Shenzhuo Formula Treatment in Patients With Macroalbuminuria Secondary to Diabetic Kidney Disease: Protocol Update and Statistical Analysis Plan

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Research Article

Keywords: Statistical analysis plan, Diabetic kidney disease, Shenzhuo Formula, Irbesartan, clinical effectiveness

Posted Date: August 27th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-717285/v1>

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Abstract

Background

Diabetic kidney disease (DKD), as one of the significant complications of diabetes, has been the focus of attention. Our previous retrospective study indicated that Shenzhou Formula (SZF) might reduce the macroalbuminuria secondary to the DKD.

Methods and design

This trial is a 24-week, randomized, multicentric, double-blinded, double-dummy clinical trial. 120 DKD patients (60 in each group) will be randomly divided randomized into two groups: SZF+ Irbesartan Simulator or Irbesartan + SZF Simulator. 24-h UP is the primary outcome measure is. The secondary outcome measures include Serum creatinine, estimated glomerular filtration rate, urinary albumin excretion rate, improvement in TCM symptoms, FBG, 2-h postprandial plasma glucose, HbA1C, Cholesterol, triglycerides, HDL, LDL, blood pressure, albumin to creatinine ratio, and the audit of diabetes-dependent quality of life 19 . Our recruitment began in May 2015, and we have enrolled 100 participants in this ongoing study, with a designed maximum sample size of 120. The interim results have been reviewed at N = 60 and continuing recruitment was recommended. This statistical analysis plan includes our approach to impute missing data, analysis primary, secondary outcomes, and safety endpoints.

Conclusion

This SAP will standardize the clinical trial's statistical analysis, avoid outcome selective reporting bias and data-driven analysis. This trial will provide further clinical evidence for SZF treatment of macroalbuminuria secondary to DKD.

Trial registration

Chinese Clinical Trial Registry, ID: ChiCTR-ICR-15006311, registered on 26 May 2013. <http://www.chictr.org.cn/showproj.aspx?proj=10862>

Background

Diabetic kidney disease (DKD) is a leading cause of chronic kidney disease (CKD) in the developed countries and is rapidly becoming the leading cause in developing countries [1]. As one of the most common complications of diabetes mellitus, DKD has been reported in 20–40% of diabetic patients in China and has been the leading cause of end stage renal disease(ESRD) in the middle-aged and elderly people replacing chronic glomerulonephritis [2–4]. Despite the increasing use of renin-angiotensin-aldosterone system(RAAS) inhibitors in recent years, the prevalence of diabetic nephropathy has not significantly changed [5, 6]. Therefore, there is an urgent need to explore drugs that can effectively prevent DKD occurrence and development.

The treatment of DKD by traditional Chinese medicine (TCM) has accumulated extensive clinical experience in recent years. TCM and angiotensin receptor blockade (ARB) treatment combination can reduce proteinuria in type 2 diabetes [7]. The treatment reported in our previous retrospective study revealed that Shenzhou Formula (SZF) could improve glomerular filtration rate (GFR) and reduce 24-h urinary protein (24h-UP) [8]. Animal experiments also showed that TCMs have protective effects on diabetic renal lesions [9]. However, the impact of SZF versus RAAS blockers in DKD remains very limited and thus requires further exploration.

We designed and implemented the trial to investigate the efficacy of and safety of SZF and irbesartan in treating DKD patients with macroalbuminuria. We hypothesized that the treatment with SZF alone could alter the macroalbuminuria secondary to diabetic kidney disease. Shenzhou Formula treatment in patients with macroalbuminuria secondary to diabetic kidney disease is a 24-week, randomized, multicentric, double-blinded, double-dummy, controlled clinical trial. The research protocol was previously reported [10]. The original protocol provides more details on the trial rationale, eligibility criteria, interventions, concomitant treatments, study visits, and data management.

Here, we describe the study's pre-determined statistical analysis plan (SAP), which will be applied when the trial ends, to prevent reporting bias and data-driven interpretation for results. The SAP (Version 2.0 20180626) was accomplished before the data analysis, and the investigators will adhere to the requirement in analyzing the data, according to "Guidelines for the Content of Statistical Analysis Plans in Clinical Trials" published in JAMA [11] (See Additional file 1 populated checklist). It includes our

approach to imputing missing data, our approach to analyzing primary, secondary outcomes, and including safety, baseline analyzes. We will also report adverse effects in total.

Study Methods

2.1 Trial design

SZF treatment in patients with macroalbuminuria secondary to diabetic kidney disease is a clinical trial conducted by 14 centers, in which 120 subjects will be recruited. In the protocol, we specified that we would include 120 subjects in 9 hospitals. We added five centers to speed up the trial, including The Second Affiliated Hospital of Shaanxi University of TCM, Xianyang; Zhengzhou hospital of TCM, Zhengzhou; Hangzhou Hospital of TCM, Hangzhou; The Affiliated Hospital to Changchun University of Chinese Medicine, Changchun; Zhejiang Hospital of TCM, Hangzhou. The newly added centers have passed the ethical review by the Ethics Committee of Guang'anmen Hospital. All investigators received intensive training on conducting the research and intervention before the recruitment to ensure the quality. The flow diagram shown in Figure.1 provides a brief description of the research process. The protocol has defined the sample size calculation [10].

2.2 Randomization and Blinding

Participants included in the study will be randomized using blocked randomization stratified by centering a 1:1 ratio to receive SZF plus Irbesartan Simulator or Irbesartan plus SZF Simulator 24weeks. According to the center of each layer, select the appropriate length. With the PROC PLAN process statement of SAS 9.4 (SAS/STAT Software 9.4, SAS Institute, Inc., Cary, NC), the random arrangement (random coding table) of 120 subjects was generated given the number of seeds. The Institute of Basic Research in Clinical Medicine of the China Academy of Chinese Medical Sciences provided the random arrangement. So did the 24-hour emergency code break and medical information. Participants, investigators, and statisticians will be unaware of treatment assignments.

SZF drugs and SZF mimic are precisely the same shape and smell. The taste, smell, color are also entirely consistent when dissolved in water. Irbesartan capsules and mimics have a consistent condition; the scent and appearance remain consistent after opening the capsule.

2.3 Interim analysis

Interim analyzes occurred when 60 patients completed the 24-week treatment, which is 50% of the planned number of cases, by independent biostatisticians. The primary, secondary outcomes and safety assessments will be tested to compare the SZF and irbesartan effect and safety. If there were concerns about the effect and safety of participants, Data Monitoring Committee would recommend continuing, stopping, or modifying the trial.

A recommendation of trial termination would be considered by the data management, clinical trial institutions, ethics committees, and sponsors if the corresponding difference in treatment effects were unlikely to be reached or intolerable adverse effects occurred. The detailed result will remain confidential to the investigators. The interim analysis occurred in September 2018, and continuing recruitment was recommended.

2.4 Criteria for trial discontinuation

Trial abortion refers to discontinuing a full trial halfway when the clinical trial has not ended as organized. The purpose of trial discontinuation is to protect subject equity, guarantee the trial quality, and avoid unnecessary economic losses. If any situation described below occurred, the trial would be terminated.

(1) Serious safety issues occur in the trial, and the trial should be promptly discontinued.

(2) Drug treatments found to be too inadequate or even ineffective in the trial to be of clinical value should be suspended, avoiding patient treatment delays and economic losses.

(3) The clinical trial protocol is found to have a significant lapse or a well-designed protocol that has undergone substantial deviations in implementation, which makes it challenging to evaluate the drug effect.

(4) The sponsor requests discontinuation (e.g., reasons for funding, administration, etc.).

(5) Withdrawal of the trial by the administration, etc.

3. Statistical principles

3.1 Overall principles

All the statistical analysis tests will be implemented based on two-side tests with a nominal alpha level of 0.05 by the SAS [12] after the completion of the trial. All confidence intervals (CIs) reports will be 95% CIs. For each outcome, the null hypothesis is that there is no difference between the intervention groups.

The description of measurement indicators will calculate the mean, standard deviation, median, minimum, maximum, interquartile range (Q3-Q1).

Continuous variables satisfying normality will be described by the mean and standard deviation, and the median and interquartile range when distribution did not follow normality. The counting indicators will be presented as the number and percentage of each category.

Inter-group comparisons for metrics will be performed with the independent two-sample t-tests (normality, homogeneity of variance) or Wilcoxon rank-sum test (non-normality, heterogeneity of variance). Comparisons within a group will be carried out using the paired t-test (normality) or paired rank-sum test (non-normality). χ^2 test or Fisher's exact probability will be needed for count metrics, and the Wilcoxon rank-sum test will be utilized for categorical variables. A generalized linear mixed model analysis (GLM) will be performed on the repeated measured outcome.

Suppose there is an imbalance in the baseline of important indicators on the efficacy analysis, such as age, gender, and the concomitant treatment. In that case, an adjustment will be required before the efficacy comparison. The covariance method will be used in continuous variables, and logistic regression analysis will be used in count metrics and hierarchical metrics.

3.2 Definition of analysis sets

3.2.1 Full Analysis Set, FAS

The patients who have accepted treatment at least once and have the primary objective after treatment will be included in the FAS.

3.2.2 Per Protocol Set, PPS

The subjects will be included in the per protocol set, selected in the FAS and received at least 50% treatment scheduled with no major protocol violations. The PPS will be determined previous to the unblinding of the data for the final analysis and will include:

All visits planned and the main data completed.

The inclusion satisfied and the exclusion inapplicable.

No significant violations of the trial protocol occurred (described in Adherence and Protocol deviations).

3.2.3 Safety Set, SS

The safety analysis will analyze all the patients who used the intervention drug at least once and had one safety assessment.

3.3 Adherence and Protocol deviations

Adherence is determined by the participants each visit point attending and the medication adherence. We will describe the proportion of participants by using frequency distributions for both groups. The medication compliance will be calculated in two

groups separately and compared between groups according to the ratio of medicine actual taken, and the drug should be taken. The medicine distributed to the patients and the medicine left untaken will be recorded every four weeks.

Significant protocol violations, including those that could affect the primary measures, like taking protocol prohibited medicine, those which present a safety risk to the participants, and/or those that are of ethical concern.

4. Trial population

4.1 Eligibility criteria

Inclusion and exclusion criteria used in the trial are presented in Table 2 of the protocol. The participants with DKD need to have macroalbuminuria and have well-controlled Serum creatinine, blood pressure, and HbA1c. Participants are excluded, including those who take the potassium-sparing diuretics or with Type 1 diabetes.

4.2 Case enrollment and completion

Enrollment and the number of completed cases will be summarized for each center. The numbers of enrolled cases and each analyzed data set will be described. Participants may withdraw from the trial intervention and/or fail to provide the follow-up data. In addition, participants may withdraw the trial consent. We will report these items (Table 1), and the total dropout rate will be compared between the two groups.

4.3 Baseline characteristics

The baseline characteristics of all participants in both groups will be outlined in Table 2. The table will describe the following variables: age, height, weight, BMI, female sex, nationality, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiration rate, drug or constitution allergic history, comorbid conditions, concomitant treatment. The sample will be described according to the full analysis set. The data of the two groups of subjects will be compared between groups to determine the equality of the baseline values of the two groups.

5. Analysis methods

5.1 Outcome measures analyzes

5.1.1 Primary outcome analyses

The primary analysis will be conducted in the full analysis set and per protocol set. The effect of SZF and its application in reducing urine protein, which is evaluated by the 24-h UP (mg/24h), is the primary concern. The distribution and changes of 24-h UP at week 0,4, 8, 12, 16,20, and week 24 of medication will be described. Intra-group and inter-group comparisons will be made. The distributions of qualitative judgments of 24-h UP at weeks 4, 8, 12, 16, 20, and 24 will be described and compared between groups. Table 3 is provided for reference in qualitatively judging the variation. The efficiency rate will be calculated by summing the rate of clinical control, obvious therapeutic effect, and with therapeutic effect (Table 4).

5.1.2 Secondary outcome analyses

The secondary outcome including Serum creatinine (SCr, umol/L) and estimated Glomerular filtration rate (eGFR, mL/(min•1.73m²), using CKD-EPI creatinine equation[13]), urinary albumin excretion rate (UAER, µg/min) „improvement in TCM symptoms , fasting blood glucose(FBG) (mmol/L) and 2-h postprandial plasma glucose(2-h PG, mmol/L), HbA1C(%),Cholesterol(mmol/L), triglycerides(mmol/L), HDL(mmol/L), LDL(mmol/L), blood pressure(mmHg) ,albumin to creatinine ratio(ACR)(mg/g) and the audit of diabetes-dependent quality of life 19 (ADDQoL)[14] and it will be conducted in the FAS and PPS. The distribution and changes of all the secondary outcomes at the baseline and the visit point will be compared between groups and within the group (Table 5).

Describe and compare the TCM symptom (physical and mental fatigue, dry mouth and throat, weakness and soreness of the lower back and knees, qi deficiency and listlessness, spontaneous perspiration, night sweat, dysphoria in chest, palms, and soles, dark purplish lips, edema) scores and the total score from the baseline and 24 weeks after medication in both groups.

The improvement of TCM syndromes will be judged according to the symptom score method, which is conducted according to the Nimodipine method [15]. Efficacy index = (Score before treatment – Score after treatment) / Score before treatment × 100%. The criteria are as follows:

Clinical control is defined as almost all symptoms disappeared after the treatment (the efficacy index ≥ 95%). The *obvious therapeutic effect* means that most clinical signs show marked improvement (the efficacy index ≥ 70%). *With therapeutic effect* means the relief of the symptoms has been experienced (the efficacy index ≥ 30%). *Invalid*: no significant improvement or symptom exacerbation (the efficacy index < 30%). The clinical efficiency will be calculated with the formula: Clinical efficiency = (Clinical control case number + Obvious therapeutic effect case number + With therapeutic effect number) / total case number × 100%.

The clinical efficiency of TCM syndrome scores after 24 weeks of treatment will be calculated for both groups (Table 6).

5.2 Safety analyzes

The safety analysis will analyze all the patients in Safety Set. The laboratory index would be listed one by one if the patients had their laboratory findings converted from normal to abnormal or aggravated and the abnormal liver and renal function occurred during the treatment, as well as the judgments of the association between the conversion and medications. The type, severity, occurrence, and relationship to intervention drug of all adverse events during treatment will be tabulated (Table 7). The number and frequency of adverse events will be calculated for both groups. The occurrence of serious adverse events and the discontinuation followed will be recorded in detail. The incidence of adverse effects (AEs) will be compared between groups.

Any AE will be classified into four levels: mild (Mild discomfort, which the participants could tolerate with no special treatment.), moderate (Moderate pain, which the participants could not handle and need special treatment with a direct impact on recovery.), and severe AEs (life-threatening or lead to death, hospitalization, extended hospitalization, to lasting or severe disability, incapacity or congenital anomaly.)

The safety assessment includes the routine blood, urine, and stool tests, electrocardiogram, liver function, renal function inspected at baseline, week 12, and week 24 (Table 8). Safety analysis will describe the distribution by qualitative judgment, which is counting the number of cases and their proportion of abnormal indexes by cross-tabulation.

5.3 Imputation of missing data

Multiple imputations will be used for subjects with missing data on the primary outcome. For the secondary and safety outcomes that may miss, the results will be analyzed according to the actual data instead of imputing the missing values or adjusting the model for missing data. Furthermore, we will conduct a per protocol analysis which excluded those with missing outcome data.

6. Changes to the original SAP

The original SAP was created based on the initial study protocol and related planned analyses. The focal point of the study protocol update and/or SAP reversion since the first version, including the additional ACR measurement, the ADDQoL were added as secondary outcomes, and an interim analysis was implemented to evaluate measures of effectiveness and safety.

7. Conclusions

The present study is a 24-week, randomized, multicentric, double-blinded, double-dummy clinical trial. Unbiased evaluation will be conducted on the clinical data in the trial to increase the credibility of the results and bring substantial evidence for further studies in the treatment of DKD.

8. Status

The trial commenced in August 2014 and is scheduled to be completed in June 2022. Currently, 100 patients have been recruited.

9. References to files

Data Management Plan and Statistical Master File developed and kept by a third-party statistical company. Trial Master Files are developed and retained by the Guang'anmen Hospital (principal investigators unit). The SOPs were developed collectively by the principal investigators and the participating centers and were preserved separately.

Abbreviations

DKD	Diabetic kidney disease
SZF	Shenzhou Formula
CKD	chronic kidney disease
ESRD	end stage renal disease
RASS	Renin-Angiotensin-Aldosterone System
TCM	traditional Chinese medicine
ARB	angiotensin receptor blockade
GFR	glomerular filtration rate
24h-UP	24-h urinary protein
SAP	statistical analysis plan
CIs	confidence intervals
GLM	generalized linear mixed model analysis
FAS	Full Analysis Set
PPS	Per Protocol Set
SS	Safety Set
UAER	urinary albumin excretion rate
FBG	fasting blood glucose
2-h PG	2-h postprandial plasma glucose
ADDQoL	the audit of diabetes-dependent quality of life 19
AEs	adverse effects
ACR	albumin to creatinine ratio

Declarations

Ethics approval and consent to participate

The trial was approved by the Ethics Committee of Guang'anmen Hospital prior to the recruitment of patients.

Consent for publication

The manuscript doesn't contain any individual person's data in any form.

Availability of data and materials

Not applicable. The trials discussed in this publication will be published or have been published separately. This project did not generate data or materials.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed in this manuscript.

Competing interests

The authors declare that they have no no conflicts of interests

Funding

This study is supported by the Fundamental Research Funds for the Central Public Welfare Research Institutes (No. ZZ0808004), and Guang's Anmen Hospital of the China Academy of Chinese Medical Science (No. 2015 s325).

Authors' contributions

All authors critically revised and contributed to the content of the updated SAP and this manuscript and approved the final submitted version.

Acknowledgments

The authors are grateful to the Data Monitoring Company (Beijing Created Medicine Technology Co., LTD) for current and initial statistical support. We also deliver our thanks to all the staff for their valuable supports in participant recruitment.

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Tables

Table 1. Withdrawals

Num	Withdrew at...	Reason withdrew	Type of withdrawal
1	xx	xx	e.g. withdrew consent
2	xx	xx	e.g. stopped intervention early, provided data at follow-up
...	xx	xx	e.g. stopped intervention early, lost to follow-up
...	xx	xx	e.g. completed intervention, lost to follow-up
n	xx	xx	xx

Table 2. Baseline characteristics of participants prior to treatment

Characteristic	SZF, number, central tendency (variability)	Irbesartan, number, central tendency (variability)	All participants, number, central tendency (variability)	p Value
	<i>n</i> = xx	<i>n</i> = xx	<i>n</i> = xx	
Demographics				
Age(years) ^a	xx (xx)	xx (xx)	xx (xx)	.xx
Height(m) ^a	xx (xx)	xx (xx)	xx (xx)	.xx
Weight(kg) ^a	xx (xx)	xx (xx)	xx (xx)	.xx
BMI(kg/m ²) ^a	xx (xx)	xx (xx)	xx (xx)	.xx
Female sex(n,%) ^b	xx (xx%)	xx (xx%)	xx (xx%)	.xx
Nationality(China, other) ^b	xx (xx%)	xx (xx%)	xx (xx%)	.xx
Vital signs				
Heart rate(beats per minute) ^a	xx (xx)	xx (xx)	xx (xx)	.xx
Systolic blood pressure (mmHg) ^a	xx (xx)	xx (xx)	xx (xx)	.xx
Diastolic blood pressure (mmHg) ^a	xx (xx)	xx (xx)	xx (xx)	.xx
Mean arterial pressure (mmHg) ^a	xx (xx)	xx (xx)	xx (xx)	.xx
Respiration rate(breath/min) ^a	xx (xx)	xx (xx)	xx (xx)	.xx
Drug or constitution allergic history (yes or no)^b	xx (xx%)	xx (xx%)	xx (xx%)	.xx
Comorbid conditions(n%)				
Diabetic retinopathy ^b	xx (xx%)	xx (xx%)	xx (xx%)	.xx
...				
Concomitant treatment				
... ^b	xx(xx%)	xx(xx%)	xx(xx%)	.xx

a Number, mean, standard deviation

b Number, percentage.

Table 3. 24-h UP qualitative judgments classification standard

Qualitative Judgment	Standard
Clinical control	24-h UP≤0.5g
Obvious therapeutic effect	24-h UP reduction ≥50%
With therapeutic effect	24-h UP reduction ≥20%
Invalid	Fail to reach the standards above

Table 4. Analysis of primary outcome

Time point	SZF, number, mean (SD)	Irbesartan, number, mean (SD)	Mean difference (95% CI)	p Value
visit at	n = xx	n = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 4 ^a	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 8	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 16	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 20	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall SZF effect ^b				.xx

a, b: p values comparing between group differences at visit points post-randomization (a) and over the entire24-week trial (b: primary outcome).

Table 5. Secondary outcome analysis

Time point	SZF, number, mean (SD)	Irbesartan, number, mean (SD)	Mean difference (95% CI)	p Value
Scr at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 4	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 8	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 16	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 20	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall SZF effect ^a				.xx
eGFR at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 4	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 8	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 16	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 20	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall SZF effect				.xx
UAER at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 4	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 8	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 16	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 20	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall SZF effect				.xx
FBG	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 4	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 8	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 16	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 20	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.xx

Overall SZF effect				.XX
2hPG at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 4	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 8	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 16	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 20	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Overall SZF effect				.XX
TC at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Overall SZF effect				.XX
TG at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Overall SZF effect				.XX
LDL at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Overall SZF effect				.XX
HDL at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Overall SZF effect				.XX
HbA1c at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.XX
Overall SZF effect				.XX
BP at	<i>n</i> = xx	<i>n</i> = xx		

Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 4	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 8	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 16	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 20	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall SZF effect				.xx
ACR at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 4	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 8	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 16	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 20	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall SZF effect				.xx
ADDQoL at	<i>n</i> = xx	<i>n</i> = xx		
Week 0	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 12	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Week 24	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall SZF effect				.xx

^a p values comparing between-group differences over the entire 24-week trial

Table 6. TCM syndrome scores analysis

		SZF	SZF		Irbesartan	Irbesartan	
		Week 0	Week 24	p Value	Week 0	Week 24	p Value
		n = xx	n = xx		n = xx	n = xx	
Evaluation of TCM syndrome	Physical and mental fatigue	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Dry mouth and throat	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Weakness and soreness of the lower back and knees	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Qi deficiency and listlessness	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Spontaneous perspiration	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Night sweat	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Dysphoria in chest, palms, and soles	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Dark purplish lips	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Edema	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
Efficacy index	Clinical control	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx
	Obvious therapeutic effect	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx
	With therapeutic effect	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx
	Invalid	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx
	Overall clinical efficiency	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx

Table 7. List of all adverse effects reported during the trial

Description	SZF, number	Irbesartan, number	Severity	Related to trial
xx	xx	xx	xx	xx
xx	xx	xx	xx	xx
xx	xx	xx	xx	xx

Table 8. Safety assessment

		0W			12W			24W		
		SZF	Irbesartan	p value	SZF	Irbesartan	p value	SZF	Irbesartan	p value
		(n=xx)	(n=xx)		(n=xx)	(n=xx)		(n=xx)	(n=xx)	
Haematology	Red blood cell	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	White blood cell	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Hemoglobin	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Platelet	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
Urine test	Glucose	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Ketone	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Occult blood	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Erythrocytes	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Leukocytes	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
Stool routine	Faecal leukocytes	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Feces occult blood	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
Blood chemistry	ALT	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	AST	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	ALP	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	GGT	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	TBIL	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	UA	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	β2-microglobulin	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Serum albumin	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Potassium	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
	Blood urea nitrogen	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx	xx (xx)	xx (xx)	.xx
Electrocardiogram		xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx

Adverse events	Mild	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx
	Moderate	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx
	Severe	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx
	Overall AEs	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx	xx (xx%)	xx (xx%)	.xx

Study Period

study period									
	enrollment	allocation	intervention						
Time point(weeks)	-2	0	4	8	12	16	20	24	
Eligibility screen	√								
Written informed consent		√							
Physical examination	√								
Medical history	√								
24 h urinary protein	√	√	√	√	√	√	√	√	
UAER/ACR		√	√	√	√	√	√	√	
FBG, 2hPG	√	√			√				√
HbA1c	√	√	√	√	√	√	√	√	
BP	√	√	√	√	√	√	√	√	
TC, TG, LDL-C, HDL-C		√			√				√
Routine blood and CRP,urine, and stool		√			√				√
ALT,AST, ALP GGL, TBIL		√			√				√
BUN, Serum Cr, β2-MG,UA		√	√	√	√	√	√	√	
Electrocardiogram		√			√				√
Adverse events		√	√	√	√	√	√	√	
ADDQoL		√			√				√

Figures

Figure 1

Flow diagram of the study

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AdditionalFile1.docx](#)