Protocol Abstract

Sponsor/Company:	Innovent Biologics (Suzhou) Co., Ltd.
Investigational Drug:	IBI305
Active Ingredient:	Recombinant humanized anti-VEGF monoclonal antibody
Study Title:	Biosimilar Candidate IBI305 plus Paclitaxel/Carboplatin for the Treatment of Non-squamous Non-small Cell Lung Cancer
Protocol No.:	CIBI305A301
Coordinating Investigator:	Zhang Li
Coordinating Center:	Sun Yat-Sen University Cancer Center

Study Duration: Each subject will receive treatment every 3 weeks until progressive disease (PD), intolerable toxicity, withdrawal of informed consent, loss to follow-up, or death (whichever comes first). The end of this study will be the18th month after randomization of the last subject.	Phase: III

Study Objectives:

Primary Objective:

- To compare the objective response rate (ORR) in subjects with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) treated by IBI305 and bevacizumab in combination with paclitaxel/carboplatin

Secondary Objectives:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) in subjects with advanced or recurrent non-squamous NSCLC treated by IBI305 and bevacizumab in combination with paclitaxel/carboplatin
- To compare the safety and immunogenicity of IBI305 and bevacizumab in combination with paclitaxel/carboplatin for treatment of advanced or recurrent non-squamous NSCLC

Exploratory Objectives:

- To compare the population pharmacokinetics (PPK) of IBI305 and bevacizumab in subjects

with advanced or recurrent non-squamous NSCLC

- To compare the pharmacodynamics (PD) of IBI305 and bevacizumab in subjects with advanced or recurrent non-squamous NSCLC

Study Design:

This is a multicenter, randomized, double-blind and phase III study. A total of 436 subjects with non-squamous NSCLC will be enrolled, randomized in a ratio of 1:1 to either IBI305 in combination with paclitaxel/carboplatin group or bevacizumab in combination with paclitaxel/carboplatin group, and stratified according to age (<60 vs. ≥60 years old) and epidermal growth factor receptor (EGFR) status (wild type vs. unknown).

Each treatment cycle will be 3 weeks for both experimental groups. On D1 of each treatment cycle, subjects will be administered 15 mg/kg of either IBI305 or bevacizumab in combination with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, or death (whichever comes first), after which subjects will discontinue paclitaxel/carboplatin and continue with either IBI305 or bevacizumab monotherapy as maintenance treatment. The maintenance monotherapy will continue every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

During the study, a CT or an MRI will be performed every 6 weeks (± 7 days) and be determined whether the study treatment will be continue by investigators at each center through tumor assessments until PD, withdrawal of informed consent, loss to follow-up, death, start of other anti-tumor therapies, or end of study. If the subjects discontinue the study treatment for reasons other than PD, tumor assessments will be continued until PD, withdrawal of informed consent, loss to follow-up, death, start of other anti-tumor therapies, or end of study. If the subjects discontinue the study treatment for PD, the investigators will make telephone follow-up every 12 weeks (± 7 days) to collect the information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, loss to follow-up, death, or end of study.

Number of Subjects:	436
Diagnostic and Key Inclusion Criteria:	Inclusion Criteria: Subjects meeting all the following criteria will be enrolled: 1) Signing the informed consent form. 2) Males or females ≥ 18 and ≤ 75 years old. 3) Inoperable, locally advanced (stage IIIB), metastatic (stage IV), or

	recurrent non-squamous NSCLC verified by histology or cytology (mixed tumors should be classified according to the predominant cell type). 4) EGFR wild type or non-sensitive mutation type verified by histology or cytology. 5) At least one measurable lesion as the target lesion (based on RECIST version 1.1 criteria). 6) Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1. 7) Survival ≥ 6 months. 8) Laboratory results during screening: a) Count of Blood cells: white blood cell (WBC) count ≥ 3.0 x 10^9/L, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 90 g/L. b) Hepatic function tests: total bilirubin (TBIL) < 1.5 x upper limit of normal (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x ULN in subjects with non-liver metastases, < 5 x ULN in subjects with hepatic metastases. c) Renal function tests: serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 mL/min, and urinary protein < 2+ in routine urinalysis. For subjects with urinary protein ≥ 2+ at baseline in routine urinalysis, 24-hour urine should be collected and total protein content should be < 1 g. d) International normalized ratio (INR) ≤ 1.5, and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN within 7 days prior to study treatment. 9) Being compliant with study protocol. 10) Female subjects of childbearing age, and male subjects and their heterosexual partners agreeing to take effective contraceptive measures (such as abstinence, surgical sterilization, contraceptives, medroxyprogesterone injection, and contraceptive implants) during the study and 6 months after administration of the study drugs.

	Exclusion Criteria: Subjects meeting any one of the followings will not be enrolled: 1) History of systemic chemotherapy or targeted therapy (such as monoclonal antibody and tyrosine kinase inhibitors) for the current stage of disease (stage IIIB, stage IV, or recurrent disease unsuitable for multimodal therapy). Previous surgery and radiotherapy are accepted if meeting the corresponding therapy criteria in this protocol. Subjects with disease recurrence within 6 months of adjuvant therapy. 2) Mixed non-small cell and small cell cancer, or adenosquamous carcinoma predominantly containing squamous cell carcinoma component. 3) EGFR sensitive mutation type (including exon 18 point mutation (G719X), 19 exon deletion, and 21 exon point mutation (L858R and L816Q)) verified by histology or cytology. Subjects with unknown EGFR status for any reason are eligible. 4) History of hemoptysis (> 2.5 mL) within 3 months prior to screening. 5) Signs of great vessels invasion via imaging. Subjects with tumors that are adjacent to, have surrounded, or have invaded the lumens of great vessels (such as pulmonary artery or superior vena cava) determined by investigators or radiologists. 6) Subjects with symptomatic central nervous system (CNS) metastasis. Subjects with asymptomatic brain metastasis or with stable disease after brain metastasis treatment are eligible if all of the following criteria are met: measurable lesions other than CNS; no midbrain, pons, cerebellum, medulla oblongata, or spinal cord metastasis; no history of intracranial hemorrhage. 7) History of radical thoracic radiotherapy within 28 days prior to enrollment; history of palliative radiation for bone lesions other than in the thoracic region within 2 weeks prior to the first dose of study treatment. 8) Subjects with severe unhealed wound ulcers or fractures, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study. 9) History of minor surgery (outpatient or inpatient surgery requiring

	local anesthesia, including central line insertion) within 48 hours prior to the first dose of study treatment. 10) Current or recent (within 10 days prior to the first dose of study treatment) use of aspirin (> 325 mg/day) or other non-steroidal anti-inflammatory drugs known to inhibit platelet function for 10 consecutive days. 11) Current or recent (within 10 days prior to the first dose of study treatment) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for treatment for 10 consecutive days. However, anticoagulants for prophylaxis are accepted. 12) Subjects with inherited hemorrhage or coagulation disorders, or history of thrombosis. 13) Subjects with uncontrolled hypertension (systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg) despite treatment, or history of hypertensive crisis or hypertensive encephalopathy. 14) Subjects with any unstable systemic disease, including but not limited to active infections, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), congestive heart failure (≥ Class II by New York Heart Association (NYHA) Functional Classification), severe arrhythmia requiring medication, and hepatic, renal, or metabolic diseases. 15) History of the followings within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, or abdominal abscess. 16) Subjects with tracheoesophageal fistula. 17) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments). 18) Subjects with interstitial lung disease or active pneumonia shown on CT during screening. 19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma

	in situ, basal or squamous cell carcinoma, localized prostate cancer treated by radical srugery, ductal carcinoma in situ treated by radical srugery, and papillary thyroid carcinoma. 20) Subjects with active autoimmune disease. 21) Positive test result of hepatitis B surface antigen (HBsAg), and peripheral blood hepatitis B virus deoxyribonucleic acid (HBV DNA) titer ≥ 1 x 10^3 copies/L or ≥ 200 IU/mL. Subjects with positive test result of HBsAg but peripheral blood HBV DNA titer < 1 x 10^3 copies/L or < 200 IU/mL are eligible if the investigators determine that the hepatitis B is stable and dose not increase the risks in subjects. 22) Positive test results of hepatitis C virus antibody (HCV-Ab), human immunodeficiency virus antibody (HIV-Ab), or syphilis. 23) Subjects with known history of allergic diseases or allergic physique. 24) History of treatment with any other study drugs or participation in any other interventional studies within 30 days prior to screening. 25) History of alcohol or drug abuse. 26) Female subjects who are pregnant/lactating, or planning to be pregnant/lactating during the study. 27) Known allergies to bevacizumab or its any excipients, or any other chemotherapeutic agents. 28) Other situations determined by investigators that the subjects are ineligible for inclusion.

Investigational Drug, Dosage, and Route of Administration:	IBI305: 15 mg/kg in combination with chemotherapy and 7.5 mg/kg maintenance monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).
Control Drug, Dosage, and Route of Administration:	Bevacizumab: 15 mg/kg in combination with chemotherapy and 7.5 mg/kg maintenance monotherapy, administered via intravenous infusion on D1 of evey 3-week treatment cycle until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).
Chemotherapy:	Paclitaxel: 175 mg/m^2 administered via intravenous infusion on D1 of evey 3-week treatment cycle for up to 6 cycles until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, or death. Carboplatin: areas under the concentration-time curve (AUC) = 6.0, administered via infusion on D1 of evey 3-week treatment cycle for up to 6 cycles until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, or death.

Evaluation Criteria:

Efficacy Endpoints:

Primary Efficacy Endpoint:

- ORR

Secondary Efficacy Endpoints:

- DOR
- PFS
- DCR
- OS

Safety Endpoints:

- Vital signs
- Physical examination

- Laboratory tests (count of blood cells, blood chemistry, and routine urinalysis)
- 12-lead electrocardiography (ECG)
- Adverse event (AE, including treatment-emergent AE (TEAE)), AE of special interest (AESI) (hypertension, proteinuria, gastrointestinal perforation, hemorrhage (cerebral hemorrhage, hematuria, and upper gastrointestinal hemorrhage), cardiotoxicity, and thrombosis), and serious AE (SAE)
- Immunogenicity: positive rates of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)

PK/PD Endpoints:

- PPK (including steady-state trough concentrations after repeated doses)
- Changes of serum VEGF at different time points

Statistics:

Sample Size Calculation:

A sample size of 218 subjects for each group (426 subjects in total) will provide 80% power to confirm the clinical equivalence between IBI305 nd bevacizumab in combination with paclitaxel/carboplatin. Estimation parameters for sample size: significance level for two one-sided test = 0.05; ORR for subjects in both IBI305 and bevacizumab groups ≈ 50.0%; equivalence margins for ORR ratio = (0.75, 1/0.75). Based on the above estimations, a number of 218 subjects for each group is required (436 subjects in total).

Efficacy Analysis:

Clinical equivalence will be evaluated by comparing the 90% CIs of ORR ratio between IBI305 and bevacizumab with the equivalence margins of (0.75, 1/0.75). The ORRs and 95% CIs of two groups, ORR difference and 90% CI, and ORR ratio and 90% CI will be estimated by the generalized linear model (GLM, including groups and stratification factors).

The median survivals and survival curves will be estimated by the Kaplan-Meier method. The hazard ratios and 95% CI of two groups will be estimated by the Cox model. DORs and PFSs will be analyzed by the same method as the median survivals. DCRs will be analyzed by the same method as the primary efficacy endpoint without equivalence test.

Safety Analysis:

All AEs will be categorized by Medical Dictionary for Regulatory Activities (MedDRA) codes and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All TEAEs,

TEAEs ≥ grade 3, SAEs, drug-related TEAEs, drug-related SAEs, TEAEs resulting in the termination of study drugs, TEAEs resulting in the termination of study, and AESIs will be listed based on system organ class, preferred terms, and groups and summarized the numbers of corresponding subjects and percentages. Besides, the severity of TEAEs and relevance to the study drugs will also be summarized system organ class, preferred terms, and treatment groups.

Observed values and changes from baseline of vital signs, physical examinations, laboratory tests, and 12-lead ECGs will be analyzed with descriptive statistics. Baseline results and the worse results during the study will be presented using cross tabulation.

The numbers and percentages of subjects with ADAs and NAbs will be summarized according to groups.

PK/PD Exploratory Analysis: Primarily will use descriptive statistics, and inter-group comparisons will be performed if necessary.

Table 1. Study Schedule

Periods	Screening Period	Treatment Period (21 Days = 1 Treatment Cycle)							After Treatment		
		Combination Therapy						Maintenance Therapy	End of Treatment Visit (28 Days After the Last Dose)	Follow-Up for PD[a]	Follow-Up for Survival[b] (Every 12 Weeks After PD)
Cycles (C) and Days (D)	D-28 to D 1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	C7 to Termination of Treatment			
Time Window (Days)	-	-	± 3	± 3	± 3	± 3	± 3	± 3	± 7	-	± 7
Visits	1	2	3	4	5	6	7	8–N			
Informed Consent	x										
Inclusion and Exclusion Criteria	x	x									
Demographics	x										
Medical History (Including Smoking History)	x										
NSCLC Treatment History	x										
Vital Signs	x	x	x	x	x	x	x	x	x	x	
Height and Weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG PS Score	x										
Physical Examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Count of Blood Cells[d]	x	x	x	x	x	x	x	x	x		
Routine Coagulation Tests	x										
BloodChemistry[d]	x	x	x	x	x	x	x	x	x		

Periods	Screening Period	Treatment Period (21 Days = 1 Treatment Cycle)							After Treatment		
		Combination Therapy						Maintenance Therapy	End of Treatment Visit (28 Days After the Last Dose)	Follow-Up for PD[a]	Follow-Up for Survival[b] (Every 12 Weeks After PD)
Cycles (C) and Days (D)	D-28 to D 1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	C7 to Termination of Treatment			
Time Window (Days)	-	-	± 3	± 3	± 3	± 3	± 3	± 3	± 7	-	± 7
Visits	1	2	3	4	5	6	7	8–N			
Routine Urinalysis[d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy Test[f]	x								x		
Immunogenicity[g]		x			x				x		
HBV, HCV, HIV, and Syphilis Test	x										
Imaging Test (CT/MRI)[h]	x			x		x		x	x	x	
Tumor Sample Collection for EGFR Mutation Testing[i]	x										
Randomization		x									
Study Drug (IBI305/Bevacizumab)[j]		x	x	x	x	x	x	x			
Chemotherapy (Paclitaxel/Carboplatin)[k]		x	x	x	x	x	x				
Concomitant Medication	x	x	x	x	x	x	x	x	x		
AEs	x	x	x	x	x	x	x	x	x		
Subsequent Anti-Tumor Therapy									x	x	x
Follow-Up for Survival									x	x	x

Periods	Screening Period	Treatment Period (21 Days = 1 Treatment Cycle)							After Treatment		
		Combination Therapy						Maintenance Therapy	End of Treatment Visit (28 Days After the Last Dose)	Follow-Up for PD[a]	Follow-Up for Survival[b] (Every 12 Weeks After PD)
Cycles (C) and Days (D)	D-28 to D 1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	C7 to Termination of Treatment			
Time Window (Days)	-	-	± 3	± 3	± 3	± 3	± 3	± 3	± 7	-	± 7
Visits	1	2	3	4	5	6	7	8–N			
PK		x	x		x	x	x				
VEGF Test		x	x				x		x		

a. If the study drugs are discontinued for reasons other than PD, the **end of treatment visit** in study sites will be conducted in 28 days after the last dose of study drug, and tumor assessments should be conducted every 6 weeks (± 7 days) until PD (after which, follow-up for PD will be conducted), withdraw of informed consent, loss to follow-up, death, start of other anti-tumor therapies, or end of study.

b. For subjects with PD, survival information will be collected every 12 weeks (84 ± 7 days) by telephone follow-up until withdrawal of informed consent, loss to follow-up, death, or end of study. Subsequent anti-tumor therapies should be documented in the electronic case report forms (eCRFs).

c. Only weight is required.

d. Clinical laboratory tests will be conducted at the laboratories of each study site. If the laboratory tests (count of blood cells, blood chemistry, and routine urinalysis) are performed within 7 days prior to the first dose, the results will be used as the baseline data. During the visits after baseline, all laboratory tests should be completed within 3 days prior to administration.

e. Urinary protein should be tested prior to each dose of IBI305/bevacizumab.

f. Blood/urine pregnancy test will be performed in female subjects of childbearing age.

g. Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: within 1 hour prior to the first dose of the study drug (IBI305/bevacizumab) in C1, within 1 hour prior to the dose in C4, and at the **end of treatment visit**. Serum samples of positive ADAs should be further tested for NAbs. Samples will be analyzed at the designated central laboratory.

h. Imaging test (CT or MRI) of the head, chest, abdomen, and pelvic cavity should be completed at baseline. Retests are not required if the tests have been performed within 28 days prior to the first dose, unless the investigators suspect changes in tumor burden. Imaging tests should be performed every 6 weeks (± 7 days), and completed within 7 days prior to the scheduled visits until PD, withdrawal of informed consent, loss to follow-up, death, start of other anti-tumor therapies, or end of study. Subsequent imaging test method should be consistent with the baseline method, and the chest, abdomen, and pelvic cavity scans are required.

i. EGFR mutation testing will be performed in all subjects.

j. IBI305 or bevacizumab will be administered 15 mg/kg in combination with chemotherapy and 7.5 mg/kg maintenance monotherapy on D1 of evey 3-week treatment cycle until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first). After the completion of all assessments, the study drugs will be administered prior to chemotherapy. The first dose of study drugs should be administered within 24 hours after randomization.

k. Carboplatin + paclitaxel will be administered on D1 of evey 3-week treatment cycle for up to 6 cycles until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, or death. After the administration of study drugs, paclitaxel will be administered followed by carboplatin.

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1 Introduction

1.1 Background

1.1.1 Disease background

Lung cancer has the highest incidence and mortality globally among all cancers. According to the global cancer statistics released by the International Agency for Research on Cancer in 2012 (GLOBCAN 2012), among all new cancer cases, 1.8 million people were diagnosed with lung cancer (13%), where 58% occurred in underdeveloped areas[1]. According to the data released by National Central Cancer Registry of China in 2015, lung cancer was the most common malignant tumor in China in 2011, accounting for an estimated 650,000 new cases annually. Additionally, lung cancer is also the most frequent cause of cancer-related death, accounting for an estimated 520,000 deaths annually[2]. Lack of effective treatments of lung cancer is the main reason for poor prognosis. Thus, there is huge demand for new lung cancer drugs.

85-90% of lung cancer are non-small cell lung cancer (NSCLC), and most patients are diagnosed at an advanced stage[3]. According to the Chinese Guideline on the Diagnosis and Treatment of Primary Lung Cancer, anatomic pulmonary resection is the mainstay of treatment of early lung cancer[4]. However, some patients develop distant metastasis despite of surgery, ultimately leading to death[5]. For almost all clearly diagnosed stage IV, most stage IIIB, and some stage IIIA NSCLC that are inoperable[4], a multimodal therapy based on systemic therapy is often used to maximize the patient survival, control the progressive disease (PD), and improve the quality of life[6].

In recent years, anti-tumor therapies have entered a new era with the emergency of targeted drugs. Some have shown good efficacy in treatment of advanced NSCLC. These targeted drugs include monoclonal antibodies and tyrosine kinase inhibitors (TKIs), mostly targeting epidermal growth factor receptors (EGFRs) and vascular endothelial growth factor (VEGF), such as bevacizumab, cetuximab, gefitinib, erlotinib, and icotinib. Monoclonal antibodies have become the drugs of choice in various treatment guidelines due to the good targeting ability, low drug resistance, and good patient tolerability. Bevacizumab combination chemotherapy is a first-line therapy of NSCLC recommended by the National Comprehensive Cancer Network (NCCN)[7], Additionally, bevacizumab in combination with paclitaxel/carboplatin has also been approved as the first-line therapy of unresectable advanced, metastatic, or recurrent non-squamous NSCLC by China Food and Drug Administration (CFDA) on Jul. 9, 2015[6].

Compared with traditional chemotherapy that directly inhibits or kills tumor cells, anti-angiogenic drugs have the following unique advantages[8]:

- The targets are genetically stable vascular endothelial cells (VECs) rather than highly heterogeneous tumor cells, thus leading to lower drug resistance;
- The number of tumor-induced VECs is far less than that of tumor cells, and the efficacy is preferable targeting on VECs and their cytokines;

- Normal VECs are quiescent, whereas tumor VECs are active in proliferation. Anti-angiogenic therapy targets activated cells and avoids damage to normal VECs, thus leading to better targeting ability;
- Anti-angiogenic therapy can normalize the tumor vessels, reducing the pressure in tumor tissues. This enhances the delivery of chemotherapeutic agents into tumor tissues, thus increasing the efficacy.

Angiogenesis is a basic biological characteristic of tumors. The growth of both solid and hematologic tumors are depended on angiogenesis instead of the specific tumor cells Therefore, the anti-angiogenic therapy is broad-spectrum and applicable for various tumors.

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to human VEGF and inhibits its activity. Bevacizumab contains human framework regions and fragment antigen-binding of a humanized murine antibody that binds to VEGF, inhibiting the interaction of VEGF with its receptors, Flt-1 and KDR, on the surface of endothelial cells. By inactivating VEGF to prevent the angiogenesis, tumor growth is thereby inhibited[9].

In a study conducted by the Eastern Cooperative Oncology Group (ECOG), compared with chemotherapy alone (paclitaxel/carboplatin), bevacizumab in combination with paclitaxel/carboplatin significantly increased the overall survival (OS) (median: 12.3 vs. 10.3 months), progression-free survival (PFS) (median: 6.2 vs. 4.5 months), and overall response rate (35 % vs. 15%) in patients with advanced, metastatic, or recurrent non-squamous NSCLC[10]. In another foreign AVAiL study, different doses of bevacizumab (7 and 15 mg/kg) in combination with chemotherapy (cisplatin and gemcitabine) and placebo combine with chemotherapy were compared for the treatment of non-squamous NSCLC. The study found that the two bevacizumab groups had significantly increased PSF [median: 6.7 (7.5 mg/kg combination chemotherapy group) vs. 6.5 (15 mg/kg combination chemotherapy group) vs. 6.1 months (placebo combination chemotherapy group)] and overall response rate [37.8% (7.5 mg/kg combination chemotherapy group) vs. 34.6% (15 mg/kg combination chemotherapy group) vs. 21.6% (placebo combination chemotherapy group)] in patients with locally advanced, metastatic, or recurrent non-squamous NSCLC.[11]. In a BEYOND study conducted in China, compared with placebo in combination with paclitaxel/carboplatin, bevacizumab in combination with paclitaxel/carboplatin significantly increased the PFS (median: 9.2 vs. 6.5 months), OS (median: 24.3 vs. 17.7 months), and overall response rate (54% vs. 26%) in patients with advanced or recurrent non-squamous NSCLC.[12].

In China, the antibodies and fusion proteins targeting VEGF are research hotspots. However, since 2006, the clinical efficacies of various drugs has not been verified and no products have been launched to the market Due to the complexity of macromolecular drugs and limitation of drug development capability, advanced technologies in antibody development, production, and quality control is required to develop high-quality VEGF inhibitors that are safe and effective. IBI305 has showed high similarity to bevacizumab in various pharmaceutical and preclinical studies (refer to Investigator's Brochure [IB]). Besides, the efficacy and safety of bevacizumab for treatment of locally advanced, metastatic, or recurrent lung cancer have been verified. The relevant domestic and external pivotal clinical studies are referable for the protocol design of IBI305 clinical study. In summary, the clinical

study of IBI305 for treatment of NSCLC has a solid foundation and relatively low risks. The successful development of IBI305 indicates an additional first-line targeted drug for the lung cancer treatment in China, providing doctors and patients with more therapeutic options.

1.1.2 Investigational drug

1.1.2.1 Description

IBI305 is a recombinant humanized anti-VEGF monoclonal antibody injection developed byInnovent Biologics (Suzhou) Co., Ltd. (hereinafter referred to as the sponsor) that specifically binds to human VEGF. The molecular weight of IBI305 is 149 kDa. IBI305 specifically binds to VEGF-A, inhibits the interaction of VEGF-A to VEGF-R1 and VEGF-R2, blocks the signaling pathways such as PI3K-Akt/PKB and Ras-Raf-MEK-ERK. IBI305 also inhibits the growth, proliferation, and migration of VECs and angiogenesis, decreases the vascular permeability, blocks the blood supply to tumor tissues, inhibit the proliferation and metastasis of tumor cells, and induces the apoptosis of tumor cells, thereby generates anti-tumor effects. The main active ingredient is recombinant humanized anti-VEGF monoclonal antibody and excipients include sodium acetate, sorbitol, and polysorbate 80[13]. Refer to the Investigator's Brochure for the detailed structure and physicochemical properties of IBI305.

1.1.2.2 Preclinical studies

Pharmaceutical study

The pharmaceutical studies showed that the stability, primary structure, higher-order structure, oligosaccharide distribution, charge variants, and product-related impurities of IBI305 are highly similar to those of bevacizumab, and the process-related impurities meet the proposed specification. Therefore, IBI305 is considered to have highly similar protein properties and product quality to bevacizumab[13].

Pharmacodynamic study

In vitro and in vivo pharmacodynamic (PD) studies of IBI305 showed the following findings:

1) Target: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A with an affinity constant same as that of bevacizumab, indicating that IBI305 is a specific human VEGF blocker against the clear target.
2) Specificity: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A, medium-affinity binding to canine VEGF-A, but low-affinity binding to human VEGF-B, VEGF-C, VEGF-D, PIGF, suggesting that IBI305 recognizes specific targets and has low off-target toxicity risk; no obvious affinity to mouse VEGF-$A_{164}$and rat VEGF-A_{164}, suggesting that IBI305 has high species specificity.
3) Mechanism of action: IBI305 specifically binds to VEGF-A and inhibits the activation of VEGFR-2 and ERK1/2, blocks the proliferation and migration of HUVEC, and inhibits the sprouting from rat aortic ring, suggesting that IBI305 antagonizes VEGF-A-induced signaling pathway to block the proliferation and migration of VECs

and inhibit angiogenesis, which leads to the reduction of nutritional supply and metastasis of tumor.

4) Anti-tumor effects: IBI305 significantly inhibits the growth of human colon cancer LS174T and lung cancer NCI-H460 cells in xenograft nude mice, indicating that IBI305 has significant anti-tumor effects.

Results from in vitro and in vivo studies of IBI305 showed highly similarity with bevacizumab, demonstrating that the target, mechanism of action, and anti-tumor effects of IBI305 are highly similar to bevacizumab[13].

Pharmacokinetic studies

In vitro and in vivo pharmacokinetic (PK) studies of IBI305 showed the following findings:

1) IBI305 showed no cross-reactivity with normal human tissues and cynomolgus monkey tissues, and only cross-reacts with the positive-control, i.e. human angiosarcoma tissue, suggesting that IBI305 is highly specific to cancer tissues rather than normal human tissues and has very low on-target toxicity.
2) Linearity: With single dose or repeated doses of IBI305 (2–50 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed significant linear PK, thus reducing the suddenly rising toxicity risks with increased clinical doses.
3) Immunogenicity: With single dose and repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed abnormal changes of drug concentration-time curves in several animals. The anti-drug antibody (ADA) test results showed that IBI305 has a medium immunogenicity.
4) Accumulation: With repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed that 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 that the drug may be accumulated in body.

The results of tissue cross-reactivity and PK/toxicokinetic studies in cynomolgus monkeys indicated that IBI305 and bevacizumab have similar characteristics in tissue cross-reactivity and PK/toxicokinetics[13].

Toxicological study

Toxicological studies of IBI305 showed the follwing findings:

1) Single dose: With single dose of IBI305 (up to 300 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed good tolerability without any abnormal clinical symptoms and toxicity. The dose was about 48 times the proposed clinical dose for human based on body surface area. In the safety pharmacology test, with single-dose of IVI305 (50 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed no significant effects on the central nervous system (CNS), respiratory system, and cardiovascular system, suggesting that the single dose of

IBI305 via intravenous injection has a high safety.

2) Repeated doses:With repeated doses of IBI305 (up to 50 mg/kg) via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, equivalent to 20 times the proposed clinical dose for human (based on the weight), the test showed extremely mild to mild linear growth arrest of metaphyseal lines at knee joint and disordered chondrocyte proliferation, extremely mild increase in macrophage count in white pulp of spleen, pulmonary (including bronchial) hemorrhage, and deposits of hemosiderin in lymphoid tissue of bronchial mucosa, indicating that the target organ toxicities were mainly in the bone, spleen, and lungs.
3) Immunotoxicity and immunogenicity: With repeated doses of IBI305 via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, the tests showed medium immunotoxicity to the spleen. Different doses of IBI305 may result in the production of ADAs, a portion of which are neutralizing antibodies (NAbs), indicating that IBI305 has medium immunotoxicity and immunogenicity.
4) Local irritation test: With repeated doses of IBI305 via intravenous injection in cynomolgus monkeys, the test showed no irritation at the injection site, suggesting that administration of IBI305 via intravenous injection is safe and feasible.
5) In vitro hemolysis assay: With maximum proposed clinical concentration of IBI305 (9 mg/mL), the assay showed no hemolysis, suggesting that IBI305 is suitable for intravenous injection.

IBI305 has high similarity with bevacizumab in safety pharmacology, long-term toxicity, immunotoxicity, immunogenicity, local irritation, and hemolysis[13].

1.2 Study Principles and Risk/Benefit Assessment

1.2.1 Study principlesand dose selection

Biosimilars refer to therapeutic biological products which are similar to approved reference drugs in terms of quality, safety, and efficacy[14]. IBI305, developed and sold in the market by the sponsor, is a bevacizumab biosimilar, and has the same administration method and indications as bevacizumab.

This study is conducted in accordance with the "Guidelines on Development and Evaluation of Biosimilars (for Trial Implementation)" by China Food and Drug Administration[14]. The doses of IBI305 selected in this study are based the preclinical studies that showed high similarity between IBI305 and bevacizumab in pharmacology, PD, PK, and toxicology (refer to the Investigator's Brochure for details). Besides, the efficacy and safety of bevacizumab for treatment of advanced, metastatic, or recurrent non-squamous NSCLC have been verified, and the indications have also been approved in China. Therefore, the doses and administration method of IBI305 in this study is the same as those of bevacizumab, i.e. 15 mg/kg in combination with chemotherapy(paclitaxel/carboplatin) and 7.5 mg/kg maintenance monotherapy, both administered via intravenous infusion on D1 of evey 3-week treatment cycle. This study is designed to further verify that IBI305 and bevacizumab have similar clinical efficacy, safety, and immunogenicity in patients with

advanced, metastatic, or recurrent non-squamous NSCLC.

1.2.2 **Risk/benefit assessment**

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

The treatment-related risks of bevacizumab are detailed in its prescribing information. This study is the first human study of IBI305 that unexpected adverse reactions will be possible. The design of this study ensures the minimized subject risks by close monitoring of the adverse events (AEs) before, during, and after the infusion of study drugs. Once an adverse reaction occurs, the investigator will immediately take appropriate action for the subject safety.

The platinum-based therapy is the standard first-line therapy of advanced NSCLC[4]. This study uses the combination of paclitaxel/carboplatin, ensuring the basic anti-tumor therapy for subjects.

2 Study Objectives

2.1 Primary Objective

To compare the objective response rate (ORR) in subjects with advanced or recurrent non-squamous NSCLC treated by IBI305 and bevacizumab in combination with paclitaxel/carboplatin

2.2 Secondary Objectives

The secondary objectives include:

- To compare the duration of response (DOR), PFS, disease control rate (DCR), and OS in subjects with advanced or recurrent non-squamous NSCLC treated by IBI305 and bevacizumab in combination with paclitaxel/carboplatin
- To compare the safety and immunogenicity of IBI305 and bevacizumab in combination with paclitaxel/carboplatin for treatment of advanced or recurrent non-squamous NSCLC

2.3 Exploratory Objectives:

- To compare the population pharmacokinetics (PPK) of IBI305 and bevacizumab in subjects with advanced or recurrent non-squamous NSCLC
- To compare the PD of IBI305 and bevacizumab in subjects with advanced or recurrent non-squamous NSCLC

3 Study Design

3.1 Study Design Overview

This is a multicenter, randomized, double-blind, parallel-controlled, and phase III study. A total of 436 subjects across 35 study sites with non-squamous NSCLC will be enrolled, randomized in a ratio of 1:1 to either IBI305 in combination with paclitaxel/carboplatin group or bevacizumab in combination with paclitaxel/carboplatin group, and stratified according to age (<60 vs. ≥60 years old) and epidermal growth factor receptor (EGFR) status (wild type vs. unknown). Each treatment cycle will be 3 weeks for both experimental groups. On D1 of each treatment cycle, subjects will be administered 15 mg/kg of either IBI305 or bevacizumab in combination with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, or death (whichever comes first), after which subjects will discontinue paclitaxel/carboplatin and continue with either IBI305 or bevacizumab as maintenance monotherapy. The maintenance monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

After the study drugs are discontinued, the **end of treatment visit** in study sites will be conducted in 28 days (± 7 days) after the last dose of study drug. If the subjects discontinue the study treatment for reasons other than PD, subsequent follow-up will be continued until PD, withdrawal of informed consent, loss to follow-up, death, start of other anti-tumor therapies, or end of study. If the subjects discontinue the study treatment for PD, the investigators will make telephone follow-up every 12 weeks (± 7 days) to collect the information of subsequent anti-tumor therapies and survival.

A CT or an MRI will be performed every 6 weeks (± 7 days) until PD, withdrawal of informed consent, loss to follow-up, death, start of other anti-tumor therapies, or end of study. Subsequent imaging test method should be consistent with the baseline method, and the chest, abdomen, and pelvic cavity scans are required. Each test should be completed within 7 days prior to the last visit, and assessed by the investigators based on RECIST version 1.1 criteria to determine whether the subject should continue with the next round of treatment. An independent tumor review committee (Section 11.1.1) will also assess the tumor response according to RECIST version 1.1.If the subjects discontinue the study treatment for reasons other than PD, subsequent tumor assessments will be continued according to the study procedure until PD, withdrawal of informed consent, loss to follow-up, death, start of other anti-tumor therapies, or end of study.

Refer to Figure 1 for study design.

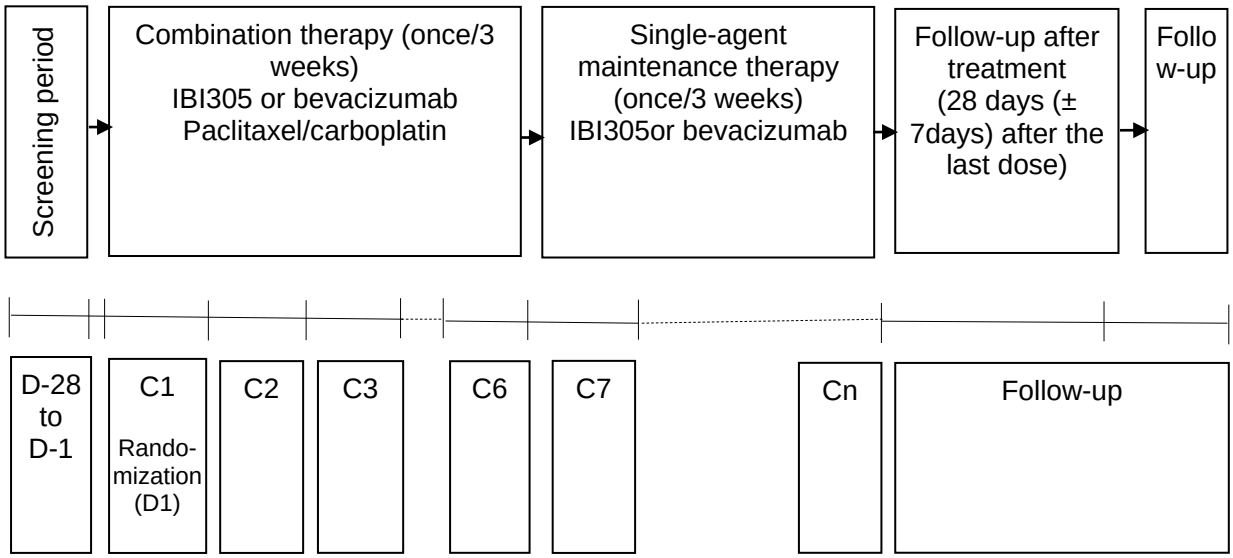

Figure 1. Study Design Schematic

3.2 Study Design Discussion

This is a randomized and double-blind study, which avoids the selection bias, and the tumor assessments will be performed according to the CT/MRI imaging based on RECIST version 1.1 to ensure the consistency of assessments.

4 Study Population

4.1 Inclusion Criteria

Subjects meeting all the following criteria will be enrolled:

1) Signing the informed consent form.
2) Males or females ≥ 18 and ≤ 75 years old.
3) Inoperable, locally advanced (stage IIIB), metastatic (stage IV), or recurrent non-squamous NSCLC verified by histology or cytology (mixed tumors should be classified according to the predominant cell type).
4) EGFR wild type or non-sensitive mutation type verified by histology or cytology.
5) At least one measurable lesion as the target lesion (based on RECIST version 1.1 criteria).
6) ECOG PS 0 or 1.
7) Survival ≥ 6 months.
8) Laboratory results during screening:
    a) Count of blood cells: white blood cell (WBC) count ≥ 3.0 x 10^9/L, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 90 g/L.
    b) Hepatic function tests: total bilirubin (TBIL) < 1.5 x upper limit of normal (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x ULN in subjects with non-liver metastases, < 5 x ULN in subjects with hepatic metastases.
    c) Renal function tests: serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 mL/min, and urinary protein < 2+ in routine urinalysis. For subjects with urinary protein ≥ 2+ at baseline in routine urinalysis, 24-hour urine should be collected and total protein content should be < 1 g.
    d) International normalized ratio (INR) ≤ 1.5, and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN within 7 days prior to study treatment.
9) Being compliant with study protocol.
10) Female subjects of childbearing age, and male subjects and their heterosexual partners agreeing to take effective contraceptive measures (such as abstinence, surgical sterilization, contraceptives, medroxyprogesterone injection, and contraceptive implants) during the study and 6 months after administration of the study drugs.

4.2 Exclusion Criteria

Subjects meeting any one of the followings will not be enrolled:

1) History of systemic chemotherapy or targeted therapy (such as monoclonal antibody and tyrosine kinase inhibitors) for the current stage of disease (stage IIIB, stage IV, or recurrent disease unsuitable for multimodal therapy). Previous surgery and radiotherapy are accepted if meeting the corresponding therapy criteria in this protocol. Subjects with disease recurrence within 6 months of adjuvant therapy.
2) Mixed non-small cell and small cell cancer, or adenosquamous carcinoma predominantly containing squamous cell carcinoma component.
3) EGFR sensitive mutation type (including exon 18 point mutation (G719X), 19 exon deletion, and 21 exon point mutation (L858R and L816Q)) verified by histology or cytology. Subjects with unknown EGFR status for any reason are eligible.
4) History of hemoptysis (> 2.5 mL) within 3 months prior to screening.
5) Signs of great vessels invasion via imaging. Subjects with tumors that are adjacent to, have surrounded, or have invaded the lumens of great vessels (such as pulmonary artery or superior vena cava) determined by investigators or radiologists.
6) Symptomatic CNS metastasis. Subjects with asymptomatic brain metastasis or with stable disease after brain metastasis treatment are eligible if all of the following criteria are met: measurable lesions other than CNS; no midbrain, pons, cerebellum, medulla oblongata, or spinal cord metastasis; no history of intracranial hemorrhage.
7) History of radical thoracic radiotherapy within 28 days prior to enrollment; history of palliative radiation for bone lesions other than in the thoracic region within 2 weeks prior to the first dose of study treatment.
8) Subjects with severe unhealed wound ulcers or fractures, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study.
9) History of minor surgery (outpatient or inpatient surgery requiring local anesthesia, including central line insertion) within 48 hours prior to the first dose of study treatment.
10) Current or recent (within 10 days prior to the first dose of study treatment) use of aspirin (> 325 mg/day) or other non-steroidal anti-inflammatory drugs known to inhibit platelet function for 10 consecutive days.
11) Current or recent (within 10 days prior to the first dose of study treatment) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for treatment for 10 consecutive days. However, anticoagulants for prophylaxis are accepted.

12) Subjects with inherited hemorrhage or coagulation disorders, or history of thrombosis.

13) Subjects with uncontrolled hypertension (systolic blood pressure (BP) > 140 mmHg and/or diastolic BP > 90 mmHg) despite treatment, or history of hypertensive crisis or hypertensive encephalopathy.

14) Subjects with any unstable systemic disease, including but not limited to active infections, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), congestive heart failure (≥ Class II by New York Heart Association (NYHA) Functional Classification), severe arrhythmia requiring medication, and hepatic, renal, or metabolic diseases.

15) History of the followings within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, or abdominal abscess.

16) Subjects with tracheoesophageal fistula.

17) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments).

18) Subjects with interstitial lung disease or active pneumonia shown on CT during screening.

19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell carcinoma, localized prostate cancer treated by radical srugery, ductal carcinoma in situ treated by radical srugery, and papillary thyroid carcinoma.

20) Subjects with active autoimmune disease.

21) Positive test result of hepatitis B surface antigen (HBsAg), and peripheral blood hepatitis B virus deoxyribonucleic acid (HBV -DNA) titer ≥ 1×10^3 copies/L or ≥ 200 IU/mL. Subjects with positive test result of HBsAg but peripheral blood HBV DNA titer < 1×10^3 copies/L or < 200 IU/mL are eligible if the investigators determine that the hepatitis B is stable and does not increase the risks in subjects.

22) Positive test results of hepatitis C virus antibody (HCV-Ab), human immunodeficiency virus antibody (HIV-Ab), or syphilis.

23) Subjects with known history of allergic diseases or allergic physique.

24) History of treatment with any other study drugs or participation in any other interventional studies within 30 days prior to screening.

25) History of alcohol or drug abuse.

26) Female subjects who are pregnant/lactating, or planning to be pregnant/lactating during the study.

27) Known allergies to bevacizumab or its any excipients, or any other chemotherapeutic agents.

28) Other situations determined by investigators that the subjects are ineligible for inclusion.

4.3 Screening Failure

Screening failure is that the subject who have signed the informed consent form fails to meet the inclusion criteria. Subjects with screening failure will not get a randomization number. The reasons of screening failure will be documented in the electronic case report forms (eCRFs).

4.4 Subject Restrictions

Female subjects of childbearing age must take effective contraceptive measures during the study and 6 months after the last dose.

Male subjects must take effective contraceptive measures during the study and 6 months after the last dose to avoid the pregnancy of their partners.

Refer to Section 5.9 for drug restrictions during the study.

4.5 Withdrawal and Replacement

All subjects may withdraw from the study at any study stage, regardless of whether a reason is provided. Withdrawing subjects will not be discriminated or retaliated against, and their medical treatment will not be affected.

Subjects will discontinue study treatment or withdraw from the study in the following circumstances:

- Intolerable toxicity
- PD
- Withdrawal determined by the investigators. If an intolerable AE occurs and the investigator determines the withdrawal of subject, the investigator should discontinue the study treatment, take corresponding measures, and report to the sponsor or its designated personnel.
- Withdrawal of informed consent
- Serious protocol deviation determined by the investigators and/or sponsor
- Poor protocol compliance
- Discontinuation for any reason by the investigator or sponsor
- Enrollment mistakes* (subjects who are enrolled with screening failure)

- Use of prohibited concomitant medication or other medication determined by the investigator that may result in toxicity or affect the study results
- Loss to follow-up
- Death

* If the subject is determined by the investigator and the sponsor's doctor to be medically suitable to continue with the study drugs without any risk or inconvenience, the mistakenly enrolled or randomized subject will continue with the study treatment and assessments.

In any cases, the reasons for withdrawal must be documented in the eCRFs. If the subject withdraws from the study prematurely for any reason, the investigator should make every effort to persuade the subject to receive the corresponding assessments, and continue the follow-up of all unresolved AEs based on the AE reports and follow-up requirements (Table 8):

- If the subject withdraws during the study, the series of assessments listed under the End of Treatment Visit (Section 6.9) should be performed;
- If the subject withdraws after the **end of treatment visit** and has not experienced PD, the series of assessments listed under the Follow-Up for PD (Section 6.10) should be performed (the tumor assessment is not required to be repeated if it has been performed within 6 weeks prior to this follow-up);
- If the subject withdraws during the follow-up for survival, the information of subsequent anti-tumor therapies and survival should be collected by telephone follow-up only.

The subject who withdraws the informed consent form should not be contacted unless the subject have clearly indicated the willingness to be contacted. The sponsor may use the clinical study data obtained before the withdrawal of informed consent.

Subjects who are randomized will not be replaced.

5 Study Treatment

5.1 Therapies by Study Drugs

The study drugs of this study are IBI305 and bevacizumab.

IBI305 or bevacizumab will be administered 15 mg/kg in combination with chemotherapy and 7.5 mg/kg maintenance monotherapy, administered via intravenous infusion on D1 of evey 3-week treatment cycle until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

The first dose of IBI305 or bevacizumab should be infused for 90 minutes (±15 minutes). If the subject is well-tolerated to the first infusion, the second dose will be infused in 60 minutes (±15 minutes). If the subject is well-tolerated to the 60-minute infusion, the subsequent infusions will be completed in 30 minutes (± 15 minutes).

5.2 Chemotherapy

After the administration of IBI305 or bevacizumab, paclitaxel will be administered followed by carboplatin:

Paclitaxel: 175 mg/m^2 administered via intravenous infusion for 3 hours (or adjusted according to the clinical practice of each study site) on D1 of evey 3-week treatment cycle for up to 6 cycles until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, or death.

Carboplatin: areas under the concentration-time curve (AUC) = 6.0, administered via infusion for a time adjusted according to the clinical practice of each study site on D1 of evey 3-week treatment cycle for up to 6 cycles until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, or death.

The chemotherapeutic agents are supplied by the sponsor.

Refer to Section 13.2 for formulations of body surface area, creatinine clearance, and carboplatin dose.

5.3 Dose Adjustments

5.3.1 General principles

- The reasons for dose adjustments or delayed administration, measures taken, and results should be documented in the medical records and eCRFs.
- If the concomitant symptoms exist at baseline, the investigators will determine whether the dose should be adjusted according to the change in severity of toxicity. For example, if the subject has grade 1 weakness at baseline, which is classified as grade 2 during the study treatment, the dose should be adjusted based on grade 1 toxicity since the severity increased by one grade.
- If several toxicity of different grades or severity occur simultaneously, the dose adjustment should be based on the highest grade.

- If a dose adjustment is required solely due to abnormal lab test results, the dose should be adjusted based on the measured values obtained prior to each treatment cycle.
- If the investigator determines that there is less potential for the toxicity to develop into a severe or life-threatening event, the current dose will be continued without any adjustments or treatment interruptions. In addition, dose adjustments or treatment interruptions will not be performed for non-hemolytic anemia as the symptoms can be alleviated through blood transfusions.
- If the investigator determines that a toxicity is caused by a specific therapeutic drug, the dose adjustments of other drugs are not required.
- Discontinuation of one or two therapeutic drugs before PD will not affect the subsequent therapies by the other drugs.
- Dose reductions or adjustments of IBI305 or bevacizumab are not permitted. Subsequent therapeutic dose will not be adjusted with weight, unless the subject weight variation is ≥ 10% from the baseline.
- Once the dose of any chemotherapeutic agents is reduced, the original dose should no longer be adopted.
- If any but not all of the therapeutic drug (IBI305, bevacizumab, chemotherapeutic agents) treatments is interrupted for toxicity, the treatment will be considered as a cycle.
- If the administration of any one of the chemotherapeutic agents is delayed for more than 3 weeks, the subject should permanently discontinue that drug.
- If IBI305/bevacizumab is continued/infused after a delay for more than 3 weeks, the investigators must discuss with the sponsor.

5.3.2 **Dose adjustments of study drugs**

Dose adjustments of IBI305 or bevacizumab are not permitted except for the adjustments stipulated in the study protocol (adjusted to 7.5 mg/kg during maintenance monotherapy).The dose of IBI305 or bevacizumab is calculated according to the subject weight at baseline (prior to the first dose), and remains unchanged during the study, unless the subject weight variation is ≥ 10% from the baseline.

If an infusion reaction occurs during a 60-minute infusion, the infusion time should be extended to 90 minutes for all subsequent infusions. Likewise, if an infusion reaction occurs during a 30-minute infusion, the infusion time should be extended to 60 minutes for all subsequent infusions.

IBI305 or bevacizumab in combination with paclitaxel/carboplatin will be administered every 3 weeks for 6 cycles. If the subject does not experience PD, either IBI305 or bevacizumab as maintenance monotherapy will be continued every 3 weeks until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

If IBI305 or bevacizumab is permanently discontinued due to intolerable toxicity or subject refusal to continue the study drugs during combination therapy, the subject will continue to the chemotherapy (paclitaxel/carboplatin) until 6 treatment cycles are completed as determined by the investigator. If any of the chemotherapeutic agents (paclitaxel or carboplatin) is prematurely discontinued due to intolerable toxicity, IBI305 or bevacizumab can be continued until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, or death (whichever comes first).

When a grade 3 or 4 IBI305- or bevacizumab-related toxicity occurs, the investigators should determine whether IBI305 or bevacizumab will be continued according to the followings:

First occurrence:

- IBI305 or bevacizumab administration should be interrupted until the symptoms return to baseline levels or at least are reduced to ≤ Common Terminology Criteria for Adverse Events (CTCAE) grade 1 (except for special circumstances listed below).

  Note that when grade 4 febrile neutropenia and/or thrombocytopenia occur(s), IBI305 or bevacizumab administration should be interrupted until the symptoms return to baseline levels or at least are reduced to ≤ CTCAE grade 1, since these events increase the risk of hemorrhage.

Re-occurrence in re-administration:

- If grade 3 IBI305- or bevacizumab-related toxicity occurs again, the investigators should assess the subject risks/benefits of study treatment continuation. If the toxicity re-occurs again upon the re-administration, IBI305 or bevacizumab should be permanently discontinued
- If grade 4 IBI305- or bevacizumab-related toxicity occurs again, IBI305 or bevacizumab should be permanently discontinued.

Measures should be taken in the following special circumstances (classified based on CTCAE version 4.03):

Hemorrhage

- Subjects with grade 3 or 4 hemorrhages should be treated accordingly and permanently discontinue the study treatment.
- Thrombosis/embolism
  - Subjects with arterial thrombosis of any severity grades should permanently discontinue the study treatment.
  - Subjects with grade 4 venous thrombosis should permanently discontinue the study treatment.
  - Subjects with grade 3 venous thrombosis should interrupt the study treatment. If therapeutic dose of anticoagulant therapy will last for < 2 weeks, the study

treatment should be interrupted until the anticoagulant treatment is completed. If therapeutic dose of anticoagulant therapy will last for > 2 weeks, IBI305 or bevacizumab administration should be for 2 weeks, and the study treatment can be restarted during anticoagulant therapy if the following criteria are met:

- INR is within the target range (usually 2–3) prior to restarting the study treatment.
- Subject must not have experienced grade 3 or 4 hemorrhage since enrollment.
- No signs of great vessel invasion or adjacency to great vessels from previous tumor assessments.

Note: Therapeutic dose of anticoagulant therapy is defined as the escalating dose of warfarin or other anticoagulants until INR is maintained at least 1.5 (usually 2–3). The warfarin dose should be documented in the eCRF. INR should be monitored during the anticoagulant therapy.

Hypertension

BP should be measured frequently to monitor the occurrence and exacerbation of hypertension. Subjects should remain at resting position for at least 5 minutes before BP measurement.

Definition of hypertension: pathologically increased BP with repeated measurements persistently over 140/90 mmHg.

Table 2. Hypertension severity grades and interventions in CTCAE version 4.03

CTCAE		Interventions
Grade 1	Prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg)	Intervention not indicated
Grade 2	Stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg); recurrent or persistent (≥ 24 hours), symptomatic increase by > 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits (WNL);	Antihypertensive monotherapy; drug interruption; continuation of study treatment once BP falls below 140/90 mmHg indicated.
Grade 3	Stage 2 hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg)	Multiple-agent antihypertensive therapy; study treatment interruption for persistent or symptomatic hypertension; permanent study treatment discontinuation for uncontrollable hypertension indicated.
Grade 4	Life-threatening consequences (e.g.	Urgent intervention and

	malignant hypertension, transient or permanent neurological deficit, and hypertensive crisis)	permanent study treatment discontinuation indicated

The dose of antihypertensive agents should be documented during each visit. If the subject remains hypertensive despite treatment discontinuation, BP and antihypertensive drug used should be monitored every 3 months until BP returns to normal or end of study.

Posterior reversible encephalopathy syndrome (PRES)

There have been a few reports of subjects with signs and symptoms consistent with PRES after study treatment. This is a rare neurological disease. Signs and symptoms include epilepsy, headache, altered mental status, visual impairment, or cortical blindness, with or without hypertension. Subjects with PRES should permanently discontinue the study treatment.

Proteinuria

Routine urinalysis should be performed prior to each dose of IBI305/bevacizumab unless 24-hour urinary protein test has already been done.

First occurrence of proteinuria:

Routine urinalysis should be performed if urinary protein:

- < 2+: continue study treatment as scheduled, no additional tests indicated.
- ≥ 2+ (routine urinalysis): perform 24-hour urinary protein test within 3 days prior to administration:
  - 24-hour urinary protein ≤ 2 g: continue study treatment as scheduled and perform routine urinalysis before each scheduled dose.
  - 24-hour urinary protein > 2 g: delay study treatment until 24-hour urinary protein ≤ 2 g and perform 24-hour urinary protein test prior to each subsequent dose until urinary protein ≤ 1 g/24 hours. Interrupt study treatment only when 24-hour urinary protein > 2 g.

Second and subsequent occurrence of proteinuria:

- < 3+ (routine urinalysis): continue study treatment as scheduled, no additional tests indicated.
- ≥ 3+ (routine urinalysis): perform 24-hour urinary protein test within 3 days prior to administration:
  - 24-hour urinary protein ≤ 2 g: continue study treatment as scheduled.
  - 24-hour urinary protein > 2 g: delay study treatment until 24-hour urinary protein ≤ 2 g and perform 24-hour urinary protein test prior to each subsequent dose until urinary protein ≤ 1 g/24 hours. Interrupt study treatment only when 24-hour urinary protein > 2 g.

- Nephrotic syndrome (Grade 4): permanently discontinue the study treatment.

Gastrointestinal perforation

If gastrointestinal perforation occurs, appropriate measures should be taken and the study treatment should be permanently discontinued.

Wound healing complications

Study treatment should not begin within 28 days of a major surgery, or before the surgical wound has fully healed. If a complication of wound healing occurs during study treatment, the study treatment should be interrupted until the wound has fully healed. If an elective surgery is required, the study treatment should be interrupted.

Abdominal abscess or fistula

If abdominal abscess or fistula occurs, the study treatment should be discontinued. However, the investigator will determine whether study treatment will be continued if the above AE is resolved.

Infusion-related and allergic reactions:

Infusion-related reactions after the first dose of the study drug is uncommon (< 3%), and the incidence of a severe reaction is only around 0.2%.

If a mild (grade 1 or 2) reaction (such as fever, chills, headache, and nausea) occurs, pretreatment prior to subsequent administration should be performed and infusion time should not be reduced. If the subject is well-tolerated during infusion after pretreatment, the infusion time can be reduced by 30 minutes (+ 10 minutes) for subsequent administration with pretreatment. If an infusion-related AE occurs during a 60-minute infusion, the subsequent infusion should be completed within 90 minutes (+ 15 minutes) with pretreatment. Likewise, if an infusion-related AE occurs during a 30-minute infusion, the subsequent infusion should be completed in 60 minutes (+ 10 minutes) with pretreatment. If a subject has a grade 3 infusion-related reaction, the study treatment should be interrupted and not be restarted on the same day. However, since there lacks the dose adjustment method for grade 3 infusion-related reactions, the investigators will decide to either discontinue the study drug or perform pretreatment, and complete the infusion within 90 minutes (+ 15 minutes). If an adverse reaction still occurs during a 90-minute infusion, the infusion should be continued slowing down and then gradually returned to a 90-minute infusion. If the investigator is uncertain about the handling, the study treatment should be discontinued. When the study treatment is restarted, the subject should be closely monitored based on routine clinical practice until the possible time of adverse reaction has passed. If a subject has a grade 4 infusion-related reaction, the study treatment should be discontinued.

An allergic reaction is defined as the vascular collapse or shock (systolic BP < 90 mmHg, unresponsive to rehydration) that occurs within 30 minutes of a study drug infusion caused by an allergy, with or without respiratory distress. Skin reactions include pruritus, urticaria, and angioedema. Subjects with allergic reactions should discontinue the study treatment.

5.3.3 **Dose adjustments of chemotherapy**

Paclitaxel and carboplatin should be administered according to the study site guidelines and local prescribing information. For the specific information for use, preparation, and storage of paclitaxel and carboplatin, refer to the prescribing information and local dosing information. Carboplatin-based chemotherapies have a relatively high incidence of emesis. Therefore, antiemetics for prophylaxis can be used.

Hematological toxicity:

ANC (reduce dose only when febrile neutropenia occurs. ANC must be ≥ 1.5 x 10^9/L and platelet count must be ≥ 100 x 10^9/L on D1 of each treatment cycle). Once the chemotherapeuti dose is reduced due to febrile neutropenia or thrombocytopenia (platelet count < 25 x 10^9/L or 50 x 10^9/L with hemorrhage or blood transfusion required), the original dose should no longer be adopted. If the dose reduction is required for the third time, the chemotherapy should be immediately discontinued.

Table 3. Dose Adjustments of Paclitaxel/Carboplatin (Febrile Neutropenia and Thrombocytopenia)

	Dose Adjustments of Paclitaxel/Carboplatin		
	First Occurrence	Re-Occurrence After Dose Adjustment	Re-occurrence After Two Dose Adjustments
Febrile Neutropenia (Regardless of Duration)	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5	Paclitaxel = 100 mg/m^2 Carboplatin = AUC 3	Chemotherapy discontinuation
Lowest Level After Last Dose < 25 x 10^9/L or < 50 x 10^9/L with hemorrhage or blood transfusion required	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5	Paclitaxel = 100 mg/m^2 Carboplatin = AUC 3	Chemotherapy discontinuation

If the dose adjustment is required when ANC and thrombocytopenia occur concurrently, the low-dose chemotherapy should be adopted.

Chemotherapy may be delayed for up to 3 weeks. If after the chemotherapy has been delayed for 3 weeks, ANC does not reach ≥ 1.5 x 10^9/L and platelet count does not reach ≥ 100 x 10^9/L on D1 of the scheduled chemotherapy, the chemotherapy should be permanently discontinued. If the above values have been reached, the next course of chemotherapy should be continued.

The investigator should monitor the subject closely for toxicity with particular attention to early and evident signs of myelosuppression, infection, or febrile neutropenia to timely and

appropriately treat the complications.

Subjects should be informed to pay attention to these signs and receive treatment as soon as possible.

If the chemotherapy must be interrupted due to hematological toxicity, the complete blood count should be performed regularly (including WBC differentials) until all the counts reach the minimum requirements for treatment continuation. Thereafter the scheduled treatment plan will be performed.

Dose adjustments are not required for anemia. However, treatment based on guidelines of each clinic should be performed.

Gastrointestinal toxicity

Antiemetics will be used to control nausea and/or emesis. If grade 3 or 4 nausea and/or emesis occur(s) despite of antiemetics, the chemotherapeutic dose should be reduced by 20% for the next treatment cycle. The dose should be returned to the initial level as possible if the subject is tolerated.

If the subject experiences stomatitis on D1 of any treatment cycle, the chemotherapy should be interrupted until the symptoms resolve. If the stomatitis has not resolved after 3 weeks, the chemotherapy should be permanently discontinued (refer to CTCAE version 4.03). If an acute Grade 3 stomatitis occurs, the chemotherapeutic dose should be reduced to 75% of the proposed dose when symptoms resolve.

Hepatotoxicity (Paclitaxel)

The paclitaxel dose should be determined based on the lab values measured on D1 of each treatment cycle.

Table 4. Paclitaxel dose adjustments (hepatotoxicity)

AST		TBIL	Paclitaxel Dose
≤ 5 x UNL	and	WNL	175 mg/m^2
> 5 x UNL	or	> UNL 1.5 x UN	150 mg/m^2
		> 1.5 x UN	0

If paclitaxel interrupted due to hepatotoxicity, carboplatin should also be interrupted until paclitaxel is restarted. Paclitaxel will be interrupted for up to 3 weeks. If the subject's hepatic function does not return to the acceptable ranges in 3 weeks, paclitaxel should be permanently discontinued. The carboplatin dose will not be adjusted when hepatotoxicity occurs.

The investigators should avoid PD due to abnormal hepatic enzyme levels as possible. If PD occurs, all the study drugs should be permanently discontinued, including chemotherapy.

Cardiovascular toxicity (paclitaxel)

The arrhythmia in subjects was infrequent in previous clinical studies. However, most subjects were asymptomatic and electrocardiographic monitoring is not required. Transient asymptomatic bradycardia was observed in 29% of subjects, but significant atrioventricular block was rare. Cardiac events should be treated as the followings:

- Transient asymptomatic bradycardia: no intervention indicated.
- Symptomatic arrhythmia during infusion: stop paclitaxel infusion and perform routine treatment of arrhythmia. Discontinue subsequent paclitaxel treatment. Document this AE in the AE Report Form of eCRF.
- Chest pain and/or symptomatic hypotension (< 90/60 mmHg or rehydration therapy required): discontinue the paclitaxel infusion. Perform electrocardiography (ECG). If hypersensitivity reaction is suspected, administer diphenhydramine and dexamethasone via intravenous infusion. If the chest pain is not considered as cardiogenic, epinephrine or bronchodilators will be administered. Document this AE in the AE Report Form of eCRF. Discontinue subsequent paclitaxel treatment and provide symptomatic treatment. Consult a cardiologist if needed.

Neurotoxicity (paclitaxel)

The dose of paclitaxel should be adjusted according to Table 5 when neuropathy occurs. The dose adjustment of carboplatin is not needed when neurotoxicity occurs.

Table 5. Paclitaxel dose adjustments (neurotoxicity)

Toxicity Grade (CTCAE version 4.03)	Paclitaxel Dose Adjustments
Grade 1 or Below	175 mg/m^2
2	Interrupt treatment until return to grade 1, then reduce dose to 140 mg/m^2 (20% of reduction) and restart infusion.
Grade 3 or Above	Interrupt treatment until return to grade 1, then reduce dose to 125 mg/m^2 (30% of reduction) and restart infusion.

Once the dose is reduced due to neurotoxicity, the original dose should no longer be adopted. If the neurotoxicity does not return to grade 1 after paclitaxel interruption for 3 weeks, paclitaxel should be permanently discontinued.

Allergic reactions/hypersensitivity reactions (paclitaxel)

Note: Prophylaxis for hypersensitivity reactions (see below) and close monitoring of vital signs are recommended for subjects with history of mild to moderate hypersensitivity reactions when hypersensitivity reactions reoccur.

- Mild symptoms: complete paclitaxel infusion. Closely monitor. No treatment indicated.

- Moderate symptoms: Interrupt paclitaxel infusion, administer diphenhydramine 25–50 mg and dexamethasone 10 mg via intravenous infusion. Once symptoms have resolved, resume paclitaxel infusion at a slower rate (20 mL/hour for 15 minutes, then at 40 mL/hour for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete). Document this AE in the AE Report Form of eCRF. If symptoms reoccur, interrupt the paclitaxel infusion and permanently discontinue subsequent paclitaxel infusion.
- Severe and life-threatening symptoms: Interrupt paclitaxel infusion, administer diphenhydramine and dexamethasone via intravenous infusion (as above). Use epinephrine or bronchodilators if indicated. Document this AE in the AE Report Form of eCRF. Permanently discontinue paclitaxel infusion.

Moderate to severe hypersensitivity reactions should be documented as AE.

Other toxicities

If other unmentioned grade 3–4 toxicities occur, the chemotherapy should be interrupted until symptoms resolve or return to grade 1. Thereafter restart the infusion at 50% of the original dose (which should no longer be adopted). If the toxicity does not return to grade 1 after interruption for 3 weeks, the chemotherapy should be permanently discontinued. Dose adjustments are not recommended for grade 1 and 2 toxicities.

5.4 Study Drug Properties

IBI305 is a bevacizumab biosimilar. The active ingredient of both drugs is recombinant humanized anti-VEGF monoclonal antibody; Bevacizumab is the standard commercially available drug, provided by the sponsor.

Refer to Table 6 for detailed study drug information.

Table 6. Study drugs

Study Drugs	Dosage Form and Strength	Exicipients	Description	Manufacturer
IBI305	4 mL: 100 mg	Sodium acetate, sorbitol, and polysorbate 80	Sterile solution for intravenous injection pH 5.2 Clear, colorless solution, no foreign matters, flocs, and precipitation	Innovent Biologics, Inc.
Bevacizumab	4 mL: 100 mg	*α,α*-trehalose dihydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate, polysorbate 20, and sterile water for injection	Sterile solution for intravenous injection pH 5.9–6.3 Clear to slightly opalescent, colorless to light brown	Roche Pharma (Schweiz) Ltd.

5.5 Preparation and Dispensation

IBI305 or bevacizumab is diluted in 0.9% sodium chloride solution under sterile conditions by the pharmacist or research nurse prior to administration. Check the particles and discoloration prior to administration.

The investigator should ensure that the pharmacist or research nurse administers the study drugs according to study protocol.

5.6 Packaging, Labeling, and Storage

The sponsor should package and label the study drugs according to appropriate local regulations.

All study drugs (IBI305 and bevacizumab) should be stored at 2–8 ℃ and away from light. The study drugs should be stored at a safe zone only accessible by authorized staff prior to dispensation to the subjects.

5.7 Subject Allocation

After confirming that the subject meets all of the inclusion and exclusion criteria, the study site will log in Interactive Web Response System (IWRS) and enter the subject information into the IWRS. The IWRS will allocate a random number to the subject and provide a medication number. This study will use stratified randomization with variables including age (< 60 vs. ≥ 60 years old) and EGFR status (wild vs. unknown type).

5.8 Blinding

This is a randomized, double-blind, parallel-controlled study in which only relevant individuals have access to the random numbers. A non-blinded pharmacist or research nurse will prepare the medications since IBI305 and bevacizumab do not have identical appearance. The pharmacist or research nurse responsible for preparing the medication must not reveal the allocation information to the subjects, their families, or other staff, including the investigators and research staff.

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

Emergency unblinding: In case of an emergency where the investigator must know the medication given to a particular subject, the investigator will unblind the subject via the IWRS and immediately inform the sponsor and CRO. The reasons for unblinding, date, and outcomes should be documented in the source document and eCRF of the subject.

5.9 Concomitant Medications and Therapies

All medications except for the study drugs, including other chemotherapies not specified in the study, Chinese herbal medicines, and other non-traditional therapies, are considered concomitant medications. All concomitant medications used within 30 days prior to screening should be documented in the eCRFs, including the information of generic name, route of administration, start date, end date, and indication.

5.9.1 **Prohibited therapies**

Except for IBI305, bevacizumab, paclitaxel, and carboplatin, all the other anti-tumor therapies are prohibited during the study, including any Chinese herbal medicine, radiation, or other investigational drugs.

Severe myelosuppression may occur after chemotherapy. Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) should not be used prophylatically during the first treatment cycle.

5.9.2 **Permitted therapies**

Prophylactic use of antiemetics, glucocorticoids, and other therapies of toxicity are permitted during the study. Unconventional treatments (such as acupuncture) and vitamins/microelements are permitted if their use does not affect the study endpoints as determined by the investigators.

To avoid severe myelosuppression that may occur after chemotherapy, G-CSF or GM-CSF can be used prophylatically starting from the second treatment cycle.

Necessary anti-viral therapy is permitted.

Stable antiepileptic therapy is permitted.

Radiotherapy of bone metastases is acceptable only if the radiation field excludes the target lesion.

5.9.3 **Therapies after study treatment**

Subsequent therapy after the end of study treatment should be determined by the subject's attending doctor.

5.10 Treatment Compliance

Subjects should receive treatment at the study site. The dose and time of administration of IBI305 or bevacizumab and paclitaxel/carboplatin should be documented in the source records and eCRFs during each treatment cycle. Reasons for dose adjustments, therapy delay, and therapy discontinuation should be documented. Treatment compliance is monitored by medication dispensing and return records, medical records, and eCRFs.

5.11 Medication Return and Destruction

The containers, vials, infusion bags, and syringes of used and partially used drugs can be destroyed on-site according to the appropriate guidelines and operating procedures established by study sites and local agencies.

Unless the contents have significant safety issues requiring immediate destruction in accordance with local regulations, all the unused drugs should be returned and destroyed based on the requirements of sponsor.

5.12 Study Drug Records

The designated personnel of the study sites should make timely records of receiving, dispensing, using, storing, returning, and destroying the study drugs in accordance with the relevant regulations and guidelines.

6 Study Procedure

Refer to 表 1 for details of study procedures.

6.1 Screening Visits (D -28 to D -1)

Complete the screening visits within 28 days prior to study treatment commencement. The following procedures must be completed during screening to ensure that subject meets the requirements for participating in this study:

- Signing of the informed consent form
- Recording the demographics (including age, ethnicity, and sex)
- Recording the medical history (including smoking history)
- Recording the history of anti-tumor therapies
- Recording the concomitant medications (within 30 days prior to screening)
- Recording the vital signs
- Measuring the height and weight (include BMI)
- ECOG PS score
- Physical examination
- 12-lead ECG
- Hepatitis B, anti-HCV, anti-HIV, and syphilis
- Clinical laboratory tests (count of blood cells, coagulation tests, blood chemistry, and routine urinalysis)
- Blood/urine pregnancy test (for female subjects of childbearing age only)
- Imaging tests (CT or MRI: head, chest, abdomen, and pelvis cavity)*
- EGFR mutation testing#
- Confirming the inclusion/exclusion Criteria
- Recording the AEs and concomitant medications

Retests are not required if the tests have been performed within 28 days prior to the first dose, unless the investigators suspect changes in tumor burden. Imaging results during screening will be used as the baseline data. Subsequent imaging test

method should be consistent with the baseline method, and the chest, abdomen, and pelvic cavity scans are required.

[#] If the subject has been tested for EGFR of tumor sample at the study site with documentation, the subject will not be required for retest.

6.2 Baseline Visits (C1D1)

D1 refers to the day of receiving the first dose of the study drugs. Eligible subjects meeting the inclusion criteria will return to the study site and complete the following procedures:

- Recording the vital signs
- Measuring the weight
- Physical examination
- Clinical laboratory tests (count of blood cells, blood chemistry, and routine urinalysis) to confirm that the inclusion/exclusion criteria are met

* If the laboratory tests (count of blood cells, blood chemistry, and routine urinalysis) are performed within 7 days prior to the first dose, the results will be used as the baseline data.

If the subject meets the inclusion criteria, the following procedures should be complete:

- Randomization
- Immunogenicity test (within 1 hour prior to study drug infusion)
- Study drug administration (IBI305 or Bevacizumab)
- PK blood sampling of chemotherapeutic agent administration (paclitaxel/carboplatin) [within1 hour prior to study drug infusion and immediately after study drug infusion (+ 5 minutes)]
- VEGF blood sampling (within 1 hour prior to study drug infusion)
- Recording the AEs and concomitant medications

6.3 C2 (Week 4 ± 3 Days)

Subjects should return to the study site 3 weeks (± 3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Recording the vital signs
- Measuring the weight
- Physical examination
- 12-lead ECG
- Clinical laboratory tests (count of blood cells, blood chemistry, and routine urinalysis)

- PK blood sampling (within 1 hour prior to study drug infusion)
- VEGF blood sampling (within 1 hour prior to study drug infusion)
- Study drug administration (IBI305 or Bevacizumab)
- Chemotherapeutic agents administration (paclitaxel/carboplatin)
- Recording the AEs and concomitant medications

6.4 C3 (Week 7 ± 3 Days)

Subjects should return to the study site 3 weeks (± 3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Recording the vital signs
- Measuring the weight
- Physical examination
- 12-lead ECG
- Clinical laboratory tests (count of blood cells, blood chemistry, and routine urinalysis)
- Study drug administration (IBI305 or Bevacizumab)
- Chemotherapeutic agents administration (paclitaxel/carboplatin)
- Recording the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (± 7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.5 C4 (Week 10 ± 3 Days)

Subjects should return to the study site 3 weeks (± 3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Recording the vital signs
- Measuring the weight
- Physical examination
- 12-lead ECG
- Clinical laboratory tests (count of blood cells, blood chemistry, and routine urinalysis)
- PK blood sampling (within 1 hour prior to study drug infusion)
- Immunogenicity test (within 1 hour prior to study drug infusion)
- Study drug administration (IBI305 or Bevacizumab)

- Chemotherapeutic agents administration (paclitaxel/carboplatin)
- Recording the AEs and concomitant medications

6.6 C5 (Week 13 ± 3 Days)

Subjects should return to the study site 3 weeks (± 3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Recording the vital signs
- Measuring the weight
- Physical examination
- 12-lead ECG
- Clinical laboratory tests (count of blood cells, blood chemistry, and routine urinalysis)
- PK blood sampling (within 1 hour prior to study drug infusion)
- Study drug administration (IBI305 or Bevacizumab)
- Chemotherapeutic agents administration (paclitaxel/carboplatin)
- Recording the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (± 7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.7 C6 (Week 16 ± 3 Days)

Subjects should return to the study site 3 weeks (± 3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Recording the vital signs
- Measuring the weight
- Physical examination
- 12-lead ECG
- Clinical laboratory tests (count of blood cells, blood chemistry, and routine urinalysis)
- PK blood sampling (within 1 hour prior to study drug infusion)
- VEGF blood sampling (within 1 hour prior to study drug infusion)
- Study drug administration (IBI305 or Bevacizumab)
- Chemotherapeutic agents administration (paclitaxel/carboplatin)
- Recording the AEs and concomitant medications

6.8 C7 and subsequent treatment cycles (± 3 Days)

Subjects should return to the study site 3 weeks (± 3 days) after the last infusion of the study drug. Maintenance monotherapy will start from week 7 and the dose of study drug will be adjusted to 7.5 mg/kg. Subjects should complete the following procedures during this visit:

- Recording the vital signs
- Measuring the weight
- Physical examination
- 12-lead ECG
- Clinical laboratory tests (count of blood cells, blood chemistry, and routine urinalysis)
- Study drug administration (IBI305 or Bevacizumab)
- Recording the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (± 7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.9 End of Treatment Visit

The **end of treatment visit** in study sites will be conducted in 28 days (± 7 days) after the last dose of study drug. Subjects should complete the following procedures during this visit:

- Recording the vital signs
- Measuring the weight
- Physical examination
- Clinical laboratory tests (count of blood cells, blood chemistry, and routine urinalysis)
- Immunogenicity test
- PD Blood Sampling
- Blood/urine pregnancy test (for female subjects of childbearing age only)
- Tumor assessment (CT or MRI, completed within 7 days prior to this visit; not required to be repeated if it has been performed within 6 weeks prior to this follow-up)
- Subsequent anti-tumor therapy
- Recording the AEs and concomitant medications

If the subject has not experienced PD, the subsequent follow-up for PD will be performed (Section 6.10).If the subject has experienced PD, the subsequent follow-up for survival will be performed (Section 6.11).

6.10 Follow-Up for PD

If the study drugs are discontinued for reasons other than PD, the **end of treatment visit** in study sites will be conducted in 28 days after the last dose of study drug, and tumor assessments should be conducted every 6 weeks (± 7 days) until PD (after which, follow-up for survival will be conducted) [Section 6.11]), withdraw of informed consent, loss to follow-up, death, start of other anti-tumor therapies, or end of study.During this follow-up, vital sign and weight measurements will be performed, and any subsequent anti-tumor therapies will be documented.

6.11 Follow-Up for Survival

The investigator will make telephone follow-up every 12 weeks (± 7 days) to collect the information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, loss to follow-up, death, or end of study.

6.12 Study Completion

The end of this study will be the18th month after randomization of the last subject. If the subjects continue to receive the study drug treatment before this cut-off time, the treatment should be discontinued and the **end of treatment visit** should be completed (Section 6.9).

6.13 Tumor Assessment

Imaging test (CT or MRI) of the head, chest, abdomen, and pelvic cavity should be completed at baseline. Retests are not required if the tests have been performed within 28 days prior to the first dose, unless the investigators suspect changes in tumor burden. Imaging tests should be performed every 6 weeks (± 7 days), and completed within 7 days prior to the scheduled visits until PD, withdrawal of informed consent, loss to follow-up, death, start of other anti-tumor therapies, or end of study. Subsequent imaging test method should be consistent with the baseline method, and the chest, abdomen, and pelvic cavity scans are required.

The investigator should perform a tumor assessment based on RECIST version 1.1 (Section 13.3) prior to each dose to determine that whether the subject should continue with the next round of treatment. An independent review committee will also assess the tumor response (Section 11.1.1).Imaging tests will not be rescheduled if the study drugs or chemotherapeutic agents are interrupted due to toxicities. Every effort should be made to continue the schedule for imaging tests even for subjects who discontinue one or two study treatment(s) due to drug-related toxicities.

If subject experience PD according to the RECIST version 1.1 criteria, the attending doctor should discuss with the subject regarding subsequent routine cancer therapies.

6.14 Clinical laboratory evaluations

Clinical laboratory tests will be conducted at the laboratories of each study site. Sample collection and analysis should be performed according to the requirements of each laboratory.

The following laboratory tests should be conducted according to the study procedures (Table 1):

- Count of blood cells: hemoglobin, hematocrit, WBC count and differentials (including neutrophil and absolute lymphocyte count), platelet count, and red blood cell count
- Coagulation tests (baseline): INR, aPTT, or PTT
- Blood chemistry: creatinine, blood urea, total protein, albumin, TBIL, alkaline phosphatase, AST, ALT, fasting blood glucose, potassium, sodium, chlorine, calcium, phosphorus, and magnesium
- Routine urinalysis: specific gravity, pH, urinary glucose, urinary protein, occult blood and urinary WBCs
- Pregnancy test: blood/urine pregnancy tests for all female subjects of childbearing age during screening and at the **end of treatment visit**.

The above tests should be conducted at the laboratories of each study site.

During the visits after baseline, all laboratory tests should be completed within 3 days prior to administration. During the study, the frequency of these laboratory tests will be increased if safety is a concern. The investigator should review the laboratory test results throughout the study to determine whether the results are clinically significant. The investigator should assess the changes in laboratory test results. Any abnormal laboratory findings that are considered clinically significant by the investigator should be documented as AEs.

6.15 Vital Signs, Physical Examination and Other Safety Assessments

6.15.1 Vital signs

Vital signs include pulse, BP, temperature, and respiratory rate. Subjects should rest for at least 5 minutes prior to vital sign measurements.

Vital signs should be measured according to the study schedule (Table 1). During the study, the investigator may increase the frequency of vital sign measurement if safety is a concern.

6.15.2 Height and weight

Height is only measured during screening. Weight is measure during each visit.

6.15.3 Physical examination

The following organs/systems should be examined according to the study schedule

(Table 1): general condition, head (eyes, ears, nose, throat), neck and thyroid, respiratory system, cardiovascular system, abdomen, nervous system, skeletal muscles and limbs, lymphatic system, and skin.

6.15.4 **12-Lead ECG**

12-lead ECG will be performed during screening and at each dosing visit during the study.

ECG parameters such as heart rate, PR interval, QRS complex, QT interval, and QTc interval should be recorded. Subjects should remain in supine position for at least 5 minutes prior to 12-Lead ECG. All ECG should be evaluated by qualified doctors. All clinically significant abnormal findings should be reported as AEs.

6.15.5 **Immunogenicity evaluation**

Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: within 1 hour prior to the first dose of the study drug (IBI305/bevacizumab) in C1, within 1 hour prior to the administration of the study drug in C4, and at the **end of treatment visit**. Serum samples of positive ADAs should be further tested for NAbs. Samples will be analyzed at the designated central laboratory.

6.15.6 **PK/PD**

6.15.6.1 PK

Study sites that are implementing version 2.0 or any later version of the study protocol should collect PK samples until 140 subjects in this study meet the requirements for PPK assessment (notified by the sponsor in writing). There are 6 PK sampling time points: within 1 hour before the first dose of the study drug (IBI305/bevacizumab) in C1, immediately after the first infusion (within 5 minutes), within 1 hour prior to the dose in C2, within 1 hour prior to the dose in C4, within 1 hour prior to the dose in C5, and within 1 hour prior to the dose in C6. Serum will be separated from the samples at the study site and the serum samols will be analyzed at the designated central laboratory.

6.15.6.2 PD

Study sites that are implementing version 2.0 or any later version of the study protocol should collect PD samples until 140 subjects in this study meet the requirements for VEGF testing (notified by the sponsor in writing). There are 4 VEGF sampling time points: within 1 hour prior to the first dose of the study drug (IBI305/bevacizumab) in C1, within 1 hour prior to the dose in C2, within 1 hour prior to the dose in C6, and at the **end of treatment visit**. Samples will be analyzed at the designated central laboratory.

6.15.7 **EGFR mutation testing**

EGFR mutation testing histologically or cytologically will be performed in all subjects (if the subject has been tested for EGFR at the study site histologically or cytologically with documentation, the subject will not be required to be retested). The testing will be conducted at the laboratory of each study site or a qualified third-party laboratory.

7 Study Evaluation

7.1 Efficacy Evaluation

7.1.1 Primary efficacy endpoints

- ORR

The ORR should be evaluated based on RECIST version 1.1, which is defined as the proportion of subjects with tumor size reduction of a predefined amount and for a minimum time period, including those who have a complete response (CR) or partial response (PR). The cut-off date for data included in the primary efficacy evaluation is the 18th week after the last subject is randomized.

7.1.2 Secondary efficacy endpoints

- DOR
- PFS
- DCR
- OS

Each indicator is evaluated using RECIST version 1.1.

DOR is defined as the time of initial response (CR or PR) until PD or death. If the subject with CR or PR does not experience PD or death, the subject will be censored at the date of the last imaging test.

PFS is defined as the time of randomization until PD or death. If the subject does not experience PD or death, the subject will be censored at the date of the last imaging test.

DCR is defined as the proportion of subjects with tumor size reduction or stabilization over a certain time period, including those who have achieved CR, PR, and SD.

OS is defined as the time of randomization until death for all causes. At the end of the study, subjects who are still alive or lost to follow-up will be censored at the last contacted date.

7.2 Safety Evaluation

7.2.1 AEs

7.2.1.1 Definitions

AEs

An AE refers to any untoward medical occurrence in a subject after signing the informed consent form, and does not necessarily have a causal relationship with the treatment. Thus, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not considered drug related.

Abnormalities resulting from PD are not considered as AEs.

SAE

An SAE refers to an AE meeting at least one of the followings:

(1) Results in death, except for death caused by PD.

(2) Life-threatening (a life-threatening event is defined as an AE when the subject is at immediate risk of death at the time, but does not include the one that may lead to death only when the event worsens).

(3) Requires hospitalization or prolonged hospitalization, excluding an emergency or outpatient visit. Subjects with existing diseases or conditions prior to the enrollment that do not worsen during the study, and having hospitalization and/or surgery that was scheduled before the study or during the study are not considered as SAEs. Hospitalizations resulting from PD are not considered as AEs.

(4) Results in permanent or serious disability/incapacity.

(5) Results in congenital anomalies/birth defects

(6) Other important medical events: The event that does not result in death, is not life-threatening or does not require hospitalization, but jeopardizes the health of subjects and require medical intervention to prevent the SAEs above, is considered as an SAE.

7.2.1.2 Severity of AEs

The severity of AEs is evaluated using the 5-level criteria of NCI CTCAE version 4.03.

For AEs not included in CTCAE version 4.03, use the following CTCAE general guidelines:

- Grade 1 Mild; asymptomatic or mild signs; clinical or diagnostic observations only; medical intervention not indicated.
- Grade 2 Moderate; minimal, local or non-invasive intervention required; limiting age-appropriate instrumental activities of daily living (e.g., cooking, shopping, using the telephone and managing money, etc.).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g. bathing, dressing and undressing, feeding self, using the toilet, and taking medications), but not bedridden.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

7.2.1.3 Relationship between AEs and study drugs

The relationship between the study drugs and AEs can be determined using the followings:

Table 7. Correlation between AEs and study drugs

Correlation	Criteria
Related	• The AE occurrence has a reasonable time relationship with administration time; • The investigational drug can more reasonably explain the AE than the other causes (such as concurrent disease, environment, toxicity, or other treatment received); • The AE resolves or is alleviated after treatment interruption or dose reduction; • The event meets the recognized pharmacological AE type; • The AE dose not occur after re-administration.
Probably Related	• The AE occurrence has a reasonable time relationship with administration time; • The investigational drug provide more reasonable explanations on the AE than the other causes (such as concurrent disease, environment, toxicity, or other treatment received); • The AE resolves or is alleviated after treatment interruption or dose reduction; (if applicable);
Probably Unrelated	• Other causes provide more reasonable explanations on the AE than the study drugs (such as concurrent disease, environment, toxicity, or other treatment received); • The AE does not resolve or be alleviated after treatment interruption or dose reduction (if applicable), or the situation is unclear; • The AE dose not occur after re-administration or the situation is unclear.
Unrelated	• The AE occurrence has a reasonable time relationship with administration time, or • Other causes provide evident explanations (such as: concurrent disease, environmental, toxicity, or other treatment received by the subject).
Unable to Determine	• The above information is unclear and cannot be determined based on the available information. Further follow-up information is not accessible to the investigator.

7.2.1.4 Reporting SAEs

SAEs that occur from the signing of informed consent form until 90 days (inclusive) after the last dose should be reported. The investigator must fill out the "CFDA SAE Report Form", regardless of whether it is the initial report or a follow-up report, and sign and date the form. The investigator must report the SAE to the sponsor, CFDA, and ethics committee within 24 hours of noticing the event. Refer to the table below for contact details.

For SAEs occurring outside of the above-mentioned period, those considered related to the study drug should also be reported to the sponsor.

The investigator must submit the completed SAE report form to the sponsor within 24 hours of noticing the event. The investigator should urgently perform visit on missing information and provide a complete SAE report for events that result in death or are

life-threatening.

The investigator should also report the event to the CFDA, health administration departments, and ethics committees in accordance with the regulations.

When submitting the SAE report by mail, it is recommended for the investigator to encrypt the report file and send the report file and password in separate emails.

Table. SAE report contacts

Agency	Contact	Fax/Telephone/Address
Hospital Name	Ethics Committee	Hospital Fax/Telephone
Innovent Biologics, Inc.	Clinical Study Department PV	Fax: 021-31652800 Email: drugsafety@innoventbio.com
Office of Drug Research and Supervision, Department of Drug and Cosmetics Registration, China Food and Drug Administration		Address: Building 2, No. 26, Xuanwumen West Street, Xicheng District, Beijing Postal Code: 100053 Telephone: 010-88330732 Fax: 010-88363228
Medical Administrative Department, Health Administration		Address: No. 38, Lishi Road, Xicheng District, Beijing Telephone: 010-68792001 Fax: 010-68792734
Province, Autonomous Region, Municipality Food and Drug Administration	Based on the requirements of the food and drug administration department of each province, autonomous region or municipality	

7.2.1.5 Handling and Visits of AEs

The investigator is responsible for proper medical treatment of all AEs (including recommend treatment measures such as interruption/discontinuation of the study drugs, dose adjustments, study drug continuation, etc). When an AE occurs, the investigator should actively take appropriate measures to ensure the safety of the subject. All AEs observed from the signing of the informed consent form to the time specified in the protocol (Table 8) should be documented, reported, and visited in accordance with protocol requirements.

Any SAE that occurs beyond the time specified in the protocol (Table 8) but is determined to be related to the study drugs should be reported to the sponsor.

7.2.1.6 AE of Special Interest (AESI) and expedited reporting

The AESI for this study include:

- Gastrointestinal perforation
- Surgical and wound healing complications
- Hemorrhage
- Fistula
- Hypertension
- Thrombosis
- Posterior reversible encephalopathy syndrome (PRES)
- Proteinuria
- Infusion reactions
- Ovarian failure
- Congestive heart failure

If the criteria for SAE is met, the SAE report should be submitted to the sponsor within the specified time limit (See Section 7.2.1.4).

7.2.1.7 Pregnancy

Bevacizumab may be harmful to the fetus. Subjects or female partners of male subjects must use an effective form of contraception during the 6 months after the last dose.

During the study, if a female subject exposed to the study drug becomes pregnant, she must discontinue study treatment. The investigator must report to the sponsor within 24 hours of noticing the event and submit the Innovent clinical Study Pregnancy Report/Follow-Up Form.

During the study, if a female partner of a male subject exposed to the study drug becomes pregnant, the subject will continue in the study. The investigator must report to the sponsor within 24 hours of noticing the event and submit the Innovent clinical Study Pregnancy Report/Follow-Up Form.

The investigator must continuously monitor and visit on the outcome of the pregnancy until 8 weeks after the subject gives birth. The outcome should be reported to the sponsor.

If the outcome of the pregnancy is stillbirth, spontaneous abortion, fetal malformation (any congenital anomaly/birth defects), or medical abortion, it should be considered a SAE and the event requires to be reported in accordance with SAE procedures and time limits.

If the subject also experiences a SAE during the pregnancy, the CFDA SAE Report Form should also be filled out and reported according to SAE's procedures.

7.2.1.8 Time limits of documenting and reporting AEs

All AEs (including SAEs or non-SAEs) that occur from the signing of the informed consent form to the time specified by the study (Table 8) should be documented in the eCRFs under AEs, regardless of severity.

Table 8. Reporting and visits on AEs

	Reporting Time Limit	**Visit Time Limit**
AEs	From signing the informed consent form to 90 days after the last dose (if the subject begins other anti-tumor therapies, only AEs related to the study drugs should be collected).	Until resolved or stable determined by the investigator
Pregnancy	From the first dose to 6 months after the last dose	Until the end of the pregnancy, and visit according to the protocol on the health status of the newborn for at least 2 months

7.2.1.9 Precautions for AE documentation

Diagnosis, signs, and symptoms

Document the definite diagnosis, if there is one, rather than just listing the independent signs and symptoms (e.g. hepatic failure rather than jaundice, elevated transaminase, and asterixis). However, if the signs and symptoms cannot be attributed to a definitive diagnosis, each independent event should be documented in the eCRFs as an AE or SAE. Update the report with visit information if a diagnosis is confirmed later on.

AEs secondary to other events

Generally, AEs secondary to other events (such as result of another event or clinical sequelae) should be documented as the primary event, unless the event is severe or an SAE. However, clinically significant secondary events should be recorded as independent adverse events in the eCRFs if they occur at different time than the primary event. If the relationship between events is unclear, document them as separate events in the eCRFs.

Ongoing or recurrent AEs

An ongoing AE refers to an event that does not resolve and is ongoing between two assessment time points. These AEs should only be documented once in the eCRFs. The initial severity should be documented, and the information should be updated if the event exacerbates.

Recurring AEs refer to AE that have resolved between the two time points of assessment but subsequently occur again. These events should be independently documented in the eCRFs.

Abnormal laboratory or vital signs

Any abnormal laboratory finding that is clinically significant should be reported as an AE. The investigator is responsible for reviewing all the abnormal laboratory results, and determine whether the findings should be reported as AEs.

Death

During the entire course of the study, all deaths that occur within 90 days after the last dose should be documented in the eCRFs and Mortality Report Form, regardless of the casual relationship with the study treatment

If the cause of death is known, record the cause of death as an AE and the outcome of the event as a death and submit an SAE report; if the cause of death is unclear, the AE should be recorded as Death of Unknown Cause in the AE form, and submit the SAE report as Death of Unknown Cause. The exact cause of the death should be further investigated.

Pre-existing medical conditions

Symptoms/signs present during the screening period will be recorded and reported as adverse events only if their severity, frequency, or property becomes aggravated (except for worsening of the studied disease). The relative change should be documented, such as increased frequency of headaches.

Hospitalization and prolonged hospitalization, or surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, except for the following situations:

- Hospitalization or prolonged hospitalization as required by study protocol (such as for dose administration or efficacy evaluation).
- Hospitalization due to a pre-existing medical condition that remains stable, e.g. elective surgery/therapy scheduled prior to the study.

However, elective surgery/therapy required because of the exacerbated condition during the study (e.g. surgery/therapy required earlier than scheduled) should be considered as an AE.

The investigator should document all the necessary information, including AE term (diagnosis, if tdiagnosis not available, then document the signs and symptoms, including any abnormal laboratory findings), start date, end date, severity, an AESI or not, measures taken for the study drug, treatment provided for the AE, outcome, and relationship with the study drug. If the signs and symptoms cannot be attributed to a definitive diagnosis, each AE should be documented independently.

PD

PD is defined as the worsening of subject condition caused by the primary tumor that the study drug is targeting, the appearance of new lesions, or the progression of the primary

lesion. PD will not be reported as an AE. Any deaths, life-threatening events, hospitalization or prolonged hospitalization, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by PD will not be reported as an SAE.

8 Statistics

8.1 Determination of Sample Size

A sample size of 218 subjects for each group (426 subjects in total) will provide 80% power to confirm the clinical equivalence between IBI305 nd bevacizumab in combination with paclitaxel/carboplatin.The sample size estimation is based on the following hypotheses:

- The ORRs between IBI305 and bevacizumab group are equivalent.
- The ORR of bevacizumab group is 50.0%.
- The acceptable range of equivalence margins for ORR ratio is (0.75, 1/0.75).
- The significance level of two one-sided test is 0.05.
- The randomization ratio is 1:1.

Based on the above hypotheses, a number of 218 subjects for each group is required (436 subjects in total). Sample size was estimated using the PASS 2013.

8.2 Statistical Analysis Populations

Intention-to-treat (ITT): all randomized subjects.

Full analysis set (FAS): includes all randomized and evaluable subjects who have received at least one dose of the study drugs. This dataset is used as the primary analysis dataset for the efficacy evaluation.

Per-protocol set (PP): subset of subjects in the FAS who have completed the minimum-exposure study treatment and are compliant with the protocol. This dataset is used as the secondary analysis dataset for the efficacy evaluation.

Safety set (SS): includes all randomized subjects who have received at least one dose of the study treatment and have safety evaluation data. This dataset is used for safety evaluation of this study.

PK analysis set (PKAS): includes subjects in the FAS with at least one PPK measured value.

PD analysis set (PDAS): includes subjects in the FAS with at least one PD measured value.

8.3 General Principles for Statistical Analysis

For continuous variables, descriptive statistics should include the count, mean, standard deviation, median, maximum, and minimum. For categorical variables, descriptive statistics should include the number and percentage of subjects. The results of this study will be analyzed using SAS 9.4.

8.4 Statistical Analysis Methods

8.4.1 Covariate adjustment

The study is stratified by age and EGFR status. These factors are considered in the analysis of the primary and secondary efficacy endpoint models (GLM or Cox).

8.4.2 Handling of dropouts or missing data

The handling of dropouts and missing data are described in the statistical analysis plan.

8.4.3 Multicenter study

Since this is a multicenter study, the primary endpoint (ORR) will be listed according to study sites and treatment groups. However, individual equivalence analysis will not be conducted. Data from study sites with ITT < 5 subjects per treatment group should be combined. Details will be discussed at the data review meeting.

8.4.4 Multiple comparisons and adjustments

αAdjustments for multiple comparisons are not considered.

8.5 Statistical Analysis

8.5.1 Subject distribution

Refer to Figure 1. Study Design Schematic for the visit procedure of subjects. 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.

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

8.5.2 Demographics and other baseline characteristics

Demographic information such as age, height, sex, and weight, and other baseline characteristics such as disease history (including NSCLC diagnosis, staging, previous cancer treatment, and target and nontarget lesions) are summarized using descriptive statistics.

8.5.3 Compliance and drug exposure analysis

The required dose and actual dose will be documented in the eCRFs. Subject compliance is determined by the ratio of the number of actual doses (times) to the number of required doses (times). Subject compliance will be categorized by < 80%, 80–120%, and > 120%. The number and percentage of patients in each category will be shown.

8.5.4 Efficacy analysis

The efficacy is analyzed using the FAS and the results of PP set will also be provided.

8.5.4.1 Primary efficacy analysis

The primary objective of this study is to examine the clinical equivalence of IBI305 and bevacizumab in combination with paclitaxel/carboplatin for treatment of advanced or recurrent non-squamous NSCLC. The primary endpoint is ORR, which is defined as the rate of confirmed CR or PR. Target and non-target lesions are evaluated by confirmed radiological methods and assessed according to RECIST version 1.1. Subjects without tumor assessments after baseline will be considered as not assessable. Subjects eligible to have either CR or PR assessment must have at least one measurable lesion that can be assessed by RECIST version 1.1. Clinical equivalence as demonstrated by ORR should be based on the assessments by IRRC. The assessment results by investigators will be used for sensitivity analysis.

Clinical equivalence will be evaluated by comparing the 90% CIs of ORR ratio between IBI305 and bevacizumab with the equivalence margins of (0.75, 1/0.75). The ORRs and 95% CIs of two groups, ORR difference and 90% CI, and ORR ratio and 90% CI will be estimated by the generalized linear model (GLM, including groups and stratification factors).

8.5.4.2 Secondary efficacy analysis

The secondary efficacy endpoints of this study include DOR, DCR, PFS, and OS.

DCR is defined as the rate of complete response (CR), partial response (PR), and stable disease (SD). Target and non-target lesions are evaluated by confirmed radiological methods and assessed according to RECIST version 1.1.

DOR is defined as the time of initial response (CR or PR) until PD or death. If the subject with CR or PR does not experience PD or death, the subject will be censored at the date of the last imaging test.

OS refers to the time from randomization to death (of any cause). Subjects who are still alive at the time of analysis are censored at the last contacted date. PFS refers to the time from randomization to the first documentation of PD or death (whichever occurs first). Subjects who have not experience PD or death are censored at the date of the last tumor assessment. Subjects without tumor assessments after baseline are censored at the date of randomization.

The median OS and 95% CI are estimated using Kaplan-Meier methods and the survival curve is plotted. The hazard ratio and 95% CI of two groups will be estimated by the Cox model, which includes the treatment group and stratification variables. DOR and PFS are analyzed by the same method as OS. DCR is analyzed by the same method as the primary efficacy endpoint without equivalence test.

8.5.4.3 Sensitivity analysis

Fixed and random effects are considered in the model analysis (GLM or Cox) of the primary and secondary efficacy endpoints.

8.5.4.4 Antibody and efficacy analysis

Subjects who produce antibodies during the study are listed. The difference in efficacy between subjects who produced antibodies versus subjects who do not produce antibodies will be compared if needed.

Changes in PK parameters and steady-state trough concentrations of subjects with positive ADA are analyzed.

8.5.5 Exploratory analysis

PD: describe the changes in serum VEGF levels at different time points, and inter-group comparisons when necessary (based on PD analysis set).

Steady-state trough concentrations: describe trough concentrations, and inter-group comparisons when necessary (based on PPK analysis set).

8.5.6 Interim analysis

No interim analysis is planned.

8.5.7 Stratified analysis

Efficacy analysis of different levels of subjects is conducted based on the random stratification factors.

8.5.8 Safety analysis

The safety analysis is based on the safety analysis set.

8.5.8.1 AEs

All AEs will be categorized by Medical Dictionary for Regulatory Activities (MedDRA) codes and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All TEAEs, TEAEs ≥ grade 3, SAEs, drug-related TEAEs, drug-related SAEs, TEAEs resulting in the termination of study drugs, TEAEs resulting in the termination of study, and AESIs will be listed based on system organ class, preferred terms, and groups and summarized the numbers of corresponding subjects and percentages. Besides, the severity of TEAEs and relevance to the study drugs will also be summarized system organ class, preferred terms, and treatment groups.

8.5.8.2 Laboratory tests

Descriptive statistical analysis of all laboratory findings and changes from baseline are shown based on time points and treatment groups. Abnormal laboratory findings are listed.

8.5.8.3 ECG

Descriptive statistical analysis of ECG findings and relative changes from baseline are shown.

8.5.8.4 Vital signs, physical examinations and other safety-related examinations

Descriptive statistics of vital signs and relative changes from baseline are shown.

Results of physical examinations are listed by treatment groups.

8.5.8.5 Concomitant medications

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

(1) All medications used at the time of the first dose or after the first dose of the study drug;

(2) All medications started before and continued after the first dose of the study drug.

Concomitant medications are listed by treatment groups.

9 Quality Assurance and Quality Control

In accordance with the guidelines of the GCP, it is the responsibility of the sponsor to implement and maintain a quality assurance and quality control system in accordance with the appropriate standard operating procedures to ensure the implementation of clinical trials and the truthfulness of the data, and to collect, record and report compliance with the protocol, GCP and corresponding regulatory requirements.

9.1 Clinical Monitor

The CRO authorized by the sponsor will conduct a clinical monitor of the study. The CRA should conduct the monitor according to the standard operating procedures of the sponsor or CRO and have the same rights and responsibilities as the sponsor's monitor. The auditor shall maintain regular communication with the investigator, the trial authorised personnel and the sponsor.

Before the study begins, the CRA will assess the competency of each research center and report issues related to facilities, technical equipment, or medical staff to the sponsor. During the course of the study, the CRA will be responsible for monitoring whether the investigator has obtained written informed consent from all subjects and whether the data records are correct and complete. At the same time, the CRA will also compare the data input to the eCRF with the original data and inform the investigator of errors or omissions. The CRA will also control the compliance of the research center's program and test procedures, arrange for the supply of research drugs, and ensure that the drugs are kept in the proper conditions. The monitor visit will be conducted in accordance with the requirements of relevant laws and regulations. From the time the subjects are enrolled, each center will receive regular monitoring visits. After each visit to the investigator, the auditor should submit a written report to the sponsor.

9.2 Data Management / Coding

This study will use an electronic data collection (EDC) system, and the research data will be entered into the eCRF by the investigator or authorized researcher. Investigator and authorized researchers will be properly trained and appropriate security measures will be taken for the equipment used, etc., prior to the start of the research center or data entry.
Data entry for eCRF should be completed as soon as possible during or after the visit and updated at any time to ensure that it reflects the latest developments of the participants in the study. To avoid differences in outcome assessment by different evaluators, it is recommended that the same subject's baseline and all subsequent efficacy and safety assessments be performed by the same individual. Investigators are required to review the data to ensure the accuracy and correctness of all data entered into the eCRF. If some assessments are not made during the study, or if certain information is unavailable, not applicable, or unknown, the investigator should record it in the eCRF. The investigator should electronically sign the verified data.

The CRA will review the eCRF and assess its completeness and consistency, and the CRA will compare the eCRF with the original documents to ensure consistency of key data. All data entry, corrections and modifications will be the responsibility of the investigator or his designee. The data in the eCRF is submitted to the data server and any changes to the data are recorded in the audit trail, ie the reason for the change, the name of the operator, the time and date of the modification will be recorded. The roles and authorities of the staff responsible for data entry in the research center will be predetermined. If there is any data

challenge, the CRA or data management staff will issue a challenge in the EDC and the research center staff will be responsible for the Q&A. The EDC system will record the audit trail of the challenge, including the name, time and date of the investigator.
Unless otherwise stated, eCRF will only be used as a form to collect data, not as a source. The original document is used by the investigator or hospital, relevant to the subject, and demonstrates the presence, inclusion criteria, and all records of participation in the study, including laboratory records, ECG results, and pharmacy drug delivery records. , subject folder, etc.

The investigator is responsible for maintaining all original documents and for CRA to monitor them at each visit. In addition, regardless of the length of time the enrolled subjects participated in the study, the investigator must submit a complete eCRF for each enrolled subject. The protocol number and subject number of all supporting documents (such as laboratory records or hospital records) submitted with eCRF should be carefully verified, and all personal privacy information (including the subject's name) should be deleted or made illegible. To protect the privacy of the subject. The investigator verifies that the record has been reviewed by an electronic signature record and that the data of the record is accurate. The electronic signature will be completed using the investigator's user ID and password. The system will automatically attach the date and time of the signature. The investigator must not share the user ID and password with other people. If you need to change the data in the eCRF, you should follow the workflow defined by the EDC system. All changes and reasons for the changes will be recorded in the audit trail.
Adverse events, concomitant diseases/history will be coded. The dictionary for coding will be described in the Clinical Research Summary Report (CSR).
9.3 Quality Assurance Audit

During the course of the study, the sponsor or the representative authorized by the sponsor will conduct quality assurance audits of the research center, research database and related research documents. At the same time, the corresponding regulatory agency may also inspect the research center, research database and related research documents at its own discretion. When the investigator receives the inspection notice from the regulatory body, he or she must immediately inform the sponsor.
The quality assurance department of the sponsor conducts an audit of the clinical trial institution. The audit includes: the supply of the drug, the required test documents, the record of the informed consent process, and the consistency of the medical report form with the original documents. The content and scope of the audit can also be increased depending on the situation. After reasonable notice, the investigator shall allow the auditors commissioned by the sponsor to conduct inspections related to the trials and inspections conducted by the regulatory authorities. The primary purpose of an audit or inspection is to inspect all study related procedure and documents, and ensure that the study is conducted according to protocol GCP and Declaration of Helsinki. Investigators should have direct access to all test files, original records, and raw data.

10 Ethics

10.1 Ethics Committee

The sponsor or the representative authorized by the sponsor will prepare the relevant documents to be submitted to the Research Center's Ethics Committee (EC), including the trial protocol, informed consent, investigator's manual, subject recruitment materials or advertising and other regulatory requirements. Documents must be submitted to the appropriate EC for approval. Prior to the start of the study, written approval from the Research Center EC must be obtained and provided to the sponsor. The EC's approval must specify the name, serial number, version number and version number of the other study (eg informed consent) and the date of approval. The investigator is required to notify the sponsor of the EC's written comments regarding delays, suspensions, and re-approval.

The research center must follow the requirements of the Center's EC. It may include revision of the protocol, revision of the informed consent form, revision of the subject's recruitment materials, submission of the EC for approval, local safety report requirements, regular reporting and update in accordance with EC regulations, and submission of the final report. All the above documents and EC approvals must be provided to the sponsor or its designee.

10.2 Ethics of the study

Access to the research process and informed consent is subject to the Helsinki Declaration, relevant GCP requirements, and laws and regulations related to drug and data protection in China.

GCP provides ethical, scientific, global quality standards for the design, implementation, documentation, and reporting of clinical studies involving human subjects. This study will be conducted in accordance with the GCP and relevant national regulations and in accordance with the relevant ethical principles of the Helsinki Declaration to protect the rights, safety and health of the subjects.

The investigator is required to follow the procedures specified in this protocol and should not change it without the permission of the sponsor. Any protocol deviation will be reported to the EC, the sponsor, or the regulatory body.

10.3 Subject Information and Informed Consent

Before the start of any research process, informed consent (ICF) is used to explain the risks and benefits of this study to potential participants, and the language of informed consent should be straightforward. The ICF statement should make it clear that informed consent is voluntary and clearly identifies the risks and benefits of participating in the study, and the subject may withdraw from the study at any time. The investigator can only enroll the subject if he or she fully explains the details of the study, the subject's question is satisfactorily answered, and sufficient time is given for consideration and the written consent of the subject or his legal representative is obtained. All signed informed consent must be in the investigator's document or in the subject's folder.

The investigator is responsible for interpreting the informed consent of the subject and obtaining informed and dated informed consent from the subject or his or her legal representative prior to the start of the study. After signing, the investigator should send the subject a copy of the signed informed consent form. The investigator is required to document the process of informed consent in the original test document.

10.4 Subject Data Protection

ICF will contain (or in some cases, together with separate files) information about data protection and privacy protection.

Take precautions to ensure the confidentiality of the documents and prevent the identification of the subject. However, under special circumstances, some people may see

the genetic data and personal identification number of a subject. For example, in the event of a medical emergency, the sponsor, his representative doctor, or the investigator knows the subject identification code and has access to the subject's genetic data. In addition, relevant regulatory agencies require access to relevant documents.

11 Research Management

11.1 Data Processing and Record Saving
The documents in the clinical trial (plan and protocol revision, completed eCRF, signed ICF, etc.) are to be preserved and managed as required by the GCP. The research center should keep these documents for 5 years after the end of the study.
Study documents should be reasonably preserved for future visits or data traceability. Security and environmental risks should be considered when saving files.

No research documents will be destroyed without the written permission of the sponsor and the investigator. The investigator/research center may transfer the research documents to other parties who comply with the document retention requirements or transfer to other locations that meet the requirements only after notifying the sponsor and obtaining their written consent.
11.2 Raw Data / File Access Rights
The investigator agrees that the sponsor, CRO, and relevant authorized regulatory agencies have direct access to all research-related documents, including subject medical records.
11.3 Protocol revision
Any possible revisions to the protocol during the course of the study will be communicated and agreed by the sponsor and the investigator. The sponsor should ensure that the protocol revision is submitted to the regulatory body in a timely manner.
All revisions to the protocol should be maintained as a supplement to the protocol. Any changes to the protocol must be submitted to the Ethics Committee for approval or filing in accordance with the ethics committee's rules. If necessary, it should also be submitted to the regulatory authority for approval and approved by the EC and regulatory authorities (if required) (except for changes to the protocol to eliminate direct hazards to the test subjects).

11.4 Investigator Responsibilities
The investigator will follow the protocol, the ethical principles of the Helsinki Declaration, the Chinese GCP and the corresponding regulatory requirements for this study.
The detailed responsibilities of the relevant investigators are listed in Chapter 5 (Investigator's Responsibilities) of the Chinese GCP (Order No. 3).
11.5 Publication Policy
All data generated in this study are confidential information of the sponsor. The sponsor has the right to publish the research results. Information about sponsor and investigator publication policies will be described in the clinical trial protocol.
All information about this trial (not limited to the following documents: protocol, investigator's manual) must be kept strictly confidential. Investigators must recognize that the scientific or medical information derived from this trial may be of commercial value to the sponsor. The investigator should keep the information and data related to this test confidential. If you want to publicly publish the information related to this test or the conclusions obtained from the test, you must consult with the sponsor in advance and obtain the written consent of the sponsor. In order to protect their rights and interests, the sponsor may require the investigator not to publish information about the trial before the trial product is approved for marketing.
The sponsor has the right to publish or publish information or data related to the trial or to report it to the drug administration. If the sponsor needs to have the name of the investigator

in the publication, publication or advertising content, the investigator's consent should be obtained

11.6 Finance and Insurance

The sponsor will purchase insurance for the participants in the study in accordance with local regulations and minimum requirements. Insurance related terms will be saved in the research folder.

12 Reference

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13. IBI305 Investigator's Brochure.Innovent Biologics (Suzhou) Co., Ltd. May 11, 2016.

14. China Food and Drug Administration. Guidelines on Development and Evaluation of Biosimilars (for Trial Implementation). Accessed on Apr. 21, 2016 from: http://www.sda.gov.cn/WS01/CL1616/115104.html

13 APPENDICES

13.1 APPENDICES 1

ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

13.2 APPENDICES 2

Calculation of Body Surface Area

Body surface are (m^2) = 0.00616 height (cm) + 0.01286 weight (kg) - 0.1529

Calculation of Creatinine Clearance (Cockroft-Gault Equation)

Ccr (mL/min) = [(140 - age) x weight (kg)]/[72 x Scr (mg/dL)]

Female subjects: results x 0.85

1 mg/dL = 88.41 μmol/L

Calculation of Carboplatin Dose (Calvert Formula)

Carboplatin dose (mg) = AUC (mg/mL/min) × [CrCl (mL/min) + 25]

Note: During the study, if the carboplatin dose calculated using the Calvert equation excessively exceeds the usual clinical dose, choose one of the following two methods to ensure the patient safety:

1. Retest the serum creatinine and re-calculate the dose (preferred option).
2. Based on clinical experience, the investigator may choose the highest dose tolerated by the subject. The dose should remain unchanged for the subsequent cycles.

13.3 APPENDICES 3

RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1 CRITERIA FOR EVALUATING RESPONSE IN SOLID TUMORS
RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be used utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.
* As published in the European Journal of Cancer:
E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S.Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J.
Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version
1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

14 Signature Page for Investigator

Title: A randomized, double-blind, multicenter and phase III study comparing the efficacy and safety of IBI305 and bevacizumab in combination with paclitaxel/carboplatin for treatment of treatment-naive subjects with advanced or recurrent non-squamous non-small cell lung cancer

Protocol No.: CIBI305A301

This protocol is a trade secret owned byInnovent Biologics (Suzhou) Co., Ltd. I have read and fully understood this protocol, and agree to conduct this study in accordance with the requirements found in this protocol and the Good Clinical Practice, and in compliance with relevant laws and regulations and the Declaration of Helsinki. Also, I promise not to reveal any confidential information to a third-party without the written consent fromInnovent Biologics (Suzhou) Co., Ltd..

Instructions for investigators: please sign and date this page, print the name of the investigator, position, and study site, and return the signed form toInnovent Biologics (Suzhou) Co., Ltd.

I have read the entire contents of this study protocol and shall perform the study as required:

Signature of Investigator: _____ Date: _____

Print Name: _____

Title of Investigator: _____

Study Site/Address: _____

_____

_____