Statistical Analysis Plan

A Randomized, Double-blind, Multicenter, Phase III Study to Evaluate the Efficacy and Safety of IBI305 Plus Paclitaxel/Carboplatin Compared to Bevacizumab Plus Paclitaxel/Carboplatin in Treatment-naive Subjects with Advanced or Recurrent Non-squamous Non-small Cell Lung Cancer

Generic Name of the Investigational Drug:	Recombinant Humanized Anti-VEGF Monoclonal Antibody for Injection (IBI305)
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd.
Statistical Analysis Institution:	WuXi Clinical Development Services (Shanghai) Co., Ltd.
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Signature Page for Approval

The following signers approved the Statistical Analysis Plan:

Signature	Date
Name: Zeng Huaxi	
Department/Title: Clinical Information/Senior Biostatistician	
Institution: WuXi Clinical Development Services (Shanghai) Co., Ltd.	

Signature	Date
Name: Luo Zhaoyu	
Department/Position: Clinical Information Department/Senior Biostatistics Director	
Institution: WuXi Clinical Development Services (Shanghai) Co., Ltd.	

Signature	Date
Name: Yanyan Zhang	
Department/Title: Clinical Operation/Project Manager	
Institution: WuXi Clinical Development Services (Shanghai) Co., Ltd.	

Signature	Date
Name: Xing Sun	
Department/Title: Senior Director, Biostatistics	
Institution: Innovent Biotechnology (Suzhou) Co., Ltd.	

Contents

1. Introduction

This statistical analysis plan (SAP) is intended to describe the statistical analysis methods employed in the clinical trial, protocol number CIBI305A301. The clinical trial is proposed to evaluate the efficacy and safety of IBI305 plus paclitaxel/carboplatin compared to bevacizumab plus paclitaxel/carboplatin in the treatment of advanced or recurrent non-squamous NSCLC.

The Statistical Analysis Plan is based on the Clinical Study Protocol version 3.2 (date: November 5, 2018), and Case Report form (CRF) version 1.0 (date: Oct 24, 2016). Any revision of the trial protocol or CRF would result in update of the Statistical Analysis Plan as required.

This SAP must be finalized prior to the final data lock upon approval of the sponsor.

1.1 Changes of Planned Statistical Analysis for the Study

The immunogenicity analysis set (ADA-AS) was added to this SAP, defined as subjects in the SS population who have at least one valid anti-drug antibody assay after the use of study drug. The definition of pharmacokinetic analysis set (PKAS) was changed to subjects in the SS population with at least one PK value. Pharmacodynamic analysis set (PDAS) was changed to subjects in the SS population with at least one PD value.

2. Objective of the Trial

Primary Objective: To compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin compared to bevacizumab plus paclitaxel/carboplatin in the treatment of advanced or recurrent non-squamous NSCLC.

Secondary Objectives:

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

3. Design of the Trial

This is a randomized, double-blind, multicenter Phase 3 study. It is planned to enroll 436 subjects with non-squamous NSCLC and randomize them in a 1:1 ratio, to IBI305 plus paclitaxel/carboplatin arm or bevacizumab plus paclitaxel/carboplatin arm with stratification factors including age (< 60 years vs. ≥ 60 years) and EGFR status (wild-type vs. unknown type).

With every 3 weeks as a treatment cycle, both arms are given 15 mg/kg of IBI305 or bevacizumab plus paclitaxel/carboplatin on Day 1 of each cycle. A maximum of 6 cycles of combination therapy may be given in the absence of progressive disease (PD), intolerable toxicity, withdrawal of consent, loss to follow-up or death (whichever occurs first). Subsequently the subjects will receive single-agent maintenance therapy, i.e., stop paclitaxel/carboplatin and continue treatment with IBI305 or bevacizumab. The single-agent maintenance therapy continues in a 3-week cycle, administered 7.5 mg/kg on Day 1 of each cycle until PD, intolerable toxicity, withdrawal of consent, end of study, loss to follow-up or death, whichever occurs first.

During the study, subjects will undergo CT or MRI examination every 6 weeks (±7 days) for tumor assessment by the investigator at each site to confirm whether to continue the study treatment until PD, withdrawal of consent, loss to follow-up, death, other anti-tumor treatment or end of study. If the study treatment is terminated for reasons other than PD, tumor assessment should be continued for the subject until PD, withdrawal of consent, loss to follow-up, death, other anti-tumor treatment or end of study. If the treatment is terminated due to PD, the investigator will perform telephone visits for the subject every 12 weeks (±7 days) to collect subsequent anti -tumor treatment and survival information of the subject until death, withdrawal of consent, loss to follow-up or end of study.

Flowchart:

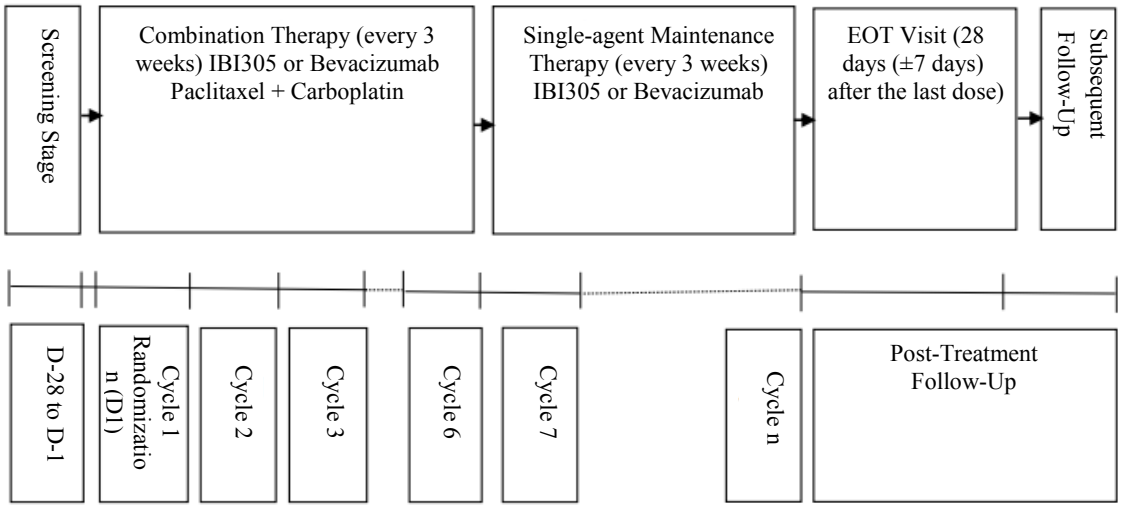

Figure 1. Principle for Study Design

3.1 Estimation of Sample Size

Two hundred and eighteen (218) subjects in each arm (436 subjects in total) achieving a 80% power can confirm the clinical equivalence between IBI305 plus paclitaxel/carboplatin and bevacizumab plus paclitaxel/carboplatin.

This sample size is estimated based on the following assumptions:

- ORR is equal between IBI305 and bevacizumab arms
- ORR of bevacizumab arm is set as 50.0%
- The equivalence cutoff of ORR ratio is assumed (0.75, 1/0.75)
- The significance level for two one-sided tests is 0.05 (one-sided)
- The randomization ratio is 1:1

Based on the above assumptions, each group needs 218 subjects (436 subjects in total). The sample size is estimated using software PASS2013.

3.2 Randomization

Subject random number: This study is a randomized, double-blind, active-controlled multicenter Phase 3 study. It is planned to enroll 436 subjects with non-squamous NSCLC at about 35 site across the nation and randomize them, in a 1:1 ratio, to IBI305 plus paclitaxel/carboplatin arm or bevacizumab plus paclitaxel/carboplatin arm with stratification factors including age (< 60 years vs. ≥ 60 years) and EGFR status (wild-type vs. unknown type), a total of four combinations. The randomization list and labels will be

prepared 4 times the total number of subjects enrolled (in case of accidental drug loss or unbalanced enrollment in stratified subgroups), i.e., randomization list and labels for 436 subjects are prepared in each stratified subgroup (1: < 60 years, wild-type EGFR; 2: < 60 years, EGFR unknown; 3: ≥ 60 years, wild-type EGFR; 4: ≥ 60 years, EGFR unknown). The block randomization will be used, and subjects in each block will be randomized in a 1:1 ratio to receive IBI305 and bevacizumab.

Drug random number: IBI305 or bevacizumab plus paclitaxel/carboplatin will be administered at 15 mg/kg on Day 1 of each 3-week treatment cycle. A maximum of 6 cycles of combination therapy may be given in the absence of PD, intolerable toxicity, withdrawal of consent, loss to follow-up or death (whichever occurs first). The study drug (IBI305 or bevacizumab) for injection is available in strength of 100 mg/vial. It is estimated that each subject (e.g., 60 kg) requires an average of 9 vials in each cycle and approximately 54 vials for 6 cycles. For a total of 436 subjects with non-squamous NSCLC to be enrolled, about 23,544 vials will be needed, and 6 significant digits are taken as the drug random number (XXXXXX). The Statistical Analysis Institution must produce drug randomization no. and grouping information, based on the random number for drugs, required for blinding, validity term of the drugs, and corresponding quantity of the drugs, provided by the Sponsor.

4. Study Endpoints

4.1 Efficacy Endpoints

1) Primary efficacy endpoint

- Objective response rate (ORR)

ORR is evaluated according to RECIST v1.1, which is defined as the proportion of subjects who achieve a reduction of tumor volume to the pre-specified value maintaining for the minimum time limit, including those with complete response (CR) and partial response (PR). The analysis data cutoff date for assessing primary efficacy endpoint is 18 weeks after randomization of the last subject.

$$\text{ORR} = \frac{\text{Number of } CR + PR \text{ subjects}}{\text{Total number of analysis population}} \times 100\%$$

2) Secondary efficacy endpoints

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

All indices, except for OS, are evaluated according to RECIST v1.1.

DOR is defined, for CR or PR subjects, as the duration from first tumor assessment as CR or PR to PD or death before PD; if the CR or PR subject does not have PD or death before PD, the date of last imaging assessment is censored date.

PFS is defined as the duration from randomization to PD or death before PD; if no PD or death before PD occurs, the date of last imaging assessment is censored date.

DCR is defined as the proportion of subjects whose tumor is reduced or stabilized maintaining for a certain period of time, including subjects with CR, PR, and stable disease (SD). The analysis data cutoff date for assessing DCR is 18 weeks after randomization of the last subject.

$$\text{DCR} = \frac{\text{Number of } CR+PR+SD \text{ subjects}}{\text{Total number of analysis population}} \times 100\%$$

OS is defined as the duration from randomization to patient death for various reasons. If the subject is surviving or lost to follow-up as of the end of study, the censored date will be the date of their last contact.

4.2 Safety Endpoints

- Vital signs
- Physical examination
- Laboratory tests (Hematology Test, blood biochemistry, and urine test)
- 12-Lead ECG
- Adverse events (AE, including treatment-emergent adverse event [TEAE]), adverse events of special interest (hypertension, proteinuria, gastrointestinal perforation, hemorrhages [cerebral hemorrhage, hematuria, and upper gastrointestinal hemorrhage], cardiotoxicity and thrombosis), and serious adverse events (SAE)
- Immunogenicity: ADA-positive rate and neutralizing antibody positive rate

4.3 PK/PD Endpoints

- Population PK including trough steady-state concentration after multiple dose
- Changes of serum vascular endothelial growth factor (VEGF) at different time points

5. Definition

5.1 Baseline

Trial baseline value: For safety endpoints, it is defined as the last non-missing measurement before first dose of study drug; for efficacy endpoints, it is defined as the last non-missing measurement before randomization. If the last non-missing measurement cannot be judged by time and corresponding scheduled visit measurement is non-missing, corresponding scheduled visit measurement is used.

5.2 Change Since Baseline

Change from baseline: Defined as the difference of measured value from baseline value

- Change since Baseline = Measured Value at Visit X - Baseline Value

The percentage since baseline is calculated as:

- Percent of change from baseline = (Measurement at visit X - Baseline value)/Baseline value ×100%

5.3 Number of Research Days

Study day: Calculated from the day the subject takes study drug, the day of using the study drug is regarded as Day1, indicating the time from the first dose of study drug to the start/end of test or occurrence of event (e.g., progressive disease, death).

If the event occurs on or after the day of using study drug: Study day = Date of event - Date of using study drug + 1;

If the event occurs before the day of using study drug: Study day = Date of event - Date of using study drug.

6. Analysis Dataset

Intention-To-Treat (ITT):

Includes all randomized subjects.

The data set will be used to summarize major protocol violations and disposition of subjects and populations.

Full analysis set (FullAnalysisSet, FAS):

Includes all evaluable subjects who are randomized and have received at least one dose of

study drug. The data set is the primary analysis set for efficacy evaluation and will be additionally used to summarize demographics and other baseline characteristics, including medical history and treatment history.

After discussion at blind data review meeting, the following three categories of subjects will be excluded from full analysis set:

1. Subjects who experience allergy on the first dose, do not receive a full combination dose, and are immediately withdrawn from the study.
2. Second-line patients who are wrongly enrolled.
3. Subjects whose baseline lesions are not measurable as determined by central imaging.

Per Protocol (PP):

On the basis of FAS, the subjects who have completed the pre-specified minimum exposure to study drug without pre-specified major protocol violation. The data set is the secondary analysis set for efficacy evaluation.

Safety dataset (SafetySet, SS):

All subjects who have received at least one dose of any study drug after randomization and have post-medication data for safety evaluation. The data set is used to evaluate the safety in this study.

Pharmacokinetic Analysis Set (PKAS):

Subjects in the SS population who have at least one PK value.

Pharmacodynamic analysis set (PDAS):

Subjects in the SS population who have at least one PD value.

Immunogenicity Analysis Set (ADA-AS):

Subjects in the SS population who have at least one valid anti-drug antibody assay after the use of study drug.

7. Interim Analysis

No interim analysis is planned for this study.

8. Data Management and Review

The data used for final data are cleaned data.

8.1 Data Processing and Transfer

Electronic case report form (eCRF) data will be exported from Electronic Data Capture (EDC) system by data management team and transmitted as SAS datasets to statistical

programming team.

In addition to data screening based on data management protocol, the programmer programming to generate analysis datasets and graphs provides additional data screening for the data collected. The expected data problems will be exported and confirmed as "problems" by the SAS Log, and picked out by SAS Macro and transferred to the Data Management Department.

Prior to database lock, a further data screening will be provided for review of charts produced, based on the cleaned subset of the subjects. Prior to database lock, those charts will be discussed in the data review conference with the Sponsor, to confirm any data problem and seek for correction.

A final blind data review meeting will be held prior to final data locking. At the final blind data review meeting, the criteria for major protocol violations will be reviewed, especially those for major protocol violations to be excluded from PP set, and final decision will be made.

9. Statistical Method

9.1 General Considerations for Statistical Analysis

9.1.1 General Rules

For continuous variables, descriptive statistics will include count, mean, standard deviation, median, minimum and maximum; for categorical variables, descriptive statistics will include the number and percentage of each category.

Unless otherwise specified, the default significance level is 5%; all tests are two-sided.

9.1.2 Hypothesis testing:

This is a clinical equivalence study between IBI305 and bevacizumab, with objective response rate (ORR) as the primary endpoint. The equivalence hypothesis testing is:

H_0: $\pi_{\text{test arm}}/\pi_{\text{control arm}} \leq 0.75$	H_0: $\pi_{\text{test arm}}/\pi_{\text{control arm}} \geq 1/0.75$
H_1: $\pi_{\text{test arm}}/\pi_{\text{control arm}} > 0.75$	H_1: $\pi_{\text{test arm}}/\pi_{\text{control arm}}$
$\alpha = 0.05$ (one-sided)	$\alpha = 0.05$ (one-sided)

The confidence interval method is used to judge the equivalence: If 90%CI of between-group ORR ratio (test arm to control arm) is within (0.75, 1/0.75), it is considered that the

clinical equivalence of test arm with control arm is established. The between-group ORR ratio and 90% confidence interval are estimated using a generalized linear model (GLM): Group and stratification factors, age (< 60 years vs. ≥ 60 years) and EGFR status (wild-type vs. unknown type) are included in the model.

9.1.3 Handling of Missing Data

Safety data: Missing data are not imputed. Missing data are imputed only when time is divided for summary analysis.

For categorical variables, subjects with missing data will not be included in the percentage calculation unless otherwise specified. The number of subjects with missing data will be presented.

Calculation of treatment duration when the date of last dose of study drug is missing

For the calculation of treatment duration, the date of last study drug infusion should be consistent with that of last dose on the dosing page of CRF. If date of last dose on the dosing page is missing on CRF, the treatment duration should be counted as missing.

The last infusion should be clearly recorded on CRF and not be estimated by the date of returning remaining medicinal product.

Handling of missing and partially missing dosing time for concomitant medication

Dose start and end times will not be imputed. If the date or time of a dose is missing or partially missing, and it cannot determine whether the dose is administered before or after the first dose of study drug, the dose will be considered as prior concomitant medication.

Handling of missing and partially missing onset date and time of adverse event

Missing and partially missing onset date and time of adverse event will be imputed in case that the adverse event will be classified as treatment-emergent adverse event when the information does not indicate that the adverse event starts earlier than the first dose of study drug or later than treatment-emergent adverse event. The completely missing end date and time of adverse event will not be imputed, and partially missing end date and time of adverse event will be imputed. The above mentioned data imputation is only used for the division of adverse events and will not be presented in listings. The date and time of adverse event outcome will not be imputed except for analyses involving calculation of duration of adverse event.

Imputation rules for AE onset date missing:

- If year and month are known and earlier than month and year of the first dose of study drug, the last day of known month will be used for imputation.
- If the year and month are known and exactly the same month and year of the first dose of study drug, the start date of AE is the date of first dose of study drug (date refers to "mm-dd").
- If year and month are known and later than month and year of the first dose of study drug, the first day of known month will be used for imputation.
- If only the year is known and earlier than year of the first dose of study, it is imputed as "December 31".
- If only the year is known and exactly the same year of the first dose of study drug, the start date of AE is the date of first dose of study drug (date refers to "mm-dd").
- If only the year is known and later than year of the first dose of study, it is imputed as "January 1".
- If the day, month, and year are all missing, the date of first dose of study drug is taken as the corresponding start date.
- If the imputed start date is after the end date, the end date will be taken as the corresponding start date.
- It is considered as missing in other cases.

Missing of AE end date

- If year and month are known, the last day of known month will be used for imputation.
- If only the year is known, it is imputed as "December 31".
- For AE of subjects who died eventually, the AE end date should be an earlier date between date of death and imputed end date.
- It is considered as missing in other cases.

Handling of adverse events with missing date and time of first dose

When both date and time of the first dose of study drug are missing, all adverse events occurring on or after the day of randomization should be regarded as treatment-emergent adverse events. The treatment duration is counted as missing. If the subject's first dose date is complete but time is missing, whether it is a treatment-emergent adverse event is determined according to the date.

Handling of adverse events with missing relationship to study drug

If relationship to study drug is missing, the relationship of adverse event to study drug will be considered as possible in the relationship table, but missing data will not be imputed.

Handling of potentially clinically significant abnormalities

Subjects with missing baseline data will be classified in "normal/missing baseline" category.

Measurements marked as invalid by the laboratory will not be included in the analysis.

Efficacy data: Except for censoring rules specified in Section 9.4, any missing values will not be imputed for primary and secondary efficacy analyses. For ORR and DCR in FAS and PP sets, subjects without tumor assessment after baseline period will be considered as non-evaluable (NE) according to RECIST criteria.

9.1.4 Export of Statistical Results

All statistical results will be exported directly by SAS. See separate documents for samples of the figures, tables, and listings. The export template is used to standardize the programmer's work. In this Plan, it is not required to revise and review any non-substantial or modificatory adjustment to the export template that does not influence the Plan.

Unless otherwise specified, in the description P-values are presented to 4 decimal places, mean, median, Q1, Q3 to +1 decimal place in the original data format, minimum and maximum to the same decimal places as original data recorded in the database, and SD to +2 decimal places in the original data format. Percent (%) is presented to 1 decimal place, rate ratio to 2 decimal places, hazard ratio to 2 decimal places, and confidence interval to 3 decimal places.

9.1.5 Multicenter Study

As this study is a multicenter study, the primary endpoint (ORR) will also be tabulated by site and group, but no separate equivalence analysis will be performed by site. Sites with < 5 ITT subjects per treatment group will be combined for analysis and specific site combined analysis will be discussed at the data review meeting.

9.2 Disposition of Subjects

The disposition of subjects is summarized for all subjects. The number and percentage of subjects with screen failure, reasons for screen failure, number and percentage of subjects enrolled, still receiving study drug, stopping study drug, completing the study as planned, withdrawing from the study prematurely and not completing the study will be calculated

by arm and site. Subjects withdraw early will be summarized by the main causes for withdrawal from the trial. Number and percentage of subjects will be calculated by group, according to disposition of subjects in the analysis populations.

A listing of subject disposition by arm and subject number will be provided.

9.2.1 Protocol Deviations

A listing of protocol violations by trial arm and subject number will be provided.

In case of any other protocol violation, case discussion meeting should be held as needed or based on the opinions of principal investigator or statistician at the final blind data review meeting to decide corresponding treatment (classified as major protocol violation, whether it affects efficacy analysis, and minor protocol violation)

9.3 Demographics and Other Baseline Characteristics

Analyses of demographics and other baseline characteristics are based on FAS. Randomized but not included patient information will be listed separately for FAS set. Between-group differences in demographics and other baseline characteristics will not be statistically tested. If significant difference is observed in a specific variable, for continuous variables, t-test is used to calculate the statistics and P value for differences; for categorical variables, chi-square test or Fisher's exact test is used to calculate P values for differences.

9.3.1 Demographics

Descriptive statistical analysis will be performed for demographic variables by trial arm. The following information will be tabulated and summarized.

- Age (years) = Integer [(Date of Signature of the Informed Consent - Date of Birth + 1)/365.25].
- Sex: male, female
- Nationality: Han Nationality, Other
- Height (cm)
- Body Weight (kg)
- Body Mass Index BMI (kg/m^2)
- Body surface area (m^2) = 0.00616 height (cm) + 0.01286 weight (kg) - 0.1529
- Smoking history
- Baseline ECOG (Eastern Cooperative Oncology Group) performance status

The demographics list is provided by trial group and subject serial no.

9.3.2 Past history, surgical history and prior treatment

Past history and surgical history will be coded using Medical Dictionary for Regulatory Affairs (MedDRA) V19.1 and tabulated by preferred term and group.

The primary tumor history will be summarized in this study, including the following information:

- Time interval from diagnosis date to randomization date (months) = (Date of randomization - Date of diagnosing primary disease + 1)/30.25, rounded to one decimal place
- Disease stage: Locally advanced, metastatic, local advanced and metastatic
- Diagnostic method: Histology, cytology
- Tissue type
- Differentiation: Well differentiated (G1), moderately differentiated (G2), poorly differentiated (G3), undifferentiated (G4), grade cannot be assessed (GX)
- Malignant pleural effusion: Yes, no
- TNM staging
- Clinical staging
- Relapse: yes, no
- EGFR status: wild-type, unknown

The number of subjects receiving at least one prior tumor therapy (chemotherapy, radiotherapy and surgery) will be summarized separately, and the treatment information will be pooled. For chemotherapy regimens and radiotherapy sites, coded data will be categorized by clinical team to determine the specific categories presented in the form.

All past history, surgical history, primary tumor history and prior tumor therapy will be listed.

9.3.3 Prior and Concurrent Medications

Prior and concomitant drug name will be coded using WHO-Drug (version date: June 1, 2016 or later) and ATC, and summarized by ATC code and trial arm.

“Prior” medications are drugs that are used and stopped prior to the first dose of the investigational drug.

“Concurrent” medications are drugs of which:

- All medications started on or after the first dose of study drug;

- All concomitant medications starting before the first dose of study drug and continued after the first dose of study drug are tabulated by treatment group.

A listing of all prior and concomitant medications will be provided.

9.3.4 Other Baseline Tests

Baseline ECOG scores are pooled and listings are provided.

9.4 Efficacy Analysis

Efficacy analysis is primarily based on FAS, and PP set will serve as sensitivity analysis dataset for efficacy analysis.

9.4.1 Primary Efficacy Analysis

The primary study objective is to examine the clinical equivalence of IBI305 plus paclitaxel/carboplatin compared to bevacizumab plus paclitaxel/carboplatin in the treatment of advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) with objective response rate (ORR) as primary endpoint. ORR is defined as the rate of confirmed complete response (CR) or partial response (PR), assessed by validated radiological methods for target lesions and non-target lesions, and judged according to RECIST v1.1. Subjects who have no tumor assessment after baseline period will be considered as non-evaluable according to RECIST criteria. Subjects eligible for complete or partial response assessment must have at least one available lesion measured by RECISTv1.1.

The assessment of ORR in clinical equivalence evaluation is the results based on independent tumor assessment committee (refer to Protocol Appendix III: RECIST V1.1 for the assessment criteria and process of independent tumor assessment committee), and the investigator's assessment result will be used for sensitivity analysis.

The clinical equivalence will be determined by whether the 90%CI of ORR ratio of IBI305 to bevacizumab is within the equivalence cutoff (0.75, 1/0.75) of ORR ratio. Generalized linear model (GLM, including group and stratification factors, age (< 60 years vs. ≥ 60 years) and EGFR status (wild-type vs. unknown)) is used to estimate the ORR and corresponding 95%CI of two groups, ORR ratio between two groups and corresponding 90% and 95%CI. The difference in ORR between two groups and corresponding 90% and 95%CI are also estimated by the GLM model. In the analysis of actual data, too less subjects in the subgroup according to baseline EGFR will cause the GLM not converging,

then the baseline EGFR will not be included in the GLM.

9.4.2 Secondary Efficacy Analysis

The secondary efficacy analysis will be based on the results assessed by independent tumor assessment committee, and the investigator's assessment will be used for sensitivity analysis.

9.4.2.1 Disease Control Rate (DCR)

DCR is defined as the rate of confirmed complete response (CR), partial response (PR) and stable disease (SD) assessed by validated imaging methods for target lesions and non-target lesions, and judged according to RECIST v1.1. The analysis of DCR is the same as that for primary efficacy endpoint, but equivalence test is not performed.

9.4.2.2 Duration of Response (DOR)

DOR is defined, for CR or PR subjects, as the duration from first tumor assessment as CR or PR to PD or death before PD; if the CR or PR subject does not have PD or death before PD, the date of last imaging assessment is censored date. If the subject experiences progression or death missing two or more consecutive tumor assessments, the time of last evaluable tumor data is taken as censored date. If the subject receives other anti-tumor therapy prior to PD, the date of last imaging examination for other anti-tumor therapy is taken as censored date.

Duration of response (months) = (Date of PD or death before PD or censored date - Date of first tumor assessment as CR or PR + 1)/30.25, rounded to two decimal places

Kaplan-Meier method is used to estimate median DOR and its 95% confidence interval, and the survival curve is plotted. Hazard ratio (HR) of two groups, 90% and 95% confidence intervals are estimated from a Cox model, which includes group and stratification factors.

9.4.2.3 Progression-free Survival (PFS)

PFS is defined as the duration from the date of randomization to the date of first documented PD or death before PD, whichever occurs first. For subjects who have no progression or death before PD, the date of last tumor assessment will be taken as censored date. For subjects who have no tumor assessment after baseline period, the date of randomization will be taken as censored date. If the subject experiences progression or death missing two or more consecutive tumor assessments, the time of last evaluable tumor

data is taken as censored date. If the subject receives other anti-tumor therapy prior to PD, the date of last imaging examination for other anti-tumor therapy is taken as censored date.
Progression-free survival (months) = (Date of event - Date of randomization + 1)/30.25, rounded to two decimal places
Kaplan-Meier method is used to estimate median PFS and its 95% confidence interval, and the survival curve is plotted. Hazard ratio (HR) of two groups, 90% and 95% confidence intervals are estimated from a Cox model, which includes group and stratification factors.

9.4.2.4 Overall Survival (OS)

OS is defined as the duration from the date of randomization to date of death (from any causes). For subjects who have not been reported dead at the time of analysis, their last known surviving date will be taken as censored date.
Overall survival (months) = (Date of event - Date of randomization + 1)/30.25, rounded to two decimal places
Kaplan-Meier method is used to estimate median OS and its 95% confidence interval, and the survival curve is plotted. Hazard ratio (HR) of two groups, 90% and 95% confidence intervals are estimated from a Cox model, which includes group and stratification factors.

9.4.3 Sensitivity Analysis

The analyses of primary and secondary efficacy endpoints will be repeated based on investigator assessment.
Based on the assessment of independent tumor assessment committee, center effect (fixed or random) is included in the model (GLM or Cox) analysis of primary efficacy endpoint and secondary efficacy endpoints, and the significance of center effect is tested.
Analysis of primary and secondary efficacy based on central imaging and investigator assessment will be performed on PP set.

9.4.4 Subgroup Analysis

Subgroup analysis will be performed for ORR by stratification factors, presented with a forest plot, and the analysis of ORR for treatment group is provided. Subgroups include:

- Age (< 60 years vs. ≥ 60 years)
- Gender (male vs female)
- EGFR status (wild type vs. unknown)
- ECOG score (0 vs 1)

- Smoking (yes vs no vs ex-smoking)
- Tumor staging (stage IIIB vs stage IV)
- Relapse (yes vs no)

9.5 Subsequent Anti-tumor Therapy

Subsequent anti-tumor therapy will be tabulated by subject group and summarized by treatment session and type (chemotherapy, radiotherapy and surgery). For chemotherapy regimens and radiotherapy sites, coded data will be categorized by clinical team to determine the specific categories presented in the form.

A listing of all subsequent anti-tumor therapies will be provided.

9.6 Safety Analysis

The safety analysis is based on the safety analysis set.

Safety observation period starts from the patient signing the informed consent and is divided into the following 3 periods:

- Pre-treatment period: From signing of informed consent to the first dose of study drug.
- Treatment period: From the first dose of study drug to 30 days after the last dose of study drug.
- Post-treatment period: From 31 days after the last dose of study drug to the end of follow-up period. A listing of all AEs in three observation periods will be provided. Tabular summary of AEs in treatment period will be provided.

9.6.1 Drug Exposure and Compliance Analysis

The total exposure to medications (combination therapy and separately administered IBI305/bevacizumab) is calculated, and P value of the difference is calculated using t-test. The following summaries will be provided for combination therapy period (first 6 cycles), single-agent maintenance period (continuous treatment) and overall:

- Number of cycles
- Duration of treatment (weeks)
- Cumulative exposure (mg)
- Actual number of injections
- Number of dose delays or adjustments
- Relative injected dose intensity (%)
- Compliance with number of injections (%)

Duration of treatment (weeks) in this study is defined as:

Duration of treatment = (Date of last injection - Date of first injection + 1)/7

Treatment compliance is defined as:

Relative injected dose intensity = (Cumulative actual total dose/Cumulative planned total dose) ×100

Compliance with number of injections = (Cumulative actual total injections/Cumulative planned total injections) ×100

The actual number of injections is the planned number of injections when combination therapy period continues for 4 to 6 cycles. For medication with monoclonal antibody less than 4 cycles, the planned number of injections is 4. Treatment compliance is summarized only for combination therapy period.

Subjects are further classified by compliance: <80%; ≥80% and ≤20%; >120%.

9.6.2 Adverse Events

All adverse events (AEs) will be classified in accordance with the System Organ Class (SOC) and preferred terms of the ICH Medical Dictionary for Regulatory Activities (MedDRA).

Severity

Severity of each TEAE will be classified as one of 5 grades (Grades 1-5) in accordance with the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCICTCAE) V4.03, and the incidence (frequency and percentage) will be provided by SOC and PT.

TEAEs with missing CTCAE grade in severity after first dose of study drug are classified as severe. If a subject reports one TEAE more than once in SOC/PT, then AE with the maximum severity will be used in the summary of corresponding severities.

Relationship with the Investigational Drug

The investigator will indicate the relationship with the investigational drug, classified as “Related”, “Possibly Related”, “Unlikely Related”, “Unrelated”, and “Cannot be Judged”. TEAE with missing relationship with the investigational drug would be considered as “Possibly Related” with the investigational drug. If a subject reports the same one AE more than once in SOC/PT, then AE with the maximum severity will be used in the summary of corresponding relationships. Relevant TEAEs in the summary table include TEAEs which

are “Related”, “Possibly related”, and “Cannot be judged” with the investigational drug.

Observation period of adverse events

All AEs, regardless of severity and relationship to study treatment, from signing of informed consent to the end of follow-up period should be recorded on the corresponding page or interface of CRF.

Adverse events are classified as follows:

- Pre-treatment AE: Any AE reported during pre-treatment period,
- Treatment-emergent adverse event (TEAE): AE reported during treatment period as defined above,
- Post-treatment AE: AE reported during post-treatment period.

Adverse event analysis mainly focuses on TEAE. A listing of all AEs will be provided.

Analysis of treatment-emergent adverse events

The following summary of TEAE is generated for the treated population:

- An overview of TEAE outlines the number (%) of patients who experience any of the following events

- TEAE
- Grade 3 and above TEAE
- Serious TEAE
- TEAE leading to trial discontinuation
- TEAE resulting in dose reduction
- TEAE leading to death
- TEAE leading to permanent discontinuation of treatment
- Adverse event of special interest

- All TEAEs are coded by primary SOC and PT, and the number (%) of patients experiencing at least 1 TEAE is presented. TEAEs are sorted by internationally recognized (ICH recommended) SOC order in decreasing incidence of PT within each SOC by IBI305 group. This ranking applies to all other tables unless otherwise specified.
- All TEAEs related to study drug are coded by primary SOC and PT, and the number (%) of patients experiencing at least 1 TEAE is presented; SOCs are sorted by internationally recognized order, and PTs in each IBI305 group within SOC are sorted

by decreasing incidence.

A listing of TEAEs in all patients will be provided.

Analysis of all serious treatment-emergent adverse events

The following summaries of serious TEAEs are given for the treated population:

- All serious TEAEs are coded by primary SOC, PT, and most serious grade. The number (%) of patients experiencing at least 1 TEAE is presented and sorted by internationally recognized order of SOC and decreasing incidence of PT within each SOC by IBI305 group.
- All serious TEAEs related to study drug are coded by primary SOC, PT, and most serious grade. The number (%) of patients experiencing at least 1 TEAE is presented and sorted by internationally recognized order of SOC and decreasing incidence of PT within each SOC by IBI305 group.
- A listing of all SAEs is provided.

Analysis of all treatment-emergent adverse events leading to dose modification

The following summaries of TEAEs leading to dose modification are given to the treated population:

- All treatment-emergent adverse events leading to dose reduction, dose interruption, dose omission and cycle delay will be categorized by primary SOC, PT and the most serious grade. The number (%) of patients will be given and sorted by internationally recognized order of SOCs and decreasing incidence of PT within each SOC.
- A listing of all TEAEs leading to dose modification will be provided.

Analysis of all treatment-emergent adverse events leading to treatment discontinuation

The following summaries of TEAEs leading to treatment discontinuation are given to the treated population.

- All treatment-emergent adverse events leading to treatment discontinuation will be categorized by primary SOC, PT and the most serious grade. The number (%) of patients will be given and sorted by internationally recognized order of SOCs and decreasing incidence of PT within each SOC.
- A listing of all TEAEs leading to treatment discontinuation will be provided.

In the table for overall incidences of adverse events, patients with the same AE once but with different severities will be only counted once in the frequency table; its maximum

severity will be used, applicable for SOC and PT.

A listing of all adverse events (including"non-treatment-emergent adverse events") will be provided.

Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESIs) will be summarized and listed by incidence (frequency and percentage). Including the following adverse events:

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

For infusion reaction, duration of TEAE, and the interval form the injection time of the drug will be summarized, which are calculated as follows:

- Duration of infusion reaction (min) = End date/time of infusion reaction - Start date/time of infusion reaction
- Interval (min) from the Injection Time of the Drug = Start Date and Time of the Infusion Reaction - Date and Time of the Last Infusion prior to Start of the Infusion Reaction

Major Adverse Events

A significant adverse event is any adverse event, other than serious adverse event, that requires corrective medical action (discontinuation, dose reduction, and symptomatic treatment). Tabulated analysis will be made.

Death

The observation period for death is the observation period defined above.

- On-study death: Death occurred during the study

- On-treatment death: Death occurred during the treatment

The following summaries of deaths are given for the treated population:

- The number (%) of patients who died is statistically analyzed by study period (on-study and on-treatment), and the cause of death should be indicated if it is available on the death report form.
- Treatment-emergent adverse events leading to death, regardless of relationship to study medication, are categorized by primary SOC and PT, number (%) of patients will be given; SOC is sorted by internationally recognized order and PT is sorted by alphabetical order within each SOC and the most serious NCI grade.

9.6.3 Clinical laboratory Test Value

Only safety laboratory tests specified in the protocol will be analyzed.

For continuous trial data, summary statistics (number, mean, standard deviation, median, minimum and maximum) of measured values and changes from baseline will be presented by cycle and trial arm.

The frequency of patients with each grade of laboratory abnormality during on-treatment period is summarized for each cycle. For patients with multiple abnormalities in the same laboratory variable during on-treatment period, the maximum grade (most serious) for each patient is used.

A listing of all laboratory parameters will be presented.

The last non-missing measurement before the use of study drug is referred to as baseline measurement. The treatment period for all laboratory parameters starts from day 1 of study medication.

For the last cycle, evaluations performed between day 2 of the cycle and 30 days after last dose (whichever occurs later) are assigned to the last cycle.

For a given parameter, a patient is considered evaluable if he/she has at least one measurement for the parameter during treatment. The baseline laboratory evaluation results, and the worst results during the trial will be summarized in cross table.

A listing of all laboratory values and abnormal values will be provided.

9.6.4 Vital Signs

For parameters of vital signs, measured values and changes since baseline will be summarized by planned time point and trial group. Abnormal values of vital signs will be

summarized.

See the table below for abnormal values of vital signs:

Parameter	Unit	Low	High
Systolic blood pressure	mmHg	<=90 mmHg, or change <= -20 mmHg since baseline	≥140 mmHg, and change ≥20mmHg since baseline
Diastolic blood pressure	mmHg	<=50 mmHg, and change <= -15 mmHg since baseline	≥90 mmHg, and change ≥15mmHg since baseline
Pulse	Bpm	<=50 bpm, and change <= -15 bpm since baseline	≥120 bpm, and change ≥ 15bpm since baseline
Body temperature	℃	NA	≥37.5℃, and change ≥1.1℃ since baseline
Body weight	Kg	Percentage change <= -10.0% since baseline	Percentage change ≥ 10.0% since baseline

A list for all parameter values of vital signs, and for abnormal values will be provided

Trend charts for changes in systolic and diastolic blood pressures are presented by scheduled time point and trial arm.

9.6.5 12-Lead ECG

For parameters of 12-lead ECG, measured values and changes since baseline will be summarized by planned time point and trial group. The baseline laboratory evaluation results of 12-lead ECG, and the worst results during the trial will be summarized in cross table.

Refer to the following definitions for summary of abnormal QTc intervals:

Absolute values of QTc intervals will be classified as:

- >450 msec
- >480 msec
- >500 msec

Changes of QTc intervals since baseline will be classified as:

- Prolongation > 30 msec
- Prolongation > 60 msec

A list of all parameter values and prolonged QTc intervals will be provided.

9.6.6 Physical Examination

Physical examination results will not be summarized. A list of all physical examination results will be provided and abnormal values will be indicated.

9.6.7 Immunogenicity

The positive rates of anti-drug antibody (ADA) and neutralizing antibody (Nab) in patients

who have at least one valid anti-drug antibody assay after study medication will be summarized by scheduled time point and trial arm, and post-baseline positive rates will also be summarized. A listing of all immunogenicity test values will be provided.

9.6.8 Other Tests

The following additional safety tests will be only presented as listings.

- Blood pregnancy test

9.7 Pharmacokinetic Analysis

Population pharmacokinetic analysis is not included in this statistical analysis plan.

Descriptive statistics and coefficient of variation (CV) of plasma concentration at each time point are summarized by trial arm and a listing will be provided. For the calculation of descriptive statistics, if the plasma concentration is below the lower limit of quantification, it will be set as 0. The mean concentration-time profiles will be presented graphically by trial arm.

9.8 Pharmacodynamic Analysis

The pharmacodynamic analysis set is used for analysis.

The measured levels of serum VEGF will be summarized by scheduled time point and trial arm, and a listing will be provided.

10. Quality Control

To ensure that TFL results are delivered each time at high quality level, the quality control procedure of TFL will be defined detailedly in the Quality Control Plan Document.

Appendix 1. Abbreviations

AE	Adverse Events
AESI	Adverse Event of Special Interest
ATC	Anatomic Therapeutic Chemical Classification
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
FAS	Full Analysis Set
GLM	Generalized Linear Model
HR	Hazard Ratio
ICH	International Conference of Harmonization
ITT	Intent-To-Treat
MedDRA	ICH Medical Dictionary for Regulatory Activities
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDAS	Pharmacodynamic Analysis Set
PFS	Progression-free Survival
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PP	Per Protocol
PR	Partial Response
PRES	Posterior Reversible Encephalopathy Syndrome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Organ System
SD	Stable Disease
SS	Safety Dataset
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure, and List
VEGF	Vascular Endothelial Growth Factor
WHO-DD	World Health Organization Drug Dictionaries

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