Clinical Trial Approval Number: 2016L04809

Protocol Title: A RANDOMIZED, DOUBLE-BLIND, CONTROLLED SINGLE-DOSE PHASE I CLINICAL STUDY OF IBI305 VERSUS BEVACIZUMAB TO ASSESS PHARMACOKINETICS, SAFETY, TOLERABILITY, AND IMMUNOGENICITY IN HEALTHY MALE SUBJECTS

Protocol Number: CIBI305A201

Version: v 1.0

Version Date: Aug. 3, 2016

Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

Study Center: Phase I Clinical Trial Laboratory, The First Hospital of Jilin University

Principal Investigator (PI): Ding Yanhua

NCT Number：NCT03083990

documents to be provided in future and indicated to be confidential in nature.

PROTOCOL SIGNATURE PAGE

I hereby agree to

- endeavor to conduct this study in strict accordance with this protocol, Good Clinical Practice (GCP), and applicable laws and regulations.
- keep all data information provided by the sponsor pursuant to the requirement for confidentiality, and that such information has to be indicated to be confidential before being submitted to the Ethics Committee.

I have read this protocol and agree all the information therein.

Sponsor's Medical Director: Zhou Hui

Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

Signature:  Date: 2016.8.4

Principal Investigator: Ding Yanhua

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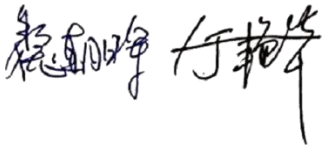
Signature:  Date: 2016.8.9

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LIST OF ABBREVIATIONS

AE	AEs
ADA	Anti-drug antibody
AESI	Adverse events of special interest (AESIs)
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
$AUC_{0-\infty}$	Area under the serum concentration–time curve from time 0 to infinity (∞)
AUC_{0-t}	Area under the serum concentration–time curve from time 0 to t
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CFDA	China Food and Drug Administration (now National Medical Products Administration)
CI	Confidence interval
CL	Plasma clearance
C_{max}	Maximum serum concentration
CRA	Clinical research associate
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBP	Diastolic blood pressure
D-D	D-dimer
DM	Data Manager
ECG	ECG
eCRF	Electronic case report form
EDC	Electronic Data Capture in clinical trials
GCP	Good Clinical Practice
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International normalized ratio
NAb	Neutralizing antibody

PK	Pharmacokinetics:
PKAS	Pharmacokinetic analysis set
PT	Preferred Term
PTT	Partial thromboplastin time
QA	Quality Assurance
SAE	Serious adverse event
SBP	Systolic blood pressure
SDV	Source data verification
SOP	Standard Operation Procedure
SS	Safety set
$t_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse events
VEGF	Vascular endothelial growth factor
V	Apparent volume of distribution
WHO-DD	World Health Organization Drug Dictionary

STUDY PROTOCOL AND AMENDMENTS

Not applicable.

PROTOCOL SYNOPSIS

Study title:	A randomized, double-blind, parallel-controlled Phase I clinical trial of single-dose IBI305 vs. bevacizumab to assess pharmacokinetic (PK) profile, safety, tolerability, and immunogenicity in healthy male subjects
Brief summary:	The primary objective of this study is to demonstrate PK similarities between IBI305 and bevacizumab in healthy volunteers after a single intravenous infusion. In this study, PK similarities are evaluated by comparing the AUC_{0-t} and $AUC_{0-\infty}$ of IBI305 with that of bevacizumab. In addition, safety, tolerability, and immunogenicity of IBI305 is assessed.
Study drugs:	Investigational drug: Recombinant anti-vascular endothelial growth factor (VEGF) humanized monoclonal antibody (IBI305) injection, with strength of 4 mL/100 mg. Control drug: Bevacizumab injection, with strength of 4 mL/100 mg
Project number:	CIBI305A201
Study phase:	Phase I
Study duration:	Each subject receives a single dose of IBI305 or bevacizumab and participates in the study for a period up to about 16 weeks (including 2-week screening period)
Subject population:	A total of 100 healthy male subjects
Inclusion criteria:	Subjects must meet all of the following inclusion criteria to be enrolled in the study: 1. Fully understand the study objectives and have a basic understanding of the pharmacological effects of the study drugs and potential adverse reactions; voluntarily sign a written informed consent form (ICF) in accordance with the Declaration of Helsinki 2. Healthy male subjects aged ≥ 18 years and ≤ 50 years 3. Body weight ≥ 50 kg and ≤ 100 kg, and body mass index (BMI) ≥ 19 and ≤ 28 kg/m^2 4. Various systemic laboratory parameters within the normal range, or abnormal test results deemed clinically insignificant by the investigator 5. Subjects agree that they and their partners will take effective contraceptive measures (such as sexual abstinence, sterilization, contraceptives, injection of medroxyprogesterone, or contraceptive implants, etc.) during the study and within 6 months after the infusion of the study drug.
Exclusion criteria:	Subjects meeting any of the followings are not enrolled in the study: 1. A history of hypertension or abnormal blood pressure measured at screening/baseline [systolic blood pressure (SBP) > 140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg confirmed by one repeat measurement on the same day] 2. Proteinuria deemed clinically significant by the investigator (urine protein 2+ or above by urinalysis) or a history of proteinuria 3. Received any antibody or protein therapy targeting VEGF or VEGF receptor in the past 1 year

	4. Used any biological product or inoculated with any live virus vaccine within 3 months prior to the infusion of the study drug, or used any monoclonal antibody within 12 months 5. With inherited bleeding tendency or coagulopathy, or a history of thrombosis or hemorrhagic disorder 6. A history of gastrointestinal perforation or gastrointestinal fistula 7. With unhealed wounds, ulcers or fractures, or underwent any major surgery within 2 months prior to randomization or expected to undergo any major surgery during the study or within 2 months after the end of the study 8. Used any prescribed or over-the-counter drug or any nutritional supplement within 5 half-lives of such drug or nutritional supplement or within 2 weeks prior to the administration of the study drug (whichever is longer). Use of herbal health products should be discontinued 28 days prior to the administration of the study drug 9. Tested positive for HBsAg, hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody, or treponema pallidum (TP) antibody 10. Known allergy to bevacizumab or any excipient of bevacizumab 11. Known history of allergic disorders or allergic constitution 12. Has donated blood 3 months prior to the infusion of the study drug 13. Treated with any other study drug or participated in another interventional clinical trial within 3 months prior to screening 14. A history of alcohol abuse or drug abuse within 12 months prior to screening; the subject fails to abstain from alcoholism within 72 h pre-dose and throughout the study 15. A history of psychosis 16. Subject whose spouse is planning to become pregnant 17. Unable to complete the study in accordance with the protocol during the study 18. Other circumstances deemed inappropriate for enrollment by the investigator
Planned enrollment:	This study plans to enroll a total of 100 subjects. Subjects are randomly assigned to the IBI305 or bevacizumab groups at a ratio of 1:1, i.e., subjects in IBI305 group : subjects in bevacizumab group = 50:50.
Study groups:	$^{35}_{17}$ A. IBI305 group: IBI305; single dose, 3 mg/kg, intravenously infused for 90 min $^{35}_{17}$ B. Bevacizumab group: bevacizumab; single dose, 3 mg/kg, intravenously infused for 90 min
Primary endpoint analysis:	$^{35}_{17}$ Area under the serum concentration–time curve from time 0 to t (AUC_{0-t}) $^{35}_{17}$ Area under the serum concentration–time curve from time 0 to infinity (∞) ($AUC_{0-\infty}$)

Secondary endpoint analysis:	Maximum serum concentration observed post-dose (C_{max}) Elimination half-life ($t_{1/2}$) Clearance (CL) Apparent volume of distribution (V)
Safety assessment	Vital signs; Physical examination; Laboratory tests (blood routine examination, blood chemistry, coagulation, and urinalysis) 12-lead ECG AEs Immunogenicity: ADA positive rate and Nab positive rate
Calculation of sample size:	50 subjects per group (100 subjects in total) shall provide a power-of-test of 85% to confirm the bioequivalence between IBI305 and bevacizumab. In estimation of this sample size, it is assumed that the significance level of two one-sided tests is 0.05, the coefficient of variation (CV) is 35%, and the dropout rate is 10%. IBI305 can be deemed equivalent to bevacizumab if 90% CI of the reference therapeutic ratio of ln-transformed AUC_{0-t} to ln-transformed $AUC_{0-\infty}$ is 80–125%.
Pharmacokinetic analysis:	Mean concentration is plotted against blood sampling time point to obtain a plasma concentration vs. time curve. PK parameters are calculated by non-compartmental analysis (NCA). PK analysis is carried out based on PK analysis set (PKAS). AUC_{0-t} and $AUC_{0-\infty}$ served as primary PK endpoints, while the other PK parameters serve as secondary PK endpoints. Plasma concentrations at each scheduled blood sampling time point is analyzed using descriptive statistics [number of subjects (N), arithmetic mean, standard deviation (SD), CV, minimum, median, and maximum]. Concentrations below the lower limit of quantitation (LLoQ) are replaced with "0" to facilitate descriptive statistical analysis. PK plasma concentrations are analyzed using descriptive statistics by group. Mean and individual plasma concentration vs. time curves after intravenous infusion of IBI305 and bevacizumab are plotted. The ln-transformed primary PK endpoints (AUC_{0-t} and $AUC_{0-\infty}$) are analyzed using an analysis of variance (ANOVA) model. The difference in the least square mean (LSM) between IBI305 and bevacizumab as well as corresponding 90% CI are calculated. Inverse transformation is applied to calculate geometric mean ratios (GMRs) and their 90% CIs. IBI305 can be deemed equivalent to bevacizumab if 90% CIs of the GMRs (IBI305/Bevacizumab) of AUC_{0-t} and $AUC_{0-\infty}$ are between 0.8 and 1.25.

Setting of blood sampling time points:	PK analysis Blood sampling time points: prior to infusion (within 60 min), immediately after infusion (within 5 min), and at 4 h (± 10 min), 12 h (± 20 min), 24 h (± 1 h) (D2), 48 h (± 1 h) (D3), 96 h (± 1 h) (D5), 168 h (± 8 h) (D8), 336 h (± 12 h) (D15), 504 h (± 24 h) (D22), 672 h (± 24 h) (D29), 1008 h (± 48 h) (D43), 1344 h (± 48 h) (D57), 1512 h (± 48 h) (D64), 1680 h (± 48 h) (D71), and 2016 h (± 48 h) (D85) after the start of infusion ADA/NAb assay Blood sampling time points: prior to infusion (within 60 min) and at 336 h (± 12 h) (D15), 1008 h (± 48 h) (D43), 1680 h (± 48 h) (D71), and 2352 h (± 48 h) (D99) after the start of infusion
Safety analysis	All adverse events (AEs) are classified using MedDRA codes and graded according to CTCAE version 4.03. Numbers and percentages of all subjects with treatment-emergent AEs (TEAEs), Grade 3 or greater TEAEs, serious adverse events (SAEs), drug-related TEAEs, drug-related SAEs, TEAEs leading to study discontinuation, TEAEs leading to study termination, and AEs of special interest (AESIs) are summarized by system organ class (SOC), preferred term (PT), and group. In addition, the severity of TEAEs and their causality with the study drug are also be summarized by SOC, PT, and group. For vital signs, physical examinations, laboratory tests, and 12-lead ECG, their measurements and changes from baseline are analyzed using descriptive statistics. The number and percentage of subjects who develop anti-drug antibodies and neutralizing antibodies during the study are summarized by treatment group.

1 BACKGROUND

1.1 Investigational Drug

1.1.1 Description of IBI305

IBI305 is a recombinant anti-VEGF humanized monoclonal antibody injection developed by Innovent Biologics (Suzhou) Co., Ltd. (hereinafter referred to as the sponsor), which is capable of binding specifically to human VEGF. With a molecular mass of about 149 kDa, IBI305 is capable of binding specifically to VEGF-A, inhibiting the binding of VEGF-A to VEGF-R1 and VEGF-R2, blocking the signaling pathways such as PI3K-Akt/PKB and Ras-Raf-MEK-ERK, inhibiting the growth, proliferation, and migration of vascular endothelial cells (VECs) and angiogenesis, decreasing the vascular permeability, blocking the blood supply to tumor tissues, inhibiting the proliferation and metastasis of tumor cells, and inducing the apoptosis of tumor cells, so as to produce anti-tumor effect. The active ingredient is recombinant anti-VEGF humanized monoclonal antibody, while the excipients include sodium acetate, sorbitol, and polysorbate 80[r1]. Refer to the Investigator's Brochure for the detailed structure and physicochemical properties of IBI305.

1.1.2 Preclinical studies

Pharmaceutical studies

The Chemistry, Manufacturing, and Control (CMC) study of IBI305 has shown that IBI305 is similar to bevacizumab in stability: They are identical in primary structure, highly similar to each other in higher-order structures, similar in oligosaccharide distribution, charge variants distribution, and product-related impurities, and all data of process-related impurities are within the proposed specification range. Therefore, it can be deduced that IBI305 is highly similar to bevacizumab in protein properties and product quality[r1].

Pharmacodynamic studies

The *in vitro* and *in vivo* pharmacodynamic (PD) studies of IBI305 have shown that,

1) Targets: IBI305 enables specific high-affinity binding to recombinant human VEGF-A with an affinity constant similar to that of bevacizumab, indicating that, like bevacizumab, IBI305 is also a specific human VEGF blocker with definite targets of action.
2) Specificity: IBI305 could have specific high-affinity binding to human VEGF-A and certain affinity to canine VEGF-A, but had low affinity to human VEGF-B, human VEGF-C, human VEGF-D, and human PIGF, suggesting that IBI305 recognizes specific targets and has low risk of off-target toxicity. No significant affinity to mouse VEGF-

$A_{164}$and rat VEGF-A_{164}, suggesting that IBI305 has high species specificity.

3) Mechanism of action: By binding to VEGF-A specifically, IBI305 could inhibit the activation of VEGFR-2 and ERK1/2, block the proliferation and migration of HUVEC, and inhibit the sprouting from rat aortic ring. The above findings suggested that IBI305 blocks the proliferation and migration of VECs and inhibits neovascularization by antagonizing VEGF-A-mediated signaling pathway, so as to reduce nutritional supply to tumor tissues and metastasis of tumor.

4) Anti-tumor effect: IBI305 is able to significantly inhibit the growth of human colon cancer Ls174t and lung cancer NCI-H460 cells in xenograft-bearing nude mice, indicating that IBI305 has significant anti-tumor effect.

Results of the *in vitro* and *in vivo* studies of IBI305 were highly similar to those of the synchronously designed study of bevacizumab, suggesting that IBI305 is highly similar to bevacizumab in targets of action, mechanism of action, and effect[r1].

Pharmacokinetic studies

The *in vitro* and *in vivo* pharmacokinetic (PK) studies of IBI305 have shown that,

1) Tissue specificity: IBI305 had no cross-reactivity with normal human tissues and cynomolgus monkey tissues, except cross-reactivity with the positive-control, i.e., human angiosarcoma tissue, suggesting high tissue targeting specificity of IBI305 so that IBI305 acts on tumor issues only rather than normal human tissues and has thus very low target-related toxicity.

2) Linearity: Significant linear PK profile was observed in single-dose or repeated-dose intravenous injection of IBI305 (2–50 mg/kg) in cynomolgus monkeys, thus significantly reducing the risk of abrupt increase in toxicity with increasing clinical dose.

3) Immunogenicity: After single-dose and repeated-dose intravenous injection of IBI305 or bevacizumab in cynomolgus monkeys, abnormal variations in plasma concentration vs. time curve were observed in particular animals, in combination with the anti-drug antibody test, indicating that IBI305 is immunogenic to some extent; at the same dose, IBI305 and bevacizumab are similar in immunogenicity.

4) Accumulation: After repeated-dose intravenous injection of IBI305 or bevacizumab in cynomolgus monkeys, the drug exposure of the last dose was significantly higher than that of the first dose, and steady-state drug concentration after repeated doses was higher than that after a single dose, suggesting probable *in vivo* drug

accumulation.

The results of tissue cross-reactivity and PK/TK studies in cynomolgus monkeys showed that IBI305 is similar to bevacizumab in tissue cross-reactivity and PK/TK profiles[r1].

Toxicological studies

Toxicological studies of IBI305 have shown that,

1) Single dose: A single intravenous infusion of IBI305 (up to 300 mg/kg) in cynomolgus monkeys showed good tolerability without any abnormal clinical symptom or toxicity. As converted based on body surface area, the dose is about 48 times the proposed clinical dose for human. In the safety pharmacology study, a single intravenous injection of IBI305 (50 mg/kg) in cynomolgus monkeys had no significant impact on the central nervous system (CNS), respiratory system, and cardiovascular system, This finding suggested very high safety in a single intravenous injection of IBI305.
2) Repeated doses: Repeated intravenous injection of IBI305 (up to 50 mg/kg) in cynomolgus monkeys twice weekly for 9 consecutive doses equivalent to 20 times the proposed dose for human (based on body weight) had only resulted in minimal to mild linear growth arrest of metaphyses at knee joints and chondrocytosis associated with disordered arrangement, minimal tingible-body macrophagocytosis in white pulp of the spleen, pulmonary (including bronchial) hemorrhage, and hemosiderin hyperpigmentation in lymphoid tissue of bronchial mucosa, thus the main target organs of toxicity are the bone, spleen, and lungs.
3) Immunotoxicity and immunogenicity: Repeated intravenous injection of IBI305 in cynomolgus monkeys twice weekly for 9 consecutive doses was immunotoxic to the spleen to some extent. IBI305 at each dose was likely to produce ADA, a portion of which were neutralizing antibodies (NAbs), indicating that IBI305 is immunotoxic and immunogenic to some extents.
4) Local irritation study: After repeated intravenous injection of IBI305 in cynomolgus monkeys, no injection site irritation was observed, suggesting that administration of IBI305 by intravenous injection is safe and feasible.
5) *In vitro* hemolysis assay: When IBI305 was administered at the maximum proposed clinical concentration (9 mg/mL), no hemolysis occurred, suggesting that IBI305 is suitable for intravenous injection.

The results of safety pharmacology study, chronic toxicity study, immunotoxicity study, immunogenicity study, local irritation study, and hemolysis assay of IBI305 were highly similar

to those of synchronously designed studies of bevacizumab injection, respectively[1].

1.1.3 Clinical study

Preclinical studies have demonstrated that IBI305 is highly similar to bevacizumab in CMC, PD, PK, and toxicology. This finding lays solid foundation for the test of IBI305 in human. Based on the results of preliminary *in vivo* and *in vitro* studies, this study was conducted to compare the PK, safety, tolerability, and immunogenicity of IBI305 vs. bevacizumab in healthy males. A Phase III study will be conducted to compare the efficacy, safety, and immunogenicity of IBI305 plus paclitaxel/carboplatin vs. bevacizumab plus paclitaxel/carboplatin in treatment-naive patients with advanced or recurrent non-squamous cell non-small cell lung cancer (NSCLC).

1.2 Study Principle and Risk/Benefit Assessment

1.2.1 Study principle

A biosimilar refers to a therapeutic biological product analogous to a market-approved RLD in terms of quality, safety, and efficacy[2]. Developed by the sponsor, IBI305 is a biosimilar of the commercially available bevacizumab, which can be administered via the same administration method as bevacizumab, to treat advanced, metastatic or recurrent NSCLC.

This study is conducted in accordance with the "Technical Guidelines on Development and Evaluation of Biosimilars (Tentative)" issued by CFDA (now NMPA)[r2]. Based on preclinical *in vitro*, *in vivo*, and toxicological studies, IBI305 is similar to bevacizumab in CMC, PD, PK, and toxicological profiles.

1.2.2 Justification for the selection of bevacizumab

The RLD in this study is bevacizumab. At doses of 1–10 mg/kg, PK of bevacizumab exhibited linear relationship with the dose[3,4]. Therefore, the dose for this study can be selected within the above dose range. In balanced consideration of the safety of healthy subjects, it is essential to obtain PK parameters of IBI305/bevacizumab, including AUC, and PK parameters of IBI305 can be compared with that of bevacizumab, hence a low dose, i.e., 3 mg/kg, is chosen as the dose for this study.

1.2.3 Risk/Benefit assessment

Developed by the sponsor, IBI305 is a biosimilar of bevacizumab. Based on the clinical pharmacology and toxicity profile of IBI305, the risks and benefits are expected to be similar to those of bevacizumab.

For treatment-related risks of bevacizumab, please refer to its patient package insert[r4].

Only healthy male subjects are enrolled in this study and they will not receive any therapeutic effect from this study. As unexpected adverse reactions may occur during the study, the following measures are taken to ensure minimal hazard to the subjects: Adverse events (AE) occurring before, during, and after infusion are closely observed, and once any related adverse reaction occurs, the study physician would take corresponding measures immediately to guarantee the safety of the subject; in addition, the subject would stay at the study center until 96 h (D5) after the start of infusion and leave the study center only after completing related examinations, so that prompt treatment can be administered in the case of any emergency.

1.3 About This Study

This study was intended to assess the PK, safety, tolerability, and immunogenicity of IBI305 vs. bevacizumab in healthy male subjects.

1.3.1 Study objectives

Primary objective: To perform PK comparability study after single-dose infusion of IBI305 or bevacizumab in healthy male subjects.

Secondary objectives: To compare the safety, tolerability, and immunogenicity of IBI305 vs. bevacizumab after single-dose infusion of IBI305 or bevacizumab in healthy male subjects.

1.3.2 Study design

This study is a randomized, double-blind, controlled single-dose Phase I study. As planned, 100 healthy male subjects aged 18–50 years are randomly assigned to the IBI305 group or bevacizumab group at a ratio of 1:1. Subjects receive a single dose of bevacizumab or IBI305 (3 mg/kg) via intravenous infusion, before PK analysis and immunogenicity (ADA/NAb) assay are performed.

Refer to **Figure 1** for the study design.

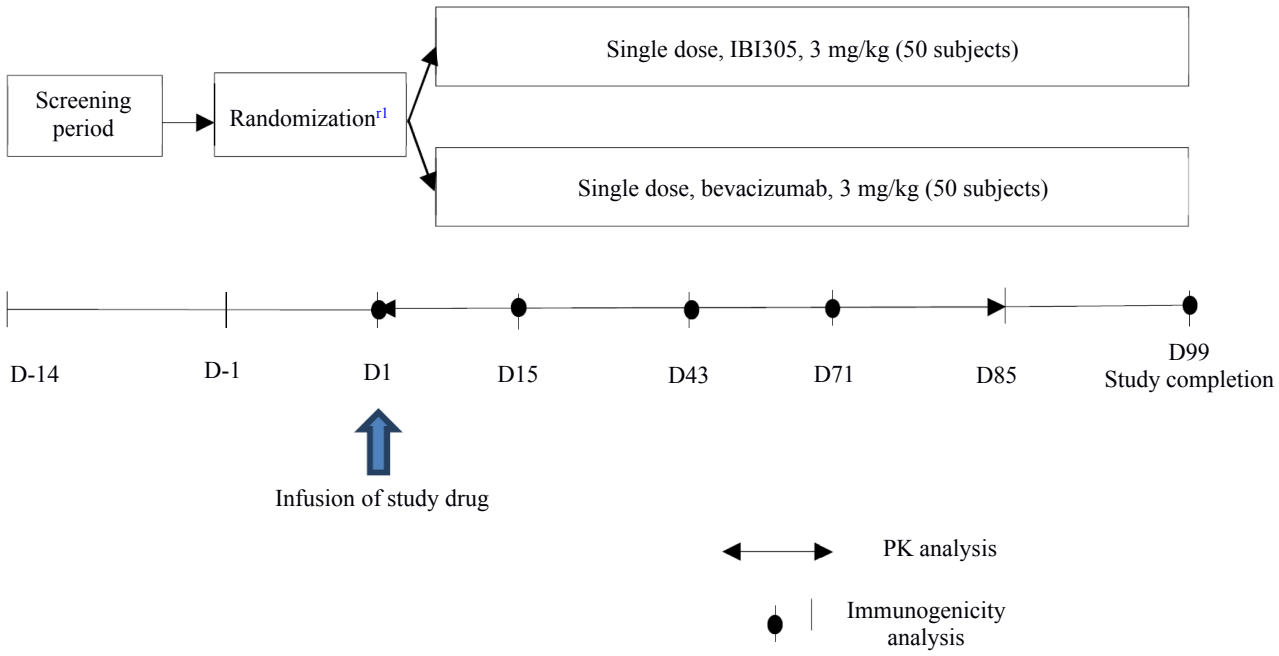

Figure 1. Schematic of study design.

[1] Randomization can be carried out after the review of inclusion/exclusion criteria on D-1 and prior to administration.

Discussion of study design

This is a randomized double-blind study, which eliminates biases in subject grouping, AE observation, follow-up, etc. The half-life of bevacizumab is about 20 days[r4], thus a duration of about 4 half-lives (85 days) is selected to guarantee a full understanding of PK profile.

Primary endpoint analysis

- Area under the serum concentration–time curve from time 0 to t (AUC_{0-t})
- Area under the serum concentration–time curve from time 0 to infinity (∞) ($AUC_{0-\infty}$)

Secondary endpoint analysis

- Maximum serum concentration observed post-dose (C_{max})
- Elimination half-life ($t_{1/2}$)
- Clearance (CL)
- Apparent volume of distribution (V)

2 SELECTION OF SUBJECT POPULATION

Subject population: Healthy male volunteers.

2.1 Number of Subjects

Fifty subjects per group (100 subjects in total) shall provide a power-of-test of 85% to confirm the bioequivalence between IBI305 and bevacizumab. The following assumptions were made in the estimation of sample size: two one-sided test has 5% significance level, coefficient of variation (CV) is 35%, and the dropout rate is 10%. IBI305 can be deemed equivalent to bevacizumab if 90% CI of the reference therapeutic ratio of ln-transformed AUC_{0-t} to ln-transformed $AUC_{0-\infty}$ is 80–125%.

If dropout rate of the subjects during the study is greater than 10% (more than 10 subjects cannot be involved in PK analysis), then more eligible subjects will be enrolled to ensure that there are 90 PK data-centered cases.

2.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled in the study:

1) Fully understand the study objectives and have a basic understanding of the pharmacological effects of the study drugs and potential adverse reactions; voluntarily sign a written ICF in accordance with the Declaration of Helsinki
2) Healthy male subjects aged ≥ 18 years and ≤ 50 years
3) Body weight ≥ 50 kg and ≤ 100 kg, and body mass index (BMI) ≥ 19 kg/m^2 and ≤ 28 kg/m^2
4) Various systemic laboratory parameters within the normal range, or abnormal test results deemed clinically insignificant by the investigator
5) Subjects agree that they and their partners will take effective contraceptive measures (such as sexual abstinence, sterilization, contraceptives, injection of medroxyprogesterone, or contraceptive implants, etc.) during the study and within 6 months after the infusion of the study drug

2.3 Exclusion Criteria

Subjects meeting any of the followings are not enrolled in the study:

1) A history of hypertension or abnormal blood pressure measured at screening/baseline (SBP > 140 mmHg and/or DBP > 90 mmHg confirmed by one repeat measurement on the same day)

2) Proteinuria deemed clinically significant by the investigator (urine protein 2+ or above by urinalysis) or a history of proteinuria
3) Received any antibody or protein therapy targeting VEGF or VEGF receptor in the past 1 year
4) Used any biological product or inoculated with any live virus vaccine within 3 months prior to the infusion of the study drug, or used any monoclonal antibody within 12 months
5) With inherited bleeding tendency or coagulopathy, or a history of thrombosis or hemorrhagic disorder
6) A history of gastrointestinal perforation or gastrointestinal fistula
7) With unhealed wounds, ulcers or fractures, or underwent any major surgery within 2 months prior to randomization or expected to undergo any major surgery during the study or within 2 months after the end of the study
8) Used any prescribed or over-the-counter drug or any nutritional supplement within 5 half-lives of such drug or nutritional supplement or within 2 weeks prior to the administration of the study drug (whichever is longer). Use of herbal health products should be discontinued 28 days prior to the administration of the study drug
9) Tested positive for HBsAg, hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody, or treponema pallidum (TP) antibody
10) Known allergy to bevacizumab or any excipient of bevacizumab
11) Known history of allergic disorders or allergic constitution
12) Has donated blood 3 months prior to the infusion of the study drug
13) Treated with any other study drug or participated in another interventional clinical trial within 3 months prior to screening
14) A history of alcohol abuse or drug abuse within 12 months prior to screening; the subject fails to abstain from alcoholism within 72 h pre-dose and throughout the study
15) A history of psychosis
16) Subject whose spouse is planning to become pregnant
17) Unable to complete the study in accordance with the protocol during the study
18) Other circumstances deemed inappropriate for enrollment by the investigator

2.4 Screening Failure

Screening failure occurs when a subject who has signed the informed consent form fails to meet the inclusion criteria. In the event of screening failure, the demographic data of the ineligible subject and noncompliance with the inclusion/exclusion criteria should be documented in the source document and electronic case report form (eCRF). Subjects who failed screening due to any transient disease are allowed to undergo another screening.

2.5 Subject Restrictions

The subjects agree that they and their partners will take effective contraceptive measures during the study and within at least 6 months after study medication to avoid pregnancy.

For restrictions on medication during the study, please refer to Section 3.5.

2.6 Withdrawal and Replacement

All subjects might withdraw from this study at any time, with or without providing a reason. Subjects who withdraw from the study would not be subject to discrimination or retaliation, and their medical treatment would not be affected. If a subject who fails to meet inclusion criteria is inadvertently enrolled, the investigator must notify the sponsor or its representative immediately to discuss the safety and health status of the subject, and whether the subject should continue participating in the study. When consensus is not achieved, the subject has to withdraw from the study and where possible, undergo follow-up.

In addition, subjects might withdraw from the study in the following circumstances:

- Subjects voluntarily withdraw from the study;
- Subjects who use other drugs that affect the trial results (as assessed by the investigator);
- Subjects with drug allergies or serious adverse events, and are deemed unsuitable by the investigator to continue the trial;
- Subjects who experience diseases or other conditions during the trial which prevente them from continuing the trial;
- Subjects with significant deviations or other reasons (such as loss to follow-up) during the clinical trial that makes it difficult to assess drug efficacy;
- Subjects who should withdraw from the study as determined by the study doctor;
- Study termination by the investigator or sponsor for any reason;

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17 The government department or ethics committee discontinues the study for any reason.

Subjects who withdraw from the study are required to complete the withdrawal procedure according to the visit flow chart. Subjects who withdraw from the study would not be replaced.

Subjects who withdraw their informed consent are not be contacted again unless they clearly indicate the willingness to be contacted. The sponsor could use the clinical trial data obtained from the subjects before their withdrawal of the informed consent.

Subjects should be examined and observed as much as possible upon withdrawal. At the same time, the date of withdrawal, reason for withdrawal, and the tests and observation results at the time of withdrawal are documented in the source document and eCRF. If necessary, the subject can be appropriately treated and followed up until the symptoms (test values) return to the state before initialization of the clinical study or until there is no medical issue, and the results will be documented in the source document and eCRF.

3 STUDY DRUGS

The study drugs in this study are IBI305 and bevacizumab.

IBI305 is a biosimilar of bevacizumab. Both drugs contain humanized anti-VEGF monoclonal antibody as the active ingredient. Bevacizumab is a standard commercially available drug. Both drugs were provided by the sponsor.

3.1 Investigational Drug

Name: IBI305

Appearance: Sterile solution for intravenous injection with pH 5.2. Clear colorless liquid that is free of foreign matter, floc, and precipitate

Strength: 4 mL/100 mg

Source: Innovent Biologics (Suzhou) Co., Ltd.

3.2 Control Drug

Name: Bevacizumab

Appearance: Sterile solution for intravenous injection with pH 5.9–6.3. Clear to slightly opalescent, colorless to light brown liquid

Strength: 4 mL/100 mg

Source: Roche Pharma (Schweiz) Ltd.

3.3 Group Assignment and Blinding

After the eligibility (meet all inclusion criteria) of a subject has been verified, the operator at the study center logs into the Interactive Web Response System (IWRS) and enters the subject information into IWRS, which allocates a random number to the subject and provides a medication number of the drug to be received by the subject.

This study is a randomized, double-blind, controlled single-dose Phase I study. As IBI305 and bevacizumab cannot be made to appear identical, the study center has to designate non-blinded pharmacists and research nurses to prepare the study drugs and complete relevant records. The non-blinded research nurses and pharmacists responsible for preparing and verifying the study drug are not allowed to disclose any information regarding treatment allocation to the subjects, their families, or other personnel including the physicians and relevant study personnel.

Unblinding: Subject unblinding should only be performed after database locking.

Emergency unblinding: In emergencies where the investigator has to be aware of the medication administered to a subject, the investigator should perform emergency unblinding for the subject and notify the sponsor and the contract research organization (CRO) immediately. Moreover, the investigator should document the reason for unblinding, date of unblinding, and outcome of unblinding in the source document and eCRF of the subject.

3.4 Method of Drug Administration

In this study, each subject receives single doses (3 mg/kg) of IBI305 or bevacizumab via intravenous infusion for 90 min. The dose needed by each subject is calculated based on body weight of the subject: Dose (mg) = 3 mg/kg × Body weight of the subject (kg). The calculated dose is then converted into the required volume of the drug. An equal volume of liquid will be drawn from a 100 mL infusion bag containing 0.9% normal saline and then discarded or used to flush the infusion device. Based on the calculated required volume, the corresponding drug volume is drawn and added into the infusion bag. The solution in the infusion bag is gently mixed by inversion and avoided the formation of foam, drug agglomerates, and precipitates.

Subjects should remain in bed from the start of infusion to 2 h after completion of the infusion. When the infusion is completed, 30 mL of 0.9% normal saline is used to flush the injection line according to routine clinical practice.

If an infusion-related reaction occurs, it should be handled according to routine clinical practice at the study site.

In the event of suspension of infusion/adjustment of infusion rate due to any infusion-related reaction in a subject, PK blood samples will still be collected at the scheduled time points.

3.5 Concomitant Medications and Therapies

All medications except the study drugs, including Chinese herbal medicines and other non-traditional therapies, are considered as concomitant medications. All concomitant medications within 30 days prior to subject screening should be documented in eCRF, including their generic name, route of administration, start date, end date, and indications.

3.5.1 Permitted concomitant medications and therapies

Use of acetaminophen at the daily recommended dose (≤ 2 g/24 h and ≤ 1 g/4 h) is permitted.

3.5.2 Prohibited concomitant medications and therapies

Use of prescribed or over-the-counter formulations, including antacids, analgesics (except acetaminophen), dietary supplements, or herbal medicines, is not permitted during the study,

unless required to treat AEs or current medical issues.

3.5.3 Emergency treatments

During the study, the investigator must ensure that adequate treatment is administered when any adverse reaction occurs.

3.6 Drug Management

As IBI305 and bevacizumab cannot be made to appear identical, the study center has to designate non-blinded pharmacists and research nurses to prepare the study drugs and complete relevant records. After the verification of AE and SAE data, used portions of IBI305 and bevacizumab are destroyed on site according to the relevant operating procedures, and the destruction log is filled out by the study center. Unused portions of IBI305 and bevacizumab are tallied up by the study center and returned to the sponsor to be destroyed. Infusion-related containers, empty vials, and syringes can be destructed on site and documented in accordance with applicable guidelines and operating procedures established by the study center and local and institutional authorities.

The non-blinded clinical research associate (CRA) is responsible for verifying the supply, transport, reception, storage, distribution, destruction, recovery, and related records of the study drugs used in the clinical study.

3.7 Packaging, Labeling, Storage, and Tallying

Study drugs (IBI305 and bevacizumab) should be packed and labeled in accordance with relevant regulations. Study drugs should be stored according to the specifications on the drug labels.

IBI305 and bevacizumab are stored at 2–8 °C in the dark before being transported via cold-chain logistics to each center without being frozen or shaken. Upon the receipt of study drugs, the person designated by the study center should check transportation temperature, tally drugs up, verify and sign the receipt, and the related records should be retained in the investigator's folder. Drug storage temperature should be recorded on a daily basis, and the following items should be recorded on the inventory log: Date of receipt, quantity, lot numbers, quantity released, and remaining stock.

Study drugs can only be handled by authorized persons. Volume of drugs required by the subject is calculated based on 3 mg/kg. IBI305 and bevacizumab are diluted with 0.9% sodium chloride to obtain 100 mL for immediate infusion. In the event that intravenous infusion cannot be performed immediately on account of the subject or any other reason, the prepared solutions can

be stored at 2–8 °C but the intravenous infusion must be completed within 12 h. Otherwise, the solutions should be destroyed at the study center and documented by a drug administrator.

4 TRIAL PROCESS FLOW

This is a randomized, double-blind, controlled Phase I trial. The study plans to enroll 100 healthy male subjects aged 18–50 years, who will be randomly assigned at a ratio of 1:1 to receive single intravenous infusion (3 mg/kg) of IBI305 or bevacizumab.

The schedule of procedures is detailed in **Table 1**.

T1Table 1. Schedule of study procedures.

	Screening		Admission									Follow-up										
Visit	**1**	**2**	**3**							**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Days of visits	**Screening period**		**D1–D2 (h)**							**D3**	**D5**	**D8**	**D15**	**D22**	**D29**	**D43**	**D57**	**D64**	**D71**	**D85**	**D99**	**Withdrawal**
	D-14 to D-2	**D-1**	**Before infusion[a]**	**0**	**Immediately after infusion**	**4**	**8**	**12**	**24**	**48**	**96**	**168**	**336**	**504**	**672**	**1008**	**1344**	**1512**	**1680**	**2016**	**2352**	
Admission to study site		X																				
Discharge from study site											X											
Signing of informed consent form	X																					
Inclusion/exclusion criteria	X	X																				
Demographic characteristics	X																					
Body weight and height	X	X[b]																			X[b]	X[b]
Medical history/previous medication	X	X																				
Vital signs[c]	X	X	X[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[c]	X	X							X		X		X		X		X		X		X	X
Blood routine examination[c,e]	X	X[f]							X		X		X		X		X		X		X	X
Urinalysis[c,g]	X	X[f]							X		X		X		X		X		X		X	X
Blood chemistry[c,h]	X	X[f]							X		X		X		X		X		X		X	X
Coagulation[c,i]	X	X[f]							X		X		X		X		X		X		X	X
HBV Assay	X																					

	Screening		Admission									Follow-up										
Visit	**1**	**2**	**3**							**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Days of visits	**Screening period**		**D1–D2 (h)**							**D3**	**D5**	**D8**	**D15**	**D22**	**D29**	**D43**	**D57**	**D64**	**D71**	**D85**	**D99**	**Withdrawal**
	D-14 to D-2	**D-1**	**Before infusion[a]**	**0**	**Immediately after infusion**	**4**	**8**	**12**	**24**	**48**	**96**	**168**	**336**	**504**	**672**	**1008**	**1344**	**1512**	**1680**	**2016**	**2352**	
Treponema pallidum antibody	X																					
Anti-HCV antibody assay	X																					
Anti-HIV antibody assay	X																					
12-lead ECG[c]	X	X	X[d]		X	X	X	X	X	X	X		X	X		X	X		X		X	X
Randomization and grouping		X[j]																				
Administration via intravenous infusion				X																		
PK blood sampling[c,k]			X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
ADA/NAb blood sampling[c,l]			X										X			X			X		X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetics; ADA = anti-drug antibody; NAb = neutralizing antibody.

a. 60 min prior to infusion;

b. Body weight measurement only;

c. If multiple evaluations are to be carried out at the same time, then samples/data should be collected or acquired in the following order under non-rescue situations: blood sampling, 12-lead ECG, vital signs, and physical examination;

d. For vital signs and 12-lead ECG, the measurements obtained within 60 min prior to the infusion will be used as baseline values;

e. Hematology tests include hemoglobin, hematocrit, differential white blood cell (WBC) count (neutrophil count, absolute lymphocyte count, monocyte count, eosinophil count, and basophil count), platelet count, and red blood cell (RBC) count;

f. If blood routien test, urinalysis, blood chemistry, and coagulation test are carried out within 7 days prior to the infusion, then screening results can serve as baseline data, and such examinations may be not required at this visit; otherwise, repeat examinations will be required;

g. Urinalysis consists of specific gravity (SG) of urine, pH value, urine ketone body, urine glucose, urine protein, urine nitrite, urine occult blood, urine WBC, urobilinogen, and urine bilirubin;

h. Blood chemistry consists of creatinine, blood urea nitrogen, total protein, albumin, total bilirubin, triglycerides, total cholesterol, alkaline phosphatase (ALP), AST, ALT, fasting blood glucose, sodium, potassium, chlorine, calcium, phosphorus, and magnesium;

i. Coagulation test consists of international normalized ratio (INR), activated partial thromboplastin time (APTT) and partial thromboplastin time (PTT), and D-dimer (D-D);

j. Randomization can be carried out after the review of inclusion/exclusion criteria on D-1 and prior to administration;

k. PK blood sampling time points: prior to infusion (within 60 min), immediately after the infusion (within 5 min), and at 4 h (± 10 min), 12 h (± 20 min), 24 h (± 1 h) (D2), 48 h (± 1 h) (D3), 96 h (± 1 h) (D5), 168 h (± 8 h) (D8), 336 h (± 12 h) (D15), 504 h (± 24 h) (D22), 672 h (± 24 h) (D29), 1008 h (± 48 h) (D43), 1344 h (± 48 h) (D57), 1512 h (± 48 h) (D64), 1680 h (± 48 h) (D71), and 2016 h (± 48 h) (D85) after the start of the infusion;

l. ADA/NAb blood sampling time points: prior to infusion (within 60 min) and at 336 h (± 12 h) (D15), 1008 h (± 48 h) (D43), 1680 h (± 48 h) (D71), and 2352 h (± 48 h) (D99) after the start of the infusion.

4.1 Visiting Procedure

4.1.1 Screening period (D-14 to D-1 pre-dose)

Screening visits are completed from D-14 to D-2 prior to the start of study medication. The following procedure must be completed at each screening visit to ensure that the subject meets the requirements for enrollment in this study:

- Signing of informed consent form
- Check against the inclusion/exclusion criteria
- Record demographic data (sex, ethnicity, age, etc.)
- Measure body weight and height
- Record medical history and previous medications (within 30 days prior to screening)
- Vital signs
- Physical examination
- Laboratory tests (blood routine examination, coagulation, blood chemistry, and urinalysis)
- HBV assay, anti-HCV antibody assay, anti-HIV antibody assay, and anti-TP antibody assay
- 12-lead ECG
- Recording the AEs and concomitant medications

The investigator will assess all results of screening visits. Only subjects who meet the inclusion criteria but not any of the exclusion criteria could proceed to the next visit. Subjects not eligible for enrollment are asked to withdraw from the study and deemed as screening failure. The investigator should document all the reasons for withdrawal/screening failure of subjects.

The subjects are admitted to the study center on D-1 (1 day prior to infusion of study drug) until their discharge on D5. Each subject is required to complete the following procedure on D-1:

- Check against the inclusion/exclusion criteria
- Randomization*
- Measure body weight and calculate dosage amount
- Record medical history and previous medications

- Vital signs
- Physical examination
- Laboratory tests (blood routine examination, coagulation, blood chemistry, and urinalysis)§
- 12-lead ECG
- Recording the AEs and concomitant medications

* Randomization can be carried out after the review of inclusion/exclusion criteria on D-1 and prior to administration on D1

§ If laboratory screening tests (blood routine examination, coagulation, blood chemistry, and urinalysis) are performed within 7 days prior to infusion of the study drug, then the results of the screening tests could serve as baseline data and such tests are not required at this visit.

4.1.2 D1

After fasting overnight for at least 8 h, each subject should complete the following procedure before the infusion of study drug:

- PK and immunogenicity blood sampling
- 12-lead ECG*
- Vital signs*
- Recording the AEs and concomitant medications

* 12-Lead ECG and vital signs: Measurements prior to infusion are used as baseline values.

After the start of study drug infusion, the following procedure must be completed:

- PK blood sampling (immediately post-dose, and at 4 h and 12 h after the start of infusion)
- 12-Lead ECG (immediately post-dose, and at 4 h, 8 h, and 12 h after the start of infusion)
- Vital signs (immediately post-dose, and at 4 h, 8 h, and 12 h after the start of infusion)
- Recording the AEs and concomitant medications

Note: Subjects need to fast for 8 h prior to infusion and do not consume fluids from 1 h pre-dose to 1 h post-dose. A standard meal is offered by the study center 1 h after the completion of

infusion.

4.1.3 D2

Each subject needs to complete the following procedure:

- PK blood sampling (24 h after the start of infusion)
- Laboratory tests (blood routine examination, blood chemistry, coagulation, and urinalysis)
- 12-Lead ECG
- Vital signs
- Physical examination
- Recording the AEs and concomitant medications

4.1.4 D3

Each subject needs to complete the following procedure:

- PK blood sampling (48 h after the start of infusion)
- 12-Lead ECG
- Vital signs
- Recording the AEs and concomitant medications

4.1.5 D5

Each subject needs to complete the following procedure:

- PK blood sampling (96 h after the start of infusion)
- Laboratory tests (blood routine examination, blood chemistry, coagulation, and urinalysis)
- 12-Lead ECG
- Vital signs
- Physical examination
- Recording the AEs and concomitant medications
- Discharge from study site

Subjects do not stay at the study center from D5 on.

4.1.6 D8

Subjects pay a return visit to the study center on D8. Subjects should complete the following procedures during this visit:

- PK blood sampling (168 h after the start of infusion)
- Vital signs
- Recording the AEs and concomitant medications

4.1.7 D15

Subjects pay a return visit to the study center on D15. Subjects should complete the following procedures during this visit:

- PK and immunogenicity blood sampling (336 h after the start of infusion)
- Laboratory tests (blood routine examination, blood chemistry, coagulation, and urinalysis)
- 12-Lead ECG
- Vital signs
- Physical examination
- Recording the AEs and concomitant medications

4.1.8 D22

Subjects pay a return visit to the study center on D22. Subjects should complete the following procedures during this visit:

- PK blood sampling (504 h after the start of infusion)
- 12-Lead ECG
- Vital signs
- Recording the AEs and concomitant medications

4.1.9 D29

Subjects pay a return visit to the study center on D29. Subjects should complete the following procedures during this visit:

- PK blood sampling (672 h after the start of infusion)
- Laboratory tests (blood routine examination, blood chemistry, coagulation, and urinalysis)
- Vital signs
- Physical examination
- Recording the AEs and concomitant medications

4.1.10 D43

Subjects pay a return visit to the study center on D43. Subjects should complete the following procedures during this visit:

- PK and immunogenicity blood sampling (1008 h after the start of infusion)
- 12-Lead ECG
- Vital signs
- Recording the AEs and concomitant medications

4.1.11 D57

Subjects pay a return visit to the study center on D57. Subjects should complete the following procedures during this visit:

- PK blood sampling (1344 h after the start of infusion)
- Laboratory tests (blood routine examination, blood chemistry, coagulation, and urinalysis)
- 12-Lead ECG
- Vital signs
- Physical examination
- Recording the AEs and concomitant medications

4.1.12 D64

Subjects pay a return visit to the study center on D64. Subjects should complete the following procedures during this visit:

- PK blood sampling (1512 h after the start of infusion)

- Vital signs
- Recording the AEs and concomitant medications

4.1.13 D71

Subjects pay a return visit to the study center on D71. Subjects should complete the following procedures during this visit:

- PK and immunogenicity blood sampling (1680 h after the start of infusion)
- Laboratory tests (blood routine examination, blood chemistry, coagulation, and urinalysis)
- 12-Lead ECG
- Vital signs
- Physical examination
- Recording the AEs and concomitant medications

4.1.14 D85

Subjects pay a return visit to the study center on D85. Subjects should complete the following procedures during this visit:

- PK blood sampling (2016 h after the start of infusion)
- Vital signs
- Recording the AEs and concomitant medications

4.1.15 D99 (Study completion)

Subjects pay a return visit to the study center on D99. Subjects should complete the following procedures during this visit:

- Immunogenicity blood sampling (2352 h after the start of infusion)
- Laboratory tests (blood routine examination, blood chemistry, coagulation, and urinalysis)
- 12-Lead ECG
- Vital signs
- Physical examination

- Body weight measurement
- Recording the AEs and concomitant medications

4.1.16 Withdrawal

To terminate the study prematurely, a subject is required to complete the following procedure:

- PK and immunogenicity blood sampling
- Laboratory tests (blood routine examination, blood chemistry, coagulation, and urinalysis)
- 12-Lead ECG
- Vital signs
- Body weight measurement
- Physical examination
- Recording the AEs and concomitant medications

4.2 Dietary Restrictions

Subjects are informed not to consume food or drink caffeinated food or beverages (e.g., chocolate, tea, coffee, cola, energy drinks, etc.), not to take methylxanthine, grapefruit, and grapefruit juice, and not to consume alcohol or cigarettes from 48 h prior to the administration of study drug to the end of this study.

While hospitalized in the Phase I ward, the subjects are provided with standard meals and drinks. On the day of study drug administration, each subject should have fasted for 8 h prior to the infusion and deprived of fluids from 1 h pre-dose to 1 h post-dose. A standard meal is provided by the study center 1 h after the completion of infusion.

4.3 Activities and Exercises

Subjects should refrain from high-intensity exercises, sauna, steam bath, and sunbathing during the study. Subjects should remain in bed from the start of study drug infusion to 2 h after completion of the infusion. During the study, subjects should also avoid TCM physical therapies, such as skin scraping and cupping.

4.4 Other Restrictions

No vaccine regardless of dosage form may be used.

Any concomitant medication should be determined by the investigator in comprehensive consideration of medical condition and its impact on study outcome, as shown in Section 3.5.

Subjects may not donate sperms throughout the study and within 3 months after completion of the study.

Subjects must agree that they and their partners will take effective contraceptive measures (such as sexual abstinence, sterilization, contraceptives, injection of medroxyprogesterone, or contraceptive implants, etc.) during the study and within 6 months after the infusion of the study drug.

5 PHARMACOKINETICS AND IMMUNOGENICITY STUDIES

5.1 Collection and Handling of Blood Samples

PK blood samples are collected at the following time points: prior to infusion (within 60 min), immediately after infusion completion (within 5 min), and at 4 h (± 10 min), 12 h (± 20 min), 24 h (± 1 h) (D2), 48 h (± 1 h) (D3), 96 h (± 1 h) (D5), 168 h (± 8 h) (D8), 336 h (± 12 h) (D15), 504 h (± 24 h) (D22), 672 h (± 24 h) (D29), 1008 h (± 48 h) (D43), 1344 h (± 48 h) (D57), 1512 h (± 48 h) (D64), 1680 h (± 48 h) (D71), and 2016 h (± 48 h) (D85) after the start of the infusion. Collection date and time of each blood sample is documented in eCRF.

Immunogenicity (ADA/NAb) blood samples are collected at the following time points: prior to infusion (within 60 min) and at 336 h (± 12 h) (D15), 1008 h (± 48 h) (D43), 1680 h (± 48 h) (D71), and 2352 h (± 48 h) (D99) after the start of the infusion. Collection date and time of each blood sample is documented in eCRF.

Since hemolysis of a sample affects the assay of its drug concentration, the sample hemolysis is paid attention to during the blood sampling process. The relevant nurses receive training prior to blood sample collection to ensure gentle manipulation during blood sampling. Personnel in charge of centrifugation should communicate with the blood sampling nurses in a timely manner to minimize the rate of hemolysis.

Note: For the frozen storage of samples, it is recommended to use a medical cryogenic freezer with small fluctuation of temperature; a cryogenic freezer with a defrost cycle function should not be used to prevent repeated freeze-thaw.

Blood samples are stored in a freezer at -80 °C (-80 °C ± 10 °C) at the clinical study center until they are taken out and sent to the analysis center. Serum samples in sample tubes are transported in styrofoam packages containing a sufficient amount of dry ice to ensure the samples remain frozen for at least 24 h. Under such conditions, the frozen samples were promptly sent to various central laboratories. The blood samples for PK and NAb assays will be delivered to United-Power Pharma Tech Co., Ltd. for analysis, while the blood samples for ADA assay will be delivered to Wuxi AppTec (Shanghai) Co., Ltd. for analysis. Detailed description of sample collection, handling, labeling, storage, transportation, and analysis is listed in laboratory manual of the center.

5.2 Pharmacokinetic Blood Sampling Time Windows

Time windows for PK blood sampling are shown in **Table 2**.

T2T2Table 2. PK blood sampling time windows.

Blood sampling point (based on start time of infusion)	Allowed time window
Before infusion	Within 60 min
Immediately at the end of infusion	+ 5 min
4 h after the start of infusion	± 10 min
12 h after the start of infusion	± 20 min
24 h (D2), 48 h (D3), and 96 h (D5) after the start of infusion	± 1 hr
168 h after the start of infusion (D8)	± 8 hr
Blood sampling point (based on start time of infusion)	Allowed time window
336 h after the start of infusion (D15)	± 12 hr
504 h (D22) and 672 h (D29) after the start of infusion	± 24 hr
1008 h (D43)–2016 h (D85) after the start of infusion	± 48 hr

5.3 Bioanalysis

The blood samples for PK and NAb assays will be delivered to United-Power Pharma Tech Co., Ltd. for analysis, while the blood samples for ADA assay will be delivered to Wuxi AppTec (Shanghai) Co., Ltd. for analysis. Verification methods and the final report of sample analysis will be provided separately and included in study-related documents.

6 CALCULATION OF PHARMACOKINETIC PARAMETERS

PK parameters are calculated using WinNonlin v6.4. PK parameters, which include:

– Area under the serum concentration–time curve from time 0 to t (AUC_{0-t})

– Area under the serum concentration–time curve from time 0 to infinity (∞) ($AUC_{0-\infty}$)

– Maximum serum concentration observed post-dose (C_{max})

– Elimination half-life ($t_{1/2}$)

– Clearance (CL)

– Volume of distribution (V)

7 SAFETY EVALUATION

Patients who have signed the ICF are required to undergo safety assessment [vital signs, physical examination, body height, body weight, AEs, ECG, blood routine examination, urinalysis, blood chemistry (liver function, kidney function, electrolyte, blood lipid, and blood glucose), and coagulation, etc.]. The time interval to be assessed should span from the time of ICF signing to the end of the study, and AEs or SAEs occurring during this period should be followed up until they return to normal or are stabilized. All reported AEs are listed and analyzed.

7.1 Assessment of Physical Examination and Laboratory Safety Parameters

Changes in laboratory measurements of each subject relative to baseline values are evaluated, each laboratory abnormality is evaluated for clinical significance, and clinically significant abnormalities relative to baseline value are documented as AEs in the case report form. Clinically significant laboratory measurements during screening should be documented as AEs.

Physical examination

The investigator or any other authorized qualified investigator conduct specified physical examination, including the following: general condition, skin, head, neck, ears, eyes, nose, mouth, throat, respiratory organs/lungs, cardiovascular system, gastrointestinal tract/abdomen, genitourinary system, lymphatic system, musculoskeletal system/limbs, nerves, and others. During each visit, the investigator documentes symptoms reported by the subject and abnormalities observed in physical examination. All clinically significant abnormalities are reported as AEs.

Monitoring of vital signs

At each visit, vital signs of each subject (including axillary temperature, heart rate, and blood pressure) were monitored, documented, and evaluated. All clinically significant abnormalities should be reported as AEs. During the study, the investigator could carry out more vital sign measurements based on actual conditions (e.g., for safety reasons).

12-lead ECG

12-lead ECG is carried out at specified time points. Frequency of ECG could be increased during the study, according to the opinion of the investigator.

ECG parameters such as heart rate, PR interval, QRS complex duration, QT interval, and QTc interval should be documented. Subjects should rest in the supine position for at least 5 min prior to 12-lead ECG examination. All ECG are evaluated by qualified physicians. All clinically significant abnormalities should be reported as AEs.

Hematological parameters

To determine the maximum level of myelosuppression due to study drug, the most serious changes in neutrophil count, WBC count, platelet count, and the level of hemoglobin occurring throughout the study will be summarized and analyzed as per NCI CTCAE version 4.03. The number of subjects with Grade 3 or 4 hematological toxicity post-dose and corresponding incidence rate should be listed and analyzed.

Clinical biochemical parameters

Measurements of ALP, ALT, AST, total bilirubin, and creatinine are summarized and analyzed according to NCI CTCAE version 4.03, to evaluate the effects of the study drug on liver and kidney functions in the subjects. The number of subjects with the most serious changes in liver and kidney functions throughout the study and their incidence rates should be summarized and analyzed according to NCI CTCAE version 4.03. The number of subjects with Grade 3 or 4 blood chemistry abnormalities post-dose and their incidence rates should be listed.

Immunogenicity evaluation

Within 60 min prior to infusion, and on D15, D43, D71, and D99, blood samples are collected for ADA assay and NAb assay (**Table 1**). Tests are conducted in the relevant site laboratory. Detailed description of sample collection, handling, labeling, storage, transportation, and analysis is listed in laboratory manual of the center.

Assessment of other toxicities

The clinical investigator analyzes and documentes toxicities observed during the study in the AE log or SAE log in accordance with the study protocol. AEs happening from the start of treatment to the end of each visit, as graded by the clinical physician, should be summarized and analyzed.

7.2 AEs

7.2.1 Definition

AEs

An AE refers to any untoward medical occurrence in a subject involved in a clinical study and may not have a definite causal relationship with the treatment. Thus, an AE can be any adverse and unexpected sign (including laboratory abnormalities), symptom, or any disease with temporal dependence on study medication, regardless of causality with the study drug.

Serious adverse event

An SAE refers to any unfavorable medical occurrence in a clinical study (may not have a definite causal relationship with the study drug), which meets at least one of the following criteria:

(1) Events resulting in death.

(2) Life-threatening events (a "life-threatening" AE is defined as an AE that will lead to immediate death of the subject upon its onset, excluding the AEs that will lead to death only upon further progression).

(3) Events requiring hospitalization or prolonged length of stay. The following circumstances are excluded herein: Hospitalization and/or surgery that had been scheduled before or during the study for a pre-existing illness or disease prior to enrollment (which does not worsen during the study), hospitalization for the sake of medical insurance reimbursement rather than an illness, elective surgery, or conditions not requiring hospitalization or SAE reporting in the opinion of the study physician.

(4) Events leading to permanent or serious disability/incapacity.

(5) Events leading to congenital abnormalities/birth defects.

(6) Other significant medical events: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious, when based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.2.2 Severity of AEs

Severity of AEs are evaluated according to CTCAE version 4.03 and graded as follows:

- Grade 1 Mild; asymptomatic or with mild symptoms; clinical or diagnostic observation only, medical intervention not indicated
- Grade 2 Moderate; minimal, local or non-invasive intervention required; limiting age-appropriate instrumental activities of daily living (the instrumental activities of daily living refer to cooking, buying sundry goods or clothes, using the telephone, managing money matters, etc.)
- Grade 3 Serious or medically significant, but not immediately life-threatening; leading to hospitalization or prolonged length of stay; disabling; limiting self-care activities of daily living (the self-care activities of daily living refer to bathing, dressing

and undressing, feeding oneself, using the toilet, taking medications, but not bedridden)

- Grade 4 Life-threatening; urgent intervention indicated
- Grade 5 AE-related death

7.2.3 Relationship between AEs and study drugs

There are five types of causal relationships between the investigational product and AE: Related, possibly related, possibly unrelated, unrelated, and not evaluable. The evaluation method is detailed as follows (**Table 3**):

T3Table 3. Assessment of causality between the investigational drug and AE.

Causality	Criteria
Related	AE occurrence has a reasonable temporal relationship with administration time; AE has significant reasonable causal relationship with the investigational drug, as compared to any other cause (e.g., concurrent disease, environment, toxicity, or other therapy received, etc.) AE is resolved or alleviated after discontinuation or dose reduction The event meets the definition of any known AE type related to a suspected drug or its analog AE recurs after re-administration
Possibly Related	AE occurrence has a reasonable temporal relationship with administration time; AE has equally reasonable causal relationship with the investigational drug, as compared to any other cause (e.g., concurrent disease, environment, toxicity, or other therapy received, etc.). AE is resolved or alleviated after discontinuation or dose reduction (if applicable)
Possibly Unrelated	AE has more reasonable causal relationship with other causes (e.g., concurrent disease, environment, toxicity, or other therapy received, etc.), as compared to the investigational drug AE is not resolved or alleviated after discontinuation or dose reduction (if applicable) or in the event of unclear circumstances AE does not recur after re-administration or in the event of unclear circumstances
Unrelated	AE occurrence has no reasonable temporal relationship with administration time, or AE has significant causal relationship with other factors (such as concurrent disease, environment, toxicity, or other therapy received by the subject, etc.)
Cannot Evaluable	The above information is unclear, the AE is not evaluable based on existing information in the opinion of the investigator, and the investigator fails to get further follow-up information

7.2.4 SAE Reporting

Any SAE occurring during the study, regardless of causality with treatment, should be reported according to SAE reporting procedure issued by relevant regulatory authority or an Independent Ethics Committee (IEC). The investigator should make clinical diagnosis where possible based on vital signs and symptoms of the subject, and when such diagnosis is definite, the investigator should report the diagnosis result rather than symptoms.

The investigator should take the following measures:

- Take appropriate medical measures immediately;
- Send the completed SAE report immediately (within 24 h after the study center becomes aware of this event or the latest information of this event) by fax to the sponsor: 021-31652800. The sponsor's email address for SAE reporting: drugsafety@innoventbio.com (when reporting SAE via email, it is recommended to encrypt the SAE report and send the sponsor the password in a second email);
- Document this SAE in the AE log and SAE log of eCRF and in the source document;
- This signed and dated SAE form will be immediately (in 24 h) sent by the investigator to the IEC, CFDA (now NMPA), health department, and local drug administration authorities;
- Follow up and document the SAE process until the event has been resolved or recovered to an outcome that follow-up is no longer required in the opinion of the investigator.

In addition, the sponsor or a representative thereof (e.g., CRO) should report the SAE to the corresponding regulatory authority and other investigators in accordance with requirements of the regulatory authority and local regulations.

7.2.5 Handling of AEs and visits

The investigator is obliged to conduct proper medical treatment of any AE (pointing out the treatment methods, such as interruption/discontinuation of study medication, dose modification, administering drug therapy, etc.). When an AE occurs, the investigator should actively take appropriate measures to ensure the safety of the subject. Any AE observed from the signing of ICF to the protocol-specified time (**Table 4**) should be followed up.

Any SAE occurring beyond the protocol-specified time (**Table 4**), if deemed by the investigator to be related to the study drug, should be reported to the sponsor.

7.2.6 Adverse events of special interest (AESI)

The AESI for this study include:

- Hypertension
- Proteinuria
- Gastrointestinal perforation
- Hemorrhage event
- Cardiotoxicity
- Phlebitis
- Thrombus
- Intestinal fistula
- Posterior reversible encephalopathy syndrome
- Hypersensitivity reaction, infusion-related reaction

The above AESIs should be closely observed and promptly managed by the investigator during the study. If criteria for SAE is met, AESIs should be reported to the sponsor in accordance with the SAE reporting procedure within the specified duration.

7.2.7 Pregnancy

In the event that the female partner of a subject gets pregnant within 6 months after the start of study medication, the investigator should be notified immediately and is required to submit the completed pregnancy report to the sponsor within 24 h, in accordance with the SAE reporting procedure. The investigator should discuss with the subject and the partner thereof about the risk of continuing such pregnancy and its impact on the fetuses. The pregnancy should be monitored until the completion of pregnancy. Any other SAE occurring during pregnancy should be reported in accordance with the SAE reporting procedure. In the event of any congenital abnormality/birth defect or any other SAE, a SAE report should be filled out and submitted in accordance with the SAE reporting procedure.

7.2.8 Collection, documentation, and reporting of AEs

All AEs occurring from the time of signing the ICF until a study-specified time (**Table 4**), regardless of severity, should be collected and documented in the AE page of eCRF (all SAEs and non-SAEs). Clinically significant laboratory findings during screening should also be

documented as AEs.

The investigator should enter all essential information, including AE description, start date, end date, severity level, countermeasures, outcome, and causal relationship between severity and the investigational drug, and should document each AE separately.

T4Table 4. AE reporting and follow-up.

	Reporting Time Limit	**Visit Time Limit**
AEs	From signing of ICF to the end of visit	Until the event is resolved or has reached an outcome that can be reasonably interpreted without the need of further follow-up in the opinion of the investigator (e.g., recovering or not recoverable, etc.)
Adverse events of special interest (AESIs)	From signing of ICF to the end of visit	Until the event is resolved or has reached an outcome that can be reasonably interpreted without the need of further follow-up in the opinion of the investigator (e.g., recovering or not recoverable, etc.)
Serious adverse event	From signing of ICF to the end of visit	Until the event is resolved or has reached an outcome that can be reasonably interpreted without the need of further follow-up in the opinion of the investigator (e.g., recovering or not recoverable, etc.)
The subject's partner becomes pregnant	From the first dose to 6 months after administration of study drug	Until outcome of this event

8 DATA MANAGEMENT

Data in this study are acquired in the form of eCRF.

8.1 Data Traceability and eCRF Completion and Transfer

Only subject number can be shown in the eCRF system. As part of the related study report, eCRF is used to document clinical study information of the subject. The eCRF is completed by the investigator or an authorized person (which should be indicated in the study authorization form). Prior to database locking, the eCRF should be electronically signed by the investigator or the authorized person to state that all information in the eCRF system is true.

After each examination in the clinical study, an eCRF has to be completed to document the physical condition of the subject.

Medical record and other records of the subject are kept by the investigator. These records should contain the source data, copies of laboratory data, and other medical testing results (e.g., ECG).

During the study, subject information is not directly documented in eCRF system but in the source document of each subject as part of the source data, and later is transcribed to the eCRF system.

Data in this study is managed by the data department of WuXi Clinical Development Services (Shanghai) Co., Ltd., in order to ensure that the clinical study data are true, complete, private, and traceable.

All data in eCRF originated from the source document and are filled out by the investigator or any person designated by the investigator to ensure information integrity and accuracy. Along with any modification or correction of data in eCRF system, names of the data modifier and dates of changes are automatically recorded.

Once completed, eCRF should be submitted via internet in a timely manner, and the data in eCRF system is subjected to source data verification (SDV), review by data manager (DM), and query to verify that they are unquestionable, and have to be acknowledged by the investigator by e-signing prior to data locking.

8.2 Database Creation

The data department of Wuxi Clinical Development Services (Shanghai) Co., Ltd. should create a database in accordance with FDA 21 CFR Part 11 to manage traces of system login, data entry, modification, and deletion, and such database should be created as per CDISC standard, where possible.

After the final data are verified in a data review meeting, the PI, sponsor, and statistician co-sign the related documents and lock the database. In principle, the locked database may not be altered any longer. Any issue found after data locking should be verified. Following verification, corrections may be made in the statistical analysis procedure, and a written record should be retained.

8.3 Data Verification

Data verification consists of computerized edit check, manual check, and data verification meeting. Any data query in the verification should be promptly corrected by the investigator or any person designated by the investigator.

8.4 Data Quality Assurance

Quality assurance of data is organized, conducted, and reported pursuant to the study protocol and SOPs released by the sponsor. In ICH E6, quality assurance (QA) is defined as "all proposed systematic actions intended to ensure that the conduct of the study and generation, documentation, and reporting of the data comply with GCP and applicable regulatory requirements". In this study, quality control (QC) and data validation procedures are used to ensure the reliability and accuracy of the clinical database. Data entry, collation, clarification, and validation procedures that all relevant research staff must follow are detailed in the monitoring plan and data management plan, to ensure compliance with GCP and GLP.

8.5 Database Locking

Following review and verification of the created database, the database is jointly locked by the PI, sponsor, and statistician. In principle, the locked database may not be altered any longer. Any issue found after data locking should be verified. Following verification, corrections may be made in the statistical analysis procedure, and a written record should be retained.

Thereafter, the database is statistically analyzed by the statistician according to the statistical analysis plan, and a statistical analysis report is provided.

8.6 Blind Verification and Unblinding

ICH Biostatistics Guideline E9 recommends investigators to perform blind verification before unblinding for two purposes:

- To discuss each issue in the blinded state to determine dataset size
- To review study data in the blinded state

Study groups are unblinded after the minutes of the verification meeting are signed and dated. Prior to unblinding, one written credential for confirmation of database locking is submitted by

the head statistician.

9 DATA ANALYSIS AND STATISTICAL METHODS

Statistical analytical procedure and information used in this study are detailed in a separate statistical analysis plan. In the event of protocol amendment and that such amendment will have major impact on statistical analytical procedure and information in the opinion of the sponsor and/or PI, the statistical analysis plan should be revised accordingly to remain consistent with this protocol.

9.1 Sample Size Determination

Fifty subjects per group (100 subjects in total) shall provide a power-of-test of 85% to confirm the bioequivalence between IBI305 and bevacizumab. The following assumptions are made in the estimation of sample size: two one-sided test has 5% significance level, coefficient of variation (CV) is 35%, and the dropout rate is 10%. IBI305 can be deemed equivalent to bevacizumab if 90% CI of the reference therapeutic ratio of ln-transformed AUC_{0-t} to ln-transformed $AUC_{0-\infty}$ is 80–125%.

9.2 General Analysis

For continuous variables, descriptive statistics should include the count, mean, standard deviation, median, maximum, and minimum. For categorical variables, descriptive statistics consists of frequency and absolute or relative rate. Statistical analysis in this study is conducted using SAS.

Data of dropout subjects are included in the analyses of primary and secondary endpoints. The procedure for the handling of missing data is detailed in the statistical analysis plan.

9.3 Analysis Sets

Safety analysis set (SS): Include all randomized subjects who receive the study drug with available post-medication safety evaluation data. Subjects are analyzed by group. SS is used in all safety analyses.

PK analysis set (PKAS): Include all randomized subjects who receive the study drug, for whom at least AUC_{0-t} and $AUC_{0-\infty}$ could be reliably calculated, the absorption, distribution, metabolism, and elimination of the study drug are not seriously affected, and positive ADA is detected at baseline. PKAS is used as the primary analysis set in PK equivalence analysis. PKAS and SS are used in demographics and baseline characterization.

Immunogenicity assay dataset: Include all enrolled subjects who receive the study drug with available post-medication immunogenicity assessment data.

9.4 Subject Distribution

The schedule of subject visit procedure is shown in **Table 1**. The number and percentage of patients who have completed or dropped out of the study (including the reason for dropouts such as loss to follow-up, AEs, and poor compliance) are summarized based on treatment groups.

The number and percentage of subjects in each analysis set are calculated based on treatment groups.

For subjects completing the study, dropout subjects, and their distribution in each analysis set, the number and percentage of subjects are calculated by study center.

The number and percentage of protocol violations are calculated based on treatment groups.

9.5 Demographics and Other Baseline Characteristics

Demographic characteristics such as age, height, gender, and weight, and other baseline characteristics such as disease history are analyzed using descriptive statistics.

9.6 Compliance and Drug Exposure Analysis

Drug exposure levels in the subjects are analyzed using descriptive statistics by group.

9.7 Pharmacokinetic Analysis

PK analysis is based on PKAS.

9.7.1 Analysis of Primary PK Endpoints

The primary objective of this study was to check the bioequivalence between IBI305 and bevacizumab. The ln-transformed primary PK endpoints (AUC_{0-t} and $AUC_{0-\infty}$) are analyzed using an ANOVA model. The difference in the least square mean (LSM) between IBI305 and bevacizumab as well as corresponding 90% CI are calculated. Inverse transformation is applied to calculate geometric mean ratios (GMRs) and their 90% CIs. IBI305 can be deemed equivalent to bevacizumab if 90% CIs of the GMRs (IBI305/Bevacizumab) of AUC_{0-t} and $AUC_{0-\infty}$ are between 0.8 and 1.25.

9.7.2 Analysis of Secondary PK Endpoint

The secondary PK endpoint for this study is C_{max}. The difference in the least square mean of ln-transformed C_{max} between IBI305 and bevacizumab and corresponding 90% CI is calculated by using the ANOVA model, and the GMR and its 90% CI are calculated using inverse transformation.

9.8 Safety Analysis

Safety analysis is based on the safety analysis set.

9.8.1 AEs

All AEs are classified by code according to MedDRA and graded according to CTCAE version 4.03. Numbers and percentages of all subjects with treatment-emergent AEs (TEAEs), Grade 3 or greater TEAEs, serious adverse events (SAEs), drug-related TEAEs, drug-related SAEs, TEAEs leading to study discontinuation, TEAEs leading to study termination, and AEs of special interest (AESIs) are summarized by system organ class (SOC), preferred term (PT), and group. In addition, the severity of TEAEs and the causality with the study drug are also summarized by SOC, PT, and group.

9.8.2 Laboratory tests

All laboratory measurements and their changes relative to baseline are analyzed by scheduled time point and group using descriptive statistics. A cross-classification table is used to describe normal values and abnormalities after infusion, and the laboratory abnormalities are tabulated.

9.8.3 ECG

ECG measurements and their changes relative to baseline are analyzed using descriptive statistics.

9.8.4 Vital signs, physical examination and other safety-related examinations

Vital signs and their changes relative to baseline are analyzed using descriptive statistics.

Results of physical examination are listed by group.

9.8.5 Concomitant medications

Concomitant medications are non-study medications that meet one of the followings:

(1) All other drugs received after study medication.

(2) Other drugs that are administered prior to study medication and continue to be used after study medication.

The concomitant medications are coded according to the World Health Organization Drug Dictionary (WHO-DD), and the number and percentage of cases are calculated by Anatomical Therapeutic Chemical classification (ATC), PT, and group.

9.9 Interim Analysis

One interim analysis is planned in the study to evaluate the safety data only without adjusting α.

The analysis is carried out when the first 50 subjects complete observation on D29.

10 STUDY MANAGEMENT

10.1 Statement

This clinical study iscarried out in accordance with the moral, ethical, and scientific principles specified in the *Declaration of Helsinki* and GCP, as well as the design and requirements in the protocol.

10.2 Ethics

Before the drugs are delivered to the investigator, a copy of Ethics Committee Approval and a list of documents for review have to be submitted to the sponsor. The Ethics Committee Approval should be accompanied by a list of names of all EC members involved in approval discussion and their respective responsibilities.

After the EC has approved this study protocol, the sponsor should submit this clinical study protocol to CFDA (now NMPA) for registration.

Prior to initialization, the clinical trial has to be approved by the EC and relevant regulatory authority.

Any modification to the study protocol should be submitted to the EC for review and approval.

In the event of any SAE or unexpected AE occurring during the clinical study, which is related to safety of the clinical study and may affect safety of the subject and the conduct of the study, the EC must be notified by the investigator.

10.3 Source Record Verification

All data obtained during the clinical study must be properly processed to guarantee the rights and privacy of the subjects involved in the clinical study. The investigator must agree to the review and audit of clinical study data carried out by the monitor/auditor/inspector, so as to validate the accuracy of source data and understand the progress of the study. If it is not possible to validate the source records, the investigator should agree to assist the monitor/auditor/inspector in further confirmation of data QC.

10.4 Quality Assurance and Review

QA audit of this clinical study should be conducted by the sponsor or any person authorized by the sponsor. GCP audit could also be conducted by the drug approval authority. The quality auditor could review all medical records, study-related documents and mails, as well as informed consent forms for this clinical trial.

10.5 Informed Consent Form

The investigator is obliged to explain the objectives, methodology, benefits, and potential risks of this clinical trial to each subject. An ICF signed by the subject must be obtained prior to any operating procedure related to the clinical trial. Informed consent should be expressed in both oral and written forms. The subject should sign and date the informed consent form in person. The subject should retain copies of the signed ICF and its information page.

By signing the ICF, the subjects agree that the sponsor, drug approval administration, auditor, and (or) monitor may check the obtained source data related to the clinical study, and the reviewers must abide by the confidentiality statement.

10.6 Liabilities and Insurance

The sponsor has insured the subjects involved in this study in accordance with local laws, and have borne the treatment cost and corresponding financial compensation for any subject having damages related to the study drug or study procedure.

10.7 Modifications to Clinical Protocol

Following the confirmation of the final study protocol, a detailed protocol modification log has to be in place and co-signed at least by the investigator and the sponsor, with version and date being indicated, for any modification made to the protocol.

All modifications to the protocol have to be approved by the EC in writing, and, if necessary, should be submitted to local drug approval authority. Simple policy-related modifications should be sent to the EC only. All the documents should be submitted to the sponsor.

10.8 Monitoring

The sponsor has designated a monitor to perform on-site monitoring. The monitor representing the sponsor or CRO authorized by the sponsor should adhere to the relevant in-house SOPs. The monitor should pay regular visits from the start of the study to the end of the study.

The monitor can access the source data related to this clinical study and check eCRF as per the relevant SOPs to ensure that the information is complete, accurate, and consistent with the source data.

The source record, eCRF, copies of laboratory data, and medical testing results should be made available for review by the CRA, auditor, and health authority at all times. The monitor should examine all eCRFs and ICFs.

10.9 Premature Termination

If the investigator and the sponsor become aware that, provided that the study is further conducted, some conditions or events are likely to jeopardize the safety and benefits of the subject, the study may be terminated after discussion among relevant personnel. Even if the above finding is absent, the sponsor may also decide to terminate the study in advance.

Reasons for premature termination include but are not limited to the following:

- Identification of unexpected significant or unacceptable risks to enrolled subjects
- Slow enrollment
- The sponsor decides to interrupt or discontinue drug development

10.10 Confidentiality

All study-related findings and documents shall be deemed confidential. The investigator and members of the research team may not disclose such information without prior written consent from the sponsor.

Privacy of the subject should be protected. Files in EDC system and documents to be submitted to the sponsor or CRO should be identified by subject number, initials, and/or date of birth, and subject name should not be shown. The investigator should maintain the confidentiality of documents that are not needed to be submitted to the sponsor or CRO but contain information from which identity of the subject can be determined (e.g., a signed ICF).

10.11 Data Retention

Medical record and other records of the subject are kept by the investigator. These records should contain inpatient medical record, source radiologic data, laboratory data, other medical testing results (e.g., ECG), and source document of this clinical trial. According to relevant regulatory requirements, the investigator should retain the source document and relevant information of the clinical study until 5 years after the completion of the study. The investigator shall retain the disk of eCRF copied data.

10.12 Publishing Policy

By signing this study protocol, the investigator has agreed that the outcome of this study can be used for registration application in or outside China, publication or the provision of information to medical professionals. Where necessary, relevant regulatory authority shall be informed of the name, address, qualification, and in-study responsibilities of the investigator.

Without prior communication with the sponsor, the investigator may not publish (in the form of poster, abstract, paper, etc.) any data related to this study. Detailed information shall be

described in other documents.

11 REFERENCES

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