CLINICAL TRIAL PROTOCOL

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

Version No.: V1.1

Version Date: 05 Feb. 2025

Clinical Research Facility: Hopeshine-Minsheng Hospital of Xinzheng

Sponsor: Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd.

Contract Research Organization: Frontage Laboratories (Shanghai) Co., Ltd.

Bioanalytical Facility: Frontage Laboratories (Shanghai) Co., Ltd.

Data Management and Statistical Facility: Frontage Laboratories (Shanghai) Co., Ltd.

Confidentiality Statement

SPONSOR SIGNATURE

I have read and approved the protocol entitled "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; Version No.: V1.1; Version Date: 05 Feb. 2025), and agree to abide by all provisions set forth therein. The trial can only be conducted after the approval of the Ethics Committee.

I agree to comply with all the obligations and responsibilities of sponsor as outlined in the clinical protocol and in accordance with the Good Clinical Practice (GCP), the Declaration of Helsinki and other relevant regulations and guidelines, and be responsible for the ultimate quality of the trial.

Sponsor: Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd.

Project Principal (Signature): Feng. Zhiguo

Date: 05 Feb. 2025.

INVESTIGATOR SIGNATURE

I have read the protocol entitled "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; Version No.: V1.1; Version Date: 05 Feb. 2025), and agree to conduct the trial as outlined in the protocol and in accordance with regulations and guidelines of GCP, the Declaration of Helsinki. This trial can only be conducted after the approval of the Ethics Committee.

I agree to comply with the obligations and responsibilities of investigator as outlined in the clinical protocol and in accordance with GCP, the Declaration of Helsinki, as well as other relevant regulations and guidelines. Any protocol amendment can only be implemented after approval from sponsor and the Ethics Committee unless the amendment is absolutely necessary for protecting safety, rights and well-being of participants in emergency.

I will keep this protocol and the related contents confidential.

The Clinical Facility: Hopeshine-Minsheng Hospital of Xinzheng

Principal Investigator (Signature): Jinxi chen

Date: 05-Feb-2025

CONTRACT RESEARCH ORGANIZATION SIGNATURE

I have read the protocol entitled "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; Version No.: V1.1; Version Date: 05 Feb. 2025), and agree to abide by all provisions set forth therein. The trial can only be conducted after the approval of the Ethics Committee.

I agree to comply with all the obligations and responsibilities of the Contract Research Organization (CRO) as predefined in the contract with sponsor and in accordance with the clinical protocol and relevant regulations and guidelines, such as GCP, the Declaration of Helsinki.

I will keep this protocol and the related contents confidential.

CRO: Frontage Laboratories (Shanghai) Co., Ltd.

Project Principal (Signature): Xiaomei Ding

Date: 05 Feb. 2025

BIOANALYTICAL FACILITY SIGNATURE

I have read the protocol entitled "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; Version No.: V1.1; Version Date: 05 Feb. 2025), and agree to abide by all provisions set forth therein. The trial can only be conducted after the approval of the Ethics Committee.

I agree to comply with all the obligations and responsibilities of bioanalytical facility as outlined in the clinical protocol and in accordance with the standard operating procedures (SOPs) of the bioanalytical laboratory, Good Laboratory Practice (GLP) and other relevant regulations and guidelines.

I will keep this protocol and the related contents confidential.

Bioanalytical Facility: Frontage Laboratories (Shanghai) Co., Ltd.

Project Principal (Signature): Xiaofeng Jia

Date: 05 Feb 25

DATA MANAGEMENT SIGNATURE

I have read the protocol entitled "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; Version No.: V1.1; Version Date: 05 Feb. 2025), and agree to abide by all provisions set forth therein. The trial can only be conducted after the approval of the Ethics Committee.

I agree to comply with all the obligations and responsibilities of data management as outlined in the clinical protocol and in accordance with the SOPs of the data management facility, GCP and other relevant regulations and guidelines.

I will keep this protocol and the related contents confidential.

Data Management Facility: Frontage Laboratories (Shanghai) Co., Ltd.

Data Management Contact (Signature): Mengjia Yang

Date: 05 Feb 2025

STATISTICAL ANALYSIS SIGNATURE

I have read the protocol entitled "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; Version No.: V1.1; Version Date: 05 Feb. 2025), and agree to abide by all provisions set forth therein. The trial can only be conducted after the approval of the Ethics Committee.

I agree to comply with all the obligations and responsibilities of statistical analysis as outlined in the clinical protocol and in accordance with the SOPs of the statistical analysis facility, GCP and other relevant regulations and guidelines.

I will keep this protocol and the related contents confidential.

Statistical Analysis Facility: Frontage Laboratories (Shanghai) Co., Ltd.

Statistical Analysis Contact (Signature): Lingshuang Meng

Date: 05 Feb. 2025

CONTACT INFORMATION

Clinical Research Facility			
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Sponsor			
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Project Principal for Data Management		Mengjia Yang	
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Project Principal for Statistical Analysis		Lingshuang Meng	
Tel	(+86) 152-3648-7091	E-mail	lingshuangmeng@frontagelab.com.cn

AMENDMENT DETAILS

Current Amendment

Amendment Number	CHS-1420-10	
Version No.	V1.1	
Version Date	05 Feb. 2025	
Number of participants enrolled	238 participants to be enrolled and none enrolled at present	
Reason(s) for Amendment	**Primary Reason:** Select from the following (multiple selections allowed): • Regulatory agency request to amend • New regulatory guidance • IRB/IEC feedback • New safety information available • Manufacturing change • Adaptive clinical trial IMP addition • Change in strategy • Change in standard of care • New data available (other than safety data) • Investigator/site feedback • Recruitment difficulty • Inconsistency and/or error in the protocol • Protocol design error ✓ **Other: Update the information of investigational products Update the sponsor information**	**Other:** Select from the following (multiple selections allowed): • Regulatory agency request to amend • New regulatory guidance • IRB/IEC feedback • New safety information available • Manufacturing change • Adaptive clinical trial IMP addition • Change in strategy • Change in standard of care • New data available (other than safety data) • Investigator/site feedback • Recruitment difficulty • Inconsistency and/or error in the protocol • Protocol design error • Other: [Describe]
Summary of the Amendment	Update the information of reference products (R) according to updated Certificate of Analysis; Update the sponsor information	
Is this amendment likely to have a substantial impact on • Safety or rights of the participants, or • On the reliability and robustness of the data generated in the clinical trial?	**No**	

Summary of Changes in the Current Amendment

Section and Name	**Description of Change**	**Brief Rationale for Change**
CONTACT INFORMATION	The sponsor is updated from "Xiangbin Tang; Tel: (+86)153-1789-3002; E-mail: tang.xiangbin@nkf-pharma.com.cn" to "Zhiguo Feng; Tel: (+86)132-8716-8303; E-mail: feng.zhiguo@nkf-pharma.com.cn"	Update project principal information of sponsor
1.1 Protocol Synopsis 6.1 Description of Trial Intervention	Update the information of reference products (R), including batch No., content, expiration Date: Batch No. is updated from 1055917 to 1256332; Content is updated from 99% to 93%; Expiration date is updated from Oct. 2025 to Apr. 2026.	Update protocol according to information on Certificate of Analysis
8.4.7 Regulatory Reporting Requirements for SAEs	The sponsor is updated from "Xiangbin Tang; Tel: (+86)153-1789-3002; E-mail: tang.xiangbin@nkf-pharma.com.cn" to "Zihan Qin; Tel: (+86)183-8045-6687; E-mail: zhqin@kindospharma.com"	Update information of sponsor

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1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

<table>
<tr><td>Protocol No.</td><td>CHS-1420-10</td></tr>
<tr><td>Protocol Title</td><td>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</td></tr>
<tr><td>Clinical Research Facility and Ethics Committee</td><td>Clinical Research Facility:
Hopeshine-Minsheng Hospital of Xinzheng
Ethics Committee:
Ethics Committee of Hopeshine-Minsheng Hospital of Xinzheng</td></tr>
<tr><td>Trial Objectives</td><td>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.</td></tr>
<tr><td>Overall Design</td><td>A single-center, randomized, single-blind, single-dose, parallel-group comparative pharmacokinetic trial.</td></tr>
<tr><td>Investigational Products</td><td>
<table>
<tr><td>Investigational Products</td><td>Test/Proposed biosimilar (T)</td><td>Reference (R)</td></tr>
<tr><td>Products Name</td><td>CHS-1420 (Autoinjector)</td><td>Adalimumab injection (Autoinjector)</td></tr>
<tr><td>Brand Name</td><td>--</td><td>HUMIRA®</td></tr>
<tr><td>Strength</td><td>40 mg/0.4 mL</td><td>40 mg/0.4 mL</td></tr>
<tr><td>Batch No.</td><td>3PPQ00641</td><td>1256332</td></tr>
<tr><td>Content</td><td>96%</td><td>93%</td></tr>
<tr><td>Dosage</td><td>40 mg</td><td>40 mg</td></tr>
<tr><td>Administration Route</td><td>Subcutaneous injection</td><td>Subcutaneous injection</td></tr>
<tr><td>Duration</td><td>A single dose</td><td>A single dose</td></tr>
<tr><td>Manufacture Date</td><td>--</td><td>--</td></tr>
<tr><td>Expiration Date/ Retest date</td><td>Apr. 2025</td><td>Apr. 2026</td></tr>
<tr><td>Storage</td><td>2-8°C. Protect it from light. Do not freeze.</td><td>2-8°C. Protect it from light. Do not freeze.</td></tr>
<tr><td>Manufacturer</td><td>Ajinomoto Althea, Inc.</td><td>AbbVie Inc.</td></tr>
</table>
</td></tr>
</table>

	Supplier	Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd.	Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd.
Administration Method	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.		
Sample Size	Two hundred and thirty-eight (238) healthy participants to be enrolled		
Trial Duration	Approximately 14 weeks including screening (about 4 weeks) and test period (about 10 weeks).		
In-Clinic Period	All participants will be confined in the clinical research facility from 1 day before the investigational product dosing to 72 hours post-dose after blood collection and safety assessment/examination. They will be allowed to leave the site upon the permission from investigators. Out-patient visits (OPVs) will be required at approximately 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.		
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.		
Trial Procedure	**Screening Period:** Before screening, participants must sign the Informed Consent Forms voluntarily. Screening tests will be conducted from Day -28 to Day -1 (1 day prior to dosing). Investigators will review the inclusion and exclusion criteria according to the results of screening and Day -1. **Observation Period:** Questionnaire will be completed before admission on Day -1 and eligible participants will be enrolled and randomized into		

	two dosing regimens. Each participant will receive a single subcutaneous dose of either the proposed biosimilar product CHS-1420 or reference product HUMIRA® according to the randomization schedule. The details are as follows: **Administration:** Following an overnight fast of at least 10 hours, one of the investigational products will be administered to the participants on Day 1 under fasting conditions 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 from 08:00 (±1 h) in the morning in turn. **PK sampling:** 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. Approximately 3.5 mL of blood will be collected at each sampling time point into vacutainer tubes containing a procoagulant followed by gentle inversions to get mixed up and then be left standing still till coagulation. The coagulated blood will be centrifugated and the serum will be transferred into two tubes and stored in a freezer at -70°C (temperature range: -90°C ~ -60°C) until analyzed. **Sampling for immunogenicity assessment:** A total of four (4) blood samples for each participant will be collected for determination of serum anti-drug antibodies (ADA) / neutralizing antibodies (Nab) at 0 h (within 30 minutes pre-dose) and Day 16, Day 30, Day 65 post-dose. Approximately 5 mL of blood will be collected at each sampling time point into vacutainer tubes containing procoagulant followed by gentle inversions to get mixed up and then be left standing still till coagulation. The coagulated blood will be centrifugated and the serum will be transferred into three tubes and stored in a freezer at -70°C (temperature range: -90°C ~ -60°C) until analyzed. **Safety tests:** Injection site assessment: within 1 h pre-dose and at 1 h, 4 h, 12 h, 24 h, 48 h post-dose. Physical examination: on Day 65 before discharge from the trial. And also, a symptom-based physical examination will be performed on Day 4 before leaving the site. Vital signs: within 1 h pre-dose and at 1 h, 2 h, 8 h, 12 h, 24 h, 48 h, 72 h post-dose, as well as on each OPV day. Laboratory tests (chemistry, hematology, urinalysis, and coagulation function as well as pregnancy tests for female participants): on Day 4, Day 16, Day 30, and Day 65.

	12-lead Electrocardiograph (ECG): on Day 65. All participants will be confined in the clinical research facility with unified management from 1 day before investigational products dosing until approximately 72 h post-dose after blood collection and safety assessment/examination. They will be allowed to leave the site after permission from investigators. Out-patient visits (OPVs) will be required at approximately 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. Before leaving, the participants will be informed by the staff of the precautions and to report any adverse events (AEs) until completion of the trial. All the AEs during the trial will be followed up until AE resolution or stabilization, or participants lost to follow up.
Inclusion Criteria	1) Able to provide signed Informed Consent Form before the trial, and fully understand the trial content, process and possible adverse drug reactions (ADRs); 2) Able to complete the trial in compliance with the protocol; 3) Participants (including males) willing to adopt effective contraceptive methods and with no pregnancy plan from 14 days before screening to 6 months after the last scheduled visit; 4) Males and females between 18 and 55 years old, inclusive; 5) At least 50 kg for participants, with a Body Mass Index (BMI) = Weight/Height^2 (kg/m^2) between 19.0-26.0 kg/m^2, inclusive; 6) No history of chronic or serious cardiac, hepatic, renal, digestive tract, nervous system, hematologic, respiratory, dermatological, mental and metabolic disorders, *etc.* **Only those who meet all the criteria listed above can be enrolled.**
Exclusion Criteria	1) With ≥ 5 cigarettes per day on average within 3 months before screening, or not able to quit smoking during the trial; 2) Allergic constitution, or allergic to the drug components and its analogues; history of allergic reaction to a biological medication; 3) A history of alcohol abuse (alcohol consumption of more than 14 units per week : 1 unit of alcohol = 285 mL beer, or 25 mL spirits, or 100 mL wine); 4) Blood donation or massive blood loss (> 400 mL) within 3 months before investigational products dosing; Or any blood donation plan from screening until 3 months after administration; 5) History of any major surgery within the past year, or history of any surgery within the past 6 months; or any elective medical procedures, including dental procedures; 6) Any history of organ transplantation;

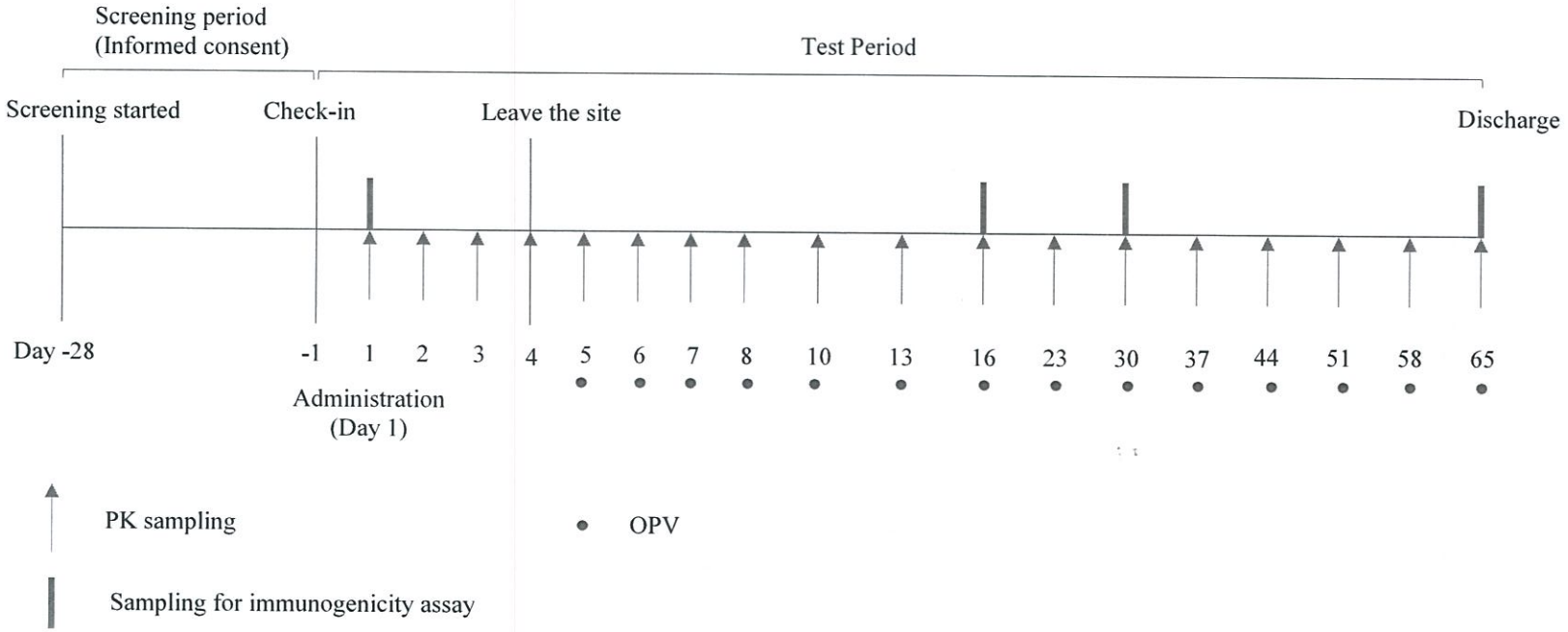
	7) Medical history of tuberculosis (or suspected tuberculosis), or with a positive tuberculosis test result; 8) Medical history of heart failure or other cardiac disorders which may lead to heart failure, e.g. coronary heart disease, hypertension, senile degenerative valvular disease, rheumatic valvular heart disease, dilated cardiomyopathy, acute severe myocarditis; 9) Medical history of immune system disorders (e.g. systemic lupus erythematosus, multiple sclerosis, *etc.*), or positive results of antinuclear antibody tests; 10) Medical history of recurrent or chronic infections (including transverse myelitis, optic neuritis, other demyelinating disorders, *etc.*), or a history of an opportunistic infection within the past year due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens; 11) History of seizure attack; 12) Medication history of TNF-α blockers e.g. Adalimumab or its analogues; 13) Any medication of monoclonal antibodies within the past year before investigational products dosing; 14) Any usage history of prescription medicines or OTCs (especially antibiotics), or Chinese herbal medicine or health supplementary within 30 days before investigational products dosing; 15) Any vaccination within 3 months before investigational products dosing, or any plan for vaccination within 3 months after investigational products administration; 16) Consumption of any special diets or food items (such as grapefruit), or strenuous exercise engagement, or other factors in the opinion of investigators affecting drug absorption, distribution, metabolism and excretion within 7 days before investigational products dosing; 17) Participation in other drug clinical trials within 3 months before investigational products dosing; 18) Any clinically significant abnormality findings, as judged by a clinical physican, such as physical examination, vital signs, electrocardiogram and laboratory tests, as well as Chest X-ray; 19) Positive results of hepatitis B surface antigen, hepatitis C antibody, and HIV antibody or syphilis; 20) Consumption of chocolate or any food/beverage containing caffeine or rich in xanthine within 48 h before investigational products dosing; 21) Consumption of any products containing alcohol within 48 h before investigational products dosing, or a positive result of the alcohol breath test; 22) A positive result of the drug abuse test, or a history of drug abuse in the past 5 years, or intake of any narcotic drugs within 3 months prior

	to the trial; 23) A positive result of the pregnancy test, or in lactation during screening or the test period for female participants; 24) Not tolerable on venipuncture, or a history of fainting on acupuncture and/or blood; 25) Special requirements and unable to follow the unified diet; 26) Unable to participate in this trial for participants' own reasons; 27) Other conditions in which participants are not suitable for the trial determined by investigators. **Those who meet any of the criteria listed above must not be enrolled.**
Withdrawal Criteria	1) Withdrawal Determined by Investigator: The withdrawal of enrolled participants determined by the Investigator in case they are not suitable to continue in the trial. A. Investigators decide that the participant should withdraw due to medical ethics; B. Investigators decide that the participant should withdraw due to AEs; C. Investigators decide that withdrawal is in the best interest of the participant; D. The participant is of poor compliance, including but not limited to: a) Failure to take the medications, blood collection and examinations as required; b) Any medication or diets that affect the safety evaluation and pharmacokinetics results; c) Smoking or drinking alcohol; d) Other behavior which may affect the trial results. 2) Voluntary withdrawal by the participant. Participants withdraw the informed consent officially, or won't take the investigational products or any tests any more although not withdrawing the informed consent officially, or lost to follow-up. Handling of Withdrawals: No matter required by the participant or determined by the principal investigator, the reason for withdrawal should be fully investigated and recorded. For safety consideration, all dosed participants who withdraw from the trial should complete safety assessment. Investigators should try to contact the participant with due diligence, "lost to follow-up" will be recorded if the participant can not be contacted after at least 3 phone calls.
Elimination Criteria	The principal investigator, sponsor and statisticians need to work together to decide the participant(s) to be excluded or not from relevant datasets before the statistical analysis. 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) After taking investigational product, the data of individual participants will be excluded from PK similarity analysis (PKSS) on condition that: a. Participants who have positive results of ADA at baseline (0 h); b. The first postdose sample provides C_{max} values; c. The pre-dose (0 h) sample provides a quantifiable concentration value; d. 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.
Termination Criteria	1) Refer to CTCAE 5.0, if more than half of the participants experience drug-related AEs of Grade 2, or more than a quarter of the participants experience drug-related AEs of Grade 3-4; or indication in which obvious intolerance; 2) Termination requested by the sponsor on the premise of full ensuring the legal rights and safety of participants; 3) Termination demanded by NMPA or Ethics Committee due to some reasons; 4) Other conditions in which the trial cannot be continued.
PK Evaluation	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 Assessment	AEs, Serious adverse events (SAEs), vital signs, physical examination, laboratory test, electrocardiogram (ECG), local reactions at the injection site, concomitant therapy, *etc.*

Immunogenicity Assessment	Incidence and severity of immunogenicity response (ADA/Nab).
Statistical Analysis	PK Analyses PK parameters estimation will be performed with WinNonlin (Version 8.4 or higher). Statistical analysis below will be performed with SAS (Version 9.4 or higher). For population included in Pharmacokinetic Concentration Set (PKCS), individual and mean concentration – time profile will be generated. Descriptive statistics will be performed on the concentration data including cases, arithmetic mean, standard deviation, *etc.* For population included in Pharmacokinetic Parameter Set (PKPS), descriptive statistics will be performed on the PK parameter data including cases, arithmetic mean, standard deviation, *etc.* For population included in Pharmacokinetic Similarity Set (PKSS), analysis of variance and the 90% confidence interval (CI) calculation will be conducted on the ln-transformed primary PK parameters C_{max}, $AUC_{0-\infty}$ And the 90% CIs of the Test/Reference geometric mean ratios (GMRs) have to fall in the range of 80% - 125% to demonstrate the PK similarity. For population included in Immunogenicity Analysis Set (IAS), data will be summarized and listed by treatment, by visit, and by treatment and visit. Based on Safety Set (SS), AEs, SAEs, vital signs evaluation, physical examination, laboratory test results, ECG, local reactions at the injection site, *etc.* will be statistically summarized and tabulated.

1.2 Trial Schema



1.3 Schedule of Activities

Procedure and assessment	Screening [1]	Check-in	CHS-1420 PK Similarity Trial																		Withdraw ahead of time [14]
			Hospitalization				OPV														
	D-28-D-1	D-1	D1	D2	D3	D4	D5	D6	D7	D8	D10	D13	D16	D23	D30	D37	D44	D51	D58	D65[13]	
Informed consent	X																				
Demographic data	X																				
Height, BMI	X																				
Weight	X																			X	X
Medical/ surgical history	X																				
Allergy history	X																				
Medication history	X	X																			
History of tobacco, alcohol and drug abuse	X																				
Chest X-ray	X																				
Antinuclear antibody	X																				
Viral screen (HIV/HBV/HCV/syphilis/tuberculosis)	X																				
Physical examination[2]	X					X														X	X
Biochemistry, hematology, urinalysis, coagulation function [3]	X					X							X		X					X	X
Serum pregnancy test (only for females)	X	X				X							X		X					X	X
ECG [4]	X																			X	X
Vital signs [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug abuse tests [6]		X													X						
Alcohol breath tests [6]		X													X						

Procedure and assessment	Screening [1]	Check-in	CHS-1420 PK Similarity Trial																		Withdraw ahead of time [14]
			Hospitalization				OPV														
	D-28-D-1	D-1	D1	D2	D3	D4	D5	D6	D7	D8	D10	D13	D16	D23	D30	D37	D44	D51	D58	D65[13]	
Admission questionnaire		X																			
Inclusion/exclusion criteria review [7]	X	X																			
Check-in		X																			
Randomization		X																			
Investigational products administration [8]			X																		
Injection site assessment [9]	X		X	X	X																
PK sampling [10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Sampling for immunogenicity assessment [11]			X										X		X					X	
AEs monitoring and recording			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication/non-drug therapy record			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge and OPV [12]						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Screening will be performed within 28 days prior to the dosing (Day 1); The serum pregnancy test won't be performed before check-in on female participants who are screened on Day -1;

[2] Physical examination will be performed at screening, on Day 65; and also, a symptom-based physical examination will be performed on Day 4 before leaving the site;

[3] Laboratory tests (biochemistry, hematology, urinalysis, coagulation function) will be performed at screening visit (the results obtained within 7 days considered acceptable), on Day 4, Day 16, Day 30, Day 65;

[4] 12-lead ECGs will be measured at screening, on Day 65;

[5] Vital signs (temperature, pulse, blood pressure) will be measured at screening, within 1 h pre-dose and at 1 h (±30 min), 2 h (±30 min), 8 h (±60 min), 12 h (±60 min), 24 h (±60 min), 48 h (±60 min), 72 h (±60 min) post-dose, as well as on each OPV day (the same requirement of timewindow for vital signs measurement on OPV days as that for PK sampling);

[6] Drug abuse tests and Alcohol breath tests will be conducted on the check-in day (Day -1), on Day 30;

[7] Investigators will review the inclusion and exclusion criteria according to the results of the screening period and Day -1;

[8] Following an overnight fast of at least 10 hours, one of the investigational products will be administered to the participants on Day 1 under fasting conditions 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 (as detailed in the dosing manual) from 08:00 (±1 h) in the morning in turn. Each participant will be dosed only once through the trial;

[9] Injection site assessment will be performed during screening, within 1 h pre-dose and at 1 h (±30 min), 4 h (±60 min), 12 h (±60 min), 24 h (±60 min), 48 h (±60 min) post-dose;

[10] PK sampling: 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. The allowed deviation from the scheduled PK sampling timepoints is as follows:

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		

[11] Sampling for immunogenicity assessment: A total of four (4) blood samples for each participant will be collected for determination of serum anti-drug antibodies (ADA) / neutralizing antibodies (Nab) at 0 h (within 30 minutes pre-dose) and Day 16, Day 30, Day 65 post-dose. The actual sampling time should be recorded;

[12] Participants will be discharged from the clinical research facility after PK sampling and required safety assessment at approximately 72 h after dosing while OPVs are required at approximately 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;

[13] Safety tests will be performed at the end of trial on Day 65 for each participant before discharge from the trial, including physical examination, laboratory tests [biochemistry, hematology, urinalysis, coagulation function, serum pregnancy test (only for females)], ECG, vital signs; and also the weight of participants will be collected;

[14] Any dosed participants who withdraw ahead of time should receive the scheduled safety tests for permission to discharge from the trial before leaving or at the time of the participants next scheduled follow-up visit, or any other time appropriate in discretion of investigators. In addition collection of weight will be performed.

2 INTRODUCTION

2.1 Purpose of Trial

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 [1].

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) [2]. 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.

2.2 Summary of Benefits and Risks

Benefits

This is 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. No benefits are expected for the individual participant. However, the trial data may support the registration application for a proposed biosimilar to HUMIRA® (Adalimumab), which can further provide an alternative therapeutic choice and benefit the indicated population.

Risks

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). Data derived from analytical studies, animal studies indicated similarity between CHS-1420 and HUMIRA®.

For individual participant, the risks of treatment with HUMIRA® (Adalimumab) can be found in the Prescribing Information [2]:

Most common adverse reactions (>10%) during HUMIRA® (Adalimumab) treatment are: infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash.

Other warnings and precautions for treatment with HUMIRA® (Adalimumab) are as follows:

- *Serious infections:* Do not start Adalimumab during an active infection. If an infection develops, monitor carefully, and stop Adalimumab if infection becomes serious.
- *Invasive fungal infections:* For patients who develop a systemic illness on Adalimumab, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic.
- *Malignancies:* Incidence of malignancies was greater in Adalimumab-treated patients than in controls.
- *Anaphylaxis or serious hypersensitivity reactions* may occur.
- *Hepatitis B virus reactivation:* Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop Adalimumab and begin anti-viral therapy.
- *Demyelinating disease:* Exacerbation or new onset, may occur.
- *Cytopenias, pancytopenia:* Advise patients to seek immediate medical attention if symptoms develop, and consider stopping Adalimumab.
- *Heart failure:* Worsening or new onset, may occur.
- *Lupus-like syndrome:* Stop Adalimumab if syndrome develops.

In one PK similarity study[3] on the proposed biosimilar to Adalimumab, following a single subcutaneous injection at dose of 40 mg in healthy participants, approximately 70% participants reported at least one adverse event of which the majority were mild or moderate in intensity. The most commonly reported TEAEs, independent of relation to

study treatment, were headache, nasopharyngitis, and rhinitis. Other adverse events included Upper respiratory tract infection, Back pain, Myalgia, Oropharyngeal pain, Fatigue, Neutropenia. There were two SAEs: an angioedema (moderate intensity), which was considered to be related to the study treatment (the proposed biosimilar product arm), and a femoral neck fracture (severe intensity), which was not considered to be related to the study treatment (US- HUMIRA arm).

For the whole clinical trial, participants will suffer venous sampling at the scheduled frequency which may lead to local reactions, e.g. swelling and stiffness, etc. In addition, there may be occurrence of blood pressure fluctuations, dizziness, nausea, even fainting, etc. upon the blood collection in clinical practice.

During the screening period, participants will be fully informed of the trial purpose, investigational product information, dosing regimen (such as dosage, administration method, period, etc.), clinical observation, frequency and procedure of blood collection, potential risks, compensation and indemnity to ensure the voluntary participation and the participant compliance. At the same time, investigators should learn participants' previous reactions and tolerance to venous blood collection to avoid enrollment of participants not tolerable with the venous sampling in the trial.

During the clinical trial, the investigator should pay close attention to the previous reported SAEs, common AEs and AEs leading to discontinuation, and make participants fully informed and establish the relevant plan of monitoring and treatment. After the treatment in each period, clinical staff should closely observe the participants for possible AEs and related symptoms.

3 TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS

3.1 Primary/Secondary Objective

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.

3.2 Associated Endpoint and Estimand

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 Estimands

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

Immunogenicity Estimands

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

4 TRIAL DESIGN

4.1 Description of 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 as indicated in Section 1.2.

4.2 Rationale for Trial Design

As a biosimilar product to Adalimumab, CHS-1420 of strength 40 mg/0.8 mL has been approved by FDA. Now an extended strength of 100 mg/mL CHS-1420, including 40 mg/0.4 mL and 80 mg/0.8 mL, will be declared. According to the guidance of Scientific Considerations in Demonstrating Biosimilarity to a Reference Product [4] and Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product [1] issued by FDA as well as the PK and immunogenicity profile of the investigational products, the communication results with FDA on CHS-1420 of strength 40 mg/0.4 mL, this comparative PK is designed, the same way as that for PK similarity study of the lower concentration CHS-1420, as a single-center, randomized, single-blind, parallel-group trial with a single subcutaneous dose of either the proposed biosimilar product (T) CHS-1420 or reference product (R) HUMIRA® under fasting conditions. In addition, safety and

immunogenicity of the two products will be also evaluated and compared.

Study population: According to the guidance of Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product issued by FDA, a study in healthy participants is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK and/or PD variability compared with a study in patients with potential confounding factors such as underlying and/or concomitant disease and concomitant medications. And healthy participants will be enrolled in this trial to assess the PK similarity between CHS-1420 and HUMIRA®.

Duration: The trial is expected to last 14 weeks including a 28-day screening period to enroll enough eligible participants. The test period will be approximately 10 weeks. According to the guidance of Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product and PK profile of Adalimumab, this parallel trial is designed to sampling up to 65 days post dose which can cover the major PK behavior according to $t_{1/2}$ of Adalimumab (approximately 2 weeks).

Pharmacokinetic endpoints: The primary PK parameters include: C_{max}, $AUC_{0-\infty}$ of serum drug (adalimumab); the secondary PK parameters include: AUC_{0-t}, $AUC_{0-65days}$, T_{max}, K_{el}, $t_{1/2}$, V_d/F, CL/F of serum drug (adalimumab) according to the guidance of Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product issued by FDA.

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

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

4.2.1 Rationale for Comparator

Hong Kong King-Friend, a subsidiary corporation of Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd. intends to submit a application under 351(k) of CHS-1420 40 mg/0.4 mL, developed as a proposed biosimilar product to Adalimumab. According to the guidance of Scientific Considerations in Demonstrating Biosimilarity to a Reference Product and the Purple Book issued by FDA, U.S.-licensed HUMIRA® (Adalimumab) 40 mg/0.4 mL manufactured by AbbVie Inc. will be selected for this trial as the reference products to assess the PK similarity, safety and immunogenicity with CHS-1420 40 mg/0.4 mL manufactured by Ajinomoto Althea, Inc.

4.2.2 Rationale for Adaptive or Novel Trial Design

Not Applicable.

4.2.3 Other Trial Design Considerations

Not Applicable.

4.3 Access to Trial Intervention After End of Trial

Not Applicable.

4.4 Start of Trial and End of Trial

Start of trial: the date when the first informed consent form is signed.

End of trial: the date when the last participant completed the last follow-up visit.

If trial termination or temporary discontinuation is indicated, the duty and obligation of the sponsor and investigators is detailed in Section 10.5.2.

5 TRIAL POPULATION

5.1 Selection of Trial Population

Healthy adult males and non-pregnant, non-lactating females of age 18 – 55 years old inclusive are to be enrolled in the trial.

5.2 Rationale for Trial Population

Healthy adult participants are to be enrolled in the trial according to the guidance of Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product issued by FDA.

5.3 Inclusion Criteria

1) Able to provide signed Informed Consent Form before the trial, and fully understand the trial content, process and possible adverse drug reactions (ADRs);
2) Able to complete the trial in compliance with the protocol;
3) Participants (including males) willing to adopt effective contraceptive methods and with no pregnancy plan from 14 days before screening to 6 months after the last scheduled visit;
4) Males and females between 18 and 55 years old, inclusive;
5) At least 50 kg for for participants, with a Body Mass Index (BMI) = Weight/Height^2 (kg/m^2) between 19.0-26.0 kg/m^2, inclusive;
6) No history of chronic or serious cardiac, hepatic, renal, digestive tract, nervous system, hematologic, respiratory, dermatological, mental and metabolic disorders, *etc.*

Only those who meet all the criteria listed above can be enrolled.

5.4 Exclusion Criteria

1) With ≥ 5 cigarettes per day on average within 3 months before screening, or not able to quit smoking during the trial;
2) Allergic constitution, or allergic to the drug components and its analogues; history of allergic reaction to a biological medication;
3) A history of alcohol abuse (alcohol consumption of more than 14 units per week : 1 unit of alcohol = 285 mL beer, or 25 mL spirits, or 100 mL wine);
4) Blood donation or massive blood loss (> 400 mL) within 3 months before investigational products dosing; Or any blood donation plan from screening until 3 months after administration;
5) History of any major surgery within the past year, or history of any surgery within the past 6 months; or any elective medical procedures, including dental procedures;
6) Any history of organ transplantation;
7) Medical history of tuberculosis (or suspected tuberculosis), or with a positive tuberculosis test result;
8) Medical history of heart failure or other cardiac disorders which may lead to heart failure, e.g. coronary heart disease, hypertension, senile degenerative valvular disease, rheumatic valvular heart disease, dilated cardiomyopathy, acute severe myocarditis;
9) Medical history of immune system disorders (e.g. systemic lupus erythematosus, multiple sclerosis, *etc.*), or positive results of antinuclear antibody tests;
10) Medical history of recurrent or chronic infections (including transverse myelitis, optic neuritis, other demyelinating disorders, *etc.*), or a history of an opportunistic infection within the past year due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens;
11) History of seizure attack;
12) Medication history of TNF-α blockers e.g. Adalimumab or its analogues;
13) Any medication of monoclonal antibodies within the past year before investigational products dosing;
14) Any usage history of prescription medicines or OTCs (especially antibiotics), or Chinese herbal medicine or health supplementary within 30 days before investigational products dosing;
15) Any vaccination within 3 months before investigational products dosing, or any plan for vaccination within 3 months after investigational products administration;
16) Consumption of any special diets or food items (such as grapefruit), or strenuous exercise engagement, or other factors in the opinion of investigators affecting drug absorption, distribution, metabolism and excretion within 7 days before investigational products dosing;
17) Participation in other drug clinical trials within 3 months before investigational

products dosing;

18) Any clinically significant abnormality findings, as judged by a clinical physican, such as physical examination, vital signs, electrocardiogram and laboratory tests, as well as Chest X-ray;
19) Positive results of hepatitis B surface antigen, hepatitis C antibody, and HIV antibody or syphilis;
20) Consumption of chocolate or any food/beverage containing caffeine or rich in xanthine within 48 h before investigational products dosing;
21) Consumption of any products containing alcohol within 48 h before investigational products dosing, or a positive result of the alcohol breath test;
22) A positive result of the drug abuse test, or a history of drug abuse in the past 5 years, or intake of any narcotic drugs within 3 months prior to the trial;
23) A positive result of the pregnancy test, or in lactation during screening or the test period for female participants;
24) Not tolerable on venipuncture, or a history of fainting on acupuncture and/or blood;
25) Special requirements and unable to follow the unified diet;
26) Unable to participate in this trial for participants' own reasons;
27) Other conditions in which participants are not suitable for the trial determined by investigators.

Those who meet any of the criteria listed above must not be enrolled.

5.5 Lifestyle Considerations

Investigator will inform participants the requirements and management rules of the clinical research facility during the trial. Participants will not be allowed to leave the clinic without permission and not allowed to bring food, cigarettes, alcohol or engage in any strenuous activities, *etc*.

5.5.1 Meals and Dietary Restrictions

Water restrictions:

Water will be prohibited from 1 hour before to 1 hour after drug administration.

Meal restrictions:

Participants will undergo an overnight fast of at least 10 hours before subcutaneous injection of the investigational products.

On the day of dosing, lunch will be provided at least 4 hours after dosing. Both lunch and dinner will be bland diet.

5.5.2 Caffeine, Alcohol, Tobacco, and Other Habits

Participants must refrain from ingesting chocolate or any food or beverages containing caffeine or rich in xanthine from 48 h before the dosing to the end of trial. Participants must refrain from consuming special food or beverage (such as grapefruit) from 7 days before the dosing to the end of trial. Participants must refrain from consuming alcohol or alcoholic food or beverage from 48 h before the dosing to the end of trial.

During in-clinic confinement period, participants will not be allowed to take any diet other than those offered by investigators at scheduled time.

Smoking is forbidden from signing the informed consent form until the end of the trial on Day 65.

5.5.3 Physical Activity

Strenuous exercise should be avoided after dosing. On the day of dosing, participants will be dosed in a lying posture throughout the dosing procedure. Keep an upright upper body position within 4 hours after investigational products administration. Avoid rubbing the administration site during the trial.

5.5.4 Other Activity

Participants (including males) should adopt effective contraceptive measurements and have no plan for pregnancy from 14 days before screening to 6 months after the last scheduled visit.

5.6 Screen Failures

Rescreening will not be performed on the screen failure in this trial.

6 TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1 Description of Trial Intervention

Investigational Products	Test/Proposed biosimilar (T)	Reference (R)
Products Name	CHS-1420 (Autoinjector)	Adalimumab injection (Autoinjector)
Brand Name	--	HUMIRA®
Strength	40 mg/0.4 mL	40 mg/0.4 mL
Batch No.	3PPQ00641	1256332
Content	96%	93%
Dosage	40 mg	40 mg
Administration Route	Subcutaneous injection	Subcutaneous injection

Investigational Products	Test/Proposed biosimilar (T)	Reference (R)
Duration	A single dose	A single dose
Manufacture Date	--	--
Expiration Date/ Retest date	Apr. 2025	Apr. 2026
Storage	2-8°C. Protect it from light. Do not freeze.	2-8°C. Protect it from light. Do not freeze.
Manufacturer	Ajinomoto Althea, Inc.	AbbVie Inc.
Supplier	Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd.	Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd.

All the investigational products will be provided from the same batch, and the immediate package should be labeled with the statement "Caution: Test/Reference Product –only used for clinical study" or other similar statement.

Sample Label for Test / Proposed Biosimilar Products

(See actual label for the specified information which will at least include)

CHS-1420 (A proposed biosimilar product to Adalimumab)

Only used for clinical trial!

【Product Code】 T—XXX
【Protocol No.】 CHS-1420-10
【Dosage form】
【Strength】
【Dosage and administration】
【Batch No.】
【Mfg. date】
【Exp. date】
【Packing specification】
【Storage】
【Mfg. by】
【Sponsor】

Note: Test / Proposed Biosimilar Products may be coded as T-XXX in which XXX is the serial No., e.g. T-001.

Sample Label for Reference Products

(See actual label for the specified information which will at least include)

HUMIRA® (Adalimumab)

Only used for clinical trial!

【Product Code】 R—XXX
【Protocol No.】 CHS-1420-10
【Dosage form】
【Strength】
【Dosage and administration】
【Batch No.】
【Mfg. date】
【Exp. date】
【Packing specification】
【Storage】
【Mfg. by】
【Sponsor】

Note: Reference product may be coded as R-XXX in which XXX is the serial No., e.g. R-001.

6.2 Rationale for Trial Intervention

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

The extended strengths to be declared of the proposed biosimilar product CHS-1420 is 40 mg/0.4 mL and 80 mg/0.8 mL, both of which share the same concentration 100 mg/mL with different volumes of drug. According to the guidance of Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product issued by FDA, the most sensitive dose should be selected to detect and to evaluate differences in the PK and PD profiles between the proposed biosimilar product and the reference product. And the dose selected should be one most likely to provide clinically meaningful and interpretable data. If a study is conducted in a patient population, the approved dose for the reference product can be the appropriate choice, because this approved dose can best demonstrate the pharmacological effects in a clinical setting. However, a lower dose on the steep part of the exposure-response curve is generally appropriate when PD is being measured or when healthy participants are selected for evaluation. Considering the approved clinical dosage of HUMIRA® (adalimumab) and other biosimilars to Adalimumab approved by FDA, a single subcutaneous dose of 40 mg will be administered. Each participant will be dosed once in the trial.

6.3 Dosing and Administration

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.

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.

6.3.1 Trial Intervention Dose Modification

No dose modification will be expected in this single-dose PK similarity assessment trial. Here is not discussing the discontinuation of trial intervention for safety or other consideration.

6.4 Treatment of Overdose

Not Applicable.

6.5 Preparation, Handling, Storage and Accountability

6.5.1 Preparation of Trial Intervention

Sponsor should not separate out the reserve samples of the proposed biosimilar and reference products before sending the products to the research facility, and the sponsor

should package the investigational products (from the same batch) properly, so that the research facility can randomly select samples for testing and samples to be reserved as reserve samples from the same batch according to the relevant guidance [5]. The reserve products should be maintained in the sponsor's original container.

6.5.2 Handling and Storage of Trial Intervention

The investigational products should be stored in a locked cabinet following the storage requirements indicated in Section 6.1. The institution should properly keep all investigational products and reserve products.

For most protein therapeutics, FDA recommends that a sponsor retain the following quantities of product and dosage units, which are expected to be sufficient for evaluation by state of the art analytical methods [6]:

- Minimum of 10 dosage units each of the proposed biosimilar product, reference product and, if applicable, non-U.S.-licensed comparator product, depending on the amount of product within each unit; in general, this should provide for a total product mass of equal to or greater than 200 mg in a volume equal to or greater than 10 mL.

Reserve samples will be stored in locked cabinets under the required conditions in clinical research facility until at least 5 years after application approval or until at least 5 years after the completion of the trial. When the clinical research facility does not have suitable storage conditions, the reserve samples can be transferred to an independent third-party with the conditions in consistent with the requirements indicated on the label of the investigational products for storage. The reserve samples must not be returned to sponsor or any third party with interests' relationship.

6.5.3 Accountability of Trial Intervention

The staff of clinical research facility should verify the information of investigational products and sign on the receiving log after receipt of proposed biosimilar/reference products. The investigational products will be administered to all randomized participants as per the randomization code. Accurate records will be maintained regarding drug distribution, drug administration and residual drug which should be with double signature.

Distribution Plan for the Investigational Products

Investigational Products	Products name (Brand name)/Strength	Receipt	Distribution	Retention
Test/Proposed biosimilar	CHS-1420 /40 mg/0.4 mL	154 autoinjectors	119 autoinjectors	26 autoinjectors for reserve samples + 9 residual samples
Reference	HUMIRA® (Adalimumab) /40 mg/0.4 mL	154 autoinjectors	119 autoinjectors	26 autoinjectors for reserve samples + 9 residual samples

6.6 Participant Assignment, Randomization and Blinding

6.6.1 Participant Assignment

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

There will be 238 healthy participants to be enrolled in the fasting trial and they will be randomized to one of two treatment groups (T, R), with an equal number of participants per treatment group.

6.6.2 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).

6.6.3 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.

6.7 Trial Intervention Compliance

During the screening period, participants will be fully informed of the trial purpose, investigational product information, trial procedure, dosing regimen (such as dosage, administration method, period, *etc.*), clinical observation, frequency and procedure of blood collection, potential risks, compensation and indemnity to ensure the voluntary participants participation and the treatment compliance. Before dosing, the participants and the drugs to be administered should be verified carefully; After dosing, any remaining drugs, the empty package and dosing apparatus should also be checked, to record the treatment compliance.

6.8 Concomitant Therapy

Unless for treatment of AEs, any medications history of TNF-α blockers e.g. Adalimumab or its analogues (except the investigational products scheduled to be dosed in the trial) were prohibited for the enrolled participants until the last scheduled visit (including OPVs); any medication of monoclonal antibodies should not be taken within one year prior to investigational products dosing to the last scheduled visit (including OPVs); any prescription medicines or OTCs (especially antibiotics), Chinese herbal medicine or health supplementary should not be taken within 30 days prior to investigational products dosing to the last scheduled visit (including OPVs); any vaccines should not be taken within 3 months prior to investigational products dosing to 3 months after investigational products administration (including OPVs). Any medication except investigational products used during the trial (including OPVs) should be recorded in source document and case report form (CRF) in details. All the non-investigational products taken by participants during the trial (including OPVs) are treated as concomitant medications. Principal Investigator or

sponsor will determine whether the participant should continue the trial according to the interaction between investigational and non-investigational products, and whether the concomitant medication may affect the PK of the investigational products.

7 DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT WITHDRAWAL FROM TRIAL

7.1 Discontinuation of Trial Intervention

The participation in the clinical trial is completely voluntary. After the investigational products are distributed, the participants can withdraw from the trial for any reason without discrimination or retaliation, and their medical treatment and rights will not be affected. Participants who withdraw are not allowed to continue the trial.

7.2 Participant Withdrawal from the Trial

1) Determined by Investigator: The withdrawal of enrolled participants determined by the Investigator in case they are not suitable to continue in the trial.
   A. Investigators decide that the participant should withdraw due to medical ethics;
   B. Investigators decide that the participant should withdraw due to AEs;
   C. Investigators decide that withdrawal is in the best interest of the participant;
   D. The participant is of poor compliance, including but not limited to:
      a) Failure to take the medications, blood collection and examinations as required;
      b) Any medication or diets that affect the safety evaluation and pharmacokinetics results;
      c) Smoking or drinking alcohol;
      d) Other behavior which may affect the trial results.

2) Voluntary withdrawal by the participant.

Participants withdraw the informed consent officially, or won't take the investigational products or any tests any more although not withdrawing the informed consent officially, or lost to follow-up.

Handling of Withdrawals: No matter required by the participant or determined by the principal investigator, the reason for withdrawal should be fully investigated and recorded. For safety consideration, all dosed participants who withdraw from the trial should complete safety assessment.

7.3 Lost to Follow-Up

Investigators should try to contact the participant with due diligence, "lost to follow-up" will be recorded if the participant can not be contacted after at least 3 phone calls.

7.4 Trial Stopping Rules

Not Applicable.

8 TRIAL ASSESSMENTS AND PROCEDURES

8.1 Screening/Baseline Assessments and Procedures

Healthy males and females of age 18 – 55 years old inclusive will be enrolled. After providing written informed consent, participants will undergo a complete collection of data within 28 days prior to investigational products dosing including:

- Demographic data (including gender, age, height, weight, BMI, nation, and race, *etc*).
- Medical /surgical history, allergy history, medication history, drug abuse history, history of tobacco and alcohol.
- Chest X-ray.
- Physical examination (detailed in Section 8.3.1)
- Vital signs (detailed in Section 8.3.2)
- ECG (detailed in Section 8.3.3)
- Clinical laboratory tests [biochemistry, hematology, urinalysis, coagulation function, antinuclear antibody, viral tests (HBV, HCV, HIV, syphilis, tuberculosis) and a serum pregnancy test (females only), see Section 13.2].
- A urine drug abuse test (Morphine, Methamphetamine, Ketamine, Tetrahydrocannabinol and Methylenedioxymethamphetamine in urine) and alcohol breath test.

Viral tests results obtained within the previous 3 months prior to investigational products dosing may be used instead of obtaining these tests at the screening visit. Among them, the urine drug abuse test and alcohol breath test will be conducted before check-in (Day -1) and retested upon OPVs on Day 30.

8.2 Efficacy Assessments and Procedures

Not Applicable.

8.3 Safety Assessments and Procedures

The safety of CHS-1420 and HUMIRA® will be assessed by AEs, SAEs, vital signs, physical examination, laboratory test results, ECG, local reactions at the injection site, concomitant therapy, *etc*.

8.3.1 Physical Examination

Physical examination will be performed at the screening visit, and before discharge from the trial on Day 65. A full physical examination includes assessment of skin, mucous membranes, lymph nodes, head, neck, chest, abdomen, spine/limbs and nervous system, *etc*. And also, a symptom-based physical examination will be performed on Day 4 before leaving the site.

Injection site assessment will be performed during screening, within 1 h pre-dose and at 1 h (±30 min), 4 h (±60 min), 12 h (±60 min), 24 h (±60 min), 48 h (±60 min) post-dose.

8.3.2 Vital Signs

Vital signs (including systolic and diastolic blood pressure, pulse rate and temperature) will be measured at screening, within 1 h pre-dose and at 1 h (±30 min), 2 h (±30 min), 8 h (±60 min), 12 h (±60 min), 24 h (±60 min), 48 h (±60 min), 72 h (±60 min) post-dose, as well as on each OPV day (the same requirement of timewindow for vital signs measurement on OPV days as that for PK sampling).

Normal reference ranges (inclusive) for vital signs are listed as follows:

- Temperature (forehead): 35.8 to 37.5°C
- Pulse rate: 50 to 100 beats per minute
- Systolic blood pressure: 90 to 140 mmHg
- Diastolic blood pressure: 60 to 90 mmHg

8.3.3 Electrocardiograms

The 12-lead ECGs will be tested at the screening visit, and before discharge from the trial on Day 65.

8.3.4 Clinical Laboratory Assessments

The clinical laboratory tests, including biochemistry, hematology, urinalysis, coagulation function, serum pregnancy test (only for females), will be performed at the screening visit (the results obtained within 7 days considered acceptable), and on Day 4, Day 16, Day 30, Day 65. In addition, serum pregnancy results for females will also be confirmed before admission on Day -1. A list of clinical laboratory assessments is included in Section 13.2.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definitions of AE and SAE

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.

8.4.2 Time Period and Frequency for Collecting AE and SAE Information

The nursing and medical staff will closely observe the participants for any AEs throughout the trial. Once dosed, any abnormalities of clinical significance e.g. clinical sign and symptom, vital signs, physical examination, ECG, laboratory test results in a participant will be collected as AEs or SAEs until completion of the trial.

Before leaving the research facility, the participants will be informed by the staff of the precautions and to report any AEs until completion of the trial.

8.4.3 Identifying AEs and SAEs

Adverse events will be monitored by nursing and medical observations of the staff and spontaneous reporting throughout the trial. The inquiry to participants for AEs from Investigators should be performed in an non-induced manner during the trial.

8.4.4 Recording of AEs and SAEs

During the trial, the AEs record form should be truthfully filled, including the time of onset, duration, severity, action taken and follow-up outcome. The AEs should be documented on the designated CRF.

Abnormal laboratory test results of no clinical significance will not be recorded as AEs or SAEs. Laboratory abnormalities (e.g. biochemistry, hematology, urinalysis, and coagulation function) and other abnormity (e.g. ECG, vital signs) of clinical significance must be recorded as AEs or SAEs. If the abnormal results are the part of a syndrome, the syndrome or diagnosis results (e.g. anemia) need to be recorded rather than laboratory test results (e.g. hemoglobin decrease).

Further details on assessing severity and causality of AEs and SAEs are in Appendix 12.3 and Appendix 12.4.

8.4.5 Follow-up of AEs and SAEs

All the AEs, whether related to the medicinal (investigational) product or not, should be followed up until the symptoms recuperate, laboratory test values return to normal or baseline level, the abnormality is irreversible or otherwise can be explained appropriately, or the participant is lost to follow up. For clinically significant abnormalities, if warranted, can be confirmed by retests. In brief the AEs during the trial should be followed up until AE resolution or stabilization, or participants lost to follow up.

8.4.6 Reporting of SAEs

When SAE occurs, the participant should be discontinued and the appropriate treatment should be provided. The investigator should inform the sponsor or the designee immediately (usually within 24 hours after awareness of the SAE) in a written form followed by detailed follow-up reports. The first report should include the following information as complete as possible: sources of the report; basic information of the participant; the investigational drug name; name, duration, severity, relationship with the investigational drug and outcomes of SAE, and any action taken. Either the first or the follow-up reports should present the participant with the clinical identification code rather than the real name, identity card number, and address.

For SAEs involving deaths, the investigator should provide the sponsor and the ethics committee with other required information, such as autopsy reports and final medical reports.

8.4.7 Regulatory Reporting Requirements for SAEs

For any SAE, the investigators must notify the contact person of Sponsor listed below upon acquiring the occurrence of an SAE:

Sponsor Contact

Zihan Qin, Project Management

Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd.

16 Xuefu Road, Nanjing High-tech Industrial Development Zone, 210032

Tel: (+86)183-8045-6687

E-mail: zhqin@kindospharma.com

8.4.8 Serious and Unexpected Adverse Reaction Reporting

Once receives safety information in spite of the source, the sponsor should immediately analyze and evaluate the severity, correlation with the investigational products, and whether it is an expected event, *etc*. If judged to be suspected unexpected serious adverse reaction, reports should be expedited and submitted to the investigators, the clinical facility, the ethics committee, the authorities e.g. NMPA or medical institutions according to the Expedited Report Standards and Procedures for Safety Data during Drug Clinical Trial issued by China CDE in April 2018. The expedited report is also recommended when consensus may not be able to be reached on the causality between AEs and the investigational drug by Sponsor and investigators and the relatedness to the investigational drug may not be excluded by either sponsor or investigators. And sponsor will perform safety reporting to FDA according to Sponsor Responsibilities — Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies issued by FDA in June 2021.

8.4.9 Adverse Events of Special Interest

Not applicable.

8.4.10 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs

Not applicable since healthy participants will be enrolled in the trial.

8.5 Pregnancy and Postpartum Information

Any pregnancy during the trial which occurs in a female participant or the partner of a male participant must be reported to the Ethics Committee by investigators within 24 h after being informed. The pregnant female participant must withdraw from the trial, and the pregnancy should be recorded, reported to the applicable agencies and followed up. When a pregnancy occurs in the partner of a male participant, the male is not required to withdraw, however, the pregnancy should be recorded, reported and followed up in the same way as the management for the pregnancy of the female participant. Results of the pregnancy should be recorded and reported. The pregnancy must be traced until at least 8 weeks after the end of pregnancy.

The pregnancy will not be treated as an AE. The pregnancy of which the outcome meets criteria for SAEs (such as spontaneous abortion, stillbirth, neonatal death, congenital malformations, ectopic pregnancy or pre-eclampsia) should be reported as SAEs. Any SAE will be reported through the SAE reporting process.

8.6 Medical Device Product Complaints for Drug/Device Combination Products

Not Applicable.

8.7 Pharmacokinetics

8.7.1 Pharmacokinetic Sampling

The whole blood and serum tubes should be labelled before sampling. The information on the label should include but not limit to the protocol number, randomization number, period, sampling time point, primary or backup sample.

Sample Label

Bar code CHS-1420-10 Participant: 10XX PK sample: Day X-X h-A	Bar code CHS-1420-10 Participant: 10XX PK sample: Day X-X h-B	Bar code CHS-1420-10 Participant: 10XX PK sample: Day X-X h

The information is as follows:
Line 1: Bar code;
Line 2: Protocol No.;
Line 3: Participant random No.;
Line 4: Indication that samples for PK analysis, and sampling day and time point (A represents the primary sample and B backup sample, both of which are serum sample tubes. It is the whole blood sample tube without A or B).

The serum drug (adalimumab) concentration will be measured and a procoagulant will be used for blood samples.

Sample Collection: 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. Approximately 3.5 mL of blood will be collected into vacutainer tubes containing the procoagulant followed by gentle inversions to get mixed up and then be left standing still till coagulation. If blood samples are obtained from an indwelling catheter rather than straight venipuncture, withdraw approximately 1 mL blood prior to obtaining the PK blood sample each time. After each blood collection, use an appropriate amount of

normal saline solution to seal the catheter.

Pre-handling of Samples: The coagulated blood samples will be centrifuged in a refrigerated centrifuger at 2-8℃. Serum will be transferred into two tubes – tube "A" for the primary assay sample and tube "B" as the backup sample. Serum will be stored in a freezer at -70°C (temperature range -90°C ~ -60°C) until shipment to the bioanalytical laboratory for analysis.

Refer to the sampling manual for detailed requirements regarding sample processing.

8.7.2 Sample Shipment and Storage

The serum samples to be tested will be transported by the cold chain logistics to Frontage Laboratories (Shanghai) Co., Ltd.. The temperature during the shipment will be monitored. Frontage Laboratories (Shanghai) Co., Ltd. is responsible for the preservation of the biosamples to be tested. The samples will be stored in a freezer (temperature range -80±10°C), and the preservation of the biosamples will be monitored and recorded according to the current specifications. Backup samples can only be transported and tested after the written approval of sponsor.

8.7.3 Bioanalysis

Serum Drug (adalimumab) concentration will be measured with the validated method by the analysts.

Method validation should be performed according to the relevant requirements ICH M10, which includes selectivity, lower limit of quantitation, calibration range (standard curve performance), accuracy, precision, matrix effect, stability in solution and biological matrix during storage and handling process, *etc*.

Sample analysis plan should be prepared prior to sample analysis. The entire analysis procedure should follow the laboratory SOPs and relevant guidelines.

Two hundred and thirty-eight (238) participants are to be enrolled. There are 24 sampling time points totally in the single-period parallel trial for each participant. Therefore, the expected number of primary samples is 5712, and incurred sample reanalysis (ISR) should be no less than 336.

8.8 Genetics

In course of the trial, sampling will be conducted on each participant for PK similarity assessment and immunogenicity comparison. And also blood will be collected for safety tests. The expected blood collection during the study before the last scheduled OPV for individual participants to be enrolled is listed as follows:

Study stage	Blood collection	Volume per test	Amount of blood loss	
			Male	Female
Screening	Antinuclear antibody test	4 mL	4 × 1 mL	4 × 1 mL
	Viral tests (HIV/HBV/HCV/syphilis)	4 mL	4 × 1 mL	4 × 1 mL
	Tuberculosis diagnosis	4 mL	4 × 1 mL	4 × 1 mL
	Biochemistry	4 mL	4 × 1 mL	4 × 1 mL
	Hematology	2 mL	2 × 1 mL	2 × 1 mL
	Coagulation function	3 mL	3 × 1 mL	3 × 1 mL
	Serum pregnancy test (only for females)	4 mL	--	4 × 1 mL
Check-in	Serum pregnancy test (only for females)	4 mL	--	4 × 1 mL
Test period	PK sampling	3.5 mL	3.5 × 24 mL	3.5 × 24 mL
	Blood withdrawn before PK sampling	1 mL	1 × 5 mL	1 × 5 mL
	Immunogenicity sampling	5 mL	5 × 4 mL	5 × 4 mL
	Safety tests - Biochemistry	4 mL	4 × 4 mL	4 × 4 mL
	Safety tests - Hematology	2 mL	2 × 4 mL	2 × 4 mL
	Safety tests - Coagulation function	3 mL	3 × 4 mL	3 × 4 mL
	Safety tests - Serum pregnancy test (only for females)	4 mL	--	4 × 4 mL
Amount of blood loss during the study			**162 mL**	**186 mL**

If warranted, participants may undergo additional blood samplings for screening and safety assessment at discretion of investigators.

The samples will be analyzed as per the laboratory requirements.

8.9 Biomarkers

Not Applicable.

8.10 Immunogenicity Assessments

The whole blood and serum tubes should be labelled before sampling. The information on the label should include but not limit to the protocol number, randomization number, period, sampling time point, primary or backup sample.

Sample Label

Bar code CHS-1420-10 Participant: 10XX IM sample: Day X-ADA	Bar code CHS-1420-10 Participant: 10XX IM sample: Day X-Nab	Bar code CHS-1420-10 Participant: 10XX IM sample: Day X-B	Bar code CHS-1420-10 Participant: 10XX IM sample: Day X

The information is as follows:
Line 1: Bar code;
Line 2: Protocol No.;
Line 3: Participant random No.;

Line 4: Indication that samples for immunogenicity assessment, and sampling day (ADA and Nab represents the primary assay samples and B for the backup sample, both of which are serum sample tubes. It is the whole blood sample tube without ADA, Nab or B).

The serum ADA/Nab will be determined and a procoagulant will be used for blood samples.

Sample Collection: A total of four (4) blood samples for each participant will be collected for determination of serum anti-drug antibodies (ADA) / neutralizing antibodies (Nab) at 0 h (within 30 minutes pre-dose) and Day 16, Day 30, Day 65 post-dose. The actual sampling time should be recorded. Approximately 5 mL of blood will be collected into vacutainer tubes containing the procoagulant followed by gentle inversions to get mixed up and then be left standing still till coagulation. If blood samples are obtained from an indwelling catheter rather than straight venipuncture, withdraw approximately 1 mL blood prior to obtaining the PK blood sample each time. After each blood collection, use an appropriate amount of normal saline solution to seal the catheter.

Pre-handling of Samples: The coagulated blood samples will be centrifuged in a refrigerated centrifuge at 2-8℃. Serum will be transferred into three tubes – tube "ADA and Nab" for the primary assay sample and tube "B" as the backup sample. Serum will be stored in a freezer at -70°C (temperature range -90°C ~ -60°C) until shipment to the bioanalytical laboratory for analysis.

Refer to the sampling manual for detailed requirements regarding sample processing.

The serum samples to be tested will be transported by the cold chain logistics to Frontage Laboratories (Shanghai) Co., Ltd.. in the same way as PK samples.

The serum ADA/Nab will be measured with the validated method by the analysts.

Two hundred and thirty-eight (238) participants are to be enrolled. There are 4 sampling time points totally in the single-period parallel trial for each participant. Therefore, the expected number of primary samples is 952 for ADA.

8.11 Medical Resource Utilization and Health Economics

Not Applicable.

9 STATISTICAL CONSIDERATIONS

Statistical analysis plan (SAP) should be prepared before statistical analysis. The statistics process should follow SOPs for statistical analysis and related guidance.

If modification of the finalized SAP is necessary, revisions should be clarified together with the sponsor. Revisions and the reasons for revisions will be recorded in the revised SAP. Ensure that the revised SAP be reviewed and approved in accordance with the same procedure as that for the original SAP.

The analysis will be conducted on all participant data after the database is locked.

9.1 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.

9.2 Analyses Supporting Primary Objective(s)

9.2.1 Statistical Model, and Method of Analysis

9.2.1.1 Pharmacokinetic Analyses

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

Parameter	Definition and Calculation
$AUC_{0\text{-}65days}$	Areas under the serum concentration versus time curve calculated to 65 days postdose; Linear trapezoidal method
$AUC_{0\text{-}\infty}$	Area under the serum concentration versus time curve extrapolated to infinity, calculated as $AUC_{0\text{-}t} + C_t / K_{el}$
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 / $AUC_{0\text{-}\infty}$
V_d/F	Apparent distribution volume; Dose / ($K_{el} \times AUC_{0\text{-}\infty}$)

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}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}65days}$, $AUC_{0\text{-}\infty}$. The number of cases, arithmetic mean, standard deviation, median, minimum, maximum 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.

9.2.1.2 Pharmacokinetic Similarity Assessment

For population included in PKSS, the primary PK parameters, C_{max}, $AUC_{0\text{-}\infty}$ 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.

9.2.2 Handling of Intercurrent Events of Primary Estimand(s)

Not Applicable.

9.2.3 Handling 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.

9.2.4 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.

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.

9.2.5 Supplementary Analysis

Not Applicable.

9.2.6 Elimination Criteria

The principal investigator, sponsor and statisticians need to work together to decide the participant(s) to be excluded or not from relevant datasets before the statistical analysis. 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) After taking investigational product, the data of individual participants will be excluded from PK similarity analysis (PKSS) on condition that:

   a. Participants who have positive results of ADA at baseline (0 h);

   b. The first postdose sample provides C_{max} values;

   c. The pre-dose (0 h) sample provides a quantifiable concentration value;

   d. 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.

9.3 Analysis Supporting Secondary Objective(s)

Safety assessment of the proposed biosimilar and reference products will be one of the secondary objectives. Analyses to support the safety assessment are shown in Section 9.5.

Immunogenicity analysis, another secondary objective:

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

Statistical analysis of safety and immunogenicity data will be performed with SAS (Version 9.4 or higher).

9.4 Analysis of Exploratory Objective(s)

Not Applicable.

9.5 Safety Analyses

Based on Safety Set (SS), statistical analysis will be conducted on the safety data. AEs, SAEs, vital signs, physical examination, laboratory test results, ECG, local reactions at the injection site, concomitant therapy, *etc.* will be statistically summarized and tabulated.

Statistical analysis of safety data will be performed with SAS (Version 9.4 or higher).

9.6 Other Analyses

9.6.1 Demographics/Other Baseline Characteristics

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

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

For gender, nation, 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.

Prior and concomitant medications will be coded using the World Health Organization (WHO)-Drug, and listed by reported term / preferred term and Anatomical Therapeutic Class classification. All prior / concomitant medications, concomitant medications / non-drug therapy taken by participant included into FAS will be listed and statistically summarized with cases and percentage.

9.7 Interim Analyses

Not Applicable.

9.8 Sample Size Determination

Based on literature information [3], 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.

9.9 Protocol Deviations

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, investigators will analyze the impact of deviations on the final data and conclusions.

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

10 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

10.1 Regulatory and Ethical Considerations

Consensus ethical principles derived from international guidelines including the Declaration of Helsinki, ICH GCP Guidelines and the local regulations where the trials will be conducted as well as other applicable laws and regulations issued by FDA where the trials will be submitted.

10.2 Committees

The trial must be approved by the Ethics Committee prior to the trial implement. The Principal Investigator and sponsor will provide the IRB/IEC with all requisite material, including the application form for ethical review, resume and qualification of PI, a sample informed consent form, protocol, CRF, Investigator brochure, recruiting materials, *etc*. Any protocol amendment must be approved by or filed to the Ethics Committee during the trial. It is the responsibility of the investigator to inform the Ethics Committee that the trial has been completed as per the relevant requirements.

10.3 Informed Consent Process

Participants must sign the written informed consent to protect their legal rights before any procedure. It's the investigators' responsibility to fully and comprehensively introduce trial objective, design, the drug effect, the expected benefit, the possible side/toxicity effects and risks to the participants. Investigators should promptly inform participants of any new information about the investigational products. Participants should be informed that the participation in the clinical trial is completely voluntary and they can withdraw from the trial at any time without any reason without punishment or loss of their rights due to withdrawal. Participants should be also informed that the investigators and sponsor have the right to read, save and statistically process their data in accordance with relevant regulations. Only participants who fully understand the risks / benefits and potential AEs, sign and date on the informed consent form can be enrolled in this trial. If the clinical protocol is modified during the trial, the informed consent form should be updated if necessary, and the participants' informed consent should be re-obtained after approval by the ethics committee.

10.4 Data Protection

All information generated in the trial will be kept strictly confidential and must not be disclosed to anyone not involved in the trial without the written permission from the sponsor.

Investigator should retain all study-related documents for the authority and sponsor

evaluation and audit, including: original medical records, informed consent forms, case report forms, the detailed distribution records of investigational drugs, *etc*. Files archived both in paper or electronic format should be traceable. The ethics committee should keep all records of ethics review, including written records of ethics review, member information, documents submitted, meeting minutes, and other related records, and all records should be kept for at least 5 years after the end of the clinical trial. The essential documents shall be retained at least 5 years after approval of marketing application or at least 5 years after the completion of the clinical trial (not for marketing application). All materials of this clinical trial are the property of sponsor, and the documents shall not be damaged without prior written agreement between the investigator and the sponsor. Notification to sponsor should be prior to any transference to another party or another place. Unless required by the regulatory authorities, the investigator shall not provide trial files to a third party in any form without the written consent of the sponsor.

10.5 Early Site Closure or Trial Termination

10.5.1 Termination Criteria

The trial will be terminated in the following conditions:

1) Refer to CTCAE 5.0, if more than half of the participants experience drug-related AEs of Grade 2, or more than a quarter of the participants experience drug-related AEs of Grade 3-4; or indication in which obvious intolerance;
2) Termination requested by the sponsor on the premise of full ensuring the legal rights and safety of participants;
3) Termination demanded by NMPA or Ethics Committee due to some reasons;
4) Other conditions in which the trial cannot be continued.

10.5.2 Responsibilities of Sponsor/Investigators following Trial Termination

If the trial is prematurely terminated or suspended, the investigator should promptly inform the trial participants, should assure appropriate therapy and follow-up for the participants. In addition:

[1] If the investigator terminates or suspends the trial without prior agreement of the sponsor, the investigator should inform the institution, the sponsor and IEC and should provide a detailed written explanation of the termination or suspension.

[2] If the sponsor terminates or suspends the trial, the sponsor should promptly inform the investigators, the institution, IEC and the regulatory authority(ies), and provide a detailed written explanation of the termination or suspension.

[3] If the IEC terminates or suspends its approval opinion of the trial, the investigator should inform the institution and the sponsor, and provide a detailed written

explanation of the termination or suspension.

11 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1 Quality Tolerance Limits

Not Applicable.

11.2 Data Quality Assurance

The sponsor and investigator should establish their own quality assurance (QA) system and perform their duties respectively. They will follow the clinical trial protocol strictly and comply with the relevant SOPs to ensure the implement of the quality control (QC) and quality assurance system.

The sponsor may perform inspection on different aspects of the clinical trial process, sample analysis, data, report and calculation process according to the actual requirement and progress of the trial and the verification results of the quality control personnel/ monitor.

11.2.1 Quality Assurance of Clinical Trial

The investigators will be trained of the clinical trial protocol to fully understand the protocol before the trial initiation. Quality control staff should inspect the clinical research facility for the essential conditions to ensure the requirements of the protocol can be met. Investigators will conduct the clinical operations conscientiously according to the SOPs of clinical research facility and the protocol requirements, and record the data accurately, timely, completely, and standardly. Quality control staff will audit the study procedures and the relevant original records. All trial documents will be collected after trial completion. Trial documents will be archived properly after quality control is finalized.

11.2.2 Quality Assurance of Bioanalytical Analysis

The bioanalytical laboratory will establish the quality assurance system, conduct independent and impartial quality audits including 100% audit on the process of data transference and calculation by quality control personnel in accordance with the sample analysis plan and SOPs and relevant guidance. The quality assurance personnel will audit the data and reports of the method validation, sample analysis process to ensure that the reports reflect bioanalytical analysis, SOPs followed and raw data.

11.2.3 Quality Assurance of Data Management

After the data entry into the eCRF, CRA 100% will check the (e)CRF data to determine whether it is complete, accurate and consistent with the original medical records. Queries should be promptly raised about data items that are questionable or inconsistent with the

original medical records. Clinical research coordinators (CRC) and investigators should have to answer the queries and verify / correct inconsistent data.

Data management staff will conduct logical inspection on the quality of data entry. Queries will be sent to investigators/CRC for verification and correction. The QC staff will verify the data management files and data in database. QA stuff will conduct audit on data management documents and process.

Frontage Laboratories (Shanghai) Co., Ltd. will conduct the data management in accordance with the SOPs, GCP and relevant guidance and provide the data management reports.

11.2.4 Quality Assurance of Statistical Analysis

Statistical analysts will conduct the statistical analysis based on current regulations, guidelines, SOPs, and the SAP. Related personnel will conduct quality control on statistical analysis process and data processing result. QA will audit the documentations during statistical analysis and data processing to ensure that they are in accordance with relevant regulations, guidelines, SOPs, and the SAP.

11.3 Source Data

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Source data are contained in source documents. Source data should be attributable, legible, contemporaneous, original, accurate, complete, consistent and durable. Changes to source data should be traceable, should not obscure the original entry, and should be explained.

12 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

12.1 Further Details and Clarifications on the AE Definition

An AE won't be recorded in the following circumstances: diseases or conditions or laboratory abnormalities that have been existing or detected prior to screening visit without further deterioration. No adverse medical incidents occur (e.g., hospitalization due to elective surgery, social reasons, and/or personal reason).

12.2 Further Details and Clarifications on the SAE Definition

Hospitalization is warranted or prolonged which will not be treated as SAEs in the following conditions:

- For diagnosis or elective surgery for the existing diseases;

- For efficacy assessment in the trial;
- For predefined course of treatment for the studied disease in the trial;
- For medical reimbursement consideration;
- Scheduled hospitalization outlined in the protocol;
- Hospitalization planned prior to the trial;
- For elective surgery not for an AE;
- For comprehensive medical examination.

12.3 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.

*If none of the criteria listed above apply, the AE intensity will be judged at the discretion of investigators according to the symptom of the participants.

12.4 Causality

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

Note:

1. The relatedness between adverse events and investigational products should be evaluated by relevant personnel with medical expertise.
2. The table above may not cover various situations in the actual work. If it cannot fully correspond to the judgment rationales in the above table, the professional judgment logic in the table can be referred to make the judgment as reasonable as possible.
3. When more information and evidence on the relatedness of adverse events and investigational products is collected during the course of the clinical trial, revision to previous decisions on the relatedness is allowed given sufficient justification provided.
4. Lack of evidence of a positive dechallenge observation may include: A negative dechallenge observation; dechallenge not performed; dechallenge not applicable.
   Lack of evidence of a positive rechallenge observation may include: A negative rechallenge observation; rechallenge not performed; rechallenge not applicable.

13 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

13.1 Contraception and Pregnancy Testing

13.1.1 Definitions Related to Childbearing Potential

Females of childbearing potential are those who have menstruation and are not proven to be sterilized (for example, the proof of a bilateral oophorectomy or hysterectomy, or menopausal for at least 12 months). Infertile females do not meet the above definition.

13.1.2 Contraception

1. Contraceptive Requirements

All participants should agree to adopt the following contraceptive practices from 14 days prior to screening until discharge from the trial on Day 65:

1) Complete abstinence [Periodic abstinence method (such as calendar method, ovulation method, symptom-ear temperature method, post-ovulation method) is not allowed];
2) Correct use of condoms;
3) Vasoligation in male participants or partners of female participants;
4) Correct use (for female participants or partners of male participants) one of:
   - Intrauterine devices (IUD) with annual failure rate <1%;
   - Female barrier method: Cervical cap or uterine cap with spermicidal agent;
   - Tubal sterilization.

The following contraceptive practices can also be adopted for female participants or partners of male participants during the 6 months after Day 65:

- Hormonal contraceptives;
- Levonorgestrel implants;
- Injection of progesterone;
- Oral contraceptives (concomitant medication of progesterone or medication of progesterone alone);
- Vaginal contraceptive ring;
- Transdermal contraceptive patch.

2. Participants must agree to abstain from donating sperm/eggs from 14 days prior to screening until 6 months after discharge from the trial on Day 65.
3. Procedures to be followed for pregnancy condition:

If a female participant (or a partner of the male participant) becomes pregnant at any time during the trial period or within 6 months after discharge from the trial on Day 65, the investigators will be notified as instructed.

13.1.3 Pregnancy Testing

Serum pregnancy tests will be performed for female participants in this trial during screening and on the day of admission (Day -1), as well as on Day 4, Day 16, Day 30, Day 65.

Female participants must have negative test results to be enrolled and continued into this trial.

13.2 Clinical Laboratory Tests

Biochemistry	**Hematology**
Glucose	White blood cell
Total cholesterol	Neutrophil cell
Triglyceride	Lymphocyte cell
High-density lipoprotein	Monocyte cell
Low-density lipoprotein	Eosinophile cell
Urea	Basophile cell
Creatinine	Neutrophil percentage
Uric Acid	Lymphocyte percentage
Alanine aminotransferase	Monocyte percentage
Aspartate aminotransferase	Eosinophile percentage
Total protein	Basophile percentage
Albumin	Red blood cell
Globulin	Hemoglobin
Albumin / Globulin	Hematocrit
Total bilirubin	Mean corpuscular volume
Direct bilirubin	Mean hemoglobin
Indirect bilirubin	Mean hemoglobin concentration
Gamma-glutamyl transferase	Red blood cell distribution width-CV
Alkaline phosphatase	Red blood cell distribution width-SD
Potassium	Platelet
Sodium	Thrombocytocrit
Chlorine	Mean platelet volume
Total calcium	Platelet volume distribution width
Phosphorus	
Magnesium	

<table>
<tr><td rowspan="3">Urinalysis
White blood cell
Ketone body
Nitrites
Urobilinogen
Bilirubin
Urine protein
Glucose
Specific gravity
Urine occult blood
pH
Vitamin C</td><td>Coagulation function
Prothrombin time
International normalized ratio
Activated partial thromboplastin time
Thrombin time
Fibrinogen</td></tr>
<tr><td>Serum pregnancy test (only for females)
Human chorionic gonadotropin</td></tr>
<tr><td>Antinuclear antibody</td><td rowspan="2">Viral tests
HBsAg
Anti-HCV
Anti-HIV
Anti-Tp</td></tr>
<tr><td>Tuberculosis diagnosis
Mycobacterium tuberculosis IgG antibody</td></tr>
</table>

13.3 Country/Region-Specific Differences

Not Applicable.

13.4 Prior Protocol Amendments

The protocol amendment should be approved by the principal investigator and sponsor, and then approved by ethics committee in case that the protocol needs to be updated after first approval by the ethics committee.

Protocol No./Amendments No.	Version No.	Version Date	Revisions
CHS-1420-10	V1.0	05 Dec. 2024	NA

14 APPENDIX: GLOSSARY OF TERMS

14.1 Abbreviations

Abbreviations	Definition
ADA	Anti-drug antibodies
ADL	Activities of daily living
ADR	Adverse drug reactions
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
CDE	Center of drug evaluation
CL/F	Clearance
CI	Confidence interval
C_{max}	Maximum serum concentration
CRA	Clinical research associate
CRC	Clinical research coordinator
CRF	Case report form
CRO	Contract research organization
ECG	Electrocardiogram
ELAM	Endothelial adhesion molecule
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMR	Geometric mean ratios
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IAS	Immunogenicity analysis set
ICAM	Intercellular cell adhesion molecule

Abbreviations	Definition
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISR	Incurred sample reanalysis
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
OPV	Out-patient visit
PI	Principal Investigator
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
PKCS	Pharmacokinetic Concentration Set
PKPS	Pharmacokinetic Parameter Set
PKSS	Pharmacokinetic Similarity Set
PT	Preferred term
QA	Quality assurance
QC	Quality control
Reference, R	Reference product
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedures
SS	Safety Set

Abbreviations	Definition
SUSAR	Suspected unexpected serious adverse reaction
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

14.2 Definition of Terms

Enrollment: Participants are randomized.

Early withdrawal: Enrolled participants who are randomized fail to complete the scheduled activities.

15 APPENDIX: REFERENCES

[1] FDA. Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. 2016.

[2] FDA: HUMIRA® (Adalimumab) Injection Prescribing Information. 2023.

[3] Oliver von Richter, Lena Lemke, Halimuniyazi Haliduola, *et al*. GP2017, an adalimumab biosimilar: pharmacokinetic similarity to its reference medicine and pharmacokinetics comparison of different administration methods[J]. Expert Opinion on Biological Therapy. 2019 Oct;19(10):1075-1083.

[4] FDA. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. 2015.

[5] FDA. Guidance for Industry: Handling and Retention of BA and BE Testing Samples. 2024.

[6] FDA. Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2). 2021.