Project Source and Number:

A Randomized Double-Blind Controlled Clinical Study of SGLT-2i Combined with Probiotic Preparation in Elderly Patients with HFpEF

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Protocol Abstract

Project Title	A Randomized Double-Blind Controlled Clinical Study of SGLT-2i Combined with Probiotic Preparation in Elderly Patients with HFpEF
Study Objective	To investigate the effects of hengliflozin combined with probiotic preparation on cardiac and renal function, intestinal barrier function, quality of life and physical function in elderly patients with HFpEF, and to explore the potential mechanism by detecting inflammatory levels.
Study Design	Prospective, randomized, placebo-controlled clinical trial
Total Sample Size	162 patients (3 groups, 54 patients in each group)
Patient Selection	Inclusion Criteria:
	(1) Age ≥60 years; (2) Relevant examinations within 6 months meet the diagnostic criteria for HFpEF; (3) NYHA cardiac function class II to III; (4) No prior use of SGLT-2 inhibitors within 6 months before enrollment; (5) No prior use of probiotic preparations within 3 months before enrollment; (6) The current anti-heart failure treatment regimen is well tolerated by the patient and has been stably implemented for at least 1 month; (7) The patient's current heart failure condition is stable without acute exacerbation; (8) Basically normal cognitive function, capable of understanding the content of assessment scales; (9) Possess basic behavioral capacity, able to perform daily activities independently or with the assistance of assistive devices; (10) Understand the purpose of the clinical trial, volunteer to participate and sign the informed consent form.
	Exclusion Criteria:

	(1) Symptoms caused by non-cardiac diseases; (2) Presence of contraindications to hengliflozin; (3) Presence of contraindications to probiotics; (4) Myocardial infarction, coronary artery bypass grafting, or any event that may reduce LVEF occurred within 6 months before enrollment (unless LVEF ≥ 50% has been confirmed); (5) Valve replacement surgery performed within 6 months before enrollment; (6) Poorly controlled blood pressure (SBP ≥ 180 mmHg or DBP ≥100 mmHg); (7) Current acute decompensated heart failure requiring treatment; (8) Resting heart rate exceeding 120 beats per minute, or complicated with malignant arrhythmia; (9) Significant coronary artery disease requiring PCI revascularization; (10) Severe renal insufficiency (serum creatinine >442 μmol/L) or receiving dialysis treatment; (11) Presence of urinary tract infection at enrollment: with symptoms and signs of urinary tract infection, such as urinary tract irritation (frequent urination, painful urination, urgent urination), suprapubic pain and tenderness, fever, lumbar pain or percussion pain, etc., and bacterial colony count in urine culture ≥10^5/ml; (12) Currently diagnosed with malignant tumor requiring treatment; (13) Current complicated with acute disease or acute exacerbation of chronic disease; (14) Participated in other interventional studies within 3 months.
Treatment Protocol	A randomized, double-blind, placebo-controlled study design is adopted. All enrolled patients meeting the inclusion/exclusion criteria are randomly assigned to Group A, Group B and Group C at a ratio of 1:1:1. On the basis of original anti-heart failure pharmacotherapy, Group A receives

	hengliflozin proline (10 mg, qd) combined with Clostridium butyricum Enterococcus triple viable tablets (400 mg, tid), Group B receives hengliflozin proline (10 mg, qd) plus placebo, and Group C receives double placebos. Patients are followed up for evaluation before treatment and 4, 8 and 12 weeks after treatment initiation, respectively. Changes in indicators such as KCCQ score, quality of life, cardiac and renal function, intestinal barrier function and physical function before and after intervention are observed. The observation endpoint is set at 12 weeks after treatment.
Efficacy Evaluation	Treatment is considered effective if any of the following conditions is met and the intergroup difference is statistically significant: ① Kansas City Cardiomyopathy Questionnaire score (KCCQ score) increases by more than 5 points compared with baseline; ② NYHA cardiac function class decreases by one grade or more; ③ NT-proBNP (or BNP) decreases by ⩾20% compared with baseline; ④ 6-minute walk distance increases by more than 5% compared with baseline; ⑤ Serum eGFR increases by 5% and urine protein/creatinine ratio decreases by 5%. Treatment is considered ineffective if none of the above criteria for indicator changes is met.
	Safety evaluation indicators: Throughout the trial, all-cause death, cardiovascular death, acute cardiovascular events, hospitalization for acute exacerbation of chronic heart failure, urinary tract infection and other potential adverse reactions related to hengliflozin proline or Clostridium butyricum Enterococcus triple viable tablets are monitored, and the incidence of adverse events directly related to the intervention measures of this study is recorded.
Statistical Methods	SPSS 26.0 software is used for statistical analysis. All statistical tests are two-sided, and $P<0.05$ is considered as the threshold for statistically significant difference. Changes from baseline (before treatment) to 12 weeks

	after treatment of primary and key secondary endpoint indicators are used for intergroup comparisons. If the data conform to normal distribution and homogeneity of variance, one-way analysis of variance (ANOVA) is used for overall comparison among the three groups; if the ANOVA result is significant, Dunnett's t-test is used for multiple comparisons, with Group C (placebo group) as the common control, to compare the differences between Group A (combined treatment group) and Group C, and between Group B (monotherapy group) and Group C, respectively. If the data do not conform to normal distribution or have heterogeneous variance, the Kruskal-Wallis H test is used for comparison among the three groups; if the result is significant, Dunn's test is further used for pairwise comparison. The chi-square test or Fisher's exact test is used for comparison of count data. Efficacy analysis is mainly based on the full analysis set (FAS), which includes all subjects randomized who have received at least one dose of study drug and have at least one post-baseline efficacy evaluation, and the analysis follows the intention-to-treat (ITT) principle. Meanwhile, the per-protocol set (PPS) is used for sensitivity analysis to verify the robustness of the results. Safety analysis is based on the safety set (SS), which includes all subjects who have received at least one dose of study drug and have undergone at least one safety assessment.
Study Period	May 1, 2026 - November 30, 2027

1. Research Background

Heart failure with preserved ejection fraction (HFpEF) is a highly heterogeneous clinical syndrome dominated by left ventricular diastolic dysfunction, with a complex and yet unelucidated pathogenesis. HFpEF accounts for approximately 40%-71% of all heart failure cases. With the intensification of population aging, its prevalence and mortality have been increasing continuously. The main therapeutic goals for HFpEF patients include relieving heart failure symptoms and signs, improving patients' quality of life, and reducing hospitalization risk. However, to date, no effective treatment has been proven to significantly reduce the mortality of HFpEF.

Sodium-dependent glucose transporters 2 (SGLT-2) inhibitors exert cardiovascular protective effects such as diuresis, improving myocardial energy metabolism, and inhibiting inflammatory response. The results of the EMPEROR-Preserved and DELIVER trials showed that SGLT2 inhibitors can reduce the composite endpoint risk of cardiovascular death or heart failure hospitalization by 20% in HFpEF patients. However, there is a lack of evidence-based medical data in the advanced elderly population. Meanwhile, weight loss induced by this class of drugs may lead to loss of adipose tissue and skeletal muscle, increasing the risk of sarcopenia and frailty in elderly patients, and may even partially offset its cardiovascular benefits.

The 2023 ESC Guidelines for Heart Failure updated SGLT2 inhibitors (dapagliflozin or empagliflozin) as Class I recommended drugs for HFpEF. Hengliflozin is the first independently developed SGLT2 inhibitor in China, which is indicated for type 2 diabetes. Early clinical trials have shown that its hypoglycemic efficacy and safety profile are favorable. A multicenter, randomized, double-blind, placebo-controlled trial of hengliflozin in dialysis patients with HFpEF (the HELD-HF study) enrolled a total of 112 patients. The results showed that the left ventricular mass index (LVMI) in the hengliflozin group decreased significantly by 3.38 g/m² from baseline, while the placebo group increased by 2.08 g/m² (intergroup difference -5.38 g/m², P=0.026). In terms of safety, the incidence of drug-related adverse events was lower in the hengliflozin group than in the placebo group (1.79% vs. 3.57%), suggesting that the drug is well tolerated in HFpEF patients with dialysis. However, the efficacy of hengliflozin in non-dialysis HFpEF patients remains unclear, and there is a particular lack of data on its application in the advanced elderly population.

Intestinal flora disorder is closely associated with systemic inflammation in HFpEF. HFpEF patients have reduced intestinal flora diversity, imbalanced flora structure, and impaired intestinal mucosal barrier function. Bacterial metabolites (such as lipopolysaccharide) enter the blood circulation, activate systemic inflammatory response, and further aggravate myocardial remodeling and diastolic dysfunction.

As a core intervention for regulating intestinal flora, probiotics can exert cardioprotective effects by inhibiting inflammation and attenuating adverse cardiac remodeling, and have potential in improving muscle health and preventing sarcopenia. Clostridium butyricum Enterococcus triple viable tablets are composed of Enterococcus, Clostridium butyricum and Saccharomyces cerevisiae. Among them, Enterococcus produces lactic acid to inhibit harmful bacteria; Clostridium butyricum produces organic acids dominated by butyric acid, which provides energy for intestinal epithelial cells and repairs the intestinal mucosal barrier; Saccharomyces cerevisiae secretes digestive enzymes to promote nutrient absorption and activate the proliferation of beneficial bacteria. The three components synergistically achieve multi-target regulation of intestinal microecology. Clinical studies have shown that this preparation has favorable efficacy and safety in the elderly population, can significantly improve the treatment efficiency of elderly functional constipation, and reduce the incidence of antibiotic-associated diarrhea in patients over 80 years old. The preliminary study of

our research group further found that on the basis of conventional anti-heart failure treatment for advanced elderly HFpEF patients, 12-week administration of Clostridium butyricum Enterococcus triple viable tablets can significantly improve patients' symptoms, cardiac function and quality of life, suggesting that regulating intestinal flora can be used as an effective adjuvant therapeutic strategy for HFpEF.

SGLT-2i exerts its effects through diuresis, anti-inflammation and improving energy metabolism, while probiotics can regulate intestinal flora, reduce inflammatory markers, and regulate immune response. The combination of the two may exert synergistic therapeutic potential, and the addition of probiotics may alleviate the potential negative impact of weight loss induced by SGLT-2i. At present, this combined strategy has not been verified in clinical trials. Therefore, this study aims to investigate the effects of hengliflozin combined with probiotic preparation on cardiac and renal function, intestinal barrier function, quality of life and physical function in elderly patients with HFpEF through a randomized double-blind controlled trial, and explore the potential mechanism by detecting inflammatory levels. This study intends to explore a novel combined treatment strategy that can effectively improve cardiorenal outcomes while minimizing the risk of aggravating frailty, so as to provide new evidence and new directions for the treatment of elderly patients with HFpEF.

2. Study Objective

This study investigates the effects of hengliflozin combined with probiotic preparation on cardiac and renal function, intestinal barrier function, quality of life and physical function in elderly patients with HFpEF through a randomized double-blind controlled trial, and explores the potential mechanism by detecting systemic inflammatory levels. This study intends to explore a novel combined treatment strategy that can effectively improve cardiorenal outcomes while minimizing the risk of aggravating frailty, so as to provide new evidence and new directions for the treatment of elderly patients with HFpEF.

3. Study Design Type, Principle and Trial Procedures

3.1 Study Design

Study design type: A randomized, double-blind, placebo-controlled, single-center clinical study.

Randomization method: Complete randomization is adopted, and patients are divided into three groups at a ratio of 1:1:1: Group A (hengliflozin combined with probiotics), Group B (hengliflozin + placebo), and Group C (double placebo). Random codes are generated and tabulated using SPSS 26.0.

Blinding design: A third party is commissioned for blinding, and a two-level blinding design is adopted: subjects are randomly coded and randomized in a blinded manner; hengliflozin, probiotics and placebo are coded, allocated and packaged in a blinded manner. The blinding code document is stored, and emergency envelopes are prepared. Unblinding is performed in two stages: first, after the trial is terminated and data is entered and locked, the third party discloses the grouping information; second, after data analysis is completed and the summary report is formed, the third party discloses the intervention allocation.

Sample size calculation: This study uses the change value of Kansas City Cardiomyopathy Questionnaire (KCCQ) score as the basis for calculation. Dunnett's test is used for analysis, the test power 1-β is set to 0.8, and the test level α is set to 0.05. Based on the previous research results of our research group and literature data, the estimated mean changes of KCCQ score in each group are: Group A (hengliflozin combined with probiotics): 8.5 points, Group B (hengliflozin + placebo): 5.8 points, Group C (double placebo): 0 points, the pooled standard deviation is 9, and the number of cases in the three groups is equal. Calculation with PASS software gives N=144. Considering a

10% dropout rate, 162 cases are finally included, with 54 cases in each group.

3.2 Study Procedures

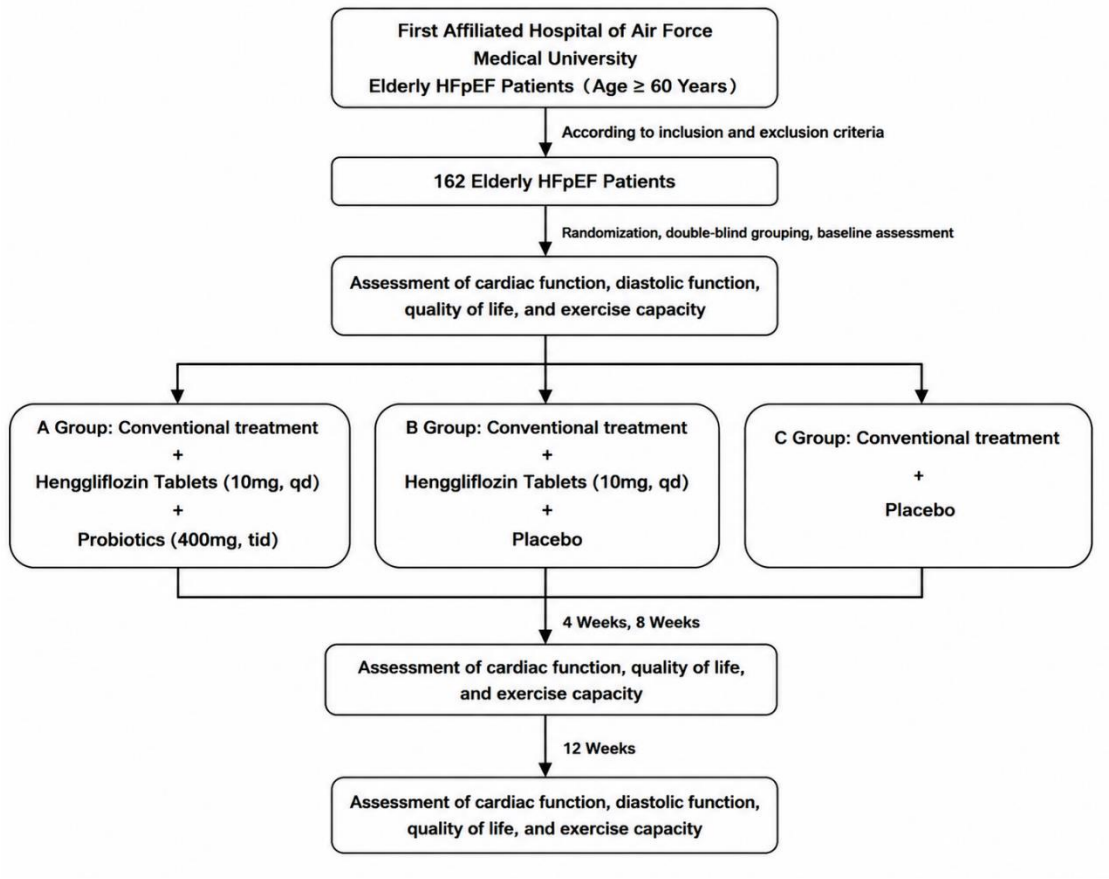


Figure 1 Research technology roadmap

4. Patient Selection

4.1 Inclusion Criteria:

(1) Age ≥60 years;

(2) Relevant examinations within 6 months meet the diagnostic criteria for HFpEF:

1) Meet the epidemiological and population characteristics of HFpEF patients;

2) Presence of heart failure symptoms and/or signs;

3) Cardiac imaging indicates LVEF ≥50%;

4) For patients with sinus rhythm: BNP ≥35 pg/ml and/or NT-proBNP ≥125 pg/ml; for patients with atrial fibrillation: BNP ≥105 pg/ml and/or NT-proBNP ≥365 pg/ml;

5) At least one of the following conditions is met:

① LVMI ≥115 g/m² (male) or 95 g/m² (female); ② LAVI ＞34 ml/m²; ③ Relative wall thickness ＞0.42; or left ventricular free wall thickness ＞12 mm; ④ E/e’ ≥14; ⑤ Septal e’ ＜7 cm/s, or lateral wall e’ ＜10 cm/s, or average e’ ＜8 cm/s; ⑥ Tricuspid regurgitation velocity ＞2.8 m/s, or pulmonary artery systolic pressure ＞35 mmHg;

(3) NYHA cardiac function class II to III;

(4) No prior use of SGLT-2 inhibitors within 6 months before enrollment;

(5) No prior use of probiotic preparations within 3 months before enrollment;

(6) The current anti-heart failure treatment regimen is well tolerated by the patient and has been stably implemented for at least 1 month;

(7) The patient's current heart failure condition is stable without acute exacerbation;

(8) Basically normal cognitive function, capable of understanding the content of assessment scales;
(9) Possess basic behavioral capacity, able to perform daily activities independently or with the assistance of assistive devices;
(10) Understand the purpose of the clinical trial, volunteer to participate and sign the informed consent form.

4.2 Exclusion Criteria:

(1) Symptoms caused by non-cardiac diseases;
(2) Presence of contraindications to hengliflozin:
1) Hypersensitivity to hengliflozin;
2) Severe renal impairment (eGFR < 30 ml/min/1.73m2), end-stage renal disease, or requiring dialysis;
(3) Those with probiotic contraindications:
1) Patients with sepsis, active gastrointestinal bleeding, perforation, etc., resulting in severe damage to the intestinal barrier due to various reasons.
2) Those diagnosed with fulminant colitis or toxic megacolon.
3) Those who cannot tolerate 50% calorie intake enteral nutrition due to severe diarrhea, significant fibrotic intestinal lumen stenosis, severe gastrointestinal bleeding, high-flow intestinal fistula, etc.
4) Patients with congenital or acquired immunodeficiency diseases.
5) Those who have received high-risk immunosuppressive or cytotoxic drug treatment recently: such as rituximab, doxorubicin, or medium to high-dose corticosteroids (20 mg/d prednisone or higher doses) for more than 4 weeks.
6) Those with severe immunosuppression: neutrophils < 1,500/mm3.
(4) Those who had suffered a myocardial infarction within 6 months before enrollment, undergone coronary artery bypass surgery, or experienced any event that may reduce LVEF (unless confirmed LVEF ≥ 50%);
(5) Those who had undergone valve replacement surgery within 6 months before enrollment;
(6) Those with poor blood pressure control (SBP ≥ 180 mmHg or DBP ≥ 100 mmHg);
(7) Those with acute decompensated heart failure requiring treatment currently;
(8) Those with resting heart rate exceeding 120 beats per minute, or concurrent malignant arrhythmias;
(9) Those with significant coronary artery lesions requiring PCI revascularization treatment;
(10) Those with severe renal insufficiency (serum creatinine > 442 μmol/L) or undergoing dialysis treatment;
(11) Those with urinary tract infections at the time of enrollment; having symptoms and signs of urinary tract irritation (urinary frequency, urinary pain, urinary urgency), pain and tenderness in the pubic area, fever, waist pain or percussion pain, and bacterial culture of urine with colony count ≥ 105/ml;
(12) Those currently suffering from malignant tumors that require treatment;
(13) Those with acute or chronic disease exacerbation currently;
(14) Those who have participated in other interventional studies within 3 months.

4.3. Exclusion criteria:

(1) Those with incomplete data affecting the evaluation of efficacy or safety;
(2) Those who did not take the prescribed medication as required by the trial;
(3) Those who used drugs that affected the efficacy of the original treatment plan during the trial;
(4) Those who underwent surgical or other intervention measures that affected the efficacy of the

original treatment plan during the trial.

4.4. Termination criteria

The patient refuses to continue participating in the study for various reasons; during the follow-up period, the patient experiences a serious cardiovascular event that cannot continue to participate in the study; suffers from other serious diseases or has an accident that causes severe physical damage or mental disorders, and cannot continue to participate in the study; experiences serious adverse reactions related to the intervention measures of this study, and cannot continue to participate in the study.

5. Research methods and technical route

5.1. Name and specification of the study medication

Proline canagliflozin tablets, trade name: Ruiqin. Molecular formula: C22H24CIFO7•C5H9NO2•H2O. Specification: 10 mg per tablet. Manufacturer: Jiangsu Hengrui Pharmaceutical Co., Ltd. Drug approval number: National Drug Approval No. H20210052. Validity period: 24 months. Storage conditions: Sealed, stored at a temperature not exceeding 25℃. Manufacturer: Kanken Pharmaceutical Industry Co., Ltd., Kanken Factory; Packaging Subcontractor: Huizhou Jiuhui Pharmaceutical Co., Ltd. Drug Approval Number: National Drug Approval Number SJ20160008. Validity Period: 36 months. Storage Conditions: Store at room temperature (10-30℃). Avoid dampness after opening.

Placebo, made from edible starch, contains no active ingredients. Manufacturer: Huizhou Jiuhui Pharmaceutical Co., Ltd.

5.2. Treatment Plan

Recruit elderly patients with HFpEF who visited the Geriatrics Department of the First Affiliated Hospital of Air Force Military Medical University or were hospitalized from May 2026 to May 2027. Use a randomized, double-blind, placebo-controlled study method. All enrolled patients who met the inclusion/exclusion criteria were randomly assigned to Group A, Group B, and Group C at a ratio of 1:1:1. Before treatment and at the 4th, 8th, and 12th weeks after treatment, follow-up evaluations were conducted on the patients. Observe changes in indicators such as KCCQ score, quality of life, heart and kidney function, intestinal barrier function, and physical function before and after intervention. The observation endpoint was 12 weeks of treatment.

5.3. Concurrent Medications

During the follow-up period, when the HFpEF condition was stable, the subjects were required to maintain the original anti-heart failure treatment plan (including but not limited to ARNI/ACEI/ARB, beta-blockers, etc.), and no unnecessary dose adjustments or discontinuation of medication were allowed. If it was necessary to adjust the treatment plan due to clinical needs, it was required to discuss with the principal investigator in advance and record the reasons for the adjustment. For concurrent medications that may affect the study endpoint (such as antibiotics, NSAIDs, glucocorticoids, anti-arrhythmic drugs, etc.), the following principles should be followed: (1) Prohibited use: Clearly prohibit the use of drugs known to aggravate HFpEF (such as non-selective COX-2 inhibitors, thiazolidinedione hypoglycemic drugs, etc.); (2) Restricted use: If it is necessary to use drugs that may interfere with the study results (such as antibiotics, increased diuretic dosage, etc.), the following conditions must be met: ① Obtain written approval from the investigator; ② Record the drug name, dose, start and end time of use, and clinical indications in the case report form (CRF); ③ Submit the drug instructions or evidence-based basis for ethical committee filing; (3) Emergency medication handling: In cases of acute events (such as infection, arrhythmia), concurrent medications should be reported to the investigator within 24 hours, and a

warning label indicating "May affect endpoint" should be marked in the CRF. Subsequent follow-ups should focus on evaluating the impact of this event on the study indicators. (4) All concurrent medication situations will be included in the final statistical analysis as a covariate for sensitivity analysis.

6. Observation Items and Testing Time Points

Conduct a comprehensive assessment of the patients before treatment and at the 4th, 8th, and 12th weeks after treatment. The assessment contents include: ① Primary outcome indicators: Kansas City Cardiomyopathy Quality of Life Questionnaire score (KCCQ score); ② Secondary outcome indicators: NYHA cardiac function classification, 6-minute walking distance, serum NT-proBNP level; changes in serum eGFR, creatinine, urea nitrogen, cystatin, urine protein/creatinine ratio, etc. ③ Other outcome indicators include: Minnesota Heart Failure Quality of Life Questionnaire score, echocardiographic indicators (LAVI, LVMI, PASP, E/e' etc.), blood routine, blood biochemistry, blood sample inflammatory indicators (NLRP3, IL-1β, TNF-α, IL-6 etc.), intestinal flora sequencing analysis, intestinal flora metabolites (SCFAs, TMAO, bile acids, indole-3-propionic acid, sulfate indoleol etc.), intestinal barrier function testing (diamine oxidase, D-lactic acid, bacterial endotoxin), vascular endothelial cell function (NO), body composition analysis, frailty assessment, sarcopenia assessment (SARC-F scale), nutritional assessment, physical function assessment (BADL scale) indicators, etc.

7. Efficacy Evaluation Criteria

If any of the following conditions is met and the difference between groups is statistically significant, it is determined as effective: ① The Kansas City Heart Failure Quality of Life Questionnaire score (KCCQ score) is increased by more than 5 points compared to the baseline value; ② NYHA cardiac function classification is reduced by one level or more; ③ NT-proBNP (or BNP) is decreased by ⩾ 20% compared to the baseline value; ④ The 6-minute walking test distance is increased by more than 5% compared to the baseline value; ⑤ Serum eGFR increases by 5% and urine protein/cr ratio decreases by 5%. If the changes in the indicators do not meet any of the above standards, it is determined as ineffective.

8. Observation of Adverse Events

1. Adverse events (AE) refer to all adverse medical events that occur after the subjects receive the trial intervention, which can manifest as symptoms, signs, diseases or abnormal laboratory tests, but do not necessarily have a causal relationship with the trial medication. Serious adverse events (SAE) refer to adverse medical events that occur after the subjects receive the trial medication, such as death, acute exacerbation of heart failure or cardiovascular events requiring hospitalization, etc.

2. Possible serious adverse events: patient death, acute exacerbation of heart failure or cardiovascular events requiring hospitalization, etc.

3. Handling of adverse events:

Require the subjects and their families to contact the researcher in time if an adverse event occurs and to seek medical treatment nearby as soon as possible. If conditions permit, they can directly come to our hospital for treatment. The details of adverse events are recorded in the pathological report form and the direct relationship with the intervention measures of this study is determined.

After a serious adverse event occurs, the researcher shall report to the ethics committee within 24 hours upon learning and submit a written report of the details of the adverse event after follow-up verification.

9. Quality Control and Quality Assurance of the Study

Before the start of the study, researchers are trained. All personnel operate strictly in accordance

with the trial protocol; researchers conduct follow-up regularly by phone, WeChat, etc., to reduce the rate of patient dropout; data recording should be timely, direct, accurate, clear, signed and dated; regular self-checks should be conducted to verify the accuracy and completeness of data recording; electronic data are entered by two people.

10. Statistical Analysis

SPSS 26.0 software is used for statistical analysis. All statistical tests are two-sided tests, and a P value < 0.05 is considered statistically significant. The main endpoint indicators and key secondary endpoint indicators are compared between groups based on the changes before and after treatment (baseline to 12 weeks) in each group. If the data are normally distributed and the variance is homogeneous, one-way analysis of variance (ANOVA) is used for overall comparison among the three groups; if the ANOVA result is significant, Dunnett's t-test is used for multiple comparisons, that is, the C group (placebo group) is used as the common control, and the differences between A group (combined treatment group) and C group, and B group (single drug treatment group) and C group are compared respectively. If the data do not conform to the normal distribution or the variance is not homogeneous, Kruskal-Wallis H test is used for comparison among the three groups; if the result is significant, Dunn's test is used for pairwise comparisons. The comparison of count data was conducted using the chi-square test or Fisher's exact probability method. The effectiveness analysis was mainly based on the full analysis set (FAS), which included all subjects who were randomly assigned, received at least one treatment of the study drug, and had at least one efficacy evaluation after the baseline. This analysis followed the intention-to-treat (ITT) principle. At the same time, a sensitivity analysis was conducted using the per-protocol set (PPS) to verify the robustness of the results. The safety analysis was based on the safety data set (SS), including all subjects who received at least one treatment of the study drug and underwent at least one safety assessment.

11. Ethics in Clinical Research

Clinical research will follow the relevant regulations of the World Medical Congress' "Helsinki Declaration" and other documents. Before the start of the study, the trial protocol must be approved by the ethics committee before the clinical research can be implemented. Before each subject is enrolled in this study, the researcher has the responsibility to fully and comprehensively introduce the purpose, procedures, potential benefits and risks of this study to the subject or their legal representative, and sign a written informed consent form. The subject should be informed that they have the right to withdraw from this study at any time. The informed consent should be retained as a clinical research document for future reference. During the research process, the personal privacy and data confidentiality of the subjects will be protected.

12. Research Progress

05/01/2026 – 06/30/2026: Develop the randomization grouping plan

07/01/2026 – 05/31/2027: Enroll HFpEF patients, implement the intervention plan, collect biological samples and clinical data

06/01/2027 – 08/31/2027: Complete the trial follow-up, analyze and process the trial data

09/01/2027 – 11/30/2027: Write the final report, publish the research results in academic journals or exchange them at academic conferences, and promote the clinical application and promotion of the results

13. Participants

Name	Position/Area of Expertise	Responsibilities	GCP Training

			(Yes/No)
Su Hui	Associate Chief Physician	Project Design and Supervision	Yes
Wang Lin	Associate Chief Physician	Recruitment of Participants	Yes
Liu Yan	Associate Chief Physician	Recruitment of Participants	Yes
Hou Liming	Resident Physician	Supervising Doctor	Yes
Ji Chenyang	Graduate Student	Collecting Data	Yes
Wang Xia	Associate Professor	Statistical Analysis	Yes

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