

## STATISTICAL ANALYSIS PLAN


**Protocol Title:** A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Phase I Clinical Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of IPG11406 in Healthy Adult Subjects

**Protocol Version/Date:** V3.1/Nov. 8, 2024

**Protocol No.:** IPG11406-C001


**Sponsor:** Nanjing Immunophage Biotech Co., Ltd.

**SAP Version/Date:** V1.0/Jan. 21, 2025

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<b>GC Project No.:</b>	NANJ201
<b>Protocol No./Sponsor:</b>	IPG11406-C001/Nanjing Immunophage Biotech Co., Ltd.
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<b>Reviewed by: Sponsor</b>			
<b>Approved by: Sponsor</b>			

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## REVISION HISTORY

Version	Date	Author	Revisions
V1.0	Jan. 21, 2025		Not applicable


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## ABBREVIATIONS

Abbreviations	Definition
ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
BDRM	Blind Data Review Meeting
BLQ	Below the limit of quantitation
BMI	Body mass index
CI	Confidence interval
CLR	Renal clearance
CRA	Clinical research associate
CRF	Case report form
CS	Abnormal with clinical significance
DBP	Diastolic blood pressure
DSS	Dataset specification
ECG	Electrocardiogram
eCRF	Electronic case report form
ES	Enrolled set
HR	Heart rate
ICE	Intercurrent event
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NCS	Abnormal without clinical significance
PK	Pharmacokinetics
PKS	Pharmacokinetic set
PT	Preferred term
QTcF	Fridericia-corrected QT interval
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical analysis system
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SMC	Safety Monitoring Committee

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<b>Abbreviations</b>	<b>Definition</b>
SOC	System organ class
SS	Safety set
TEAE	Treatment-emergent adverse event
ULQ	Upper limit of quantitation
WHO	World Health Organization

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## 1. SYNOPSIS

This is a first-in-human, randomized, double-blind, placebo-controlled, single and multiple ascending dose phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics (PK) of single and multiple ascending doses of IPG11406 in healthy adult subjects.

The SAP will be finalized before the database is locked, and any revisions after the SAP is finalized will be recorded in the Statistical Analysis Plan (SAP) Amendment Form and the Clinical Study Report. If there is any difference in the description of statistical analysis methods in different documents, the content of the SAP shall prevail.


## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Study Objectives

#### 2.1.1. Primary objectives and estimand

**Table 2- 1. Primary objectives and estimand**

<b>Objectives:</b> Part A: single ascending dose (SAD): To evaluate the safety and tolerability of a single oral dose of IPG11406. Part B: multiple ascending dose (MAD): To evaluate the safety and tolerability of multiple oral doses of IPG11406	
<b>Estimand:</b> safety of IPG11406	
<b>Treatment groups:</b> IPG11406 group and placebo group	
Estimand	Statistical analyses
Target population	Analysis datasets
Healthy adult subjects who meet the eligibility criteria and are randomized into the study (SS).	SS
Target variable	Outcome measures
Adverse events (AEs), vital signs, and clinical laboratory parameters	Descriptive statistics
Intercurrent events and treatment strategies	Processing of missing values
<ul style="list-style-type: none"> <li>ICE1 (treatment-related death): <i>treatment policy strategy</i></li> <li>ICE2 (death unrelated to the treatment): <i>treatment policy strategy</i></li> <li>ICE3 (discontinuation of study treatment due to lack of investigational medicinal product (IMP) efficacy or treatment-related AEs): <i>treatment policy strategy</i></li> <li>ICE4 (use of prohibited medications): <i>treatment policy strategy</i></li> <li>ICE5 (discontinuation of the IMP for any reason other than death, lack of efficacy, or treatment-related AEs): <i>treatment policy strategy</i></li> <li>ICE6 (dose deviations of the IMP): <i>treatment policy strategy</i></li> </ul>	<ul style="list-style-type: none"> <li>Treatment policy strategy: All observed safety data are included without data imputation under the influence of intercurrent events (ICEs).</li> </ul>

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<b>Population-level summary</b>	<b>Analytical methods</b>
The binomial distribution model is used to calculate the incidence of safety events in each dose group by cross tabulation.	Frequency and percentage will be listed for categorical variables, and the number of subjects, mean, and other descriptive statistical parameters will be listed for numerical variables.

### 2.1.2. Secondary objectives

#### Part A: single ascending dose (SAD)

- To evaluate the PK of a single oral dose of IPG11406
- To evaluate the effect of food on the PK of a single oral dose of IPG11406

#### Part B: multiple ascending dose (MAD)

- To evaluate the PK of multiple oral doses of IPG11406

### 2.1.3. Exploratory objective

#### Part A: single ascending dose (SAD)

- To evaluate the urine PK of a single oral dose of IPG11406

## 2.2. Study Endpoints

### 2.2.1. Primary endpoints

#### Part A: single ascending dose (SAD)

- Safety endpoints: AEs, vital signs, and clinical laboratory parameters.


#### Part B: multiple ascending dose (MAD)

- Safety endpoints: AEs, vital signs, and clinical laboratory parameters.

### 2.2.2. Secondary endpoints

#### Part A: single ascending dose (SAD)

- PK endpoints: maximum plasma concentration ( $C_{max}$ ), time to  $C_{max}$  ( $T_{max}$ ), half-life ( $t_{1/2}$ ), area under the plasma concentration-time curve from time 0 to the last measurable concentration ( $AUC_{0-t}$ ), area under the plasma concentration-time curve from time 0 extrapolated to infinite time ( $AUC_{0-inf}$ ), and clearance ( $CL/F$ ).

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## Part B: multiple ascending dose (MAD)

- PK endpoints (including but not limited to): steady-state maximum plasma concentration ( $C_{ss, max}$ ),  $t_{1/2}$ , steady-state time to  $C_{max}$  ( $T_{ss, max}$ ), dose interval AUC ( $AUC_{0-\tau}$ ), steady-state clearance ( $CL_{ss/F}$ ), accumulation index calculated using AUC ( $Rac_{(AUC)}$ ), and accumulation index calculated using  $C_{max}$  ( $Rac_{(C_{max})}$ ).

### 2.2.3. Exploratory endpoints

## Part A: single ascending dose (SAD)

- Determination of IPG11406 parameters in urine: renal clearance ( $CLR_{0-t}$ ), cumulative fraction excreted in urine from time 0 to t ( $Ae_{0-t}$ ), and fraction of dose excreted in urine from time 0 to t ( $Fe_{0-t}$ ).

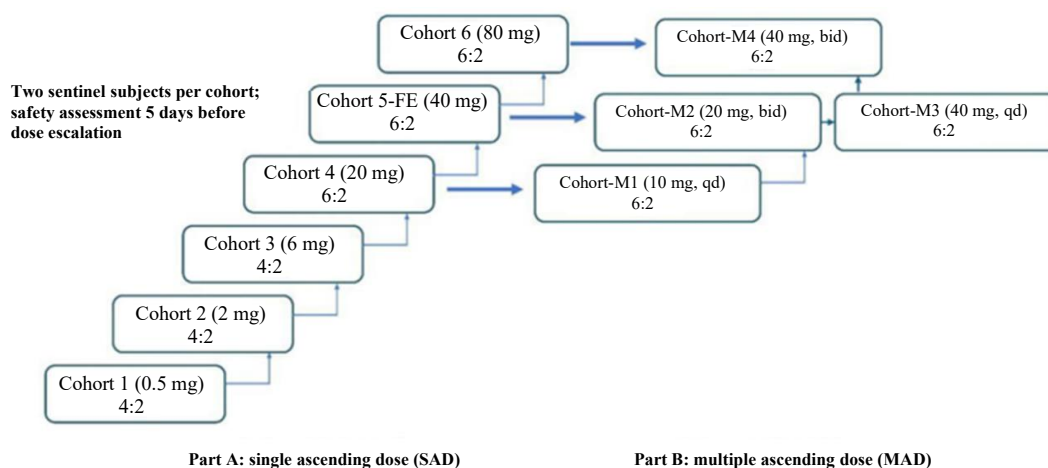
## 3. STUDY METHOD

### 3.1. Overall Design and Plan


This is a first-in-human, randomized, double-blind, placebo-controlled, single and multiple ascending dose phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics (PK) of single and multiple ascending doses of IPG11406 in healthy adult subjects.

This study is divided into two consecutive parts: Part A is an SAD part and Part B is an MAD part. Both parts include a 28-day screening period and a 7-day safety evaluation and follow-up period after the end of the dosing period.

The design patterns of Part A (SAD) and Part B (MAD) are shown in the figure below.



**Figure 3- 1. Schedule of activities**

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### Study overview of Part A:

In this study, six doses of 0.5 mg (Cohort 1), 2 mg (Cohort 2), 6 mg (Cohort 3), 20 mg (Cohort 4), 40 mg (Cohort 5), and 80 mg (Cohort 6) will be administered to subjects. In Cohorts 1 to 3, each cohort consists of 6 subjects, 2 of whom will be given a placebo and 4 of whom will be given IPG11406. In Cohorts 4 to 6, each cohort consists of 8 subjects, 2 of whom will be given a placebo and 6 of whom will be given IPG11406. All subjects will be screened within 28 days prior to dosing. Eligible subjects will be admitted to the phase I clinical study laboratory 1 day in advance for 5 days of administration and observation (hospitalization period: 6 days).

Approximately 42 healthy adult subjects will be planned to be enrolled in this part.

Two sentinel subjects will be selected randomly for each dose group and administered 48 h in advance. Among the two subjects, 1 subject will receive IPG11406 and the other subject will receive a placebo. If the 2 sentinel subjects do not exhibit any significant safety issues within 48 h, the remaining subjects will be dosed.


Subjects will be discharged on Day 5 and followed up on Day 8 after all safety assessments and PK sampling analyses are completed.

One of the cohorts (tentative Cohort 5, which may be adjusted according to the decision of the Safety Monitoring Committee (SMC) meeting) will be selected to evaluate the effect of food on PK parameters. Subjects in this cohort will receive the second dose of IPG11406 or placebo on Day 5 after the first dose following a standard high-fat meal (total calories are about 800 to 1000 kcal, and about 50% of the total calories come from fat).

The Safety Monitoring Committee (SMC) will evaluate the safety and tolerability of IPG11406 based on all safety (including follow-up data) and available PK data accumulated in a blinded manner after each cohort completes 5 days of dosing and evaluation (with food effect cohort evaluated on Day 10). Based on the evaluation results of safety and tolerability, the SMC will decide whether to administer the next dose.

### Study overview of Part B

Part B MAD study will start after the safety and tolerability evaluations of Part A (SAD) for IPG11406 are completed. Appropriate dose levels for Part B will be determined by the SMC based on the safety and tolerability data obtained in Part A. In Part B, three ascending dose levels of multiple doses will be planned to evaluate the safety and tolerability of IPG11406.

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Approximately 32 healthy adult subjects will be planned to be enrolled into four dose groups, with 8 subjects in each cohort. Subjects in Cohort M1, Cohort M2, Cohort M3, and Cohort M4 will receive the study treatment at 10 mg QD, 20 mg BID, 40 mg QD, and 40 mg BID, respectively. Among 8 subjects in each cohort, two subjects are assigned to the placebo control group and 6 subjects will receive IPG11406.

All subjects will be screened 28 days prior to dosing. Eligible subjects who pass the screening will be admitted to the phase I clinical study laboratory 1 day in advance, and then receive administration and observation for 14 days. The first dose will be administered once daily for 10 consecutive days on the morning of Day 1. During the dosing period, blood sampling will be performed as scheduled to assess the PK parameters of IPG11406.

Subjects will be discharged on Day 14 after all safety assessments and PK sampling analysis are completed, and will be followed up on Day 3 after discharge.

After completion of all safety assessments and PK sample analyses, subjects will be discharged on Day 14 and followed up on Day 3 after discharge. After each cohort completes 14 days of dosing and assessments, the SMC will evaluate the safety and tolerability of IPG11406 based on all safety data (including follow-up data) and available PK data accumulated in a blinded manner, and decide whether to proceed to the administration in the next cohort based on the evaluation results.

### 3.2. Randomization and Blinding


#### 3.2.1. Randomization

The IMP number (randomization number) of each subject will be generated by an independent statistician not involved with the study. The independent statistician will generate the IMP number (randomization number) with the stratified randomization method (the stratification factor: dose) using the PLAN procedure in SAS 9.4.

Refer to the randomization plan document for the randomization number and screening number.

#### 3.2.2. Blinding

**Blinding:** Double-blind means that the subjects, investigators, Clinical Research Associates (CRAs), and data analysts are all unaware of the allocation of the IMPs. The sponsor or its designated institution will supply the IMPs (investigational drug and placebo) and ensure that the placebo is similar to the investigational drug in appearance and weight. The investigational drug and placebo for each treatment group will be blinded by the sponsor or its designated institution,

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and the statistical analysts will randomly assign the subjects to either the investigational drug or placebo group. After blinding, the blind codes should be sealed in the envelopes in duplicate, with one copy retained by the clinical study leading site and the other by the drug registration applicant. In the event of an SAE or other emergency, the study physician may open the envelope to identify the IMP received by the subject for urgent medical intervention. This is called emergency unblinding. Emergency unblinding is also required when intolerance is considered in the tolerability evaluation after dose escalation for each cohort, in order to guide whether to continue the escalation.


**Blinding level:** This study adopts a double-blind design, that is, neither the study physicians nor the subjects can ascertain which treatment (investigational drug or placebo) the subjects will receive.

The specific operating procedures are as follows:

- In accordance with the GCP regulations on the management of IMPs, the IMPs are uniformly packaged and labeled (indicated for clinical trial use only), and the investigational drug is completely consistent with the placebo in packaging. Blinding and packaging are performed by relevant personnel.
- The drugs are individually packaged for each subject, with a dedicated person verifying the entire process and maintaining detailed records.
- After being delivered to the study site, the IMPs are stored in a designated location (drug storage area) by the drug administrator.

**Emergency envelopes and blind codes:** An emergency envelope is prepared for each subject before the start of the trial. The envelope is marked with the subject's drug number, and the letter sealed in the envelope indicates the group to which the subject belongs, for emergency unblinding. All IMPs are delivered to the study site along with the corresponding numbered emergency envelopes. The blinding process should be documented in writing and signed by all personnel involved in blinding. The blind codes must be sealed and affixed with the official seal on the spot after the drug dispensing, and stored separately by the dedicated personnel of the study site and the sponsor. The emergency unblinding envelopes are sent to the study site with the IMPs and properly kept by the dedicated personnel of the study site until the end of the trial.

**Emergency unblinding:** In case of emergency unblinding, the investigator seeks approval from the head of the study site, and opens the emergency unblinding envelope after signature and approval are obtained from the principal investigator. The relevant personnel of the sponsor

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should be notified within 24 h after unblinding and the reasons for unblinding should be explained. Emergency unblinding may be considered in the following situations (including but not limited to):

- When a subject experiences an SAE that is considered to be possibly related to the investigational drug or the placebo;
- When a subject develops a serious complication.

**Unblinding rules:** This trial should be unblinded at one time. After the database is closed, the unblinding should be performed by the investigators and the sponsor, and the relevant personnel who keep the blind codes should submit the allocation information to the statistics department for statistical analysis

### 3.3. Sample Size Calculation

**Part A (SAD):** In this part, there are 6 dose-escalation groups: 0.5 mg (Cohort 1), 2 mg (Cohort 2), 6 mg (Cohort 3), 20 mg (Cohort 4), 40 mg (Cohort 5), and 80 mg (Cohort 6). A total of 42 healthy subjects are planned to be enrolled.

**Part B (MAD):** A total of 32 healthy subjects are planned to be enrolled in 4 cohorts: Cohort M1 (10 mg, QD), Cohort M2 (20 mg, BID), Cohort M3 (40 mg, QD), and Cohort M4 (40 mg, BID). Eight subjects will be enrolled in each cohort. The dose selection and dosing frequency for the MAD cohort study may be jointly discussed and adjusted by the investigator and the sponsor based on the study results of Part A.

### 3.4. Analysis Framework

The primary objective of this study is to evaluate the safety and tolerability of PG11406. This will be achieved by descriptive statistical analysis of the safety of all dose groups.

### 3.5. Interim Analysis and Discontinuation Principles


There is no planned interim analysis.

### 3.6. Final Analysis Time

The final analysis will be performed after the SAD and MAD studies are completed.

### 3.7. Result Assessment Time

All assessments are listed in the Schedule of Activities in Table 1 to Table 6 of the protocol.

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## 4. STATISTICAL PRINCIPLES

### 4.1. Confidence Intervals and *P*-Values

- Confidence intervals (CIs) will be presented as 2-sided 95% CIs, unless otherwise specified.
- The statistical analysis will be performed using a 2-sided alpha level of 0.05, unless otherwise specified.

### 4.2. Compliance and Protocol Deviations

No protocol deviations are allowed unless the protocol is formally amended. Protocol deviations are only permissible when they are necessary to eliminate an immediate hazard to the subject. If a protocol deviation occurs, the investigator should record and notify the sponsor.

Major/significant protocol deviations are those that may significantly affect the integrity, accuracy, and/or reliability of the study data, or that may affect the rights, safety, or welfare of the subjects. The investigator must immediately notify the CRA if any potentially significant deviations are identified.

### 4.3. Analysis Population

The following analysis sets are defined for statistical analyses:

- Enrolled set (ES)


The ES includes all subjects who have signed the ICF. The ES will be used to describe subject disposition.

- Full analysis set (FAS)

It includes all subjects who are randomized and have received at least one dose of the IMP. Subjects in the FAS are analyzed based on the randomized treatment group. The FAS is used for baseline data analyses.

- Safety set (SS)

It includes subjects in the FAS who have received at least one dose of the IMP. Subjects in the SS are analyzed based on the actual treatment group. The SS is used for safety analysis.

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- Pharmacokinetic set (PKS)

It includes all enrolled subjects who have received at least one dose of IPG11406 and have at least one post-dose IPG11406 concentration result during the study, with samples that may affect the PK evaluation excluded (e.g., missed doses, wrong doses or deviations, and other treatments that may affect the PK analysis). Subjects in the PKS are analyzed based on the actual treatment group.

The assignment of all analysis sets, including decisions on the inclusion/exclusion of the PKS and other data processing issues, is agreed upon and documented in the report of the Blind Data Review Meeting (BDRM) and performed before the study database is locked.

## 5. TRIAL POPULATION

### 5.1. Screening Data

N/A.

### 5.2. Eligibility Assessment

The following are the criteria for participation in the clinical trial. Subjects must meet all of the eligibility criteria to participate in the study.

#### 5.2.1. Inclusion criteria

Refer to Section 5.1 of the protocol.

#### 5.2.2. Exclusion criteria

Refer to Section 5.2 of the protocol.


### 5.3. Enrollment

Not applicable.

### 5.4. Withdrawal

Subjects have the right to withdraw informed consent and withdraw from the study at any time for any reason.

Subjects must withdraw from the study under the following circumstances (also referred to as "criteria for termination of subject participation"):

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- 1) Subjects experience an acute disease or develop a drug-related or unrelated clinical condition during the study, and the study physician assesses that withdrawal from the study is more beneficial to the subject.
- 2) Subjects become pregnant or plan a pregnancy
- 3) The investigator may withdraw a subject from the study if the subject fails to comply with the study procedures or violates the study requirements.
- 4) Concomitant medications may interfere with the PK results of the study as judged by the investigator.
- 5) Subjects have other behaviors that affect the study results

For subjects who are withdrawn from the study or voluntarily withdraw from the study for any reason, the end-of-study medical assessment should be completed whenever possible; considering the safety of the subjects, the investigators have the right to require the subjects to stay in the study ward for monitoring until they are basically safe. The investigators should record the reason for subject withdrawal from the study in detail in the case report form (CRF). Subjects have the right to withdraw informed consent and withdraw from the study at any time for any reason.


## 6. STATISTICAL ANALYSES

### 6.1. Statistical Methodology and Precision

Unless otherwise stated, CIs and  $p$ -values will be reported two-sided and evaluated at the 5% level of significance, and  $p$ -values will be rounded to three decimal places before evaluation of statistical significance.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation (SD) or standard error (SE) (if appropriate), minimum, median, and maximum. The number of decimal places retained for each statistic is as follows:

- Mean and median: One more decimal place than electronic case report form (eCRF) data.
- SD and SE: Two more decimal places than eCRF data.
- Minimum and maximum: The same number of decimal places as the eCRF data.
- CI (e.g., for mean): The same number of decimal places as the parameter.

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For categorical data, the number and percentage of subjects will be presented. For percentages, one decimal place should be retained.

All available eCRF data will be sorted by treatment group, subject no. and date and time of evaluation/occurrence (if applicable) and presented in a data listing with study days.

Study days will be calculated from the date of the first dose of IMPs as follows: Study days = (date of event) – (date of the first dose of IMPs) + (if the date of event  $\geq$  date of the first dose of IMPs, then 1, otherwise 0). The date of the first dose of IMPs will be designated as Day 1.

Baseline value is defined as the last available value collected on or prior to the date of the first dose/exposure of IMPs/procedure. Change from baseline is defined as the difference between the value at a specific time point and the baseline value.

Analysis datasets will be generated using the analysis data model (ADaM) to facilitate data review and any necessary supplemental analyses. The analysis datasets will contain all data in the original datasets and will be used for all statistical analysis tables, figures, and listings.

The dataset specification (DSS) includes the names and definitions of the variables in the datasets.

## 6.2. Subject Disposition and Withdrawal


The disposition of subjects will be summarized overall by treatment group and for each study part, including the number and percentage of subjects who are screened, screen failed, and included in and excluded from each analysis set (with exclusion reasons), as well as those who complete or prematurely discontinue study treatment, and complete or prematurely terminate the study (including IMPs and reasons for study withdrawal).

All the above information on subject disposition will be listed.

## 6.3. Protocol Deviations

A BDRM prior to the database lock will identify subjects with any major protocol deviations. Major protocol deviations in the FAS will be summarized by deviation category. All protocol deviations will be included in the data listing. Major protocol deviations leading to exclusion of the subjects from the PKS will be marked with special symbols in the data listing. All the behaviors that violate the eligibility criteria will also be summarized.

Analysis set assignments and protocol deviation listings for all subjects, as well as a detailed listing of subjects excluded from analysis sets, will be provided.

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#### 6.4. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for each treatment group in each study part using appropriate descriptive statistics based on the FAS.

Demographic and baseline characteristics will include:

- Age (years)
- Sex: male/female
- Ethnicity: Han Chinese/Others
- Height (cm)
- Baseline weight (kg)
- Baseline BMI (kg/m<sup>2</sup>)
- Social history
- Breath alcohol test
- Drug abuse screening
- Baseline chest x-ray examination
- Four infectious disease tests

Demographics and other baseline characteristics will be listed in the order of treatment group and subject no.

#### 6.5. Medical History


Medical histories will be summarized based on the FAS.

Medical histories will be classified by system organ class (SOC) and preferred term (PT) according to the ICH Medical Dictionary for Regulatory Activities (MedDRA, version 26.1 or above) and summarized by frequency and percentage of SOC/PT.

All medical histories will be listed in chronological order by each subject and sorted by treatment group and subject no.

#### 6.6. Exposure and Compliance

Drug exposure and compliance will be summarized based on the SS. The following parameters will be summarized and analyzed based on the actual treatment group:

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- Duration of treatment (days)
- Planned dose (tablets)
- Actual dose (tablets)
- Compliance (%)

Duration of treatment (days) = Date of last dose – Date of first dose + 1.

Treatment compliance (%) = (Actual dose)/(Planned dose) × 100%.

## 6.7. Past and Concomitant Medications and Non-Drug Therapies

All past and concomitant medications will be included in the data listing.

Past medications refer to any medication discontinued before the date of the first study intervention. Subjects will continue to take all prescription medications permitted by the inclusion criteria. Concomitant medications refer to any medication discontinued between the date of first study intervention and the date of completion/withdrawal, or any medication still ongoing at the date of completion/withdrawal. Any medication starting prior to the date of first intervention in the study and ending after the date of completion/withdrawal should also be considered as concomitant medications. Past and concomitant medications will be coded using the World Health Organization Drug (WHODrug) Dictionary (Sep. 1, 2023 or above) and the Anatomical Therapeutic Chemical (ATC) classification system

Concomitant medications will be summarized by generic name and coded using the ATC classification system and WHODrug Dictionary. In the summary table, the number of subjects and percentage for each ATC classification and PT will be calculated using the total number of subjects in the SS as the denominator. ATC classifications and PTs will be sorted in descending order of the number of subjects (in alphabetical order for those with equal numbers).


Non-drug therapies will be analyzed using the same method as drug therapies and coded using MedDRA (version 26.1 or above).

## 6.8. Pharmacokinetic Analysis

### 6.8.1. Data processing description

#### 6.8.1.1. Processing of plasma concentration data below the limit of quantitation

During statistical summary, unless otherwise specified:

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- All concentration values below the limit of quantitation (BLQ) will be treated as 0 and presented as "BLQ" in the data listing.
- When PK parameters are calculated and individual plasma concentration-time curves are plotted, unless otherwise specified:
- BLQs before  $T_{max}$  will be treated as 0
- BLQs after  $T_{max}$  will be treated as missing

#### 6.8.1.2. Processing of missing values and outliers


Missing PK data will not be imputed.

Missing plasma concentration data, such as due to lost samples or other reasons, will be represented as "NA"; concentration data unavailable due to insufficient sample volume for reanalysis or other laboratory process-specified reasons will be represented as "NR". Concentrations marked as NA or NR will be treated as missing in the statistical summary.

- If PK plasma concentration data are not collected or are missing, the missing data will not be included in the statistical summary, but only displayed in the listing and treated as missing.
- If the deviation in blood sampling time has the potential to cause data deviation or the concentration value is marked as abnormal by the PK analyst, the concentration should not be included in the statistical summary, and it should be explained in the notes of the corresponding summary table.
- If PK parameters cannot be calculated from PK concentrations, they will be treated as missing values in the statistical summary table and will be presented as not calculable (NC) in the listing.
- If more than 50% of the values of a PK parameter are missing, the parameter will not be included in the statistical analysis.
- If a subject has a known bias in the estimation of a PK parameter (a protocol deviation affecting the PK endpoint), the parameter should not be included in the calculation of statistics and statistical analysis for the summary table, and it should be explained in the notes of the table.

#### 6.8.1.3. Pharmacokinetic parameter calculation rules

The calculation of PK parameters will be carried out based on the actual sampling time.

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- Samples with BLQ concentration collected before  $C_{max}$  should be calculated as 0, and those collected after  $C_{max}$  should be considered as not detectable (ND) when PK is analyzed.
- $AUC_{0-\infty}$  and  $t_{1/2}$  cannot be calculated for subjects with less than 3 non-BLQ samples in the elimination phase.
- Sampling points with abnormal plasma concentrations (such as those exceeding the time window but not marked as abnormal) should be included in the calculation of PK parameters if there are no reasonable reasons.

### 6.8.2. Pharmacokinetic parameter calculation

The plasma concentration data will be estimated using a non-compartmental analysis (NCA) with Phoenix WinNonlin V8.1 or above to calculate the PK parameters, comprehensively reflecting the metabolism of the drug in the human body.

The PK parameters will be calculated using an NCA based on the plasma concentration of each subject and the actual sampling time.

**Table 6- 1. Definitions of PK parameters**

Parameter	Definition
<b>PK parameters after the first dose:</b>	
$AUC_{0-t}$	Area under the plasma concentration-time curve from time 0 to the last measurable concentration. Calculated by the linear trapezoidal method: $AUC_{(i, i+1)} = (T_{i+1} - T_i)(C_i + C_{i+1})/2$ , where $AUC_{0-t}$ is the sum of all $AUC_{(i, i+1)}$ .
$AUC_{0-\infty}$	Area under the plasma concentration-time curve extrapolated from time 0 to infinity. $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$ , where $C_t$ is the last measurable plasma concentration and $\lambda_z$ is the terminal elimination rate constant.
$C_{max}$	Maximum plasma concentration. Obtained directly from the measured plasma concentration-time data.
$T_{max}$	Time to $C_{max}$ . Obtained directly from the measured plasma concentration-time data. Defined as the time of the first $C_{max}$ (when there are multiple maximum plasma concentrations), unless otherwise specified
$t_{1/2}$	Elimination half-life. $t_{1/2} = \ln 2/\lambda_z$ .
<b>Steady-state PK parameters:</b>	
$AUC_{0-t, ss}$	Area under the plasma concentration-time curve from the last dose to the last measurable concentration. Calculated by the linear trapezoidal method: $AUC_{(i, i+1)} = (T_{i+1} - T_i)(C_i + C_{i+1})/2$ , where $AUC_{0-t}$ is the sum of all $AUC_{(i, i+1)}$ .

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Parameter	Definition
$AUC_{0-\infty, ss}$	Area under the plasma concentration-time curve extrapolated from the last dose to infinity. $AUC_{0-\infty, ss} = AUC_{0-t, ss} + C_t/\lambda_z$ , where $C_t$ is the last measurable plasma concentration and $\lambda_z$ is the terminal elimination rate constant.
$AUC_{0-\tau}$	Area under the plasma concentration-time curve from the start of the last dose to the dose interval ( $\tau$ )
$C_{max, ss}$	Steady-state maximum plasma concentration. Obtained directly from the measured plasma concentration-time data.
$C_{min, ss}$	Steady-state minimum concentration. Obtained directly from the measured plasma concentration-time data.
$C_{av, ss}$	Steady-state mean plasma concentration during the dose interval. $C_{av, ss} = AUC_{0-\tau}/\tau$ .
$T_{max, ss}$	Steady-state time to $C_{max}$ . Obtained directly from the measured plasma concentration-time data. Defined as the time of the first occurrence of $C_{min, ss}$ (when there are multiple maximum plasma concentrations), unless otherwise specified
$t_{1/2, ss}$	Elimination half-life. $t_{1/2, ss} = \ln 2/\lambda_z$ .
$\lambda_z$	Elimination rate constant. $\lambda_z = \text{slope} \times 2.303$ , where the slope is obtained from the optimal curve of the elimination phase by the least squares method.
$V_d, ss$	Steady-state volume of distribution. Obtained from the ratio of clearance to elimination rate constant, $V_d = CL_{ss}/\lambda_z$ .
$CL_{ss}$	Steady-state clearance. Obtained from the ratio of dose to $AUC_{0-\tau}$ , $CL_{ss} = \text{Dose}/AUC_{0-\tau}$
$AUC_{Extra\%}$	Percentage of the area under the curve extrapolated. $AUC_{Extra\%} = [(AUC_{0-\infty, ss} - AUC_{0-t, ss})/AUC_{0-\infty, ss}] \times 100\%$
<b>Urine PK parameters:</b>	
$CLR_{0-t}$	Renal clearance
$Ae_{0-t}$	Cumulative urinary excretion from time 0 to t
$Fe_{0-t}$	Fraction of dose excreted in urine from time 0 to t


### 6.8.3. Statistical analysis of pharmacokinetics

The PK evaluation will be analyzed based on the PKS.

#### 6.8.3.1. Pharmacokinetic concentration data analysis

The plasma concentration data at each scheduled blood sampling time point will be summarized using descriptive statistics, including the number of subjects, the number of subjects (BLQ), mean, SD, CV, median, minimum, maximum, geometric mean, and geometric CV.

Based on the summary data of plasma concentrations at each scheduled blood sampling time point, the mean plasma concentration-time curves of different treatment groups are plotted on linear and semi-logarithmic scales, separately, with the scheduled blood sampling time points as

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the x-axis and the arithmetic mean plasma concentration at each scheduled blood sampling time point as the y-axis.  $\pm$  SD will be displayed for plasma concentrations at each scheduled blood sampling time point in the linear scale curve, but not in the logarithmic scale curve. Data from different treatment groups will be presented on the same plot.

Based on the plasma concentration data of each subject at the actual blood sampling time points, the individual plasma concentration-time curves of different treatment groups will be plotted on linear and semi-logarithmic scales with the actual blood sampling time points as the x-axis and the plasma concentration at each actual blood sampling time point as the y-axis.

Details of subjects with out-of-window blood sampling time points will be tabulated, and the time and percentage of deviation will be calculated. The plasma concentration data of each subject in different treatment groups at each scheduled blood sampling time point will be tabulated.


Urine drug concentrations will be analyzed using the same method as described above for plasma concentrations.

#### **Processing of data below the limit of quantitation:**

- BLQ plasma concentrations will be represented by "BLQ" and treated as 0 for descriptive statistics, with the number of BLQ cases at each time point indicated
- If the mean is 0, the geometric mean, CV, and geometric CV will be treated as "NA"
- The geometric mean and geometric CV of plasma concentrations will be calculated based only on the non-BLQ plasma concentrations of subjects

#### **Processing of out-of-window blood sampling time points:**

- The plasma concentration of the samples with actual blood sampling time points beyond the time window will be marked with "\*". For example, a plasma concentration value of x.xxx at the time point beyond the time window will be displayed in the data listings as x.xxx\*
- For the sample where the actual blood sampling time point is not deviated or is deviated but within the time window, the plasma concentration values will not be marked
- At the BDRM, an assessment will be performed to determine whether the samples with actual blood sampling time points beyond the time window are included in the statistical analysis. The blood sampling time points not involved in the statistical analysis will be footnoted in the summary, and the subjects with out-of-window time points will be described in the note

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- Unless otherwise specified, all the samples collected at the actual blood sampling time points should be involved in the calculation of the statistics related to the plasma concentration at the corresponding scheduled blood sampling time points

### 6.8.3.2. Analysis of pharmacokinetic parameters

#### 6.8.3.2.1. Calculation of pharmacokinetic parameters

The PK parameters of each subject will be calculated using an NCA. PK parameters will be summarized using descriptive statistics, including the number of subjects, mean, SD, CV, median, minimum, maximum, geometric mean, and geometric CV.

#### 6.8.3.2.2. Dose proportionality

The dose proportionality of IPG11406 after administration in different dose groups will be explored using the power model.

#### 6.8.3.2.3. Analysis of urine pharmacokinetic parameters

The PK parameters of IPG11406 in urine will be summarized using descriptive statistics, including the number of subjects, mean, SD, CV, median, minimum, maximum, geometric mean, and geometric CV.


## 6.9. Safety Analysis

All safety analyses will be performed based on the SS. The estimand framework in the ICH E9 supplement will be used to assess primary endpoints

The following [Table 6-2](#) shows the ICEs relevant to this study.

**Table 6-2. Intercurrent events**

Label	ICE
ICE1 (treatment-related death)	Premature discontinuation of the IMP/participation due to treatment-related death
ICE2 (death unrelated to the treatment)	Premature discontinuation of the IMP/participation due to death unrelated to the treatment
ICE3 (discontinuation of study treatment due to treatment-related AEs)	Premature discontinuation of the IMP due to treatment-related AEs
ICE4 (use of prohibited medications)	Use of any prohibited medication
ICE5 (discontinuation of the IMP for any reason other than death or treatment-related AEs)	Premature discontinuation of the IMP for any reason other than death or treatment-related AEs
ICE6 (dose deviations of the IMP)	Errors or deviations in the dose of the IMP, including incorrect doses, which are considered to have a major impact on the safety

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<b>Label</b>	<b>ICE</b>
	assessment.

The safety analysis will adopt a treatment policy strategy and will be based on the observed data without data imputation.

The primary objective and estimand of safety are shown in [Table 6-1](#).

### 6.9.1. Adverse events

All AEs will be classified by SOC and PT according to MedDRA (version 26.1 or above). A treatment-emergent adverse event (TEAE) is any AE that begins or worsens in severity on or after the date of the first dose of the IMPs.

All AEs, TEAEs, treatment-related TEAEs, CTCAE grade  $\geq 3$  TEAEs, treatment-related CTCAE grade  $\geq 3$  TEAEs, TEAEs leading to discontinuation of the IMPs, treatment-related TEAEs leading to discontinuation of the IMPs, serious adverse events (SAEs), treatment-related SAEs, and TEAEs leading to death will be summarized by SOC and PT, including the number of subjects, number of cases, and percentage.

If a subject experiences multiple identical TEAEs, the subject will be counted only once for that AE, but the number of events will be counted according to the actual number of occurrences. If a subject experiences multiple identical AEs with different severity/causality, the subject will be counted once according to the most severe/relevant category, and the number of events will be counted according to the actual number of occurrences.

A listing of all AEs will be provided.


### 6.9.2. Laboratory tests

Laboratory test data will be summarized using standard units.

Quantitative laboratory measurements reported as "< X", i.e., BLQ, or "> X", i.e., above the upper limit of quantitation (ULQ), will be converted to X for quantitative summaries, but "< X" or "> X" will be displayed as recorded in the listings.

The following summaries will be provided for laboratory data of hematology, blood chemistry, coagulation function, and urinalysis:

- Quantitative measurements will be listed by visit with actual values and changes from baseline; qualitative results will be presented in listings only;

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- Cross tabulations of changes from baseline in laboratory assessments will be presented by visit according to clinical assessment abnormalities (for quantitative measurements and clinical assessments);
- Cross tabulations of changes from baseline in laboratory assessments will be presented by CTCAE grade.

The laboratory results of all subjects will be listed.

#### **6.9.2.1. CTCAE grade of laboratory tests**

To identify potentially clinically significant laboratory values, laboratory results will be graded according to NCI CTCAE Version 5.0. All grades will be based on laboratory values only (direct or some derived, adjusted values) without regard to intervention or symptom consequences.

The following modifications will be made to the grading:


- Grade 5 refers to a fatal outcome, which cannot be determined by laboratory values alone and therefore does not appear in the scoring system.
- The other category will be presented as grade 0 and include all other laboratory values except missing values.
- Missing results will be treated as missing.

For specific parameters with CTCAE high and low direction grades (e.g., Ca, Glu, magnesium, K, and Na), the CTCAE high and low directions will be expressed separately, i.e., the high value of interest is "hyper" and the low value of interest is "hypo".

#### **6.9.3. Vital signs**

Vital signs and changes from baseline will be summarized by visit:

- Respiration (breaths/min)
- Body temperature (°C)
- Pulse (bpm)
- Systolic blood pressure (SBP, mmHg)
- Diastolic blood pressure (DBP, mmHg)

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Vital signs and weight will be summarized, including baseline, worst grade during treatment (increase or decrease), and changes from baseline. Increases or decreases in vital signs and weight will be summarized categorically according to the following table. A cross tabulation of changes from baseline in vital signs will be provided, and the results that are normal, abnormal without clinical significance (NCS), and abnormal with clinical significance (CS) will be summarized by the number of subjects (n) and percentage (%).

**Table 6-3. Category for increase or decrease of vital signs and weight**

Variable	Unit	Baseline status	Increase or decrease category
SBP	mmHg	None	Change from baseline: $\geq 40/\leq -60$ mmHg
DBP	mmHg	None	Change from baseline: $> 20/> -40$ and $\leq -20/\leq -40$ mmHg
Pulse	bpm	None	Result: $> 130/< 50$ bpm Change from baseline: $> 30/\leq -30$ bpm
Weight	kg	None	Percentage change from baseline $\geq 10\%/\leq -10\%$

The vital signs of all subjects will be listed.

#### 6.9.4. 12-lead electrocardiogram (ECG)

12-lead ECG results and changes from baseline will be summarized, including the following variables: HR, PR, QRS, QT, and QTcF.

Categorical proportions of maximum post-baseline QTcF values and maximum changes from baseline in QTcF will be summarized according to the following categories.


**Table 6-4. Criteria for significant abnormalities in ECG**

Variable	Category
Maximum post-baseline QTcF (msec)	$< 450$ ; $450 \leq \text{max} \leq 480$ ; $480 < \text{max} \leq 500$ ; $\text{max} > 500$
Maximum change from baseline in QTcF (msec)	$\leq 30$ ; $> 30$ and $\leq 60$ ; $> 60$

A listing of the ECG for all subjects will be provided. A cross tabulation of changes from baseline in ECG will be provided, and the results that are normal, abnormal without clinical significance (NCS), and abnormal with clinical significance (CS) will be summarized by the number of subjects (n) and percentage (%).

#### 6.9.5. Physical examination

A cross tabulation of changes from baseline in physical examinations will be provided, and the results that are normal, abnormal without clinical significance (NCS), and abnormal with clinical significance (CS) will be summarized by the number of subjects (n) and percentage (%).

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A listing of physical examinations for all subjects will be provided.

#### **6.9.6. 24-h ambulatory ECG**

A listing of 24-h ambulatory ECG results for all subjects will be provided.

#### **6.10. Statistical Analysis Software**

All analyses will be performed using SAS 9.4 or higher.

#### **6.11. Changes to the Planned Analyses as Specified in the Protocol**

None.

### **7. REFERENCE**

#### **7.1. Project Management Plan**

Refer to the GC Project Management Plan

#### **7.2. Statistical Service Plan**

Refer to the GC SSP

#### **7.3. Data Management Plan**

Refer to the DMP

#### **7.4. Standard Operating Procedures**

015-SOP-01 Biostatistical Supervision and Guidance


015-SOP-04 Biostatistical Randomization Process

015-SOP-05 Statistical Analysis Plan

015-SOP-06 Statistical Programming and Analysis

#### **7.5. Trial Archiving**

Not applicable

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## Appendix 1 General Principles of Program Output

### General principles for GC output tables, listings, and figures (TLFs)

All TLFs will be prepared according to George Clinical's general principles for output TLFs.

#### Date and time

The date and time format is yyyy-mm-dd hh:mm:ss.

#### Language format

SimSun

#### Display of treatment groups


The outputs will display treatment groups in the following order:

Treatment groups	Tables, listings, and figures
0.5 mg (SAD)	0.5 mg (SAD)
2 mg (SAD)	2 mg (SAD)
6 mg (SAD)	6 mg (SAD)
20 mg (SAD)	20 mg (SAD)
40 mg (SAD)	40 mg (SAD)
80 mg (SAD)	80 mg (SAD)
Placebo (SAD)	Placebo (SAD)
10 mg QD (MAD)	10 mg QD (MAD)
20 mg BID (MAD)	20 mg BID (MAD)
40 mg QD (MAD)	40 mg QD (MAD)
40 mg BID (MAD)	40 mg BID (MAD)
Placebo (MAD)	Placebo (MAD)
Screen failure	Screen failure

#### Visits

The outputs will display visits in the following order.

Long name (default)	Short name
Screening period	Screening period
D1	D1
D2	D2
D3	D3
D4	D4
D5	D5
D8	D8

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Long name (default)	Short name
D9	D9
D10	D10
D13	D13
D14	D14
D17	D17

### Listings

All listings will be output in the following order (unless otherwise specified in the template):

- Randomization group
- Study site - subject ID
- Date (if applicable)

For listings containing non-randomized subjects, the category "Screen Failure" will be marked after the randomization group.

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## Appendix 2 Principles for Processing Incomplete Dates

The original date information should be listed in the table. However, in the calculation of study days, if the date is missing, the general processing principles are as follows: If the day is missing, it should be imputed as the first day of the month; if both the day and month are missing, it should be imputed as Jan. 1.

- Criteria for TEAEs:

Start date	End date	Processing measures
Complete date	Complete date	If the AE start date is < the date of the first dose of the IMP, it is determined as a non-TEAE. If the date of the first dose of the IMP is $\leq$ the AE start date $\leq$ the date of trial completion/early withdrawal, it is determined as a TEAE.
	Partially missing	If the AE start date is < the date of the first dose of the IMP, it is determined as a non-TEAE. If the date of the first dose of the IMP is $\leq$ the AE start date $\leq$ the date of trial completion/early withdrawal, it is determined as a TEAE.
	Completely missing	If the AE start date is < the date of the first dose of the IMP, it is determined as a non-TEAE. If the date of the first dose of the IMP is $\leq$ the AE start date $\leq$ the date of trial completion/early withdrawal, it is determined as a TEAE.
Partially missing: It can be confirmed that the AE occurs before the first dose of the IMP	Complete date	Determined as a non-TEAE
	Partially missing	Determined as a non-TEAE
	Completely missing	Determined as a non-TEAE
Partially missing: It can be confirmed that the AE occurs after the first dose of the IMP and before the trial completion/early withdrawal	Complete date	If the AE end date is < the date of the first dose of the IMP, it is determined as a non-TEAE. If the AE end date is $\geq$ the date of the first dose of the IMP, it is determined as a TEAE.
	Partially missing	The end date should be imputed with the latest possible date (if the day is missing, it should be imputed with the last day of the month; if both the month and the day are missing, it should be imputed with Dec. 31 or the date of last contact, whichever is earlier); If the AE end date is < the date of the first dose of the IMP, it is determined as a non-TEAE. If the AE end date is $\geq$ the date of the first dose of the IMP, it

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Start date	End date	Processing measures
		is determined as a TEAE.
	Completely missing	Considered as a TEAE
Completely missing	Complete date	If the AE end date is < the date of the first dose of the IMP, it is determined as a non-TEAE. If the AE end date is ≥ the date of the first dose of the IMP, it is determined as a TEAE.
	Partially missing	The end date should be imputed with the latest possible date (if the day is missing, it should be imputed with the last day of the month; if both the month and the day are missing, it should be imputed with Dec. 31 or the date of last contact, whichever is earlier); If the AE end date is < the date of the first dose of the IMP, it is determined as a non-TEAE. If the AE end date is ≥ the date of the first dose of the IMP, it is determined as a TEAE.
	Completely missing	Determined as a TEAE

- Principles for classification of past and concomitant medications:

Start date	End date	Processing measures
Complete date	Complete date	If the end date is < the date of the first dose of the IMP, it is determined as a past medication; If the date of the first dose of the IMP is ≤ the end date ≤ the date of trial completion/early withdrawal, or the date of the first dose of the IMP is ≤ the start date < the date of trial completion/early withdrawal, it is determined as a concomitant medication; If the end date is > the date of trial completion/early withdrawal and the start date is < the date of the first dose of the IMP, it is determined as a concomitant medication.
	Partially missing	The end date should be imputed with the latest possible date (if the day is missing, it should be imputed with the last day of the month; if both the month and the day are missing, it should be imputed with Dec. 31 or the date of last contact, whichever is earlier); If the end date is < the date of the first dose of the IMP, it is determined as a past medication; If the date of the first dose of the IMP is ≤ the end date ≤ the date of trial completion/early withdrawal, or the date of the first dose of the IMP is ≤ the start date < the date of trial completion/early withdrawal, it is determined as a concomitant medication; If the end date is > the date of trial completion/early withdrawal and the start date is < the date of the first dose of the IMP, it is determined as a concomitant medication.
	Completely missing	If the end date is missing, it cannot be determined as a past medication. If the start date is < the date of trial completion/early withdrawal,

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Start date	End date	Processing measures
		it is determined as a concomitant medication.
Partially missing	Complete date	<p>The start date should be imputed with the earliest possible date (if the day is missing, it should be imputed with the first day of the month; if both the month and the day are missing, it should be imputed with Jan. 1);</p> <p>If the end date is &lt; the date of the first dose of the IMP, it is determined as a past medication;</p> <p>If the date of the first dose of the IMP is <math>\leq</math> the end date <math>\leq</math> the date of trial completion/early withdrawal, or the date of the first dose of the IMP is <math>\leq</math> the start date &lt; the date of trial completion/early withdrawal, it is determined as a concomitant medication;</p> <p>If the end date is &gt; the date of trial completion/early withdrawal and the start date is &lt; the date of the first dose of the IMP, it is determined as a concomitant medication.</p>
	Partially missing	<p>The start date should be imputed with the earliest possible date (if the day is missing, it should be imputed with the first day of the month; if both the month and the day are missing, it should be imputed with Jan. 1); the end date should be imputed with the latest possible date (if the day is missing, it should be imputed with the last day of the month; if both the month and the day are missing, it should be imputed with Dec. 31 or the date of last contact, whichever is earlier);</p> <p>If the end date is &lt; the date of the first dose of the IMP, it is determined as a past medication;</p> <p>If the date of the first dose of the IMP is <math>\leq</math> the end date <math>\leq</math> the date of trial completion/early withdrawal, or the date of the first dose of the IMP is <math>\leq</math> the start date &lt; the date of trial completion/early withdrawal, it is determined as a concomitant medication;</p> <p>If the end date is &gt; the date of trial completion/early withdrawal and the start date is &lt; the date of the first dose of the IMP, it is determined as a concomitant medication.</p>
	Completely missing	<p>The start date should be imputed with the earliest possible date (if the day is missing, it should be imputed with the first day of the month; if both the month and the day are missing, it should be imputed with Jan. 1);;</p> <p>If the end date is missing, it cannot be determined as a past medication.</p> <p>If the start date is &lt; the date of trial completion/early withdrawal, it is determined as a concomitant medication.</p>

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<b>Start date</b>	<b>End date</b>	<b>Processing measures</b>
Completely missing	Complete date	If the end date is < the date of the first dose of the IMP, it is determined as a past medication; If the date of the first dose of the IMP is $\leq$ the end date, it is determined as a concomitant medication.
	Partially missing	The end date should be imputed with the latest possible date (if the day is missing, it should be imputed with the last day of the month; if both the month and the day are missing, it should be imputed with Dec. 31 or the date of last contact, whichever is earlier); If the end date is < the date of the first dose of the IMP, it is determined as a past medication; If the date of the first dose of the IMP is $\leq$ the end date, it is determined as a concomitant medication.
	Completely missing	Determined as a concomitant medication