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Statistical Analysis Plan

Study CS3008(BLU-554)-101

Study Title: A Muti-center, Open-label, Multiple-dose Phase Ib/II Study to Assess the Safety, Tolerability, Pharmacokinetics, Anti-tumor Efficacy of CS3008 (BLU-554) in Combination with CS1001 in Subjects with Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)

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Protocol Title	**A Muti-center, Open-label, Multiple-dose Phase Ib/II Study to Assess the Safety, Tolerability, Pharmacokinetics, Anti-tumor Efficacy of CS3008 (BLU-554) in Combination with CS1001 in Subjects with Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)**
Protocol No.:	**CS3008(BLU-554)-101**
Investigational Drug:	**CS3008（BLU-554）; CS1001**
Version Number:	**1.0**
Sponsor:	**CStone Pharmaceuticals (Suzhou) Co., Ltd.** **CStone Pharmaceuticals (Shanghai) Co., Ltd.** **Blueprint Medicines Corporation**
Written by:	**Hangzhou Tigermed Consulting Co., Ltd.**
Finalization date:	**November 09, 2021**
Revision date	

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Signature Page

A Muti-center, Open-label, Multiple-dose Phase Ib/II Study to Assess the Safety, Tolerability, Pharmacokinetics, Anti-tumor Efficacy of CS3008(BLU-554) in Combination with CS1001 in Subjects with Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)

CS3008(BLU-554)-101

Statistical analysis plan

Version No.: 1.0

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1. BACKGROUND

This is a multi-center, open-label, multi-dose, dose-finding and extension study for evaluating the safety, tolerance, pharmacokinetics and antitumor efficacy profiles of BLU-554 in combination with CS1001 in subjects with locally advanced or metastatic HCC.

The study consists of 2 parts, including a Part 1 (phase Ib) dose escalation and part 2 (phase II) dose expansion. Part 1 is a dose escalation study for determination of the MTD (Maximum tolerated dose) and/or RP2D (Recommended Phase II dose) of BLU-554 in the combination regimen and assess primary safety and tolerance of the combination regimen. Part 2 is a dose extension study in which preliminary evaluate the antitumor efficacy and the further evaluate the safety, tolerance, PK and immunogenicity of combination regimen.

This Statistical Analysis Plan has been written based on the CS3008 (BLU-554)-101 study protocol (version number: 2.1, version date: July 28, 2020), and describes the content and methods of statistical analysis in this study in detail.

2. STUDY DESIGN

2.1 PROTOCOL SYNOPSIS

For the protocol synopsis, see Appendix 1. For more details, see the Study Flowchart in Appendix 2.

For study indicators, see the Protocol Synopsis.

2.2 SAMPLE SIZE DETERMINATION

It is planned to enroll not more than 12 subjects in the phase-Ib dose-escalation study. The observed toxicity will decide the actual sample size.

According to efficacy result of BLU-554-1101 study (data cut-off date: 16 Jun 2018), ORR was 17% (11/63) for FGF19 IHC+ subjects (1st line and above) and 0 (0/38) for FGF19 IHC-subjects. ORR of PD-1/PD-L1 monotherapy was reported around 10~20% for 1st line and 2nd line HCC subjects. Based on the data above, BLU-554 in combination with CS1001 is targeting 40% ORR for FGF19 IHC+ subjects and 30% ORR for FGF19 IHC- subjects. Combining the subjects treated at RP2D in Phase Ib and those in Phase II, gating criteria in Bayesian framework are developed as the following:

Gating based on 25 FGF19 IHC+ subjects

- A non-informative ORR prior is assumed at Beta (0.45, 0.55).
- Timing - when all 25 subjects finish at least two post-baseline tumor assessments
- Go - 12 responses or more, corresponding ORR 48%, the probability of combo ORR > 40% is 0.788.
- No go - 8 (32%) responses or fewer, the probability of combo ORR<40% is 0.797.
- Evaluate - 9 (36%) to 11 (44%) responses, evaluate other endpoints, DOR, DCR, safety, etc., and additional 15 FGF19 IHC+ subjects may be enrolled for further evaluation.

Gating based on 40 FGF19 IHC+ subjects (if enrichment of 15 FGF19 IHC+ subjects as decided)

- A non-informative ORR prior is assumed at Beta (0.45, 0.55).
- Timing - when all 40 subjects finish at least two post-baseline tumor assessments
- Go - 18 responses or more, corresponding ORR 45%, the probability of combo ORR > 40% is 0.737.
- No go - 14 (35%) responses or fewer, the probability of combo ORR<40% is 0.744.
- Evaluate - 15 (37.5%) to 17 (42.5%) responses, evaluate other endpoints, DOR, DCR, etc.

Gating based on FGF19 IHC- subjects treated at RP2D in Phase Ib

- A non-informative ORR prior is assumed at Beta (0.2, 0.8).
- Timing - only conducted if at least 6 FGF19 IHC- subjects are treated at RP2D in Phase Ib, when they finish at least two post-baseline tumor assessments
- No go - 0 response, the probability of combo ORR<30% is greater than 0.99, Phase II will only include the FGF IHC+ cohort
- Evaluate - 1 response or more, the cohort of FGF IHC- subjects will be included in Phase II

Gating based on 15 FGF19 IHC- subjects

- A non-informative ORR prior is assumed at Beta (0.2, 0.8).
- Timing - when all 15 subjects finish at least two post-baseline tumor assessments
- Go - 6 responses or more, corresponding ORR 40%, the probability of combo ORR > 30% is 0.757. If the final decision for FGF19 IHC+ subjects is “go”, FGF19 IHC- subjects

may also be included in the target population of future development.

- No go - 3 (20%) responses or fewer, the probability of combo ORR<30% is 0.845. future development will not include FGF19 IHC- subjects in the target population.
- Evaluate - 4 (26.7%) to 5 (33.3%) responses, evaluate other endpoints, DOR, DCR, etc.

The sample sizes of 25 or 40 FGF19 IHC+ subjects and 15 FGF19 IHC- subjects are selected to have reasonably high probability of ORR exceeding the target when the go criteria are met or ORR being lower than the mono therapies when no-go criteria are met.

The go and no-go criteria are set up to guide future development of the combination. **They are not binding** decision-**making rules**.

If the actual numbers of evaluable subjects are different from those planned above, the same method will be used to calculate the posteriori probability that ORR will reach the predefined target for reference in subsequent development.

2.3 TIME OF ANALYSIS

Phase Ib: Dose Escalation

The MTD and/or RP2D of two dose levels and preliminary safety evaluation of BLU-554 in the combination regimen will be determined with the starting dose of 400 mg QD (once daily). CS1001 1,200 mg Q3W (every 3 weeks) as the fixed dose will be the RP2D in the monotherapy phase I study CS1001-101. The dose escalation part will use the BOIN design.

During the study period, an SMC consisting of the principle investigator, the CRO's representatives (CRA and other relevant person) and the sponsor's representative will be established to review the safety data, PK data, efficacy data from the study and determine the escalation dose level and dosage regimen in dose escalation study so as to determine the MTD and RP2D selected for the extension study. The SMC will also decide whether or not to include unscheduled dose levels for the study.

Phase II: Dose Expansion

The primary objective of the dose expansion phase is to further evaluate the antitumor efficacy as well as the safety, tolerability, PK and immunogenicity of the combination regimen. Subjects will be enrolled into 2 groups based on FGF19 IHC expression: Group 1 will be HCC subjects with FGF19 IHC-, approximately 15 subjects will be enrolled; Group 2 will be HCC subjects with FGF19 IHC+, approximately 25 subjects will be enrolled, approximately total 40 subjects in expansion part. Data on phase Ib evaluation at RP2D will be used as the basis to determine whether to continue to enroll subjects with FGF19 IHC- in the dose expansion phase. If the statistically pre-specified continuous evaluation range is reached, additional subjects with FGF19 IHC+ may be enrolled for further evaluation. FGF19 IHC test will be performed at central laboratory with FGF19 IHC+ defined as ≥ 1% for inclusion assessment.

Archived or fresh tumor samples must be provided for FGF19 and PD-L1 IHC test which will be performed at central laboratory.

The imaging examinations of tumors shall be evaluated in accordance with RECIST v1.1. During the 1st year of the treatment, subjects will receive CT/MRI examination in the screen period and every 9 weeks (at the end of every 3 cycles). After 1 year of study, CT/MRI examinations shall be carried out once every 12 weeks (The investigator may increase the number of tumor evaluations where clinically indicated).

Subjects will be monitored for anti-tumor activity, safety, tolerability, PK profile and host immunogenicity throughout the study from the day of first administration of study drugs up to 90 days after the last administration or up to two-year treatment period of combination regimen.

2.4 OBJECTIVES AND ENDPOINTS

2.4.1 Primary Objectives and Primary Endpoints of the Study

Objectives:	Endpoints:
Primary	
Phase Ib:	
• To determine the MTD and/or RP2D of BLU-554 when being in combination with CS1001 in subject with advanced HCC. • To evaluate the safety and tolerability of BLU-554 in combination with CS1001.	• Incidence of DLT during the administration of BLU-554 in combination with CS1001. • Safety: incidence and severity of AEs and SAEs, including laboratory tests, vital signs, and ECG • Tolerance: discontinuation and reduction of study drug dose
Phase II:	
• To assess the anti-tumor efficacy of BLU-554 in combination with CS1001	• To assess ORR based on RECIST v1.1

2.4.2 Secondary Objectives and Secondary Endpoints of the Study

Objectives:	Endpoints:
Secondary	
Phase Ib	
• To assess the pharmacokinetics (PK) profile of BLU-554 in combination with CS1001.	Pharmacokinetic parameters include, but are not limited to: • When combination with BLU-554, AUC, Cmax, tmax, CLss , accumulation ratio of CS1001. • When combination with CS1001, AUC, Cmax, tmax, CLss/F, accumulation ratio of BLU-554
• To preliminary assess the anti-tumor activity of BLU-554 in combination with CS1001	• To assess ORR, DOR, DCR, TTP, PFS and OS based on RECIST v1.1
• To assess the immunogenicity of CS1001 when administered in combination with BLU-554	• Occurrence of anti-CS1001 antibody
• To correlate FGF19 and PD-L1 expression • level with efficacy of BLU-554 in combination with CS1001	• ORR, DOR, DCR, TTP, PFS and OS by FGF19 protein and PD-L1 protein level
Phase II	
• To assess the anti-tumor activity of BLU-554 in combination with CS1001.	• To assess DOR, DCR, TTP, PFS and OS based on RECIST v1.1
• To evaluate the safety and tolerability of BLU-554 in combination with CS1001.	• Safety: incidence and severity of AEs and SAEs, including laboratory tests, vital signs, and ECG • Tolerance: discontinuation and reduction of study drug dose
• To assess the pharmacokinetics (PK) profile of BLU-554 in combination with CS1001.	Pharmacokinetic parameters include, but are not limited to: • When combination with BLU-554, AUC, Cmax, tmax, CLss, accumulation ratio of CS1001. • When combination with CS1001, AUC, Cmax, tmax, CLss/F, accumulation ratio of BLU-554.
• To assess the immunogenicity of CS1001 when • administered in combination with BLU-554.	• Occurrence of anti-CS1001 antibody

• To correlate FGF19 and PD-L1 expression level with efficacy of BLU-554 in combination • with CS1001	• ORR, DOR, DCR, TTP, PFS and OS by FGF19 protein and PD-L1 protein level

3. STATISTICAL METHODS

3.1 GENERAL PRINCIPLE

For statistical analysis, all calculations will be performed using SAS statistical analysis software version 9.4 and above.

For quantitative indicators, descriptive statistics include the number of cases, mean, standard deviation, median, minimum, and maximum, and all of which, as well as geometric mean and coefficient of variation, are included in the pharmacokinetic analysis. Unless otherwise specified, the decimal places of minimums and maximums are consistent with the original data recorded in the database. Means, medians, and geometric means have one more decimal place than the original data recorded in the database, and standard deviations and coefficients of variation have two more decimal places than the original data recorded in the database. All statistics have a maximum of four decimal places.

For categorical indicators, descriptive statistics include the number and percentage of cases. Percentages are rounded to one decimal place, and the percentage is not reported if the frequency is 0.

In the statistical test, if the P value is greater than or equal to 0.0001, 4 decimal places will be retained, and if the P value is less than 0.0001, "<.0001" will be used.

Baseline is defined as the last valid measurement or recording prior to the first study treatment.

Phase Ib data will be summarized and analyzed by dose group. Phase II data will be summarized and analyzed on an aggregate basis.

3.2 ANALYSIS SETS

All analysis sets will be identified prior to database lock.

3.2.1 Safety Analysis Set (SAS)

Safety analysis set consists of all subjects receiving at least one dose of investigational product. Subjects will be divided according to the treatment they receive.

3.2.2 Efficacy Analysis Set (EAS)

Efficacy analysis set consists of all subjects with measurable baseline disease who received at least one dose of investigational product.

3.2.3 Dose-determining Set (DDS)

Dose-determining set consists of all subjects from the safety analysis set who, in Cycle 1, meet the minimum exposure criterion and complete the follow-up on Cycle 1 Day 21 or discontinue the treatment due to DLT.

A subject is considered to have met the minimum exposure criterion if in Cycle 1 the subject has received ≥75% of the treatment (not necessarily consecutively). Subjects who do not meet these minimum safety evaluation requirements are considered to be ineligible for the dose-determining set. Determination of the MTD uses subjects eligible for the dose- determining set.

3.2.4 Immunogenicity Analysis Set (IMAS)

Immunogenicity analysis set consists of all subjects receiving at least one dose of investigational product and having available ADA data.

3.2.5 Biomarker Analysis Set

Biomarker analysis set consists of all subjects receiving at least one dose of investigational product and having available biomarker data.

3.3 ANALYSIS OF STUDY IMPLEMENTATION

3.3.1 Subject Distribution

The number of subjects who have signed the informed consent form, the number of subjects who have failed the screening, and the number of subjects who have used the study drug will be calculated.

The number and percentage of subjects who have ended treatment with the study drugs BLU-554 and CS1001, as well as the number and percentage of subjects who have ended treatment due to various reasons, will be calculated respectively. The number and percentage of subjects who have withdrawn from the study, as well as the number and percentage of subjects who have withdrawn from the study for various reasons will be calculated, and the reasons for ending treatment and withdrawing from the study will be tabulated.

The number and percentage of subjects included in each analysis set will be calculated and tabulated.

3.3.2 Protocol Deviations

Based on the safety analysis set, important protocol deviations will be summarized and tabulated.

3.3.3 Combined Medications

The analysis will be based on the safety analysis set.

According to the time of the use of combined medications and study drugs, combined medications will be classified into past medications and concomitant medications.

Past medication refers to non-study medication that was started and ended before the first dose of study drug.

Concomitant medication refers to a non-study medication that meets one of the following conditions:

- Started at the same time or after the first dose of study drug.
- Started before the first dose of study drug and continued after the first dose of study drug.

Concomitant medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD) WHODrug-Global-B3 Version 202103. Past medications and concomitant medications will be summarized by 2-level Anatomical Therapeutic and Chemical classification system (ATC) and Preferred Term (PT). If a subject experiences multiple occurrences of the same ATC2 and PT, the subject will be counted only once under the ATC2 and PT.

3.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The analysis will be based on the safety analysis set.

3.4.1 Demographics

Demographic data including age, sex, race, height, weight, baseline Eastern Cooperative Oncology Group (ECOG) score, and other demographic data will be described and tabulated.

3.4.2 Medical History

Tumor diagnosis will be statistically described and tabulated.

Medical histories other than tumors will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 and summarized by System Organ Class (SOC) and Preferred Term (PT) thereunder.

3.4.3 History of Antitumor Therapy

The history of antitumor drug treatment will be coded and summarized according to the WHO-DD WHODrug-Global-B3 202103 Version.

Previous antitumor treatment regimens, including previous systemic treatment regimens, radiotherapy history, and history of tumor-related surgery/operation will be statistically described.

3.5 SAFETY ANALYSIS

3.5.1 Study Drug Exposure

The analysis will be performed based on the safety analysis set.

The number of cycles of CS1001 treatment received by patients will be summarize and statistically described, and the cumulative exposure, time of exposure (weeks), dose intensity [cumulative exposure/time of exposure (weeks)], relative dose intensity (dose intensity/planned dose intensity*100%), and dose adjustment of the study drugs CS1001 and BLU-554 will be summarized respectively.

The planned dose, the actual dose, the action taken before or during the injection, and the reason for the action will be tabulated.

3.5.2 Dose-Limiting Toxicity

The analysis will be performed based on the dose-determining set.

Dose-limiting toxicity categories will be summarized and tabulated.

3.5.3 Adverse Event

The analysis will be performed based on the safety analysis set.

Adverse events will be coded using MedDRA Version 24.0 and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

The overall occurrences of treatment-emergent adverse events (TEAEs) will be summarized, and the overall incidence of various TEAEs will be calculated.

For all treatment-emergent adverse events, grade 3 and above TEAEs, serious adverse events (SAEs), TEAEs related to the study drug, SAEs related to the study drug, immune-related TEAEs, infusion-related reactions, and TEAEs leading to discontinuation of the study drug, the number and percentage of subjects will be summarized by System Organ Class (SOC) and Preferred Term (PT). In addition, TEAEs will be summarized by System Organ Class, Preferred Term, and NCI-CTCAE severity.

TEAE is defined as (regardless of severity)

- Any adverse event following initiation of treatment
- Adverse event that exists at the time of initiation of treatment but begins to worsen following initiation of treatment
- Adverse event that has occurred and remitted prior to treatment but recurs following initiation of treatment

TEAEs leading to the adoption of actions related to the study drug need to be summarized separately based on being related or not related to the study drug.

The incidences of various treatment-emergent adverse events will be calculated by SOC and PT thereunder. The default order of adverse event incidences is an inverted order of overall incidence, by SOC first and then by PT thereunder. If the overall incidence of two adverse events is the same, the adverse events will be sorted alphabetically. If a subject experiences multiple occurrences of an adverse event with the same SOC and PT, the subject will be counted only once under the SOC and PT. The incidences of treatment-emergent adverse events will be calculated by SOC, PT and severity. If a subject experiences multiple occurrences of an adverse event with the same PT, the subject will be counted only once under the PT and only the most severe occurrence will be counted.

All adverse events, serious adverse events, grade 3 and above adverse events, adverse events related to the study drug, immune-related adverse events, adverse events leading to discontinuation of the study drug, and adverse events leading to death will be tabulated.

3.5.4 Dead

The analysis will be performed based on the safety analysis set.

All death events will be summarized and tabulated.

3.5.5 Laboratory Data

The analysis will be performed based on the safety analysis set.

At each visit, changes from baseline in quantitative laboratory test results will be summarized, and qualitative results will be summarized for specific laboratory tests.

Specific laboratory findings will be graded according to NCI CTCAE v5.0, and then a cross-tabulation of NCI CTCAE grades for the worst post-baseline measurements versus baseline will be generated.

For liver function laboratory data, the following will be summarized: alanine aminotransferase (ALT) or/and aspartate aminotransferase (AST) >= 3*upper limit of normal (ULN), and total bilirubin (TBIL) > 2*ULN or TBIL > 1.5*ULN; ALT and/or AST, ALT, AST >= 3*ULN, 5*ULN, 10*ULN, 20*ULN; TBIL > 1.5*ULN, > 2*ULN; alkaline phosphatase (ALP) > 1.5*ULN.

Abnormal clinical laboratory data results will be tabulated.

3.5.6 12-lead ECG

The analysis will be performed based on the safety analysis set.

At each visit, the overall ECG evaluation will be summarized.

All abnormal and clinically significant 12-lead ECG findings will be tabulated.

3.5.7 Echocardiogram

The analysis will be performed based on the safety analysis set.

Echocardiographic findings will be summarized.

All abnormal and clinically significant echocardiographic findings will be tabulated.

3.5.8 ECOG Score

The analysis will be performed based on the safety analysis set.

Crosstabs summarizing the highest post-baseline ECOG scores relative to baseline scores will be summarized.

3.5.9 Vital Signs

The analysis will be performed based on the safety analysis set.

Vital signs at each visit from baseline and their changes from baseline will be statistically described.

3.6 EFFICACY ANALYSIS

The analysis will be performed based on the safety analysis set.

The investigator will perform efficacy assessments according to the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).

Objective Response (ORR): The number and proportion of subjects who achieve objective tumor response (CR or PR) will be summarized. Objective response rate will be determined along with 95% confidence interval. (Clopper-Pearson method).

Progression Free Survival (PFS): PFS is defined as the time from the date of first study dose to disease progression or death (whichever occurs first). Subjects without event (no disease progression or death) will be censored at the date of "last tumor assessment". Kaplan-Meier methodology will be used to estimate median PFS, PFS rate at various time points, and their 95% confidence intervals. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time.

Duration of response (DOR): Duration of response (complete response or partial response) for responders is defined as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause (whichever occurs earlier). For subjects who do not have progressive disease following the qualifying response, duration of response will be censored on the date of last evaluable tumor assessment. Subjects without tumor assessment records after the earliest date of qualifying response will be censored on the earliest date of qualifying response. The analysis method is the same as that of PFS.

Time to Progression (TTP): TTP is defined as the time from the date of first study dose to disease progression. Subjects without event (no disease progression) will be censored at the date of "last tumor assessment". The analysis method is the same as that of PFS.

Disease Control Rate: Disease control rate (DCR) is defined as the proportion of subjects who achieve CR, PR, and SD based on RECIST v1.1. The disease control rate and its 95% confidence interval (Clopper-Pearson method) will be calculated.

Overall Survival (OS): Overall survival is defined as the time interval between the date of the first investigational product dose to the date of death from any cause. Subjects who are still alive at the analysis cutoff date will be censored at the date of the last known survival. The analysis method is the same as that of PFS.

3.7 PHARMACOKINETIC AND IMMUNOGENICITY ANALYSES

3.7.1 Pharmacokinetic Analyses

See the dedicated PK SAP.

3.7.2 Immunogenicity Analyses

Based on the immunogenicity analysis set, the immunogenicity assessment data will be presented according to the following categories.

- Number and percentage of subjects with positive ADA assays at baseline
- Number and percentage of subjects with at least one positive ADA assay at any time point following administration of the first dose
- Number and percentage of subjects with a positive treatment-induced ADA test at any time point after the first dose
- Number and percentage of subjects with a positive treatment-enhanced ADA test result at any time point after the first dose
- Number and percentage of subjects with a treatment-independent ADA test result at any time point after the first dose

- Number and percentage of subjects with an unevaluable ADA test result at any time point after first dose

- Overall ADA prevalence: total number and percentage of subjects with a positive treatment-induced ADA test result, a positive treatment-enhanced ADA test result, a treatment-independent ADA test result and an unevaluable ADA test result

- Overall ADA incidence: total number and percentage of subjects with a positive treatment-induced ADA test result and a positive treatment-enhanced ADA test result

Note: Treatment-induced ADA: The patient is ADA negative at baseline and ADA positive at any time after the first dose;

Treatment-enhanced ADA: The patient is ADA positive at baseline and has an enhanced ADA detection signal at any time point after the first dose (the immunogenicity titer is 4 times the baseline immunogenicity titer);

Treatment-independent ADA: The patient is ADA positive at baseline, and there is no enhancement in the ADA detection signal from the baseline titer at any time point after the first dose (the immunogenicity titer does not exceed the baseline immunogenicity titer), or the patient is ADA positive at baseline, and has all negative or deficient ADA test results after the first dose.

Unevaluable ADA: The patient is ADA deficient at baseline and ADA positive at least once at any time point after the first dose.

Those confirmed to be anti-CS1001 antibody positive were presented in the following categories.

- Number and percentage of subjects with a positive ADA neutralizing antibody (Nab) test result at baseline.

- Number and percentage of subjects with at least one positive Nab test result at any time point after the first dose.

3.8 BIOMARKER ANALYSES

Measurement of biomarkers, such as the expression of FGF19 and PD-L1 in tumor cells and tumor-infiltrating immune cells prior to treatment, will be presented based on available data. The correlation between measurement of the above indicators and clinical outcomes (e.g., antineoplastic efficacy) will be described in graphical and tabular forms.

3.9 MISSING VALUES

Processing of missing values: Missing values will not be imputed. The processing and censoring of missing data for the efficacy portion is described in Section 3.5. For missing dates, please refer to Appendix 3 for the specific imputation method for calculation. The dates in the list will be listed as filled on the eCRF.

3.10 INTERIM ANALYSIS

No interim analysis is planned for this study.

4. LIST OF ABBREVIATIONS

Abbreviation	Full name of abbreviations	Chinese Name
ADA	Anti-drug Antibody	抗药抗体
AE	Adverse Event	不良事件
ALP	Alkaline Phosphatase	碱性磷酸酶
ALT	Alanine Transaminase	丙氨酸氨基转移酶
AST	Aspartate Transaminase	天冬氨酸氨基转移酶
ATC	Anatomical Therapeutic Chemical	解剖学治疗学及化学分类系统
CI	Confidence Interval	置信区间
CR	Complete Response	完全缓解
CT	Computed Tomography	计算机断层
CTCAE	Common Terminology Criteria for Adverse Events	不良反应通用术语事件标准
CV	Coefficient of Variation	变异系数
DCR	Disease Control Rate	疾病控制率
DLT	Dose-Limiting Toxicity	剂量限制性毒性
DOR	Duration of Response	缓解持续时间
EAS	Efficacy Analysis Set	有效性分析集
ECOG	Eastern Cooperative Oncology Group	美国东部肿瘤协作组
ECG	Electrocardiography	12 导联心电图
eCRF	Electronic Case Report Form	电子病例报告表
IMAS	Immunogenicity Analysis Set	免疫原性分析集
MedDRA	Medical Dictionary for Regulatory Activities	国际医学用语词典
MTD	Maximum Tolerated Dose	最大耐受剂量
MRI	Magnetic Resonance Imaging	磁共振
Nab	Neutralizing Antibodies	中和抗体
NCI	National Cancer Institute	国立癌症研究所
ORR	Objective Response Rate	客观缓解率
OS	Overall Survival	总生存期
PD	Progression	疾病进展
PD-L1	Programmed Death Ligand-1	程序性死亡受配体-1
PFS	Progression-Free Survival	无进展生存期
PK	Pharmacokinetics	药代动力学
PKAS	Pharmacokinetics Analysis Set	药代动力学分析集
PR	Partial response	部分缓解
PT	Preferred Term	首选术语
RECIST	Response Evaluation Criteria in Solid Tumors	实体瘤疗效评价标准
RP2D	Recommended Phase II Dose	II 期临床推荐剂量
SAS	Safety Analysis Set	安全性分析集
SD	Standard Deviation	标准差
SMC	Safety Monitoring Committee	安全监查委员会
SOC	System Organ Class	系统器官分类
TBIL	Total Bilirubin	总胆红素
TEAE	Treatment-Emergent Adverse Event	治疗期间不良事件
TTP	Time to Progression	至疾病进展时间
ULN	Upper Limit of Normal	正常值上限
WHO-DD	WHO Drug Dictionary	世界卫生组织药物词典

APPENDIX 1: PROTOCOL SYNOPSIS

Sponsor: CStone Pharmaceuticals (Suzhou) Co., Ltd., CStone Pharmaceuticals (Shanghai) Co., Ltd., Blueprint Medicines Corporation	
Final product name: NA	
Investigational product: CS3008 (fisogatinib, BLU-554), CS1001	
Names of active substances: Fibroblast growth factor receptor 4 inhibitor, completely humanized IgG4-type recombinant anti- Programmed death ligand 1 (PD-L1) monoclonal antibody	
Title of study:	**A Muti-center, Open-label, Multiple-dose Phase Ib/II Study to Assess the Safety, Tolerability, Pharmacokinetics, Anti-tumor Efficacy of CS3008 (BLU-554) in Combination with CS1001 in Subjects with Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)**
CAT No.:	**JXHL1900045, CXSL900017**
Protocol No.:	**CS3008 (BLU-554) - 101**
Sites:	**20 sites as planned**
Duration of the study (first subject in to last subject out):	**Screening period (28 days prior to the initial administration), treatment period (at most 24 months) and follow-up period (safety follow-up period: at most 90 days; survival follow-up period: every 12 weeks until withdrawl of subjects or termination of study)**
Study Phase:	**Phase Ib/II**

This is a multi-center, open-label, multi-dose, dose-finding and extension study for evaluating the safety, tolerance, pharmacokinetics and antitumor efficacy profiles of BLU-554 in combination with CS1001 in subjects with locally advanced or metastatic HCC.

The study consists of 2 parts, including a Part 1 (phase Ib) dose escalation and part 2 (phase II) dose expansion. Part 1 is a dose escalation study for determination of the MTD (Maximum tolerated dose) and/or RP2D (Recommended Phase II dose) of BLU-554 in the combination regimen and assess primary safety and tolerance of the combination regimen. Part 2 is a dose extension study in which preliminary evaluate the antitumor efficacy and the further evaluate the safety, tolerance, PK and immunogenicity of combination regimen.

Phase 1b: Dose Escalation

Primary Objectives	**Primary Endpoints**
• To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of BLU-554 when being in combination with CS1001 in subjects with locally advanced or metastatic HCC. • To evaluate the safety and tolerability of BLU-554 in combination with CS1001.	• Incidence of DLT (Dose-limiting toxicity) during the administration of BLU-554 in combination with CS1001. • Safety: incidence and severity of AEs and SAEs, including laboratory tests, vital signs, and ECG • Tolerance: discontinuation and reduction of study drug dose
Secondary Objectives	**Secondary Endpoint**

• To assess the pharmacokinetics (PK) profile of BLU-554 in combination with CS1001.	Pharmacokinetic parameters include, but are not limited to: • When being administered in combination with BLU-554, area under the serum concentration-time curve (AUC); Maximum serum concentration (Cmax); Time to maximum serum concentration (tmax); Clearance at steady state (CLss); accumulation ratio of CS1001. • When being administered in combination with CS1001, AUC, Cmax, tmax, CLss/F, accumulation ratio of BLU-554.
• To assess the preliminary anti-tumor activity of BLU-554 in combination with CS1001.	• To assess Objective response rate (ORR), the duration of response (DOR), disease control rate (DCR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) based on RECIST v1.1.
• To assess the immunogenicity of CS1001 when being administered in combination with BLU-554.	• Occurrence of anti-CS1001 antibody
• To correlate FGF19 and PD-L1 expression level with efficacy of BLU-554 in combination with CS1001	• ORR, DOR, DCR, TTP, PFS and OS by FGF19 protein and PD-L1 protein level

Phase II: Dose expansion

Primary Objectives	**Primary Endpoints**
• To assess the anti-tumor activity of BLU-554 in combination with CS1001.	• To assess ORR based on RECIST v1.1.
Secondary Objectives	**Secondary Endpoint**
• To assess the anti-tumor activity of BLU-554 in combination with CS1001.	• To assess the DOR, DCR, TTP, PFS and OS based on RECIST v1.1
• To evaluate the safety and tolerability of BLU-554 in combination with CS1001.	• Safety: incidence and severity of AEs and SAEs, including laboratory tests, vital signs, and ECG • Tolerance: discontinuation and reduction of study drug dose
• To assess the pharmacokinetics (PK) profile of BLU-554 in combination with CS1001.	Pharmacokinetic parameters include, but are not limited to: • When being administered in combination with BLU-554, AUC, Cmax, tmax, CLss, accumulation ratio of CS1001. • When being administered in combination with CS1001, AUC, Cmax, tmax, CLss/F, accumulation ratio of BLU-554.
• To assess the immunogenicity of CS1001 when being administered in combination with BLU-554.	• Occurrence of anti-CS1001 antibody
• To correlate FGF19 and PD-L1 expression level with efficacy of BLU-554 in combination with CS1001	• ORR, DOR, DCR, TTP, PFS and OS by FGF19 protein and PD-L1 protein level

Study design:

Both Phase Ib and Phase II can be divided into 3 periods, screening period, treatment period and follow-up period:

- The screening period is the 28 days prior to the first dose.
- During the treatment period, the subjects will be administered the study drug once every 21 days (3 cycles). BLU-554 is taken orally (PO) once daily (QD); CS1001 is administered intravenously once every 21 days (Q3W). Subjects with advanced stage solid tumor will be imageologically evaluated by the investigators every 9 weeks (i.e. every 3 dosing periods) during the 1st year of treatment and every 12 weeks after treatment for more than 1 year against Response Evaluation Criteria in Solid Tumors (RECIST v1.1). The investigator may increase evaluation frequency if clinically indicated. The drug may be administered continually until presence of intolerable adverse reaction, disease progression, withdrawal of informed consent, loss to follow up, death or study termination. The duration of treatment may be up to 24 months.
- Follow-up period consists of safety follow-up period and survival follow-up period. The safety follow-up period includes 90 days after the last dose of study drug, or until the initiation of a new anti-tumor treatment, whichever occurs earlier. Survival follow-up period will be performed every 12 weeks for collection of the survival status, subsequent anti-tumor therapies and study drug-related SAEs of the subjects until the death, loss to follow-up, withdrawal or termination of study, whichever occurs first. Refer to the Section 1.2 SOA for the study schedule.

Phase Ib: Dose Escalation

The MTD and/or RP2D of BLU-554 in the combination regimen will be determined using a BOIN dose escalation design. 2 dose levels of BLU-554 will be assessed with CS1001 1,200 mg Q3W as the fixed dose (RP2D in single-dose study). The planned dose escalation scheme is shown in Table 1 with 400 mg QD as the starting dose of BLU-554. Every 21 days (3 weeks) will be considered as one cycle. DLT assessment will be done within 21 days (Cycle 1) after the administration. Using BOIN design, the target toxicity probability of the MTD is 0.3 with a maximum sample size of 12. The cohort size included 3 enrolled and treated subjects. The number can be modified based on subject's enrollment. As shown in **错误!未找到引用源。**, the starting dose is dose level 1, i.e. BLU-554 400 mg QD in combination with fixed dose CS1001 1,200 mg Q3w. After complete DLT assessment for each cohort, the dose level for the next cohort was determined according to the dose escalation/decreasing rule in **错误!未找到引用源。**. Repeat the step with every 3 subjects until a maximum sample size of 12 is reached, the dose escalation is ended (See Dose Escalation Flowchart for details). CS1001 is administered intravenously once every 3 weeks (21 days). BLU-554 is taken orally once daily from Day 1 to Day 21; In case that the two study drugs would be administered on the same day, BLU-554 should be administered firstly.

Table 1:Planned Dose Escalation Scheme

Cohort	BUL-554	CS1001
1	400 mg QD	1,200 mg Q3W
2	600 mg QD	1,200 mg Q3W

During the study period, an SMC consisting of the principle investigator, the CRO's representatives (CRA and other relevant person) and the sponsor's representative will be established to review the safety data, PK data, efficacy data from the study and determine the escalation dose level and dosage regimen in dose escalation study so as to determine the MTD and RP2D selected for the extension study. The SMC will also decide whether or not to include unscheduled dose levels for the study.

Phase II: Dose expansion:

The primary objective of the dose expansion phase is to primarily evaluate the antitumor efficacy as well as to further evaluate the safety, tolerability, PK and immunogenicity of the combination regimen. In this part, subjects will be enrolled into 2 groups according to the expression of FGF19 immunohistochemistry (IHC): Group 1 will be advanced hepatocellular carcinoma subjects with FGF19 IHC-, the cancellation of which will be based on phase Ib data (see protocol 4.1 for details); Group 2 will be advanced hepatocellular carcinoma subjects with FGF19 IHC+. In case of being within the statistically pre-defined assessment range, additional subjects may be enrolled for further evaluation (see Protocol 4.1 for details). FGF19 expression will be determined at central laboratory by immunohistochemistry (IHC) with the inclusion criteria of FGF19 IHC+ defined as ≥ 1%.
In Phase Ib and Phase II, archived or fresh tumor samples must be provided for FGF19 and PD-L1 IHC test which will be employed at central laboratory.
The tumors shall be evaluated in accordance with RECIST v1.1. During the 1st year of the treatment, subjects will receive CT/MRI examination every 9 weeks (every 3 cycles). After 1 year of treatment, CT/MRI examinations shall be carried out once every 12 weeks (The investigator may increase the frequency of tumor evaluations where clinically indicated).
The data from subjects on anti-tumor activity, safety, tolerability, PK profile and host immunogenicity will be reviewed from the day of first administration of study drugs up to 90 days after the last administration or up to two-year treatment period of combination regimen

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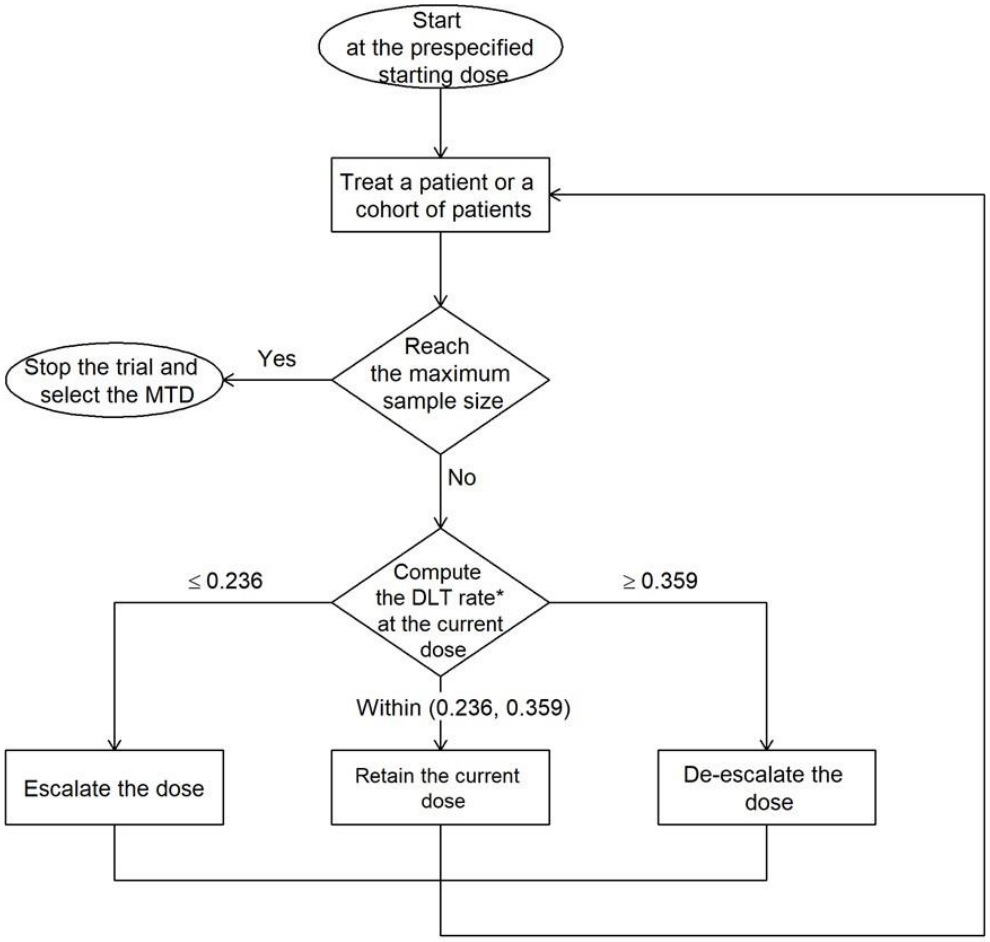
- *Dose Escalation Process:*



$$\text{* DLT rate} = \frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of patients treated at the current dose}}$$

Planned number of subjects:	Phase Ib: Approximately 12 subjects will be enrolled Phase II: Approximately 40 subjects will be enrolled
Dose limiting toxicity (DLT) definition:	Definition of DLT: All toxicity or adverse events (AEs) are graded according to NCI-CTCAE 5.0. Any AE occurring during C1 (21 days) that is not clearly caused by something other than investigational drug: Hematological toxicity: ● Grade 4 neutropenia that lasts for ＞7 days; ● Grade ≥3 febrile neutropenia (ANC<1,000/mm3, with a single temperature of ≥38.3°C or a sustained temperature of ≥38°C for more than one hour); ● Grade 3 neutropenia with infection;

	● Grade 3 thrombocytopenia with clinically significantly bleeding; ● Grade 4 thrombocytopenia; ● Grade ≥4 anemia
	Non-hematological toxicity: ● Grade ≥4 toxicity; ● Grade 3 toxicity that fails to be resolved to ≤Grade 2, with the exception of diarrhea, nausea and vomiting; ● Grade ≥3 immune-related adverse event (irAE); ● Any Grade 3 tumor flare reaction (local pain, irritation or rash at known or suspected tumor focus) that lasts for 7 days or above; ● Grade 3 or Grade 4 non-hematological laboratory abnormalities, if meet any of the followings: – need medical intervention – require hospitalization – last for >7 days and other toxicity of any grade that requires premature termination of the study as determined by the investigator and the sponsor through discussion. Definition of MTD: Based on BOIN design, MTD is the highest dose level at which 30% of the subjects experience DLT within 21 days (Cycle 1) among which at least 6 subjects are available for DLT evaluation. The RP2D will be determined by SMC based on comprehensive data of safety and tolerability, PK, pharmacodynamics, and preliminary anti-tumor efficacy obtained during the dose escalation phase. The RP2D will not exceed the MTD and will be determined at a dose escalation meeting.
Study Population:	**<u>Inclusion Criteria:</u>** To meet the conditions for participation in this clinical study, subjects must: 1. Voluntarily participate in the clinical study. Fully understand and get informed of this study and sign the Informed Consent Form (ICF). 2. ≥18 years of age on day of signing the informed consent. 3. Unresectable locally advanced or metastatic hepatocellular carcinoma as confirmed by histology or cytology. 4. Stage B or C based on Barcelona Clinic Liver Cancer (BCLC) staging system; In case of Stage B, subject must be

	ineligible for surgery and/or local therapy, or has progressed after surgery and/or local therapy or refuses surgery and/or local treatment. 5. For Phase Ib, subject has failed after or is unsuitable for the standard systemic therapy against HCC. For Phase II, subject has not previously received systemic therapy [systemic therapies mainly include: chemotherapy, molecular target drugs (e.g. tyrosine kinase inhibitors, TKI), immunotherapy (e.g. anti PD-1/PD-L1, CTLA-4 etc.), biological therapy (e.g. tumor vaccine), cytokines, etc.)]. 6. At least one measurable lesion as evaluable by RECIST version1.1, Target lesions within the field of prior efficacy irradiation or in the area of local treatment (intervention or ablation therapy) are considered measurable in case of confirmation of progression. 7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 point. 8. A-level Child-Pugh score. 9. Expected survival≥3 months. 10. For Phase Ib and II, 9 formalin fixed-paraffin embedded and unstained tumor tissue slides should be provided for FGF19 IHC and PD-L1 analysis in the central laboratory. • Patients to be enrolled in the FGF19 IHC + arm in the Phase II study must be FGF19 IHC +; • Patients to be enrolled in the FGF19 IHC - arm in the Phase II study must be FGF19 IHC – (whether this arm will be initiated or not will be decided based on Phase Ib data) 11. Clinical laboratory screening criteria: • Absolute neutrophil count (ANC)≥1.5 × 109/L • Platelet count≥ 75×10^9/L • Hemoglobin≥90 g/L • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 × ULN • Total bilirubin ≤ 2 ×ULN • International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 ×ULN (INR ≤ 1.5 × ULN and PT ≤ 1.5 × ULN, if both available) • Serum creatinine ≤ 1.5 ×ULN or creatinine clearance (CL)≥60 mL/min (Cockcroft-Gault Formula) Female: $\frac{CrCl=(140-age) \times weight\ (Kg) \times 0.85}{72\times serum\ creatinine\ (mg/dL)}$ Male: $\frac{CrCl=(140-age) \times weight\ (Kg) \times 1.00}{2\times serum\ creatinine\ (mg/dL)}$ 12. For subjects with hepatitis C virus (HCV) infection, treatment with locally approved and available anti-HCV therapy is

	required if HCV RNA is detected. 13. For subjects with hepatitis B virus (HBV) infection, HBV DNA ≤ 2,000 IU/ml at Screening. • Subject with HBV DNA (+), treatment with HBV antiviral therapy (as per the local standard of care) is required at least 14 days prior to the initiation of study. • Subject with HBsAg (+) and/or HBcAb (+), based on investigator assessment, HBV antiviral therapy may be applied if needed. 14. For female subjects of childbearing potential, serum pregnancy test must be negative within 7 days prior to randomization. Except for female subjects who have been recorded as surgically sterilized or who are postmenopausal, female subjects of childbearing potential or male subjects and their partners must agree to use effective contraception from the signature of the informed consent form (ICF) until at least 6 months after the last dose of study drug. Appendix 6: Effective Contraceptive Methods **Exclusion Criteria:** Subjects who meet any of the following criteria will not be eligible to participate in the study: 1. Portal vein tumor thrombosis in the main trunk or contralateral first branch (VP4), involvement of the inferior vena cava or the heart as revealed by imaging at baseline. 2. Prior or current history of hepatic encephalopathy. 3. History of liver surgery and/or local treatment for HCC (intervention, ablation therapy, absolute alcohol injection, etc.) or radiotherapy, etc. within 4 weeks prior to first dose. 4. Active or documented gastrointestinal bleeding within 6 months (e.g. esophageal or gastric varices, ulcer bleeding). 5. Presence of ascites detected by physical examination or clinical symptoms caused by ascites during the screening period, or ascites that need for special treatment, such as repeated drainage, or intraperitoneal drug infusion, etc. (Note: subjects with a small amount of ascites that can only be detected by imaging may be enrolled). Presence of uncontrolled pleural effusion or pericardial effusion (with clinical symptoms, requiring repeated drainage, or intrapleural or pericardial drug infusion, etc.) during the screening period. 6. Presence of meningeal metastasis or central nervous system (CNS) metastatic lesions. 7. According to the New York Heart Association (NYHA) Classification, subject has clinically significant, uncontrolled cardiovascular disease, including Grade III or IV congestive heart failure; myocardial infarction or unstable angina (within 6 months), uncontrolled hypertension (systolic blood pressure≥150 mmHg and diastolic blood pressure≥100

	mmHg) or clinically significant uncontrolled arrhythmias, including bradycardia that may result in prolonged QT (e.g. Grade II or III heart block). Left ventricular ejection fraction (LVEF)<50%. QTc interval >480 msec (corrected using Fridericia's formula). 8. Subjects who have current interstitial lung disease or noninfectious pneumonitis, and prior history of interstitial lung disease or noninfectious pneumonitis that may affect the assessment or management of study drug-related pulmonary toxicity. Presence of active tuberculosis infection. 9. Any serious acute, chronic infections that require systemic antimicrobial, antifungal or antiviral therapy at screening, excluding viral hepatitis. 10. Malabsorption syndrome or inability to take the study drug orally for other reasons. 11. Had primary malignancies other than HCC within 5 years. The following prior malignancies were excluded: completely excised skin basal cells and squamous cell carcinoma, local prostate cancer responsive to treatment, and carcinoma in situ with complete resection at any site. 12. Subject has had major surgery within 4 weeks prior to first dose (procedures such as central venous cannulation, biopsy, and feeding tube placement are not considered as major surgery). 13. Previously received FGFR4 inhibitor treatment. 14. Blood transfusion, use of hematopoietic stimulating factors [including G-CSF (granulocyte colony stimulating factor), GM- CSF (granulocyte-macrophage colony stimulating factor), EPO (erythropoietin) and TPO (thrombopoietin)] and human albumin preparations within 14 days prior to first dose. 15. Requiring corticosteroids (dose equivalent to > 10 mg/day of Prednisone) or other immunosuppressive drugs within 14 days prior to first dose for systemic therapy. Note: For the absence of active autoimmune disease, it is allowed to use inhaled or topical steroids or adrenal hormone replacement therapy with equivalent dose of ≤10 mg/day prednisone. Short-term (≤ 7 days) use of corticosteroids for prophylaxis (e.g., contrast allergy) or for the treatment of non- autoimmune diseases (e.g., delayed hypersensitivity reactions due to contact allergens) is permitted. For subjects requiring hormone therapy, the dose administration should be done at least two days before and after the injection of CS1001. 16. Use of traditional Chinese medicine (elemene, Kanglaite, Cinobufacin, Xiaoaiping, Huaier granule, Ganfule, Jinlong capsule, Aidi, etc.) with anti-liver cancer indication within 14 days prior to the first dose. 17. Subject has received potent CYP3A4 inhibitors and/or inducers within 2 weeks prior to first dose. See Appendix 8: Strong Inhibitors and Inducers of CYP3A4. 18. Concurrent HBV and HCV infection (History of HCV infection, but subjects with HCV RNA(-) can be considered

	as not being infected with HCV). 19. Subjects with human immunodeficiency virus (HIV) infection. 20. Pregnant or lactating women. 21. Subjects with a history of hypersensitivity or hypersensitivity to any of the components of the investigational drug. 22. Any previous or current clinically significant diseases, medical conditions, history of surgery, signs, or abnormal laboratory parameters that, in the opinion of the investigator, may increase the risks associated with study participation and study drug administration, or affect the subject's ability to receive study drug and reliability of study results; other circumstances that in the opinion of the investigator would preclude participation in the study. 23. Subjects who are unwilling or unable to follow the study procedures as defined. Subjects with no or limited disposing capacity and with psychiatric disorders that may affect study compliance. 24. With the exception of alopecia, all toxicities from prior anticancer therapies and other therapies did not recover to ≤ Grade 1 (per CTCAE v5.0) prior to the first dose of study drug. 25. Subjects who have received prior allogeneic stem cell or solid organ transplantation.
Definition of end of study:	All subjects completed the treatment period, EOT visit, disease progression follow-up and survival follow-up or the Sponsor terminated the study (whichever occurred first).
Test product, dose and mode of administration:	BLU-554 capsule 100 mg will be taken by oral administration once daily. CS1001 injection 600 mg/20 ml/Bottle will be given via intravenous infusion on the first day of each treatment cycle, once every 21 days (3 weeks).
Planned trial and treatment duration per subject:	No more than 35 cycles (24 months) of study treatment followed by a 90-day safety follow-up.

Statistical methods:	**Analysis Populations** Safety analysis set: consists of all subjects receiving at least one dose of investigational product. Efficacy analysis set: consists of all subjects with measurable baseline disease who received at least one dose of investigational product. It will be the primary analysis set for efficacy in this study. Note: Subjects who were screened but never started treatment will be listed, but not included in any efficacy analysis set. Therefore, these subjects will not be included in any of the summary tables. Dose-determining set: consists of all subjects from the safety analysis set who, in Cycle 1, meet the minimum exposure criterion and complete the follow-up on Cycle 1 Day 21 or discontinue the treatment due to DLT. A subject is considered to have met the minimum exposure criterion if in Cycle 1 the subject has received ≥75% of the treatment (not necessarily consecutively). Subjects who do not meet these minimum safety evaluation requirements are considered to be ineligible for the dose-determining set. Determination of the MTD uses subjects eligible for the dose-determining set. Pharmacokinetic analysis set: consists of all subjects who received at least one dose of investigational product and had at least one post-baseline pharmacokinetic assessment. Immunogenicity analysis set: consists of all subjects receiving at least one dose of investigational product and having available ADA data. Biomarker analysis set: consists of all subjects receiving at least one dose of investigational product and having available biomarker data. All analysis sets will be determined before the database is locked. **Primary Analysis Method** Safety: Safety assessments will include adverse events, vital signs, physical examination, electrocardiogram (ECG), echocardiography and laboratory tests. The incidence of DLT for each dose group will be assessed. All treatment-emergent adverse events (TEAEs) in each dose group are summarized by system organ classification and preferred terms. The relationship of the incidence and severity of all TEAEs to the investigational drug will be summarized. Descriptive summaries of laboratory tests and vital signs for each dose group will be made separately. Abnormal findings of laboratory tests, vital signs, ECG, echocardiograms will be listed. Efficacy: Efficacy assessments will be conducted according to RECIST v1.1, including ORR, PFS, DCR and DOR. The efficacy endpoint is the ORR assessed by the investigator and ORR for the subjects in each

	dose group and overall ORR will be summarized. OS and PFS will be expressed by a Kaplan-Meier curve. **<u>Sample Size Determination</u>** According to efficacy result of BLU-554-1101 study (data cut-off date: 16 Jun 2018), ORR was 17% (11/63) for FGF19 IHC+ subjects (1st line and above) and 0 (0/38) for FGF19 IHC- subjects. ORR of PD-1/PD-L1 monotherapy was reported around 10~20% for 1st line and 2nd line HCC subjects. Based on the data above, BLU-554 in combination with CS1001 is targeting 40% ORR for 1st line and 2nd line FGF19 IHC+ subjects and 30% ORR for 1st line and 2nd line FGF19 IHC- subjects. Combining all subjects treated at RP2D in Phase Ib and Phase II, gating criteria in Bayesian framework are developed as the following: <u>Gating based on 25 FGF19 IHC+ subjects</u> • A non-informative ORR prior is assumed at Beta (0.45, 0.55). • Timing - when all 25 subjects finish at least two post-baseline tumor assessments • Go - 12 responses or more, corresponding ORR 48%, the probability of combo ORR > 40% is 0.788. • No go - 8 (32%) responses or fewer, the probability of combo ORR<40% is 0.797. • Evaluate - 9 (36%) to 11 (44%) responses, evaluate other efficacy endpoints (DOR, DCR etc.) and safety. <u>Gating based on 40 FGF19 IHC+ subjects (if enrichment of 15 FGF19 IHC+ subjects as decided</u>) • A non-informative ORR prior is assumed at Beta (0.45, 0.55). • Timing - when all 40 subjects finish at least two post-baseline tumor assessments • Go - 18 responses or more, corresponding ORR 45%, the probability of combo ORR > 40% is 0.737. • No go - 14 (35%) responses or fewer, the probability of combo ORR<40% is 0.744. • Evaluate - 15 (37.5%) to 17 (42.5%) responses, evaluate other efficacy endpoints (DOR, DCR, etc.) and safety. <u>Gating based on FGF19 IHC - subjects treated at RP2D in Phase Ib</u> • A non-informative ORR prior is assumed at Beta (0.2, 0.8). • Timing - only conducted if at least 6 FGF19 IHC- subjects are treated at RP2D in Phase Ib, when they finish at least two post-

	baseline tumor assessments • No go - 0 response, the probability of combo ORR<30% is greater than 0.99, Phase II will only include the FGF IHC+ cohort • Evaluate - 1 response or more, the cohort of FGF IHC- subjects will be included in Phase II <u>Gating based on 15 FGF19 IHC- subjects</u> • A non-informative ORR prior is assumed at Beta (0.2, 0.8). • Timing - when all 15 subjects finish at least two post-baseline tumor assessments • Go - 6 responses or more, corresponding ORR 40%, the probability of combo ORR > 30% is 0.757. If the final decision for FGF19 IHC+ subjects is "go" (Gating based on 15 or 40 FGF19 IHC+ subjects, as above said), FGF19 IHC- subjects may also be included in the target population of future development. • No go - 3 (20%) responses or fewer, the probability of combo ORR<30% is 0.845. Future development will not include FGF19 IHC- subjects in the target population. • Evaluate - 4 (26.7%) to 5 (33.3%) responses, evaluate other efficacy endpoints (DOR, DCR, etc.) and safety. The sample sizes of 25 or 40 FGF19 IHC+ subjects and 15 FGF19 IHC- subjects are selected to have reasonably high probability of ORR exceeding the target when the go criteria are met or ORR being lower than the mono therapies when no-go criteria are met. The go and no-go criteria are set up to guide future development of the combination. **They are not binding decision-making rules.** If the actual numbers of evaluable subjects are different from those planned above, the same method will be used to calculate the posteriori probability that ORR will reach the predefined target for reference in subsequent development.

APPENDIX 2: SCHEDULE OF ACTIVITIES

Table 2:Study Assessments and Procedures Schedule in Dose Escalation Part (Phase Ib)

Phase Ib[a]	**Screening**	**Treatment (21d for each cycle)**								**Follow-up**			
		Cycle 1				**Cycle 2**		**≥Cycle 3**	**EOT visit [b]**	**Safety follow-up [c]**			**Survival follow-up [c]**
										1	**2**	**3**	
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**1**	**0-7 days post EOT date**	**30 days post last dose**	**60 days post last dose**	**90 days post last dose**	**Every 12 weeks post last dose**
Time Window				**±2**	**±2**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed Consent d	X												
Inclusion/Exclusion Criteria	X	X											
Demographics	X												
Medical History e	X	X											
Physical Examination f	X	X		X	X	X	X	X	X	X			
Vital Signs	X	X		X	X	X	X	X	X	X			
ECOG PS	X	X				X		X	X	X			
Serum or Urine Pregnancy Test g	X							X h	X	X			
12-lead ECG i	X	X	X			X		X	X	X			
Echocardiogram j	X	As clinically indicated							X				
Tumor Imaging k	X	**Within 1 year**: every 9 weeks ± 7 days (end of every 3 dose cycles), **after 1 year**: every 12 weeks ± 7 days; or based on the clinical needs.											
Blood test l	X	X		X	X	X	X	X	X	X			
Serum Chemistry, CK-MB l	X	X		X	X	X	X	X	X	X			
HIV, HBV, HCV m	X							X	X	X			
AFP m	X							X	X				
Coagulation l	X	X				X		X	X	X			
Routine Urine Test	X	X				X		X	X	X			

Thyroid Function n	X	X				X		X	X	X			
Tumor Sample	X o												
CS1001 Administration p		X				X		X					
BLU-554 Administration q		X											
PK blood sample r		X											
Immunogenicity Blood Sample r		X											
Subsequent anti-tumor therapy [s]										X	X	X	X
AE Monitoring	X												
SAE Monitoring [t]	X												
Concomitant Medications	X												
Survival Status u	X												

Abbreviations: AFP, Alpha-Fetoprotein; CT, computed tomography; CK-MB, creatine kinase-MB; ECOG, Eastern Cooperative Oncology Group; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; PK, pharmacokinetics.

a. All visits should be performed as noted in Table 2. Additional safety tests (e.g., blood test, ECG) may be performed whenever clinically indicated, at the Investigator's discretion. Unless otherwise indicated, all tests and procedures must be performed predose at each visit. Whenever a test result is questionable, it should be repeated immediately. Re-screening is permitted for one time, but need to decide by medical monitor and sponsor assessment.

b. The date of the End of Treatment (EOT) visit is defined as the date on which the investigator decided to stop dosing. The EOT visit should be performed 0-7 days post the EOT date. If the EOT visit and a treatment visit occur within 7 days, no tests are required for repeated items. If the EOT visit occurs within the safety follow-up window, no tests are required for repeated items. If an alternate treatment is started within 7 days of the EOT date, the EOT visit should be conducted prior to the first dose of alternate therapy. The last administration date is defined as the later last administration date of the two study drugs. It should be noted that the date on which the investigator decided to stop dosing may not coincide with the date of last dose.

c. Safety visits: For subjects who have completed treatment, a safety visit should be conducted on the 30th day (±7 days), 60 days (±7 days), and 90 days (± 7 days) post the last dose; the safety follow-up at 90 day post the last dose can be conducted at the same day as that for the first survival follow-up. Survival follow-up: subjects will be contacted by telephone or in person every 12 weeks from the last dose of study drug to collect survival status, subsequent anti-tumor therapy, and study drug-related SAEs until the death, loss of follow-up, withdrawal from the study, or study termination, whichever occurs first.

d. Consent for the study may be obtained from the subjects by written.

e. A complete medical history will be obtaining at the Screening visit. Only disease-related symptoms and changes from the previous visit need to be collected on C1D1.

f. A complete physical examination will be performed at the Screening visit. Subsequent physical examinations will be disease- and AE-focused.

g. To be performed for women with childbearing potential within 7 days of C1D1. A serum pregnancy test should be performed at Screening; thereafter, a serum or urine pregnancy test should be performed on every odd cycle (e.g., C3, C5).

h. To be performed on D1 (±4 days) of every odd cycle starting with C3.

i. ECGs (12-lead) exams will be performed after at least a 10 minute rest in the supine position. ECGs will be performed at Screening and during treatment, at EOT, and at Safety Follow-Up. In case of PK sampling, ECG should be performed for 3 consecutive times with an interval of 5 minutes each time in Cycle 1, 2

and 4. Refer to Table 4 and Table 5 for specific time. For other treatment cycles ECG should be performed at predose of any Cycle Day 1 dosing. For C1D2, ECG should be collected at predose. Frequency of ECGs may be increased if clinically indicated.

j. To be performed as clinically indicated.

k. Imaging assessment of tumors: Tumor assessment is conducted according to the standard RECIST v1.1. See the specific assessment standards in Appendix 2.

The imaging assessment method of tumors may adopt CT or MRI as decided by the investigator, however, the assessment method, machine and technical parameters should remain consistent in the entire study period; if there is no contraindication, a contrast medium should be used. The imaging results will be interpreted by the investigator or radiologist of each site. In case a tumor assessment has been conducted within 28d before initial administration and by the same method and machine in the same hospital, the result can be adopted as baseline tumor assessment. Baseline tumor assessment should cover chest, abdomen, pelvic cavity and any other site suspected of tumor lesion (such as brain, bone lesions). Subjects with bone metastases during screening should be followed up using CT/MRI/X-ray at subsequent visits. Imaging (CT or MRI) assessments per RECIST v1.1 will be performed within 28 days prior to the first dose (baseline assessment), every 9 weeks during the first year of the study, and every 12 weeks thereafter until (1) disease progression, (2) initiation of a new anti-tumor therapy, (3) withdrawal of informed consent, (4) loss of follow-up, (5) death, and (6) termination of the study, whichever occurs first. In case medication is discontinued permanently for a subject due to the reasons other than those above said (such as AEs), the tumor assessment will still be conducted as scheduled. The investigator can schedule additional imaging examination based on the subject's clinical condition. If an unscheduled tumor assessment is carried out and the disease has not progressed, subsequent tumor assessments should also be performed as scheduled. The confirmatory assessment must be completed 4 weeks after the efficacy is assessed as complete response (CR) or partial response (PR). If the investigator suspects that the progression of disease is pseudoprogression, then progression of disease must be confirmed in the imaging examination four weeks later or at the next scheduled imaging assessment time point (note: the time point of the next imaging examination may not be later than 9 weeks after the initial confirmation of progression of disease). For a subject whose treatment is stopped before any clearly- disease progression, imaging examination results should be obtained as far as possible to conduct tumor efficacy assessment. In case a subject discontinues study treatment due to disease progression (excluding pseudoprogression), it will be unnecessary to repeat the step of imaging assessment in the last visit. If the subject has completed the imaging assessment of the tumor within 28 days prior to the EOT visit or safety visit, it is not required to repeat such examinations at the two visits.

l. If the Screening visit tests are performed within 7 days of C1D1, clinical laboratory tests do not need to be repeated on C1D1 (i.e. there is a -7-day window for C1D1 labs). When laboratory tests (including blood test, blood biochemistry, myocardial enzyme, coagulation function, urinalysis, and thyroid function, if applicable) and study drug administration are scheduled to be conducted on the same day (e.g., Day 1 [D1] of each treatment cycle), the test results should be available before the administration can be scheduled. Except for the first dose, laboratory tests at each dosing visit should be completed within 3 days prior to dosing. If the subject has received relevant laboratory tests within the first 7 days of the EOT visit or safety visit 1, there is no need to repeat such tests at these two visits.

m. Screening visit will be performed at the local laboratory, which includes HCV antibody, HBsAg, HIV antibodies. Subjects with HBsAg positive will further assess HBV DNA test, subject with HCV antibody positive will further assess HCV RNA test. Subjects with HBsAg positive need to be retested for HBV DNA every 12 weeks until safety follow-up 1; subjects with HCV antibody positive need to be retested for HCV RNA every 12 weeks until safety follow-up 1; APF test will be done every 12 weeks until the EOT visit.

n. Thyroid function examination covers free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) analysis, conducted respectively in the screening period, dosing in the first and second administration cycle, dosing every two subsequent administration cycles, EOT and in the safety follow-up visit. If the thyroid function test at screening is performed within 7 days prior to the first dose (C1D1), it does not need to be repeated before the first dose (i.e., there is a -7-day window for the thyroid function test on C1D1). When thyroid function tests and study drug administration are scheduled to be conducted on the same day (eg, on Day 1 [D1] of the respective treatment cycle for thyroid function tests), the test results should be available before the administration

can be scheduled. Except for the first dose, the specified thyroid function tests performed at each dosing visit should be completed within 3 days prior to dosing. If subjects have completed the thyroid function examination within 7 days prior to the end of treatment visit or safety visit 1, there is no need to repeat such at these two visits.

o. The tumor tissue used for FGF19 and PD-L1 IHC test will be sampled at screening and be analyzed at central laboratory.

p. CS1001 will be given on D1 of each 21-day cycle. Each infusion should be completed over 60-120 minutes. The recommended infusion time for PK blood sample collection is 90 minutes, as shown in table 4 and table 5.

q. BLU-554 will be administered qd in the morning with no food intake from 2 hours before until 1 hour after study drug administration. On study visit days when PK samples are collected, subjects will take their BLU-554 dose at the site. When the 2 study drugs are administered on the same day, BLU-554 should be administered before CS1001 infusion completion. After BLU-554 is administered, the subject should be given with CS1001 through intravenous infusion as soon as possible.

r. Blood samples for PK and immunogenicity assessment refer to Table 4 and Table 5.

s. Subsequent anti-tumor treatment: Information on subsequent (after the end of study treatment) anti-tumor therapies will be collected, including the name of all components of the treatment and the start and end dates of administration.

t. If the investigator learns of any SAE (including death) in a subject after the subject has completed safety follow-up or has withdrawn from the study, and there is a reasonable cause to believe that the event is possibly related to the study drug, the investigator should notify the sponsor's pharmacovigilance team or representative.

u. Survival status: Subjects will be contacted by telephone or in person every 12 weeks from the last dose of study drug to collect survival status, subsequent anti-tumor therapy, and study drug-related SAEs until death, loss of follow-up, withdrawal from the study, or study termination, whichever occurs first.

Table 3:Study Assessments and Procedures Schedule in Expansion Part (Phase II)

Phase II[a]	**Screening**	**Treatment (21d for each cycle)**						**Follow-up**			
		Cycle 1			**Cycle 2**	**≥Cycle 3**	**EOT visit [b]**	**Safety follow-up [c]**			**Survival follow-up [c]**
								1	**2**	**3**	
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**1**	**0-7 days post EOT date**	**30 days post last dose**	**60 days post last dose**	**90 days post last dose**	**Every 12 weeks post last dose**
Time Window				**±2**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed Consent d	X										
Inclusion/exclusion Criteria	X	X									
Demographics	X										
Medical History [e]	X	X									
Physical Examination f	X	X		X	X	X	X	X			
Vital Signs	X	X		X	X	X	X	X			
ECOG PS	X	X			X	X	X	X			
Serum or Urine Pregnancy Test g	X					X h	X	X			
12-lead ECG i	X	X	X		X	X	X	X			
Echocardiogram j	X	As clinically indicated					X				
Tumor Imaging [k]	X	**Within 1 year**: every 9 weeks ± 7 days (end of every 3 dose cycles), **after 1 year**: every 12 weeks ± 7 days; or based on the clinical needs.									
Blood testl	X	X		X	X	X	X	X			
Serum Chemistry, CK-MB l	X	X		X	X	X	X	X			
HIV, HBV, HCV m	X					X	X	X			
AFPm	X					X	X				
Coagulation l	X	X			X	X	X	X			
Routine Urine Test	X	X					X				
Thyroid Function n	X	X			X	X	X	X			
Tumor Sample	X o										

CS1001 Administration p		X			X	X					
BLU-554 Administration q		X									
PK Blood Sample r		X									
Immunogenicity Blood Sample r		X									
Subsequent anti-tumor therapy [s]								X	X	X	X
AE Monitoring [t]	X										
SAE Monitoring	X										
Concomitant Medications	X										
Survival Status u	X										

Abbreviations: AFP, Alpha-Fetoprotein; CT, computed tomography; CK-MB, creatine kinase-MB; ECOG, Eastern Cooperative Oncology Group; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; PK, pharmacokinetics.

a. All visits should be performed as noted in Table 3. Additional safety tests (e.g., blood test, ECG) may be performed whenever clinically indicated, at the Investigator's discretion. Unless otherwise indicated, all tests and procedures must be performed predose at each visit. Whenever a test result is questionable, it should be repeated immediately. Re-screening is permitted for one time, but need to decide by medical monitor and sponsor assessment. Repeated screening is allowed for once and central laboratory-confirmed FGF19 IHC results obtained at screening # 1 may be used in the assessment of FGF19 IHC status at repeated screening without recollecting tumor samples for testing. It is recommended that the screening of FGF19 IHC status be performed first and then clinical screening continue when FGF19 IHC screening results are acceptable.

b. The date of the End of Treatment (EOT) visit is defined as the date on which the investigator decided to stop dosing. The EOT visit should be performed 0-7 days after the EOT date. If the EOT visit and a treatment visit occur within 7 days, no tests are required for repeated items. If the EOT visit occurs within the safety follow-up window, no tests are required for repeated items. If an alternate treatment is started within 7 days of the EOT date, the EOT visit should be conducted prior to the first dose of alternate therapy. The last administration date is defined as the later last administration date of the two study drugs. It should be noted that the date on which the investigator decided to stop dosing may not coincide with the date of last dose.

c. Safety visits: For subjects who have completed treatment, a safety visit should be conducted on the 30th day (±7 days), 60 days (±7 days), and 90 days (± 7 days) post the last dose; the safety follow-up at 90 day post the last dose can be conducted at the same day as that for the first survival follow-up. Survival follow-up: Subjects will be contacted by telephone or in person every 12 weeks from the last dose of study drug to collect survival status, subsequent anti-tumor therapy, and study drug-related SAEs until death, loss of follow-up, withdrawal from the study, or study termination, whichever occurs first.

d. Consent may be obtained from the subjects by written.

e. A complete medical history will be obtaining at the Screening visit. Only disease-related symptoms and changes from the previous visit need to be collected on C1D1.

f. A complete physical examination will be performed at the Screening visit. Subsequent physical examinations will be disease- and AE-focused.

g. To be performed for women of childbearing potential within 7 days of C1D1. A serum pregnancy test should be performed at Screening; thereafter, a serum or urine pregnancy test should be performed on every odd cycle (e.g., C3, C5).

h. To be performed on D1 (±4 days) of every odd cycle starting with C3.

i. ECGs (12-lead) exams will be performed after at least a 10 minutes rest in the supine position. ECGs will be performed at Screening and during treatment, at

EOT, and at Safety Follow-Up. In case of PK sampling, ECG test should be perfomed for 3 consecutive times with an interval of 5 minutes each time in Cycle 1, 2 and 4. Refer to Table 4 and Table 5 for specific time.For other treatment cycles ECG should be performed at predose of any Cycle Day 1 dosing. For C1D2, ECG should be collected at predose. Frequency of ECGs may be increased if clinically indicated.

j. To be performed as clinically indicated.

k. Imaging assessment of tumors: Tumor assessment is conducted according to the standard RECIST v1.1. See the specific assessment standards in Appendix 2. The imaging assessment method of tumors may adopt CT or MRI as decided by the investigator, however, the assessment method, machine and technical parameters should remain consistent in the entire study period; if there is no contraindication, a contrast medium should be used. The imaging results will be interpreted by the investigator or radiologist of each site. In case a tumor assessment has been conducted within 28d before initial administration and by thesame method and machine in the same hospital, the result can be adopted as baseline tumor assessment. Baseline tumor assessment should cover head, chest, abdomen, pelvic cavity and any other site suspected of tumor lesion (such as brain, bone lesions). Subjects with bone metastases during screening should be followed up using CT/MRI/X- ray at subsequent visits. Subjects who have no brain metastases confirmed by imaging at screening will not be required to undergo regular brain imaging at subsequent visits, which may be scheduled by the investigator as clinically indicated. Imaging (CT or MRI) assessments per RECIST v1.1 will be performed within 28 days prior to the first dose (baseline assessment), every 9 weeks during the first year of the study, and every 12 weeks thereafter until (1) the disease progression, (2) initiation of a new anti-tumor therapy, (3) withdrawal of informed consent, (4) loss of follow-up, (5) death, and (6) the termination of the study, whichever occurs first. In case medication is discontinued permanently for a subject due to the reasons other than those above said (such as AEs), the tumor assessment will still be conducted as scheduled. The investigator can schedule additional imaging examination based on the subject's clinical condition. If an unscheduled tumor assessment is carried out and the subject has not progressed, subsequent tumor assessments should also be performed as scheduled. The confirmatory assessment must be completed 4 weeks after the efficacy is assessed as complete response (CR) or partial response (PR). If the investigator suspects that the progression of disease is pseudoprogression, then progression of disease must be confirmed in the imaging examination four weeks later or at the next scheduled imaging assessment time point (note: the time point of the next imaging examination may not be later than 9 weeks after the initial confirmation of progression of disease). For a subject whose treatment is stopped before any clearly- disease progression, imaging examination results should be obtained as far as possible to conduct tumor efficacy assessment. In case a subject discontinues study treatment due to the progression of disease (excluding pseudoprogression), it will be unnecessary to repeat the step of imaging assessment in the last visit. If the subject has completed the imaging assessment of the tumor within 28 days prior to the EOT visit or safety visit, it is not required to repeat such examinations at the two visits.

l. If the Screening visit tests are performed within 7 days of C1D1, clinical laboratory tests do not need to be repeated on C1D1 (i.e. there is a -7-day window for C1D1 labs). When laboratory tests (including blood test, blood biochemistry, myocardial enzyme, coagulation function, urinalysis, and thyroid function, if applicable) and study drug administration are scheduled to be conducted on the same day (e.g., Day 1 [D1] of each treatment cycle), the test results should be available before the administration can be scheduled. Except for the first dose, laboratory tests at each dosing visit should be completed within 3 days prior to dosing. If the subject has received relevant laboratory tests within the first seven days of the EOT visit or safety visit 1, there is no need to repeat such tests at these two visits.

m. Screening visit will be performed at the local laboratory, which includes HCV antibody, HBsAg and HIV antibodies. Subjects with HBsAg positive will further assess HBV DNA test, subject with HCV antibody positive will further assess HCV RNA test. Subjects with HBsAg positive need to be retested for HBV DNA every 12 weeks until safety follow-up 1; subjects with HCV antibody positive need to be retested for HCV RNA every 12 weeks until safety follow-up 1; AFP test is required at baseline, and will be done every 12 weeks until the EOT visit..

n. Thyroid function examination covers free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) analysis, conducted respectively in the screening period, dosing in the first and second administration cycle, dosing every two subsequent administration cycles, EOT and in the safety follow-up visit. If the thyroid function test at screening is performed within 7 days prior to the first dose (C1D1), it does not need to be repeated before the first dose (i.e., there is a -7-day window for the thyroid function test on C1D1). When thyroid function tests and study drug administration are scheduled to be conducted

on the same day (eg, on Day 1 [D1] of the respective treatment cycle for thyroid function tests), the test results should be available before the administration can be scheduled. Except for the first dose, the specified thyroid function tests performed at each dosing visit should be completed within 3 days prior to dosing. If subjects have completed the thyroid function examination within 7 days prior to the end of treatment visit or safety visit, there is no need to repeat such at these two visits.

o. The tumor issue used for FGF19 and PD-L1 IHC test will be sampled at screening and be analyzed at central laboratory.

p. CS1001 will be given on D1 of each 21-day cycle. Each infusion at Cycle 1 should be completed over 60-120 minutes. The recommended infusion time for PK blood sample collection is 90 minutes, as shown in table 4 and table 5.

q. BLU-554 will be administered qd in the morning with no food intake from 2 hours before until 1 hour after study drug administration. On study visit days when PK samples are collected, subjects will take their BLU-554 dose at the site. When the 2 study drugs are administered on the same day, BLU-554 should be administered before CS1001 infusion completion. After BLU-554 is administered, the subject should be given with CS1001 through intravenous infusion as soon as possible.

r. Blood samples for PK and immunogenicity assessment refer to Table 4 and Table 5.

s. Subsequent anti-tumor treatment: Information on subsequent (after the end of study treatment) anti-tumor therapies will be collected, including the name of all components of the treatment and the start and end dates of administration.

t. If the investigator learns of any SAE (including the death) in a subject after the subject has completed safety follow-up or has withdrawn from the study, and there is a reasonable cause to believe that the event is possibly related to the study drug, the investigator should notify the sponsor's pharmacovigilance team or representative.

u. Survival status: Subjects will be contacted by telephone or in person every 12 weeks from the last dose of study drug to collect survival status, subsequent anti-tumor therapy, and study drug-related SAEs until death, loss of follow-up, withdrawal from the study, or study termination, whichever occurs first.

Table 4: Schedule for PK and Immunogenicity Blood Sampling by Study Drugs in Phase Ib

Day		BLU-554[a]			CS1001[a]				ECG[a, e]
		Time	**Time window**	**PK Sampling**	**Time**	**Time window**	**PK Sampling**	**ADA Sampling of CS1001**	
Cycle 1	D1	0 (Predose)	30 min prior to dosing	X	0 (Predose)	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosing[b]				
		30 min	± 5 min	X					
		1h	± 5 min	X					
		2h[c, e]	± 10 min	X	EOI+30 min[c, e]	± 15 min	X		X
		4h	± 15 min	X					
		6h	± 15 min	X					
		7.5h			EOI+6h	± 30 min	X		
		8h	± 30 min	X					
	D2	24h[d]	± 1h	X	EOI+22.5h[d]	± 1h	X		X
	D8	168h			EOI+168 h	± 1 day	X		
	D15	336h			EOI+336h	± 1 day	X		
Cycle 2	D1	0 (Predose)	30 min prior to dosing	X	0 (Predose)	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosingb				
		30 min	± 5 min	X					
		1h	± 5 min	X					
		2h	± 10 min	X					X
		4h	± 15 min	X					
		6h	± 15 min						
		8h	± 30 min	X					
	D2	24h[d]	± 1h	X					

Day		BLU-554[a]			CS1001[a]				ECG[a, e]
		Time	**Time window**	**PK Sampling**	**Time**	**Time window**	**PK Sampling**	**ADA Sampling of CS1001**	
Cycle 4	D1				0 (Predose	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosing[b]				
					EOI+30 min	± 15 min	X		X
					EOI+6h	± 30 min	X		
	D2				EOI+22.5h[d]	± 1 h	X		
	D8				EOI+168 h	± 1 d	X		
	D15				EOI+336h	± 1 d	X		
Cycle 5	D1				0 (Predose)	30 min prior to dosing	X	X	
C7, C10、C13 and C16, and every 8 cycles afterwards	D1				0 (Predose)	30 min prior to dosing	X	X	

Abbreviations: EOI, end of infusion; ADA, anti-drug antibody; PK, pharmacokinetics

a. It is important that PK sampling occurs as close as possible to the scheduled time. PK and immunogenicity sampling and ECG collection should be performed on the same day. Detailed sequential procedures are: 1) Scheduled triplicate ECG with an interval of at least 5 mins; 2) Vital sign measurements; 3) PK blood sampling; and 4) Any other tests and assessment required by the study.
b. After BLU-554 is administered, the subject should be intravenously infused with CS1001 as soon as possible. For PK blood sampling, the recommended infusion time of CS1001 is 90 minutes.
c. Collect two samples at one time point with BLU-554 blood sample be collected firstly and then CS1001 blood sample.
d. The 24h PK sample of BLU-554 and the EOI+22.5h PK sample of CS1001 must be collected prior to dosing on the same day.
e. Cycle 1 Day 1: "2 hours post BLU-554 dosing" ECG collection is allowed at 1 - 4 h post BLU-554 dosing; "end of CS1001 infusion + 30 min" ECG collection is allowed from the time after the completion of CS1001 infusion to 2.5 h post the completion of CS1001 infusion. If the ECG collection windows for these two time points on C1D1 do not overlap, i.e. two sets of ECG data will be collected.

Table 5:Schedule for PK and Immunogenicity Blood Sampling by Study Drugs in Phase II

Day		BLU-554[a]			CS1001[a]				ECG[a, e]
		Time	Time window	PK sampling	Time	Time window	PK sampling	ADA sampling of CS1001	
Cycle 1	D1	0 (Predose)	30 min prior to dosing	X	0 (Predose)	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosing[b]				
		2h[c, e]	±10 min	X	EOI+30 min[c, e]	± 15 min	X		X
	D2	24h[d]	± 1h	X	EOI+22.5h[d]	± 1h	X		X
Cycle 2	D1	0 (Predose)	30 min prior to dosing	X	0 (Predose)	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosing[b]				
		30 min	± 5 min	X					
		1h	± 5 min	X					
		2h	± 10 min	X					X
		4h	± 15 min	X					
		6h	± 15 min	X					
		8h	± 30 min	X					
	D2	24h[d]	± 1h	X					
Cycle 4	D1				0 (Predose)	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosing[b]				
					EOI+30 min	± 15 min	X		X
					EOI+6h	± 30 min	X		
	D2				EOI+22.5h[d]	± 1 h	X		
	D8				EOI+168 h	± 1 d	X		
	D15				EOI+336h	± 1 d	X		

Day		BLU-554[a]			CS1001[a]				ECG[a, e]
		Time	Time window	PK sampling	Time	Time window	PK sampling	ADA sampling of CS1001	
Cycle 5	D1				0 (Predose)	30 min prior to dosing	X	X	
C7, C10、C13 and C16, and every 8 cycles afterwards	D1				0 (Predose)	30 min prior to dosing	X	X	

Abbreviations: EOI, end of infusion; ADA, anti-drug antibody; PK, pharmacokinetics

a. It is important that PK sampling occurs as close as possible to the scheduled time. PK and immunogenicity sampling and ECG collection should be performed on the same day. Detailed sequential procedures are: 1) Scheduled triplicate ECG with an interval of at least 5 mins; 2) Vital sign measurements; 3) PK blood sampling; and 4) Any other tests and assessment required by the study.
b. After BLU-554 is administered, the subject should be intravenously infused with CS1001 as soon as possible. For PK blood sampling, the recommended infusion time of CS1001 is 90 minutes.
c. Collect two samples at one time point with BLU-554 blood sample be collected firstly and then CS1001 blood sample.
d. The 24h PK sample of BLU-554 and the EOI+22.5h PK sample of CS1001 must be collected prior to dosing on the same day.
e. Cycle 1 Day 1: "2 hours post BLU-554 dosing" ECG collection is allowed at 1 - 4 h post BLU-554 dosing; "end of CS1001 infusion + 30 min" ECG collection is allowed from the time after the completion of CS1001 infusion to 2.5 h after the completion of CS1001 infusion. If the ECG collection windows for these two time points on C1D1 do not overlap, i.e. two sets of ECG data will be collected.

Appendix 1 Processing of Missing Dates

Missing dates in combined medications should be imputed as follows:

For the start date, if only the day is missing, the date is defaulted to be the first day of the corresponding month, and if both the month and the day are missing, the date should be imputed as January 01. For the end date, if only the day is missing, the date is defaulted to be the last day of the corresponding month, and if both the month and the day are missing, the date should be imputed as December 31. The imputed start date should be earlier than the end date.

Missing dates for adverse events (AEs) should be imputed as follows:

1) If the AE end date is missing

- If the year and month are known, the last day of the known month should be used for imputation.

- If only the year is known, "December 31" should be used for imputation.

- For AEs leading to death, the AE end date should be the date of death or the imputed end date, whichever is earlier.

- Dates in other situations are considered as missing.

2) If the AE start date is missing

- If the year and month are known and earlier than the year and month of the first dose of the investigational drug, the last day of the known month should be used for imputation.

- If the year and month are known and equal to the year and month of the first dose of the investigational drug, the AE start date should be equal to the date of the first dose of the investigational drug (date refers to "XX month XX day").

- If the year and month are known and later than the year and month of the first dose of the investigational drug, the first day of the known month should be used for imputation.

- If the year and month are known and the year is earlier than the year of the first dose of the investigational drug, "December 31" should be used for imputation.

- If only the year is known and equal to the year of the first dose of the investigational drug, the AE start date should be equal to the date of the first dose of the investigational drug (date refers to "XX month XX day").

- If only the year is known and later than the year of the first dose of the investigational drug, "January 01" should be used for imputation.

- If the year, month, and day are all missing, the date of the first dose of the investigational drug should be used as the corresponding start date.

- If the imputed start date is later than the end date, the end date should be used as the corresponding start date.

- Dates in other situations are considered as missing.

If the date of death is incomplete:

- In the safety analysis, the death record needs to be included, and the missing date of death will not be imputed.

- In the efficacy analyses, if the year and month of the date of death are known, the first day of the month should be used for imputation. Otherwise, the date of death will not be imputed, and the death record will be censored for the calculation of time-event indicators (such as OS).