Statistical Analysis Plan

A Single-Center, Randomized, Single-Blind, Single-Dose, Parallel-Group Trial to Assess the Pharmacokinetic Similarity Between CHS-1420 40 mg/0.4 mL and HUMIRA® (Adalimumab) 40 mg/0.4 mL in Healthy Chinese Adult Participants under Fasting Conditions

Protocol No. CHS-1420-10

Sponsor:	Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd
Clinical Research Facility:	Hopeshine-Minsheng Hospital of Xinzheng
Statistical Analysis Facility:	Frontage Laboratories (Shanghai) Co., Ltd.
Version No.:	V1.0
Version Date:	26 Jun. 2025

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We have read the SAP and we agree to strictly follow the SAP requirements during the study.

Sponsor: Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd
Sponsor Project Manager: Zhiguo Feng

Signature: _____ Date: _____

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Biostatistician: Lingshuang Meng

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PK Parameter Calculation Facility: Frontage Laboratories (Shanghai) Co., Ltd.

Responsible Person：Jing Li

Signature：_____ Date：_____

Contents

GLOSSARY AND ABBREVIATIONS

Abbreviations	Definition
ADA	Anti-drug antibodies
ADL	Activities of daily living
AE	Adverse event
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the serum concentration versus time curve extrapolated to infinity
AUC_{0-t}	Area under the serum concentration versus time curve calculated to the last measurable observation
BMI	Body mass index
CL/F	Clearance
CI	Confidence interval
C_{max}	Maximum serum concentration
CRF	Case report form
ECG	Electrocardiogram
ELAM	Endothelial adhesion molecule
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMR	Geometric mean ratios
IAS	Immunogenicity analysis set
ICAM	Intercellular cell adhesion molecule
ICH	International Conference on Harmonization
K_{el}	Elimination rate constant
kg	Kilogram(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
NA	Not applicable
Nab	Neutralizing antibodies
ND	Not detectable
NR	Not reportable
NS	No sample

Abbreviations	**Definition**
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
PKCS	Pharmacokinetic Concentration Set
PKPS	Pharmacokinetic Parameter Set
PKSS	Pharmacokinetic Similarity Set
PT	Preferred term
Reference, R	Reference product
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedures
SS	Safety Set
T, Test	Test/proposed biosimilar products
T_{max}	Time to maximum serum concentration
TNF	Tumor necrosis factor
$t_{1/2}$	Half-life
VCAM	Vascular cell adhesion molecule
V_d/F	Apparent distribution volume

1 PROTOCOL SYNOPSIS

This statistical analysis plan is written based on the study protocol dated 05 Feb 2025 V1.1 and the case report form (eCRF) dated 12 Feb 2025, V1.0.

Any revisions to the study protocol will likely result in the need for this statistical analysis plan to be updated accordingly. The statistical analysis plan must be finalized prior to the final data lock and after approval by the sponsor.

1.1 Background

Biosimilarity is defined to mean that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. To support a demonstration of biosimilarity, the totality of the data and information submitted will be considered using a risk-based approach by FDA, including data from the structural and functional characterizations, nonclinical evaluations, clinical PK and/or pharmacodynamic (PD) studies, clinical immunogenicity testing and an investigation of clinical safety, and, when appropriate, clinical effectiveness. These data should be collected in a stepwise manner in development programs of a proposed biosimilar product.

HUMIRA® (Adalimumab) is a human monoclonal antibody and binds specifically to TNF-α and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the concentrations of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 × 10^{-10} M). HUMIRA® (Adalimumab) was first approved by FDA in 2002 and currently indicated for treatment of Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, Uveitis with the available marketing strengths of 80 mg/0.8 mL, and 40 mg/0.4 mL as single-dose prefilled pens and 40 mg/0.4 mL, 20 mg/0.2 mL, 10 mg/0.1 mL as single-dose prefilled glass syringes.

CHS-1420 40 mg/0.4 mL, developed by Hong Kong King-Friend, a subsidiary corporation of Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd., is designed as a biosimilar to HUMIRA® (Adalimumab). In vitro study and non-clinical study has been performed on CHS-1420. As a clinical development progarm of CHS-1420, this trial is to evaluate the pharmacokinetic similarity of the proposed biosimilar product CHS-1420 40 mg/0.4 mL manufactured by Ajinomoto Althea, Inc. and reference products HUMIRA® (Adalimumab) 40 mg/0.4 mL manufactured by AbbVie Inc. in healthy Chinese adult participants after a single subcutaneous dose treatment under fasting conditions. In addition, safety and immunogenicity of the proposed biosimilar product CHS-1420 and reference products HUMIRA® (Adalimumab) will be also compared.

1.2 Study Objectives

Primary Objective:

To evaluate the pharmacokinetic similarity of the proposed biosimilar product CHS-1420 40 mg/0.4 mL manufactured by Ajinomoto Althea, Inc. and reference products HUMIRA® (Adalimumab) 40 mg/0.4 mL manufactured by AbbVie Inc. in healthy

Chinese adult participants after a single subcutaneous dose treatment under fasting conditions.

Secondary Objective:

To assess the safety and immunogenicity of the proposed biosimilar product CHS-1420 40 mg/0.4 mL and reference products HUMIRA® (Adalimumab) 40 mg/0.4 mL in healthy Chinese adult participants.

1.3 Trial Design

This is a single-center, randomized, single-blind, single-dose, parallel-group comparative pharmacokinetic trial in healthy Chinese adult participants.

Two hundred and thirty-eight (238) participants are to be enrolled. Eligible participants will be randomized to receive one of two treatment (T or R) at the ratio of 1:1 according to the randomization schedule. Each participant will receive a single subcutaneous dose treatment of either CHS-1420 or HUMIRA® under fasting conditions in the one-period trial.

The duration of the trial is expected to be approximately 14 weeks, including screening period and test period.

1.4 Randomization

During the screening period, the screening number will be assigned to identify participants (e.g., S001). The participants will be randomized on Day -1. The stratified block randomization will be adopted. Participant random No. will be "10XX". When the randomized participant withdraws from the trial, random No. will be retained and the participant won't be enrolled again regardless of the withdrawal reason and whether a treatment has been received.

The randomization schedule will be generated by statistical department (an unblinded statistician) using SAS (Version 9.4 or higher).

1.5 Blinding and Unblinding

This is a single-blind trial. Only the designated clinical site personnel responsible for drug distribution and administration could reach the randomization code. The personnel and procedure should be blinded as following:

In course of the trial, sponsor staff, investigators in the clinical site and clinical research associates (other than those responsible for drug distribution and administration), statistician (other than unblinded statistician), data managers should be blinded to the treatment assignment. Staff who are responsible for drug distribution and administration should not conduct any protocol-specified safety assessments, e.g. AE or injection site assessments post-dose.

The participants will be blinded to the assigned treatment (T or R) through the dosing process. An eye mask will be put on for participants to avoid viewing the injection.

In addition, the identity of the dosing drug will remain blinded to the bioanalytical staff during sample analysis.

Individual participant treatment assignment should be unblinded in the case of a suspected unexpected serious adverse reaction (SUSAR) that requires knowledge of the study medication received by the participant in order to interpret the event, may be essential for medical management of the participant, and may provide critical safety information about a drug that could have implications for the ongoing conduct of the

trial. Otherwise unblinding is not allowed. Any blinding should be documented and dated. Treatment assignments for individual participants will remain blinded until after the study database has been cleaned and locked.

1.6 Sample Size Determination

Based on literature information, it is estimated that the inter-subject coefficient of variation of the primary PK parameters is approximately 44%. α is set to be 0.05; the power of detecting the PK similarity of the proposed biosimilar / reference product is 90%, the T/R GMR is assumed to be 1.05, the equivalent threshold is 0.80~1.25, taking risk of drop-out into account (approximately 15%), 238 participants are to be enrolled in the parallel trial.

1.7 Dosing and Administration

Eligible participants will be randomized to receive one of two treatments (T or R) at the ratio of 1:1 according to the randomization schedule.

Following an overnight fast of at least 10 hours, either the proposed biosimilar product (T) CHS-1420 40 mg or reference product (R) HUMIRA® 40 mg will be subcutaneously administered to participants in the right lower quadrant (left lower quadrant, if necessary, and reason for different choice of injection site should be documented) of the participants' abdomen. Participants will be dosed in a lying posture throughout the dosing procedure. Injections will be administered by a trained physician throughout the study.

Refer to the dosing manual for details of investigational products administration.

1.8 Sample Collection Time Point

A total of twenty-four (24) blood samples for each participant will be collected for determination of serum drug concentrations at 0 h (within 30 minutes pre-dose) and 2 h (Day 1), 4 h (Day 1), 8 h (Day 1), 12 h (Day 1), 24 h (Day 2), 36 h (Day 2), 48 h (Day 3), 60 h (Day 3), 72 h (Day 4), 96 h (Day 5), 120 h (Day 6), 144 h (Day 7), 168 h (Day 8), 216 h (Day 10), 288 h (Day 13), 360 h (Day 16), 528 h (Day 23), 696 h (Day 30), 864 h (Day 37), 1032 h (Day 44), 1200 h (Day 51), 1368 h (Day 58), 1536 h (Day 65) post-dose.

2 ASSOCIATED ENDPOINTS

PK Endpoints:

The primary PK endpoints are the maximum serum drug concentration (C_{max}) and areas under the serum concentration versus time curve extrapolated to infinity ($AUC_{0-\infty}$).

The secondary pharmacokinetic endpoints are areas under the serum concentration versus time curve calculated to the last measurable observation (AUC_{0-t}) and to 65 days postdose ($AUC_{0-65days}$), the time to maximum serum concentration (observed) (T_{max}), the elimination half-life ($t_{1/2}$) and terminal elimination rate constant (K_{el}), apparent distribution volume (V_d/F) and clearance (CL/F).

Safety Endpoints

AEs, Serious adverse events (SAEs), vital signs, physical examination, laboratory test, electrocardiogram (ECG), local reactions at the injection site, concomitant therapy, *etc.*

Immunogenicity Endpoints

Incidence and severity of immunogenicity response (ADA/Nab).

3 Analysis Sets

Full Analysis Set (FAS): A dataset of participants who are randomized.

Pharmacokinetic Concentration Set (PKCS): A dataset comprising at least one post-dose effective test component concentration data obtained in participants who receive one dose of the investigational drug. The dataset is for descriptively statistical analysis of the PK concentration data.

Pharmacokinetic Parameter Set (PKPS): A dataset comprising PK parameter data obtained in participants who receive one dose of the investigational drug. The dataset is for descriptively statistical analysis of the PK parameter data.

Pharmacokinetic Similarity Set (PKSS): A dataset comprising data with at least one evaluable PK parameter. This dataset is the main data set for inferring whether the proposed biosimilar product and reference product are PK similar and in this trial. PK parameters of C_{max} and $AUC_{0-\infty}$ will be analyzed. The corresponding period data will not be included in the PKSS, when the conditions occur as following: 1) Participants who have positive results of ADA at baseline (0 h); 2) The first postdose sample provides C_{max} values; 3) The pre-dose (0 h) sample provides a quantifiable concentration value; 4) Concomitant medication occur during the trial and there is clear evidence that the combination medication has an effect on the pharmacokinetics (PK) of the investigational products.

Immunogenicity Analysis Set (IAS): A dataset comprising at least one post-dose effective test immunogenicity component data obtained in participants who receive one dose of the investigational drug. This dataset is used for the immunogenicity analysis.

Safety Set (SS): A dataset of participants who receive one dose of the investigational drug with evaluable safety data. This dataset is used for the safety analysis.

4 Data Handling

4.1 Statistical Result Presentation

Conventions for presentation of numerical data:

Listings adopt actual decimals.

In descriptive statistics, Min and Max are kept with the same decimal digits as original data and N is integer.

In descriptive statistics, the arithmetic mean, median, Quartiles (Q1 & Q3), CV%, Geometric Mean, Geometric Mean CV% are kept with one more decimal place than the original data, standard deviation (SD) is kept two more decimal places than the original data. A maximum of four decimal places are kept.

When the number of decimal digits of the original data is inconsistent, the maximum number of decimal digits shall prevail.

Conventions for presentation of PK Parameters:

Values ≥ 0.0001 and < 1 will be reported with 4 decimal places (e.g., 0.0123).

Values ≥ 1 and < 10 will be reported with 3 decimal places (e.g., 1.023).

Values ≥ 10 and < 100 will be reported with 2 decimal places (e.g., 10.23).

Values ≥ 100 and < 1000 will be reported with 1 decimal place (e.g., 100.2).

Values ≥ 1000 or equal to 0 will be reported as a whole integer (e.g., 1000).

Values for T_{max} will be reported with 2 decimal places.

Values for C_{max} will use the decimal retention rule for concentration data.

Elimination Criteria

The principal investigator, sponsor and statisticians need to work together to decide the participant(s) to be excluded or not from the relevant analysis sets before data is unblinded. The judgement should be based on the degree of completion of the trial and withdrawal reasons. The relevant notes for data inclusion/exclusion should be recorded. Conditions in which data should be excluded can be as follows (not limited to):

1) Data of participants who don't meet the inclusion criteria or meet the exclusion criteria, which may affect the results;
2) Data of participants who are incompliant with the clinical protocol during the trial, which should be judged rationally according to the severity of protocol deviations;
3) Data of participants with other behavior which may affect pharmacokinetics results during the trial;

4.2 Handling of deviations in blood collection time points

In this study, the acceptable time deviation in blood sample collection is listed as below. Any sample that is collected outside of the time windows (listed below) should be recorded as a protocol deviation.

Blood Collection Time Window

Timepoint (h)	Time window	Timepoint (h)	Time window	Timepoint (h)	Time window
0	Within 30 min pre-dose	24 – 72	±18 min	528 – 1536	±240 min
2 – 4	±3 min	96 – 168	±60 min		
8 – 12	±6 min	216 – 360	±120 min		

4.3 Processing of Missing Data

For missing samples before the first quantifiable sample, the concentration values will be treated as "0". For missing samples between the two quantifiable samples or after the last quantifiable sample, the concentration values will be treated as null listed as either "Not Reportable (NR)" or "No Sample (NS)". No value will be reported and it will be just represented as "ND" which will be treated as missing data in the table for cases that PK parameters can't be acquired based on the concentration data. Other missing data may occur during safety assessment. Illogical data will be checked.

4.4 Processing of Values below the LLOQ

For samples with concentrations below the lower limit of quantification (LLOQ) will be set to 0 for pharmacokinetic analysis and descriptive statistical analysis.

4.5 Processing of Non-zero Concentration before Dosing

If the pre-dose (0 h) sample provides a quantifiable concentration value, the participants' data can be directly involved in the calculation of pharmacokinetic parameters without correction, but the participants' data will be excluded from PKSS.

5 THE STATISTICAL METHODS

5.1 Participant distribution

Participant disposition will be summarized using the number and percent of Participants according to the following aspects:

- Screened, randomized and treated participants.
- Completion of the trial, withdrawal and reasons for withdrawal.
- Number and percentage of Participant protocol violations or deviations.
- others

All the requirements in the trial protocol must be strictly followed. Any deviation from protocol and regulations in GCP will be defined as protocol deviation. If a deviation is identified, the deviation record should be filled in, and the time of occurrence, process, reason for deviation and measures taken, etc. should be recorded in detail, and the ethics committee and sponsor should be notified. In the data statistics and report, the impact of deviations on the final data and conclusions will be assessed.

When a serious protocol deviation occurs, an assessment should be made. If necessary, the sponsor can terminate this trial early.

5.2 Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all participants included into FAS.

For age, weight, height and BMI: the number of cases, arithmetic mean, standard deviation, median, quartile, min and max will be statistically summarized.

For gender, Ethnicity, race: the cases and percentage will be statistically summarized.

For medical history, surgical history: classification according to MedDRA (Version 27.0 or higher) and the cases and percentage will be statistically summarized.

For smoking/alcohol/allergy/drug abuse history, viral tests, alcohol breath tests and drug abuse tests, antinuclear antibody tests, tuberculosis diagnosis as well as chest X-ray: the cases and percentage will be statistically summarized.

5.3 Medications before Study Drug, Concomitant Medications and Concomitant Non-Drug Therapy Record

Medications before Study Drug, Concomitant Medications and Concomitant Non-Drug Therapy Record will be coded using the World Health Organization (WHO)-Drug, and listed by reported term / preferred term and Anatomical Therapeutic Class classification. Medications before Study Drug, Concomitant Medications and Concomitant Non-Drug Therapy Record taken by participant included into FAS will be listed and statistically summarized with cases and percentage.

5.4 Analysis of PK Parameters

5.4.1 Calculation of PK Parameters

The PK parameters will be estimated based on the actual sampling time with Phoenix

WinNonlin (Certara USA Inc, Version 8.4 or higher) using noncompartmental methods.

Pharmacokinetic parameters to be calculated include:

Parameter	Definition and Calculation
C_{max}	The maximum serum concentration; Observation
AUC_{0-t}	Area under the serum concentration versus time curve calculated to the last measurable observation (C_t); Linear trapezoidal method
$AUC_{0-65days}$	Areas under the serum concentration versus time curve calculated to 65 days postdose; Linear trapezoidal method
$AUC_{0-\infty}$	Area under the serum concentration versus time curve extrapolated to infinity, calculated as $AUC_{0-t} + C_t / K_{el}$
T_{max}	Time to the maximum serum concentration; Observation
K_{el}	Elimination rate constant; calculated as the absolute terminal slope of the log-transformed concentration versus time curve
$t_{1/2}$	Terminal half-life; calculated as $0.693 / K_{el}$
CL/F	Clearance; calculated as Dose / $AUC_{0-\infty}$
V_d/F	Apparent distribution volume; Dose / ($K_{el} \times AUC_{0-\infty}$)

5.4.2 Analysis of PK Parameters

For population included in PKCS, the concentration data of all participants measured for each time point will be used for descriptive statistics, including the number of cases, arithmetic mean, standard deviation, median, quartile, minimum, maximum, geometric mean and coefficient of variation. The individual and mean concentration - time curve (both in linear and semi-log scale) will be plotted. The upper standard deviations at each time point will be presented for the mean concentration – time curve.

For population included in PKPS, descriptive statistics of each PK parameter will be performed. The number of cases, arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, coefficient of variation and coefficient of variation of geometric mean will be calculated for the PK parameters of C_{max}, AUC_{0-t}, $AUC_{0-65days}$, $AUC_{0-\infty}$. The number of cases, arithmetic mean, standard deviation, median, minimum, maximum, geometric mean and coefficient of variations will be calculated for the PK parameters of T_{max}, $t_{1/2}$, K_{el}, V_d/F, and CL/F.

SAS software (version 9.4 or higher) will be used for the statistical analysis.

5.4.3 Pharmacokinetic Similarity Assessment

For population included in PKSS, the primary PK parameters, C_{max}, $AUC_{0-\infty}$ are converted by natural logarithm to perform significance test using Mixed Model, with formulation factors as fixed effects. The PK similarity of proposed biosimilar (Test) products and reference products will be evaluated by statistical analysis method of calculating 90% Cis. And the 90% CIs of the Test/Reference GMRs have to fall in the range of 80% - 125% to demonstrate the PK similarity.

T_{max} will be compared with rank test and *p* value will be provided.

The above statistical analysis will be performed using SAS 9.4 or higher.

5.4.4 Sensitivity Analysis

Outlier: Observation extremely discordant with the average level. Outlier may be

caused by the great variability of the variables, or may be an error due to a mistake which can be treated as a missing data however the mistake should be clarified.

Sensitivity Analysis: Sensitivity analyses are a series of analyses conducted against the unexpected conditions, e.g. analysis for data with missing data filled in, subgroup analysis, analysis for a different dataset, adjustment of different covariates, etc. The sensitivity analysis result will be compared with that from the due analysis to explore the robustness of inferences. Sensitivity analysis results can be a supportive data to the main analysis, however, it cannot be the primary rational to make a conclusion.

The sensitivity analysis method is the same as the pharmacokinetic similarity method.

Sensitivity analysis on the outlier or other cases can be conducted, if warranted, during the PK similarity analysis. Influence of outliers can be evaluated by comparing the assessment results in cases with the outliers excluded or not. Reasons should be explained if different conclusions are reached.

5.5 Immunogenicity Assessments

For population included in Immunogenicity Analysis Set (IAS), data will be summarized and listed by treatment, by visit, and by treatment and visit.

Incidence and severity of immunogenicity response (ADA/Nab).

5.6 Safety Analysis

5.6.1 Adverse Event

Adverse Event (AE) – Any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Event (SAE) – Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Suspected Unexpected Serious Adverse Reaction (SUSAR) – an adverse reaction that meets three criteria: suspected, unexpected and serious.

- Suspected: There is a reasonable possibility that the drug caused the adverse drug reaction.
- Unexpected: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., the reference safety information).
- Serious: See above for SAE.

Severity：

Intensity to be graded refer to CTCAE (Common Terminology Criteria for Adverse Events) 5.0 as:

DEGREE	DESCRIPTION
Grade 1	Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate, minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc.*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL. Selfcare ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Relationship to investigational products, to be classified into as: Related; Probably related; Possibly related; Unlikely; Unrelated. AEs related, probably related and possibly related to investigational products are considered to be drug related adverse reactions.

Related	• With plausible time relationship • Consistent with the known mechanism of action, properties or adverse reactions • A positive dechallenge observation • A positive rechallenge observation • Cannot be explained from other plausible aspects
Probably related	• With plausible time relationship • Consistent with the known mechanism of action, properties or adverse reactions • A positive dechallenge observation • Lack of evidence of a positive rechallenge observation • Cannot be explained from other plausible aspects
Possibly related	• With plausible time relationship • Lack of evidence of a positive rechallenge observation • Any condition in which: 1) Consistent with the known mechanism of action, properties or adverse reactions; A positive dechallenge observation; Can be explained from other plausible aspects 2) Consistent with the known mechanism of action, properties or adverse reactions; Lack of evidence of a positive dechallenge observation; Cannot be explained from other plausible aspects 3) Inconsistent with the known mechanism of action, properties or adverse reactions; A positive dechallenge observation; Cannot be explained from other plausible aspects 4) Inconsistent with the known mechanism of action, properties or adverse reactions; Lack of evidence of a positive dechallenge observation; Cannot be explained from other plausible aspects
Unlikely	• With an improbable time relationship (but not impossible) • Lack of evidence of a positive dechallenge observation • Lack of evidence of a positive rechallenge observation • Any condition in which: 1) Consistent with the known mechanism of action, properties or adverse reactions; Can be explained from other more plausible aspects 2) Inconsistent with the known mechanism of action, properties or

	adverse reactions; Can be explained from other plausible aspects
Unrelated	• Without plausible time relationship • Inconsistent with the known mechanism of action, properties or adverse reactions • Lack of evidence of a positive dechallenge observation • Lack of evidence of a positive rechallenge observation • Can be explained from other plausible aspects

Adverse events leading to withdrawal: Adverse events that selected "Yes" to " Discontinued due to Adverse Event?".

Adverse events leading to death: Adverse events of " Death related to AE / Grade 5 " intensity.

5.6.2 Laboratory Examination

Laboratory tests include biochemistry, hematology and urinalysis. Descriptive statistics is used to describe the results of biochemistry, hematology and the changes of biochemistry and hematology results from pre-dose to post-dose. The N, mean, standard deviation, median, quartile, minimum and maximum of the results will be calculated, changes from pre-dose to post-dose will be described.

The shift table is used to describe the changes of clinical evaluation before and after taking medication, and the N and percentage of participants' test results will be calculated.

List the participants with clinical significance after taking medication.

The results of laboratory tests will be tabulated.

5.6.3 Physical Examination

The shift table is used to describe the changes of the results before and after taking medication, and the N and percentage of the results of the physical examination items will be calculated.

The results of the physical examination of the participants will be tabulated.

5.6.4 Vital Signs

Descriptive statistics is used to describe each item of the participants' vital signs and the changes from pre-dose to each time point after taking medication and N, mean, standard deviation, median, quartile, minimum and maximum will be calculated.

The shift table is used to describe the changes in clinical evaluation from pre-dose to post-dose. N and percentage of the results of each test item will be calculated.

The results of the vital signs of the participants will be tabulated.

5.6.5 ECG

The shift table is used to describe the changes of ECG examination from pre-dose to post-dose, and the N and percentage of participants for ECG results will be calculated.

The results of ECG items will be tabulated.

6 REFERENCES

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- National Medical Products Administation (formerly known as CFDA):Guidance for statistical bioequivalence research.29 Oct. 2018.
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- National Medical Products Administration, "Quality Management Standards for Drug Clinical Trials," Apr. 2020

7 TABLES, LISTINGS and FIGURES

The tables, listings and figures will be provided as a separate and supportive document to this Statistical Analysis Plan.

The table, listing and figure numbers correspond to the numbers in Section 14 and Appendixes 16 of the International Conference on Harmonization (ICH) E3 model clinical study report.