Study Protocol

Title: Value of Glycated Albumin in Intervention of Glycemic Control in Patients with Type 2 Diabetes: A Multicenter, Randomized Controlled Clinical Study

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1. Research Background and Rationale for the Study

With the aging population and changes in lifestyle in China, diabetes has evolved from a rare disease to a widespread epidemic. The prevalence of diabetes surged from 0.67% in 1980 to 11.2% in 2017 [1]. As research into the disease has deepened, treatment options for diabetes have expanded significantly. However, previous studies have shown that only 35% of patients treated with oral antidiabetic drugs (OADs) alone and 26% of those treated with OADs combined with insulin achieved the target glycated hemoglobin A1c (HbA1c) level of <7% [2]. Inappropriate treatment choices may be a major factor contributing to poor glycemic control. Therefore, identifying clinical biomarkers to adjust and evaluate treatment efficacy is a crucial step in personalized diabetes management.

Currently, HbA1c and self-monitoring of blood glucose (SMBG) are commonly used clinical indicators for adjusting glycemic control. HbA1c is recommended by both international and domestic guidelines as the gold standard for assessing glycemic control [3–5]. Although HbA1c reflects the average blood glucose level over the past 2–3 months and serves as a reliable indicator of diabetes control, it is susceptible to interference from age, abnormal hemoglobin, and certain conditions such as hemolytic anemia and normal pregnancy, which accelerate red blood cell turnover and affect HbA1c measurements. For patients undergoing treatment adjustments or newly diagnosed with diabetes, HbA1c cannot promptly reflect recent changes in glycemic control. While SMBG provides real-time glucose readings, a recent randomized controlled trial published in JAMA showed that SMBG does not improve glycemic control in non-insulin-treated type 2 diabetes patients [6].

In recent years, glycated albumin (GA) has emerged as a promising biomarker for glycemic control and treatment adjustment in diabetes [7–10]. Studies have shown that GA has a half-life of 17–19 days, allowing it to reflect the average blood glucose level over the past 2–3 weeks and recent changes in glucose levels, without being affected by age, gender, diet, medications, or glucose fluctuations—thus addressing the limitations of HbA1c [11]. Recent short-term studies have found that changes in GA can predict changes in HbA1c levels three months later in newly diagnosed type 2 diabetes patients and those undergoing treatment adjustments [8]. Furthermore, preliminary results from a pilot study conducted for this research showed that patients whose treatment was adjusted based on GA had an HbA1c target achievement rate (<7%) of 76.9% after three months of follow-up, compared to 46.2% in the control group. Similarly, the achievement rate for HbA1c <6.5% was 30.8% in the GA-adjusted group versus 23.1% in the control group. Therefore, our research hypothesis is that adjusting

treatment based on GA results is more beneficial for improving patients' average blood glucose levels (HbA1c).

2. Research Objective

To validate the hypothesis that "adjusting treatment regimens based on glycated albumin (GA) test results is more effective in helping patients achieve target average blood glucose levels (HbA1c)."

3. Research Methods and Design

3.1 Study Population, Inclusion Criteria, Exclusion Criteria, and Withdrawal Criteria

3.1.1 Study Population:

A total of 200 newly diagnosed type 2 diabetes patients will be enrolled based on the 1999 WHO diagnostic criteria.

3.1.2 Inclusion Criteria:

3.1.2.1 Patients voluntarily signed informed consent forms;

3.1.2.2 Age between 20 and 70 years;

3.1.2.3 Newly diagnosed type 2 diabetes patients with a disease duration of less than 1 year and no use of antidiabetic medications in the past 3 months; HbA1c ≥7.5% and <10.5%;

3.1.3 Exclusion criteria:

3.1.3.1 Presence of proliferative retinopathy or macular degeneration requiring treatment, painful diabetic neuropathy, diabetic foot, diabetic ketoacidosis, or hyperglycemic hyperosmolar state within the past 3 months;

3.1.3.2 History or presence of the following conditions within the past 6 months:

1) Decompensated heart failure (NYHA class III or IV);

2) Myocardial infarction, coronary artery bypass grafting, or coronary artery stent implantation; 3) Uncontrolled severe arrhythmia, and deemed unsuitable for participation in this clinical trial by the investigator;

4) Hemorrhagic stroke or ischemic stroke, and deemed unsuitable for participation in this clinical trial by the investigator;

3.1.3.3 Laboratory test results meet any of the following criteria:

1) Alanine transaminase (ALT) or aspartate transaminase (AST) > 3 times the upper limit of normal;

2) Total bilirubin > 2 times the upper limit of normal;
3) Hemoglobin < 100 g/L;
4) Total protein < 60 g/L;
5) Albumin < 30 g/L;
6) Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²;

3.1.3.4 Any condition that may cause red blood cell instability and affect HbA1c testing, such as thalassemia or hemolytic anemia;

3.1.3.5 Currently has uncontrolled thyroid dysfunction;

3.1.3.6 Has received systemic steroid therapy within the past month (excluding inhaled or topical use);

3.1.3.7 Pregnant or lactating women;

3.1.3.8 Two or more episodes of severe hypoglycemia within the past year prior to screening;

3.1.3.9 Patients whom the investigator deems require initiation of sulfonylurea, glinide, insulin, or insulin analog therapy;

3.3.3.10 Patients currently receiving calcium hydroxybutyrate treatment or with a condition requiring calcium hydroxybutyrate treatment, and who the investigator believes may require additional calcium hydroxybutyrate treatment in the near future.

3.1.3.11 The investigator deems the subject unsuitable for observation.

3.1.4 Withdrawal criteria:

3.1.4.1 Withdrawal decided by the investigator

The investigator may decide to withdraw a subject from the study under the following circumstances:

1) Safety concerns arise, and the investigator believes that continuing the study may compromise the subject's safety;
2) Serious complications or adverse events occur during the study, rendering the subject unsuitable for continued participation;
3) Poor compliance by the subject or severe non-adherence to study procedures, which may affect safety or efficacy evaluation;

3.1.4.2 Subject withdrawal

Subjects may withdraw from the study at any time. Subjects may freely terminate study participation at any time without affecting further treatment. Study completion or termination should be documented in the CRF, along with all reasons for termination. Possible reasons for subject withdrawal from the study include:

1) Withdrawal of informed consent by the participant;
2) Loss to follow-up (at least three documented attempts to contact the participant must have been made prior to loss to follow-up);
3) Other circumstances leading to withdrawal from the study (e.g., change of residence rendering continued medication and follow-up impossible).

3.2 Study Population Grouping

Participants will be randomly assigned into two groups: the intervention group (Group A) and the control group (Group B), with 100 participants in each group. Randomization will be conducted using SAS software version 9.4 or higher, employing a block randomization method to generate a reproducible randomization table. Randomization will be implemented via sealed envelopes, assigning eligible participants to either Group A or Group B in a 1:1 ratio.

After randomization, physicians will prescribe antidiabetic medications according to standard clinical practice. The use of sulfonylureas, meglitinides, insulin, or insulin analogs is prohibited in this study due to the risk of hypoglycemia.

During the first month of follow-up, GA levels will be measured in Group A. Based on the principle of "GA normalization," physicians will adjust the treatment regimen accordingly (details in section 3.3.4.2). Blood samples will also be collected during the second and third months of follow-up for GA measurement, but these results will not be used to adjust treatment; they are solely for statistical analysis.

In Group B, blood samples will be collected at the same time points (1st, 2nd, and 3rd months) for GA measurement, but these results will also not be used for treatment adjustments and will be used only for statistical analysis.

3.3 Research steps and follow-up plan

The research steps and follow-up plan are shown in Figure 1 and Table 1.

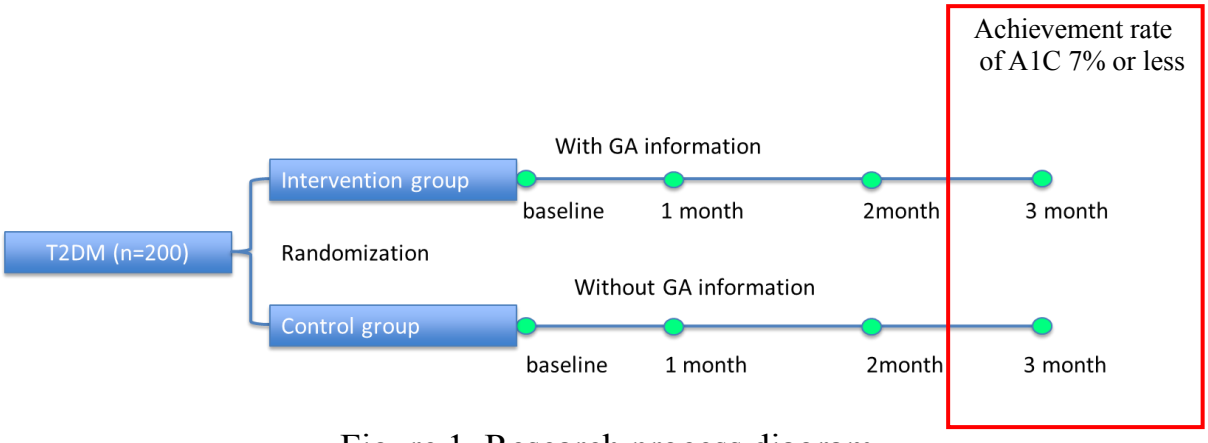

Figure 1. Research process diagram

Table 1 Research flowchart

	Screening visits	Baseline[#]	Follow-up				Measurement of GA
Visit number	1	2	3A	3B	4	5	Frozen sample
visit time	Days -7 to 0	Day 0	4 weeks (baseline: 28 ± 3 days)	4 weeks (follow-up visit 3A + 5 days) [*]	8 weeks (baseline 56 ± 3 days)	12 weeks (baseline 84 ± 3 days)	Follow-up visit completed
informed consent	X						
Demographic information (name, gender, ethnicity, date of birth)	X						
Medical history [a]	X						
Physical examination [b]	X		X[h]	X[g]	X	X	
Collect samples and perform the following laboratory tests：							
Blood glucose-related tests [c]	X[i]					X	
Complete blood count [d]	X[i]					X	
Liver and kidney function [e]	X[i]					X	
lipids [f]	X[i]					X	
Blood or urine pregnancy test	X[i]						
Blood sample collection (for GA measurement)	X		X[h]		X		
Inclusion/exclusion	X	X					

criteria							
Confirm eligibility for enrollment		X					
Randomization		X					
Treatment plan		X					
Distribution of subject diaries		X	X[h]	X[g]	X		
Check and collect participants' report			X[h]	X[g]	X	X	
GA measurement			X[g]			X	
Adjust treatment plan			X[h]	X[g]	X		
Recording medication treatment	X	X	X[h]	X[g]	X	X	
Record and review (since the previous visit) (S) AE		X	X[h]	X[g]	X	X	
study termination						X	
Determination of GA in frozen samples							X

Notes:
#If screening and baseline are conducted on the same day, all duplicate steps need only be performed once
*It is best to conduct the visit within 3 days after the 3A visit, with a maximum of 5 days
a. Medical history includes information such as disease course and treatment methods
b. Physical examination includes: height, weight, waist circumference, blood pressure, pulse (screening period); weight, waist circumference, blood pressure, pulse (follow-up period)
c. Blood glucose-related tests include: fasting blood glucose, HbA1c, fasting C-peptide, fasting insulin
d. Complete blood count: red blood cells (RBC), white blood cells (WBC), platelets (PLT), hemoglobin (HGB)
e. Liver and kidney function: total bilirubin (Tbil), alanine transaminase (ALT), aspartate transaminase (AST), total protein (TP), albumin, blood urea nitrogen (BUN) or urea (Urea), serum creatinine (Cr), uric acid (UA)
f. Lipid profile: Total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C)
g. Only for Group A participants
h. Only for Group B participants
i. If the patient has laboratory test results within the past 7 days, historical results may be used, and repeat testing is not required.

3.3.1 Visit 1 - Screening Period (Days -7 to 0)

3.3.1.1 Voluntarily sign an informed consent form;

3.3.1.2 Obtain demographic information (name, gender, ethnicity, date of birth);

3.3.1.3 Obtain relevant medical history information (disease course, treatment methods);

3.3.1.4 Physical examination (measurements: height, weight, waist circumference, blood pressure, pulse rate);

3.3.1.5 Collect samples and perform relevant tests: Blood glucose-related tests: fasting blood glucose, HbA1c, fasting C-peptide, fasting insulin; Complete blood count: red blood cells (RBC), white blood cells (WBC), platelets (PLT), hemoglobin (HGB);Liver and kidney function: total bilirubin (Tbil), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin, blood urea nitrogen (BUN) or urea, serum creatinine (Cr), uric acid (UA);Lipid profile: total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C); Pregnancy test (blood or urine) for women of childbearing age. If the patient has laboratory test results within the past 7 days, historical results may be used, and repeat testing is not required. If any results are incomplete or certain indicators exceed 7 days, additional testing must be conducted during the screening period.

3.3.1.6 Blood draw and cryopreservation (to be measured at study completion for GA determination);

3.3.1.7 Initial review of inclusion/exclusion criteria.

3.3.2 Visit 2 - Baseline (Day 0)

If screening and baseline are conducted on the same day, all duplicate steps need only be completed once.

3.3.2.1 Record and check: any AEs and SAEs, concomitant medications since the last visit[X4] (Record all concomitant medications, with particular attention to systemic corticosteroids, calcium hydroxybenzoate, and whether hypoglycemic medications were used during the period)

3.3.2.2 Further review of inclusion/exclusion criteria

3.3.2.3 Randomize patients into groups. Divide into Group A (intervention group) and Group B (control group).

3.3.2.4 Develop a diabetes treatment plan for patients according to the “Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 Edition)” [13]. Due to the risk of hypoglycemia, sulfonylureas, glinides, insulin, and insulin analogues are prohibited in this study.

3.3.2.5 Hypoglycemia: Investigators should instruct participants to complete a participant diary and monitor blood glucose levels as frequently as possible using a blood glucose meter when hypoglycemia occurs. If

hypoglycemic symptoms do not improve after carbohydrate supplementation, participants should seek medical attention at a hospital. If hypoglycemic symptoms are suspected, investigators should diagnose the condition and record it in the CRF. Investigators should classify events according to the following categories:

1) Severe hypoglycemia: An event requiring assistance from another person to administer carbohydrates, glucagon, or other resuscitation measures.
2) Documented symptomatic hypoglycemia: During the event, typical symptoms of hypoglycemia are present with measured blood glucose levels ≤70 mg/dL (3.9 mmol/L).
3) Asymptomatic hypoglycemia: An event without typical symptoms of hypoglycemia, but with a measured blood glucose concentration ≤70 mg/dL (3.9 mmol/L).
4) Possible symptomatic hypoglycemia: During the event, hypoglycemia symptoms were present without blood glucose measurement, but it is suspected that they may have been caused by a blood glucose concentration ≤70 mg/dL (3.9 mmol/L).
5) Relative hypoglycemia: Following the event, the diabetic patient reports any typical symptoms of hypoglycemia and symptoms consistent with hypoglycemia, but measured blood glucose concentration is > 70 mg/dL (3.9 mmol/L).

Researchers will collect the following items and record them in the CRF: Symptoms of hypoglycemia; duration (start and end date and time); severity grading (Grade 1 hypoglycemia: blood glucose < 3.9 mmol/L and ≥ 3.0 mmol/L; Grade 2 hypoglycemia: blood glucose < 3.0 mmol/L; Grade 3 hypoglycemia: severe event requiring assistance from others for treatment, accompanied by altered consciousness and/or physical changes, but without specific blood glucose thresholds); Measures taken (self-feeding, assistance required to eat, assistance required to go to the hospital for intravenous glucose infusion; other); Outcome; Blood glucose level measured by a blood glucose meter (at the time of hypoglycemia); Time of blood glucose measurement by a blood glucose meter (at the time of hypoglycemia);

3.3.3 Visit 3A - Follow-up Period (Baseline ± 3 days)

3.3.3.1 Patients in Group B undergo a physical examination (measurements: weight, waist circumference, blood pressure, pulse rate); blood samples are collected and frozen for storage (to be used for GA measurement at the end of the study); all data are recorded (medication changes, occurrence of hypoglycemia, other safety events).The study physician determines whether patients require medication adjustments based on clinical

guidelines (refer to Figure 2).

3.3.3.2 Patients in Group A undergo blood collection and GA measurement.

3.3.4 Visit 3B - Follow-up Period (Visit 3A + 5 days)

*Preferably within 3 days after Visit 3A, with a maximum of 5 days.

3.3.4.1 Patients in Group B will not participate in this follow-up visit.

3.3.4.2 Patients in Group A will undergo a physical examination (measurements: weight, waist circumference, blood pressure, pulse rate). The GA results for Group A patients will be communicated to the study physician and the patients. The study physician will adjust the medication based on the GA results.

Drug adjustments follow the "GA normalization" principle: if GA > 16%, the study physician increases the type of oral medication based on the 2020 Chinese Diabetes Prevention and Control Guidelines (Figure 2). Due to the risk of hypoglycemia, sulfonylureas, glinides, insulin, or insulin analogues are prohibited in this study. If GA ≤ 16%, no drug adjustments are made. However, if a patient reports hypoglycemia within the past month, the cause of hypoglycemia must be identified first and appropriate management provided. Since this study excludes sulfonylureas, glinides, insulin, or insulin analogues, the theoretical risk of hypoglycemia is extremely low. If unexplained hypoglycemia occurs, the investigator may consider reducing the dose of oral hypoglycemic agents as appropriate.

3.3.4.3 Record all data (medication status, occurrence of hypoglycemia, and other adverse events).

3.3.5 Visit 4 – Follow-up period (baseline ±3 days)

3.3.5.1 Physical examination (measurements: weight, waist circumference, blood pressure, pulse rate);

3.3.5.2 Blood samples collected and frozen for storage in both Group A and Group B (to be measured for GA at the end of the study);

3.3.5.3 Record all data (medication changes, occurrence of hypoglycemia, other safety events).

3.3.5.4 The study physician conducting this visit should generally not adjust medications. However, adjustments may be made if the patient reports adverse events related to medication. Since this study excludes sulfonylureas, glinides, insulin, and insulin analogues, the theoretical risk of hypoglycemia is extremely low. If the patient reports hypoglycemia within the past month, the cause must first be identified and appropriate management provided. If unexplained hypoglycemia occurs, the investigator may consider reducing the dose of oral hypoglycemic agents as appropriate.

3.3.6 Visit 5 - Follow-up period (baseline: 84 ± 3 days)

3.3.6.1 Physical examination (measurements: weight, waist circumference, blood pressure, pulse rate);

3.3.6.2 Collect samples and perform relevant tests: fasting blood glucose, HbA1c, fasting C-peptide, fasting insulin, glycated albumin (GA); Complete blood count: red blood cells (RBC), white blood cells (WBC), platelets (PLT), hemoglobin (HGB);Liver and kidney function: total bilirubin (Tbil), alanine transaminase (ALT), aspartate transaminase (AST), total protein (TP), albumin, blood urea nitrogen (BUN) or urea (Urea), serum creatinine (Cr), uric acid (UA);Lipid profile: Total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C);

3.3.6.3 Determine that the subject has completed the entire trial.

3.3.7 Each center measures GA frozen samples.

3.4 outcome measures

3.4.1 Primary endpoint:

Proportion of participants achieving HbA1c < 7% at Visit 5 (Week 12 ± 3 days from baseline).

3.4.2 Secondary endpoints:

3.4.2.1 Proportion of participants achieving HbA1c < 6.5% at Visit 5.

3.4.2.2 Change in HbA1c levels from baseline to Visit 5.

3.4.2.3 Incidence and frequency of hypoglycemia

3.4.2.4 Changes in pancreatic β-cell function (HOMA-β = 20 × FINS / (FPG – 3.5));

3.4.2.5 Changes in insulin resistance levels (HOMA-IR = FINS × FPG/22.5);

3.4.2.6 Changes in body weight, waist circumference, and BMI;

3.5 Sample size

100 cases each in the intervention group and the control group. Sample size calculation method:

In our previous single-center pilot study (n=40) targeting this research, the results showed that patients whose treatment regimens were adjusted based on GA achieved an HbA1c target rate (<7%) of 76.9% at 3-month follow-up, compared with 46.2% in the control group (p=0.226).Statistical significance was set at $P < 0.05$, with a statistical power of 0.8 and a 30% difference between the experimental and control groups as the calculation basis. Considering the follow-up completion rate of the pre-experimental patients (72.5%) and other factors such as a multi-center study, the target sample size for this study was determined to be 100 cases each for the intervention and control groups.

3.6 Expected overall duration of the clinical trial

Considering the time required for clinical trial sites to complete all subject enrollment, follow-up, and sample testing, it is estimated that the study will take 18 months from the first subject enrollment to database lock. If the implementation time exceeds the expected duration, the protocol will not be amended.

4. Preliminary Research Basis

In recent years, glycated albumin (GA) has gained increasing attention as an important biological marker for diabetes. The measurement of GA is not affected by albumin concentration, blood glucose levels, bilirubin levels, or lactose. Long-term frozen samples (e.g., the DCCT study, with samples frozen for up to 23 years) remain unaffected by these factors. Additionally, the clinical reference range for GA has been established [7-10]. In the latest edition of the "Chinese Clinical Application Guidelines for Blood Glucose Monitoring (2015 Edition)," glycated albumin (GA) is also proposed as a sensitive indicator of blood glucose changes [12]. Recently, a short-term study conducted by our laboratory found that changes in GA could predict changes in HbA1c levels three months later in newly diagnosed type 2 diabetes patients and type 2 diabetes patients undergoing treatment adjustments. This is the first study to report that GA can predict drug efficacy [8]. Additionally, in a preliminary small-scale pilot study conducted by our team for this research, patients whose treatment regimens were adjusted based on GA achieved an HbA1c target rate (<7%) of 76.9% after three months of follow-up, compared to 46.2% in the control group; Similarly, in the GA-adjusted treatment group, the HbA1c achievement rate (<6.5%) was 30.8%, while the control group was 23.1%.

5. Statistical Analysis

5.1 Analysis Population:

Randomized Population: All subjects who were randomly assigned to a treatment group constitute the randomized population.

Full Analysis Set (FAS): Subjects who were randomly assigned, met the study inclusion criteria, and had baseline measurements for the primary efficacy endpoint. The FAS analysis follows the intention-to-treat (ITT) principle.

Per-Protocol Set (PPS): Participants in the FAS who demonstrated good compliance and had no important protocol deviations that affected the primary efficacy assessment (specific criteria will be confirmed during data verification).

Safety Set (SS): All participants with at least one safety assessment are included in the safety analysis.

Efficacy analysis is based on the FAS and PPS, while safety analysis is based on the SS.

5.2 Statistical software used in this study:
Statistical analysis was performed using SAS version 9.4 or higher.

5.3 Baseline and Demographic Characteristics
Demographic data and other baseline characteristics between treatment groups will be described according to group. Quantitative indicators will be statistically described based on data distribution characteristics, including mean, standard deviation, median, quartiles, minimum value, and maximum value. Count data will be statistically described using various frequencies and composition ratios.

5.4 Adherence Analysis
Statistical descriptions of medication adherence records for each visit during the entire treatment period will be provided.

5.5 Analysis of Primary Endpoint Measures
- Proportion of participants with HbA1c < 7% at Visit 5 (Week 12 ± 3 days).
- The number and percentage of participants achieving HbA1c < 7% and the 95% confidence interval (CI) will be calculated.
- The difference in proportions between groups (intervention – control) and its 95% CI will be computed.
- Chi-square test or Fisher's exact test will be used for between-group comparisons.
- Sensitivity analysis: The Cochran-Mantel-Haenszel (CMH) test will be used to adjust for center effects.

5.6 Analysis of Secondary Endpoints
Secondary endpoints includes:
- Proportion with HbA1c < 6.5% at Visit 5
- Change in HbA1c from baseline
- Incidence and frequency of hypoglycemia
- Change in β-cell function (HOMA-β = 20 × FINS / (FPG – 3.5))
- Change in insulin resistance (HOMA-IR = FINS × FPG / 22.5)
- Changes in weight, waist circumference, and BMI
- Categorical variables: Chi-square or Fisher's exact test
- Continuous variables: t-test or Wilcoxon rank-sum test

5.7 Safety analysis
Safety analysis was conducted using the safety analysis set (SS) as the primary analysis set. Adverse events (AEs) and serious adverse events (SAEs) occurring during treatment were summarized and analyzed by treatment group based on

their incidence rates and severity, and classified according to major system organs and medical terminology. Other safety data, including laboratory test results, were analyzed and compared with the screening period using descriptive methods.

6. Case allocation among study centers

This trial uses a competitive enrollment method, and the case allocation plan for each study center is each center will recruit 10 subjects in the control group and 10 subjects in the intervention group, for a total of 100 subjects in the control group and 100 subjects in the intervention group.

7. Subject Protection (if applicable)

This clinical trial will be conducted in accordance with the Declaration of Helsinki (2008 revised edition) and relevant Chinese laws and regulations governing clinical trials. Prior to the commencement of the trial, approval must be obtained from the Ethics Committee, and the trial may only be conducted after such approval has been granted. Any modifications to the trial protocol must be approved by the Ethics Committee prior to implementation.

Prior to the start of the trial, an informed consent form must be provided to each participant, and they must be instructed to read it carefully. The study physician is responsible for explaining the contents of the informed consent form in detail and addressing any questions the participant may have. The participant must be fully informed about the purpose of the trial, the treatment regimen, laboratory tests, potential risks, and their rights and benefits. Participants must also be informed that they may choose alternative treatment options and withdraw from the trial at any time without facing any adverse consequences. Each patient must voluntarily sign the informed consent form before entering the trial. The study physician must ensure that all informed consent forms are properly stored in the study records. The privacy of participants must be protected, and information related to their participation in the trial must not be disclosed without authorization. If necessary, the drug regulatory authorities, ethics committee, or sponsor may review the records of participants in the trial in accordance with applicable regulations.

8. Research Management

8.1 Requirements for Investigators to Enter Data

Investigators must ensure that all data is entered into the case report form truthfully, accurately, completely, timely, and in compliance with applicable laws and regulations.

8.1.1 For all patients who have signed the informed consent form and been screened eligible for the trial, investigators must carefully and thoroughly record all observed information in the case report form, ensuring no items are left blank or omitted.

8.1.2 All data in the case report form must be verified against the original medical records of the subject to ensure accuracy.

8.1.3 The case report form serves as the original data. Any corrections must be made by striking through the original text, adding notes in the margin, and signing and dating the correction by the researcher.

8.1.4 Original laboratory test results (or copies of original laboratory test results) must be affixed to the designated section for laboratory test results in the study medical records.

8.1.5 Data that is significantly higher or lower than expected or outside the clinically acceptable range must be verified or rechecked, and the researcher must provide necessary explanations.

8.2 Database Establishment and Data Entry/Storage

8.2.1 Database Establishment: Data programmers will construct the database interface based on CRF or eCRF documentation and perform logical validation programming in accordance with the DVP.

8.2.2 Data Entry: CRCs or investigators will be responsible for data entry according to the eCRF completion guidelines.

8.2.3 Data Review: CRAs will perform SDV on the data and send any inconsistent data to the clinical team for resolution.

8.2.4 The EDC system has both system-generated and manual query modes. When abnormal data is entered, the EDC system will issue real-time alerts to prompt the data entry personnel to verify the data. Data managers will conduct manual reviews of the data and raise queries for any issues identified.

8.2.5 The clinical research implementation unit shall ensure the traceability of clinical data and retain all original data in its entirety. All original documents, data processing records, and related materials shall be retained by the participating hospitals for a period of 10 years following the completion of the clinical study.

8.3 Specimen Collection, Storage Facilities, and Laboratory Premises

The specimen collection, storage facilities, and laboratory premises for this trial are located at each center.

9 Requirements for Reporting Adverse Events

9.1 Definition of Adverse Events

(1) Adverse Event (AE): An unfavorable medical event occurring during the clinical trial, regardless of whether it is related to the trial.

(2) Serious Adverse Event (SAE): An adverse event that results in death or a serious deterioration in health, including fatal diseases or injuries, permanent defects in bodily structure or function, hospitalization or prolongation of hospitalization, medical or surgical intervention to prevent permanent defects in bodily structure or function; fetal distress, fetal death, or congenital anomalies, or congenital defects.

Note: The following situations do not constitute SAEs:

a) Hospitalization that was already planned prior to screening and did not result in a serious deterioration in health;

b) Expected, non-worsening fluctuations in pre-existing or detected abnormal conditions or diseases at the time of screening;

c) Hospitalization or prolonged hospitalization during the clinical study period as specified in the protocol (if applicable).

9.2 Reporting Procedures

(1) In the event of any adverse event, investigators shall promptly report and file a report with the principal investigator, the clinical trial institution, the ethics committee, and the sponsor.

(2) In the event of a serious adverse event during a clinical trial, investigators shall immediately take appropriate therapeutic measures for the subject, simultaneously submit a written report to the medical device clinical trial management department of the clinical trial institution to which they belong, and notify the sponsor in writing through such department. The medical device clinical trial management department shall report the incident in writing to the relevant ethics committee and the food and drug supervision department and health and family planning authority of the province, autonomous region, or municipality where the clinical trial institution is located within 24 hours. In the event of a death, the clinical trial institution and the investigator shall provide the ethics committee and the sponsor with all necessary information.

(3) For serious adverse events and device defects that may lead to serious adverse events, the sponsor shall report to the food and drug supervision and administration department and the health and family planning authority at the same level within 5 working days of becoming aware of the event, and shall notify other clinical trial institutions and investigators participating in the trial, and the medical device clinical trial management department shall promptly notify the ethics committee of the clinical trial institution.

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