application will be jointly signed and submitted by the principal investigator, DM, statisticians and other personnel. The re-locking of the database should follow the same process as the first locking of the database.

9.7 Blinding Verification and Unblinding

Not applicable.

10. Statistical Analysis

10.1 Sample Size

This trial is a phase I clinical trial and does not estimate the sample size.

This trial plans to enroll 31-78 subjects in total:

- It is expected that the dose escalation trial will enroll 19-42 subjects;
- It is expected that the expansion trial will enroll 12-36 subjects.

10.2 Statistical Analysis Set

① **Screening set:** All subjects who signed the ICF. The screening set is used to analyze the number of subjects screened, number of subjects enrolled and number of screening failures.

② **Safety set (SS):** All subjects who are enrolled and have taken the study drug. SS is used for the description of demographic data, description of baseline characteristics, safety analysis and efficacy analysis.

③ **DLT analysis set (DS):** All subjects who are enrolled and have taken the study drug, but excluding subjects who receive study drug at a dose less than 75% of the scheduled dose for reasons other than toxicities attributable to study drug during the DLT observation period. DS is used for the analysis and summary of DLT.

④ **PK analysis set (PKS):** All subjects who are enrolled, have taken the study drug, have at least one PK data for statistical analysis and have no any protocol deviation (e.g., missed dosing of BB102 tablets) that significantly affects the PK parameters [e.g., area under the concentration-time curve (AUC), C_{max}, etc.] during the treatment cycle or dosing period containing blood sampling time point. Whether a subject is included into PKS will be determined case by case on the data review meeting. PKS is used for the analysis of PK parameters.

⑤ **Biomarker analysis set (BS):** All subjects who have at least one biological sample for biomarker analysis in the SS. BS is used for the analysis of relationship between biomarker and efficacy.

10.3 General Principles for Statistics

SAS® 9.4 or updated version (SAS Institute, Inc., Cary, North Carolina) will be used for statistical analysis.

Quantitative data will be described with the number of subjects of non-missing, mean, standard deviation, median, lower quartile, upper quartile, maximum and minimum.

Qualitative data will be statistically described using the number, frequency and percentage of non-missing subjects. If necessary, the two-sided 95% confidence interval (95% CI) for the percentage

will be calculated.

Baseline of safety endpoints is the most recent data prior to the first dose (data at screening are acceptable), including laboratory tests, vital signs, ECG, physical examination and ECOG score.

Prior medical history and AEs will be coded using the MedDRA (current or updated version). Previous medications and concurrent/concomitant medications will be coded according to the WHO Drug Dictionaries (current version or updated version).

Since this study is a Phase I trial, only descriptive statistics will be provided, and no hypothesis test will be performed.

Safety, PK and efficacy analyses will be performed for the dose escalation trial and expansion trial separately. In the dose escalation trial, it will be summarized overall and by dose group. In addition, it should also be summarized by gender.

The statistical analysis methods will be described in detail in the Statistical Analysis Plan.

10.4 Statistical Methods

10.4.1 Subject disposition analysis

Information of screening failures will be tabulated and summarized.

Subjects included in each analysis set will be summarized.

For the enrolled subjects, the number of subjects with treatment discontinuation, number of subjects who terminate the study and percentage of reasons will be summarized.

10.4.2 Analysis of demographics and baseline characteristics

The demographic data and baseline characteristics will be descriptively summarized, including gender, age, race, ethnicity, body height, BMI, past medical history, medication history, history of all neoplastic diseases, history of all anti-tumor therapies, family history, surgical history, allergic history, smoking history, and history of drug abuse/dependence.

10.4.3 Analysis of compliance and concomitant medications

Descriptive statistical analysis will be performed for the planned dose and actual dose by the following formula:

Compliance (%) = actual dose/planned dose × 100%.

The frequency and percentage of concomitant medications occurring during the dosing period will be summarized. The concomitant medication of subjects will be tabulated in detail.

10.4.4 Safety analysis

Drug safety will be evaluated by analyzing the incidences of AEs, ADRs, grade ≥3 AEs and SAEs,

as well as abnormalities or changes in laboratory tests, vital signs, ECG, physical examination and ECOG score.

AEs, ADRs, grade ≥3 AEs and SAEs will be coded according to MedDRA (current or updated version), and their incidences will be summarized according to system organ class, preferred term and the severity (CTCAE, Grades 1-5), respectively. The number of subjects with different AEs will be summarized, regardless of the number of times each subject actually reported the event.

Laboratory test parameters of subjects will be summarized before and after dosing.

For vital signs, ECG and physical examination, subjects with abnormal changes during the study will be described.

For ECOG score, patients' score and change in the score will be described.

If applicable, the data listings before and after dosing will be provided, and the mean ± standard deviation will be calculated. Patients with parameters being normal pre-dose but abnormal post-dose (regardless of the clinically significance) will be listed.

10.4.5 DLT analysis

Number of subjects with DLT as well as the category, severity and incidence of DLT will be summarized.

10.4.6 PK parameters analysis

Individual concentration-time curve of BB102 (and its main metabolites, if applicable) of each subject. Moreover, mean (Mean ± SD) concentration -time curve of BB102 (and its main metabolites, if applicable) will be plotted by dose group.

The PK parameters of BB102 (and its main metabolites, if applicable) will be analyzed using the non-compartment analysis method of the Phoenix WinNonlin 8.3.1 or updated version (Pharsight Corp., Mountain View, CA, USA) software.

For the plasma PK parameters of BB102 (and its main metabolites, if applicable), descriptive statistical analysis will be performed by dose group, with the descriptive statistics including the number of samples, mean, standard deviation, coefficient of variation, minimum and maximum. If considered necessary by the investigator and the sponsor, the linear relationship between the AUC and C_{max} of BB102 (and its main metabolites, if applicable) and dose can be analyzed.

10.4.7 Analysis of food effect

Data analysis will be performed by the average bioequivalence method with fasted condition as the reference, and the exposure parameters (AUC_{0-inf}, AUC_{0-t} and C_{max}) will be log transformed using natural logarithm to calculate the geometric mean ratio of fed group to fasted group and its 90% CI. If the 90% CI of the geometric mean ratios (fed group/fasted group) of AUC_{0-inf} (or AUC_{0-}

$_t$) and C_{max} all fall within the range of 80%-125%, it can be preliminarily concluded that food has no significant effect on the bioavailability of the drug.

10.4.8 Efficacy analyses

- **ORR:** The proportion of patients with a best overall response of CR and PR as assessed per RECIST v1.1 in all patients.
- **DCR:** The proportion of patients with a best overall response of CR, PR and SD (duration ≥12 weeks) as assessed per RECIST v1.1 in all patients.
- **DOR:** The duration from the firstly documented CR or PR to the date of confirmed objective tumor progression (based on RECIST v1.1) or death for the subjects with a best overall response of CR or PR. For the patients who have no objective tumor progression or death at the end of trial, the date of the last objective tumor assessment will be taken as the censored date of DOR.
- **PFS:** The duration from the first dose of study drug to objective tumor progression (based on RECIST v1.1) or death. For the patients who have no objective tumor progression or death at the end of trial, the date of the last objective tumor assessment will be taken as the censored date of PFS.
- **OS:** The duration from the first dose of study drug to death. For patients who are alive at the end of trial, their last date known to be alive will be used as the censored date of OS.

Point estimates of ORR and DCR and their two-sided 95%CI will be calculated. The two-sided 95% CI of ORR and DCR are calculated based on the Clopper-Pearson method. Meanwhile, the number and percentage of subjects with CR, PR, SD and disease progression will be presented.

For DOR (for subjects experiencing CR and/or PR only), PFS and OS, Kaplan-Meier method will be adopted to calculate the median, lower quartile, upper quartile and two-sided 95% CI, and survival curves will be drawn.

For ORR, the estimated objective is shown in the table below.

Estimated objective:	
Population:	FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors
Treatment:	See Section 6 for details
Endpoint:	ORR
Intercurrent events and handling strategies:	• Discontinuation of study treatment or initiation of new anticancer therapy prior to CR or PR will be handled according to the while-on-treatment strategy.
Summary at the population level:	ORR and corresponding two-sided 95%CI (estimated by Clopper-Pearson method) will be calculated

For DOR, the estimated objective is shown in the table below.

Estimated objective:	
Population:	FGF19 or FGFR4 positive advanced primary HCC or other advanced solid tumors
Treatment:	See Section 6 for details
Endpoint:	DOR
Intercurrent events and handling strategies:	• Discontinuation of study treatment or initiation of new anticancer therapy prior to objective tumor progression or death will be handled according to the hypothetical strategy.
Summary at the population level:	The variables of event time will be descriptively summarized, and KM curves will be plotted

For other efficacy measures (DCR, PFS and OS), an estimation method like that of ORR or DOR will be used.

10.4.9 Biomarker analysis

The relationship between biomarker and efficacy will be analyzed, and the correlation will be inferred preliminarily.

10.4.10 C-QTcF analysis

If considered necessary by the investigator and the sponsor, C-QTcF modeling analysis will be performed based on the data features and appropriate models to explore C-QTcF and investigate the possibility of QT_C interval prolongation induced by BB102.

10.4.11 Metabolite analysis

Metabolites of BB102 will be identified. The metabolites and subjects will be tabulated.

10.4.12 Subgroup analysis

Subgroup analysis will be performed by gender.

10.4.13 Interim analysis

Not applicable.

11. Trial Management

11.1 Statement

The clinical trial should be implemented in accordance with the ethical principles of *Declaration of Helsinki*, GCP and relevant regulations on drug clinical trials.

By signing the protocol, the investigator agrees to comply with the instructions and procedures set forth in the protocol, and to comply with the principles of GCP and all local regulations and medical research.

11.2 Ethical Considerations

The investigator must submit the trial documents to the Ethics Committee of the study site for review and approval, and the Ethics Committee should deliver its approval comments to the investigator in a written form.

Before drug shipment to the investigator, a copy of approval letter from the Ethics Committee and a checklist of reviewed documents must be submitted to the sponsor. The Ethics Committee's approval letter should clearly list all the committee members involved in the review with their respective responsibilities.

After the Ethics Committee has approved the study protocol, the sponsor/CRO should register it on the clinical trial registration platform (e.g., https://www.clinicaltrials.gov/).

Amendments of study protocol must be submitted to the Ethics Committee for review and approval, and reported to drug regulatory authorities according to local requirements.

In case of reports involving death events, the investigator should provide the sponsor and Ethics Committee with other necessary information, such as autopsy report and final medical report.

The Ethics Committee should be informed of the end of study data collection.

11.3 Source Data Verification

The investigator must properly handle all data obtained during the clinical study period and guarantee the rights and privacy of subjects participating in this clinical study.

Monitoring refers to the activities to oversee the progress of a clinical trial and ensure that the clinical trial is performed, recorded and reported as per its trial protocol, SOP and applicable laws and regulations. The sponsor assigns certain monitor to perform regular monitoring to the clinical trial. According to the SOP, the monitor should confirm that the clinical study-related activities are in compliance with regulations, and confirm the certificate and resource of clinical trials, and verify the consistency of eCRF, source data and other relevant documents, and write monitoring report.

Audit refers to a type of systematic and independent inspection against relevant activities and

documents of a clinical trial. The purpose of an audit is to determine whether the implementation of the trial, the recording, analysis and reporting of data comply with the protocol, SOP and relevant laws and regulations. The sponsor should assign the personnel independent to the clinical trial, not the monitor, as the auditor. The auditor audits the clinical trial to evaluate whether trial-related activities and records comply with the trial protocol, SOP and relevant laws and regulations on drug clinical trials, and writes the audit report.

Inspection refers to the act by drug regulatory authority in conducting a review of documents, facilities, records and other aspects of a clinical trial. Inspection can be done on the study site, or at the location of the sponsor or the CRO, or any other places considered by the drug regulatory authority as essential. The drug regulatory department may carry out official review and inspection on relevant documents, facilities, records and other aspects of clinical trials. The drug regulatory authority can ask the sponsor to provide audit reports as required by work.

The investigator must allow the monitors/auditors/inspectors to review and check the required clinical study documents so as to verify the accuracy of the source data and understand the progress of this study. If the source data cannot be verified, the investigator should agree to assist the monitors/auditors/inspectors in the further confirmation of data quality control.

11.4 Quality Assurance

All drugs and materials used in all clinical studies must be on the premise of quality control. The sponsor, personnel authorized by the sponsor or related medical regulatory authorities have the right to review the clinical study in order to ensure the authenticity of the clinical study data and compliance with the provisions of the clinical study protocol.

The monitor/auditor/inspector have access to all medical records, study-related documents and correspondences, and the informed consent documents of this clinical trial. The participants of clinical study will be informed of such clinical study reviewing process, but the privacy and data materials of participants will be strictly protected.

11.4.1 Requirements for Sponsor

The sponsor is responsible for providing trial fees and Investigator’s Brochure. The contents of the Investigator’s Brochure include chemical, pharmaceutical, toxicological, pharmacological and clinical (prior and ongoing trials) documents and data. The study protocol and completion rules of eCRF will be well explained to investigators before the initiation of the clinical trial.

The sponsor must provide the investigator with study drugs with easily identified and accurate code and special labeling and ensure qualified quality. The communication methods and monitoring methods should be monitored for AEs between the sponsor and the study site to ensure that the investigator can be kept in touch at any time via telephone, fax or email.

The sponsor should designate the monitor to conduct clinical trial monitoring and timely written reporting in accordance with this protocol, monitoring plan and monitoring-related SOPs, and make sure that the clinical trial is carried out and recorded correctly as per the trial protocol. The sponsor should review and follow up on the problems in the monitoring report, and keep them in the form of a document.

11.4.2 Requirements for Investigators

The investigator should carry out this trial in compliance with the requirements of the clinical protocol, GCP and relevant laws and regulations. The investigators must make sure that the conduct of the study is completely in compliance with the ethical principles of the *Declaration of Helsinki* and relevant laws and regulations, so as to protect the rights and interests of the subject and guarantee their safety. This protocol should be reviewed and approved by the Ethics Committee of the Study Site prior to implementation. Any revisions of this protocol during the study period must also be approved by the Ethics Committee.

The investigator is responsible for obtaining the ICF signed by each subject or his/her legal guardian or impartial witness. The investigator is responsible for guaranteeing that the processes of the receipt, storage, distribution, usage, and returning of study drugs are in compliance with the trial protocol and relevant laws and regulations, and making sure that all used and unused study drugs are managed by documentation, and all drug supplies and relevant records should be monitored and confirmed by the monitor. During the clinical trial, the investigator should accept the monitoring or auditing of the clinical research associate and auditor dispatched by the sponsor as well as the inspection of the drug regulatory authorities to ensure the quality of the clinical trial. The investigator is responsible for writing the summary report, and can publish papers only after permission by the sponsor.

11.4.3 Statistical analysis

The statistical analysis plan is written by the statistical analysis institution based on the *Guidelines for Drug Clinical Trial Data Management and Statistical Analysis Plan*, *Guidelines for Biostatistics of Drug Clinical Trial*, GCP and other relevant guidelines, and it is finalized after review. After that, the statistical work is carried out according to the finalized statistical analysis plan and the current SOPs, and the process of data processing will be rechecked.

11.5 Informed Consent

ICF should be in compliance with the ethical principles of the *Declaration of Helsinki*, as well as the rules and guidelines formulated by drug regulatory authorities.

Signed ICF must be obtained from the subject before the initiation of any clinical trial-related procedures.

The investigator should be responsible for the process of informed consent. Before the screening, the investigator is responsible for explaining study objective, methods, benefits and potential risks, other alternative treatments and subjects' rights and obligations consistent with *Declaration of Helsinki* to each subject; make them understand that they are free to withdraw from the trial at any time while their personnel interests will not be impaired. Before signing the ICF, the investigator or the personnel designated by the investigator should give enough time and chance to the subject or his/her guardian to understand the details of the clinical trial, and answer the questions about the clinical trial raised by the subject or his/her guardian. The process of informed consent should be documented in the disease course records at the day of screening visit.

The verbal explanation must be given when the written informed consent form is provided for participants. The informed consent form must be dated and signed by each subject or his/her legal guardian or impartial witness. The subject will keep one copy of the signed ICF, and the other copy will be kept in the investigator site file.

If any information related to the subject’s willingness to continue participating in the trial is available during the trial, the written ICF must be updated and provided to the subject to confirm if the subject is willing to continue. Note: The approval of Ethics Committee should be obtained for the revised ICF before providing to subjects.

By signing the ICF, the subject should agree that the Ethics Committee, drug approval regulatory authorities, sponsor, auditors and/or the sponsor-authorized clinical trial monitors are allowed to check the available source data related to clinical study, and the reviewer must follow confidential statement.

11.6 Trial Protocol Revision Rules

Necessary modifications of the study protocol will be made based on available clinical trial data.

Investigators shall not revise the trial protocol without the approval of the sponsor and the Ethics Committee, except when necessary to eliminate immediate hazards to the subjects or when the change involves only management of the clinical trial (e.g., change of monitor or telephone number). The investigator should timely report the revision of the trial protocol to eliminate immediate hazards to the subjects without the approval of the Ethics Committee to the Ethics Committee and the sponsor and provide reasons, and if necessary, report to drug regulatory authorities.

"Protocol amendment history" should be written when the protocol is modified.

11.7 eCRF

DM of CRO will establish eCRF in the system. The eCRF only uses appropriate identification codes (e.g., subject screening number) to identify different subjects. Only the data of one subject

will be recorded in each eCRF. The eCRF is used for the documentation of clinical study data of subjects, and is a component of this study and relevant study reports. Entry must be therefore accurate and complete. The eCRF is entered by the investigator or an authorized person (should be specified in study authorization form). It must be ensured that all data entry is completed and stored. The investigator must provide an electronic signature to declare that all information in the eCRF is true and correct.

In a clinical study, eCRF should be completed as soon as possible after each visit to record the condition of subjects. If the information is not applicable, “NA” should be filled in; if the test item is not done, "ND" should be filled in.

11.8 Monitoring

The monitors designated by the sponsor should conduct clinical trial monitoring and timely submit written reports in accordance with this protocol, monitoring plan and monitoring-related SOPs, and make sure that the clinical trial is carried out and recorded correctly as per the trial protocol. The sponsor should review and follow up on the problems in the monitoring report, and keep them in the form of a document.

11.9 Confidentiality and Privacy of Subjects

In the process of processing the information of the clinical trial and the subjects, illegal or unauthorized access to, disclosure, dissemination, modification, damage, and loss of information should be avoided. The confidentiality of records and subject information should be guaranteed during the recording, processing and preservation of clinical trial data.

The trial staff must safeguard the privacy of subjects. Name of the subjects should not be indicated in all of the documents submitted to the sponsor. The investigator must keep the name, address and enrollment form of the subjects properly. The enrollment form is maintained by the investigator with strict confidentiality and should not be submitted to the sponsor.

11.10 Others

11.10.1 Protocol deviations

The investigator should conduct this trial according to the clinical study protocol approved by the Ethics Committee and GCP regulations.

The investigator must not revise or deviate from the trial protocol without the approval of the sponsor and the Ethics Committee, except when necessary to eliminate immediate hazards to the subjects or when the change involves only management of the trial (e.g., change of monitor or telephone number). The investigator should timely report the trial protocol deviation to eliminate immediate hazards to the subjects without the approval of the Ethics Committee to the Ethics Committee and the sponsor and provide reasons, and if necessary, report to drug regulatory

authorities.

The investigator or the personnel designated by the investigator should record and explain trial protocol deviation. The record contents include but are not limited to the occurrence time, time of awareness, event description of and actions taken for the protocol deviation. In case of a significant protocol deviation, the clinical research associate and Ethics Committee should be notified in a timely manner. If necessary, the sponsor can terminate this trial in advance.

11.10.2 Personnel training

All study-related personnel (doctors, nurses and other personnel) authorized by the investigator should accept relevant trainings, and the training records should be kept and archived,

11.10.3 Curriculum vitae of clinical investigator

All clinical investigators participating this trial or other related personnel should provide recent (within 2 years) curriculum vitae to the sponsor to be filed as related documents.

11.10.4 Qualification certificates of clinical laboratories and range of normal values

The clinical study site should provide the sponsor/CRO with copies of qualification certificates of the clinical laboratory and the range of normal values to be filed as related documents.

11.10.5 Agreement of clinical study protocol

Before the initiation of the study, the principal investigator must sign the clinical trial protocol to confirm that he/she has well understood the protocol and will conduct the clinical trial in strictly accordance with the protocol.

11.10.6 Insurance

For consideration of subject's safety, the sponsor will buy relevant liability insurance for this study. If the subject experiences health injury related to this trial, after being verified by a legal department or institution, relevant medical cost and corresponding financial compensation will be provided according to GCP and applicable national laws and policies.

12. Intellectual Property Rights and Paper Publication

All information obtained from the trial sponsor belongs to the intellectual property rights of the trial sponsor. Therefore, the clinical trial investigator and all other relevant personnel must strictly keep it confidential, and should not disclose it to any third party without the prior consent of the trial sponsor.

The study results are proprietary to the sponsor. The investigator must negotiate with the sponsor before publishing any collected or generated trial-related information. The investigator should guarantee that he/she will not publish on journals or magazines or release on academic or commercial conferences about any content related to the study and/or study results without the written permission from the sponsor. The sponsor has the right of final decision about the manuscript and publication. At the same time, the investigator should understand that the sponsor will not refuse the publication without any reason after being communicated.

In order to prevent from unconscious leakage of confidential information or unprotected inventions, the investigator must inform the sponsor in advance to discuss or review together about publications planned to be published or releases of other forms (the forms of publication/release include but are not limited to journal articles, posters, guest lectures). The investigator should provide the sponsor with the original manuscript, abstract or full text planned to be published/released at least 45 days before submitting for publication/release, and the sponsor will check for laws and regulations and intellectual property rights about the contents to be published. If it is for protection of intellectual property rights, especially before the achievement of corresponding patent, the investigator should agree to delay or cancel publication. Prior to publication, the investigator can be asked to delete any confidential information that has not been published before. Many study sites are participating in this study, unless prior consent has been obtained from the sponsor, individual should not publish any data related to the clinical study before the final report of the multi-center study has been completed. The investigator should agree that the first publication is the overall achievement of all study sites. However, if the original manuscript of overall analysis has not been submitted and published within 12 months after the completion or termination of study in all study sites, the investigator may request to publish study results of single site, but the sponsor should still be informed in advance and discussed with.

The investigator should not use the name of the sponsor and/or its designator in advertisements or advertising materials and publications before obtaining the written permission from the sponsor. At the same time, the sponsor should not use the name of the investigator in advertisements or advertising materials or publications before obtaining the written permission from the investigator and/or cooperator.

As required by the GCP, the contract signed by the sponsor and the investigator should include the

agreements about publishing articles and intellectual property rights, etc. **Note: If the description about publishing articles and intellectual property rights is different from the contract, the contract shall prevail.**

13. Clinical Data Archiving

The sponsor, investigator and clinical trial institution should keep trial documents properly in accordance with the "essential documents for clinical trials" and relevant requirements of drug regulatory authorities.

Essential documents: documents, solely or together, to evaluate the implementation process of the clinical trial and the quality of the clinical data.

According to the requirements of GCP, for clinical trials that are used to apply for drug registration, the essential documents should be kept for at least 5 years after the investigational drug has been approved for marketing; for clinical trials that are not used to apply for drug registration, the essential documents should be kept for at least 5 years after the termination of clinical trials. If the sponsor wishes to retain for a longer period of time, the retention time and methods will be discussed and decided by all three parties. It is the responsibility of the sponsor to inform the investigator/clinical trial institution of when it is no longer necessary to further retain such data. If the investigator/clinical trial institution makes any changes in document retention, the personnel or investigator responsible for document retention should contact the sponsor.

The sponsor should clarify with the investigator and the clinical trial institution about the retention time, fees and processing after expiration in the contract.

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15. Appendix

Appendix I: RECIST v1.1

This guideline describes a standard approach to solid tumour measurement and definitions for objective assessment of change in tumour size for use in adult and paediatric cancer clinical trials. It is expected these criteria will be useful in all trials where objective response is the primary study endpoint, as well as in trials where assessment of stable disease, tumour progression or time to progression analyses are undertaken, since all of these outcome measures are based on an assessment of anatomical tumour burden and its change on study. There are no assumptions in this appendix about the proportion of patients meeting the criteria for any of these endpoints which will signal that an agent or treatment regimen is active: those definitions are dependent on type of cancer in which a trial is being undertaken and the specific agent(s) under study. Protocols must include appropriate statistical sections which define the efficacy parameters upon which the trial sample size and decision criteria are based. In addition to providing definitions and criteria for assessment of tumour response, this appendix also makes recommendations regarding standard reporting of the results of trials that utilise tumour response as an endpoint.

While these guidelines may be applied in malignant brain tumour studies, there are also separate criteria published for response assessment in that setting. This appendix is not intended for use for studies of malignant lymphoma since international guidelines for response assessment in lymphoma are published separately.

Finally, many oncologists in their daily clinical practice follow their patients' malignant disease by means of repeated imaging studies and make decisions about continued therapy on the basis of both objective and symptomatic criteria. It is not intended that these RECIST guidelines play a role in that decision making, except if determined appropriate by the treating oncologist.

I. Measurability of Tumour at Baseline

1. Definitions

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows.

(1) Measurable lesions/lymph nodes

Tumour 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);

- 20mm 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 should be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

(2) Non-measurable lesions/lymph nodes

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: pathologically determined meningeal 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.

(3) Special considerations regarding lesion measurability

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

Bone lesions:

- 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 X-ray defined simple cysts should not be considered as malignant lesions (either measurable or non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to be cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, it is best to consider them as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other local

therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

2. Specifications by methods of measurements

(1) 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.

(2) Method of assessment

The same method of assessment and the same technique should be used to characterise 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 colour 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 appendix 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 that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour 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.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise 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 CA-125 response (in recurrent ovarian cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour 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 tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential ADR (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 tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

II. Tumour Response Evaluation

1. Assessment of overall tumor burden and measurable disease

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

2. Baseline documentation of "target" and "non-target" lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be

representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in previous Section 3, pathological nodes which are defined as measurable must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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

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

3. Response criteria

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

(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). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sumdiameters while on study.

(2) Special notes on the assessment of target lesions

Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <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 subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 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 default 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 is able to 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 longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

(3) Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour 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.

- **CR:** Disappearance of all non-target lesions and normalisation of tumour 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 tumour 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).

(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 tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance 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 patients 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 tumour 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 localised 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 disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

(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 tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when important when the patient's baseline lesions show 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 confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET assessments need additional study, it is 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.

4. Evaluation of best overall response

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

(1) Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 4 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (non-target) disease only, Table 5 is to be used.

Table 4 Time point response: patients 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 evaluated	No	PR
SD	Non-PD or not evaluated	No	PD
Not evaluated	Non-PD	No	Non-evaluable

Target lesions	Non-target lesions	New lesions	Overall response
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviation: CR = complete response; PR = partial response; SD = stable disease.

Table 5 Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not evaluated	No	Non-evaluable
Definite disease progression	Yes or No	PD
Any	Yes	PD

Abbreviation: CR = complete response; SD = stable disease.

Note: 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment in some trials so to assign this category when no lesions can be measured is not advised.

(2) 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 are 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 SD. 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.

(3) Best overall response: all time points

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

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last

assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this circumstance, the best overall response can be interpreted as in Table 6.

Table 6 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	Non-evaluable	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	Non-evaluable	SD provided minimum criteria for SD duration met, otherwise, NE
Non-evaluable	Non-evaluable	Non-evaluable

Abbreviation: CR = complete response; PR = partial response; SD = stable disease.

Note: 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.

(4) 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 patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of efficacy is required, repeated '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.

Patients 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, and it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 4-6.

Conditions that define 'early progression, early death and inevaluability' 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 disease 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.

5. Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6-8 weeks is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g., time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6-8 weeks on treatment or every 3-4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

6. Confirmatory measurement/duration of response (DOR)

(1) Confirmation

In non-randomised trials where response is the primary endpoint, 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. in this Special Issue). However, in all other circumstances i.e. in randomised trials (phase II or III) or studies where stable disease or disease 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.

(2) 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 disease 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.

(3) Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) 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 patients 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 RECIST to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

7. Progression-free survival/proportion progression-free

(1) Phase II trials

This RECIST guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, ‘response rate’ may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases ‘progression-free survival’ (PFS) or the ‘proportion progression-free’ at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and presence/absence of the impact of the intervention. Thus, phase II trials utilising these endpoints are best designed with a randomised control. Exceptions may exist where the behaviour patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomised trial is justifiable (see for example van Glabbeke et al.). However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

8. Independent review of response and progression

For trials where objective response (CR + PR) is the primary endpoint, and in particular where key

drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomised trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central-review-based progression time in place of investigator-based progression time due to the potential introduction of informative censoring when the former precedes the latter. An overview of these factors and other lessons learned from independent review is provided in an article by Ford et al. in this special issue.

9. Reporting best response results

(1) Phase II trials

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. CR
2. PR
3. SD
4. PD
5. Inevaluable for response: specify reasons [for example: early death, disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify)].

Normally, all eligible patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should not be based on a selected 'evaluable' subset.

Appendix II: ECOG Performance Status Score Scale

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

Appendix III: Definition of Women of Childbearing Potential and Contraceptive Requirements

- **Definition of Women of Childbearing Potential**

Women of non-child-bearing potential are defined as postmenopausal women and premenopausal women who have undergone sterilization. Sterilization includes bilateral tubal ligation or bilateral oophorectomy or hysterectomy.

1) For women of childbearing potential, human chorionic gonadotropin (HCG) will be tested. Blood HCG pregnancy test at screening visit should be completed within 7 days prior to the first dose.
2) For women ≥40 to <60 years of age and at least 12 months post-menopausal, follicle stimulating hormone, estradiol and luteinizing hormone will be tested; if necessary, anti-Mullerian hormone can be tested additionally. This test will be performed at screening only.
3) For women ≥60 years of age, a pregnancy-related test is not required.

Women of childbearing age are defined as women who have not undergone sterilization and are able to become pregnant anatomically and physiologically after menarche and before menopause.

- **Contraceptive Requirements**

For women of childbearing potential, the results of serum pregnancy should be negative at screening and baseline (if applicable).

Males of reproductive potential and females of childbearing potential must also agree to one of the following from the time of signing the ICF through the last dose of study drug:

- Total abstinence. Periodic abstinence methods (such as calendar method, ovulation method, symptom-body temperature method, post-ovulation method) are not allowed.
- One of the contraceptive methods with a failure rate of <1%:
  - Intrauterine device or intrauterine hormone release system with an annual failure rate of <1%;
  - Males undergo vasoligation;
  - Double barrier method: Condoms and/or occlusion caps (diaphragm or cervical cap/dome cap), spermicide (foam/gel/film/cream/suppository) barrier method should be used as supplementary measures

Within 6 months after the last administration, you can also accept the following contraceptive methods:

- Reasonable combined use of oral/injection/transdermal hormonal contraceptives that can

inhibit ovulation (including estrogen and progesterone);

- Reasonable use of progesterone-only oral/injection/transdermal hormonal contraceptives that can inhibit ovulation.

Appendix IV: Examples of CYP450 Related Drugs/Foods

Categories	Examples of related drugs/foods
Strong CYP3A4 inhibitors	Clarithromycin Telithromycin Itraconazole Ketoconazole Voriconazole Posaconazole Lopinavir Indinavir Nelfinavir Ritonavir Saquinavir Conivaptan Mibefradil Nefazodone Troleandomycin Grapefruit, pomelos and other citrus fruits or juice
Strong CYP3A4 inducers	Carbamazepine Efavirenz Modafinil Nevirapine Phenobarbital Phenytoin Rifampin St John's Wort
Strong CYP3A5 inhibitors	Clarithromycin Telithromycin Itraconazole Ketoconazole Voriconazole Posaconazole Lopinavir Indinavir Nelfinavir Ritonavir Saquinavir Conivaptan Mibefradil Nefazodone

	Troleandomycin Grapefruit, pomelos and other citrus fruits or juice
Strong CYP3A5 inducers	Carbamazepine Efavirenz Modafinil Nevirapine Phenobarbital Phenytoin Rifampin St John's Wort
Sensitive CYP3A4 substrates with a narrow therapeutic index	Alfentanil Cyclosporine Diergotamine Ergotamine Fentanyl Pimozide Quinidine Sirolimus Tacrolimus
Sensitive CYP2B6 substrates with a narrow therapeutic index	Bupropion, efavirenz

Note: For the drugs listed and not listed in the above list, if the investigator cannot determine whether they are strong CYP3A4 inhibitors, strong CYP3A4 inducers, strong CYP3A5 inhibitors, strong CYP3A5 inducers, sensitive CYP3A4 substrates with a narrow therapeutic index, or sensitive CYP2B6 substrates with a narrow therapeutic index, the sponsor can be contacted for discussion and decision.

List of References:

[1] FDA guidance drug interaction studies: study design, data analysis, and implication for dosing and labeling, 2006.

[2] Oncology Clinical Pharmacology internal memo: drug-drug Interactions (DDI) database, 2010.

[3] Zhou SF. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. Curr Drug Metab. 2008;9(4):310-322.

[4] https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-2

[5] http://medicine.iupui.edu/clinpharm/ddis/clinical-table/

Appendix V: Transporter Inhibitors and Substrates Examples

Categories	Examples of related drugs/foods
BCRP substrates (Narrow therapeutic index at the discretion of the investigator)	sulfasalazine rosuvastatin
P-gp substrates (Narrow therapeutic index at the discretion of the investigator)	dabigatran etexilate fexofenadine digoxin
OAT1 substrates (Narrow therapeutic index at the discretion of the investigator)	adefovir cefaclor ceftizoxime furosemide ganciclovir famotidine methotrexate oseltamivir carboxylate
OAT3 substrates (Narrow therapeutic index at the discretion of the investigator)	adefovir cefaclor ceftizoxime furosemide ganciclovir famotidine methotrexate oseltamivir carboxylate
OATP1B3 substrates (Narrow therapeutic index at the discretion of the investigator)	pravastatin repaglinide atorvastatin bosentan asunaprevir danoprevir rosuvastatin docetaxel fexofenadine glyburide nateglinide paclitaxel pitavsatatin simvastatin acid
MATE1 substrates (Narrow therapeutic index at the discretion of	Metformin

Categories	Examples of related drugs/foods
the investigator)	
MATE2-K substrates (Narrow therapeutic index at the discretion of the investigator)	Metformin
BCRP inhibitors (Strong inhibitor at the discretion of the investigator)	curcumin eltrombopag cyclosporine A
P-gp inhibitors (Strong inhibitor at the discretion of the investigator)	ranolazine verapamil itraconazole clarithromycin quinidine ritonavir elaprevir saquinavir + ritonavir

Note: For the drugs listed and not listed in the above list, if the investigator cannot determine whether they are BCRP substrates, P-gp substrates, OAT1 substrates, OAT3 substrates, OATP1B3 substrates, MATE1 substrates, MATE2-K substrates, strong BCRP inhibitors, or strong P-gp inhibitors with a narrow therapeutic index, the sponsor can be contacted for discussion and decision.

List of References:

[1] https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-2

[2] CDE Technical Guidelines for Drug Interaction Research (Trial)

Appendix VI: Drugs which May Prolong QT Interval and (or) Induce Torsade De Pointes

Categories	Common drugs
ANTIARRHYTHMIC AGENTS	Amiodarone (Cordarone ®) (Pacerone ®) Disopyramide (Norpace ®) Dofetilide (Tikosyn ®) Ibutilide (Corvert ®) Procainamide (Pronestyl ®) (Procan ®) Quinidine (Quinaglute ®) (Cardioquin ®) Sotalol (Betapace ®)
ANTIBIOTICS	Clarithromycin (Biaxin ®) Erythromycin (Erythrocin ®) (E.E.S. ®) Gatifloxacin Moxifloxacin Sparfloxacin (Zagam ®)
ANTIPSYCHOTICS	Chlorpromazine (Thorazine ®) Haloperidol (Haldol ®) Mesoridazine (Serentil ®) Pimozide (ORAPI ®) Risperidone Thioridazine (Mellaril ®) Ziprasidone
ANTIDEPRESSANTS	Amitriptyline Desipramine Doxepin Imipramine Maprotiline Venlafaxine
ANTIFUNGALS	Ketoconazole Itraconazole
ANTIMALARIALS	Chloroquine (Arelan ®) Halofantrine (Halfan ®)
ANTIEMETICS	Dolasetron Domperidone (Motillium ®) Droperidol (Inapsine ®) Ondansetron Tropisetron
Others	Arsenic trioxide (Trisenox ®) Bepridil (Vascor ®) Methadone (Methadose ®) Pentamidine (NebuPent ®) Cisapride (Propulsid ®) Tacrolimus