CLINICAL STUDY PROTOCOL

Finerenone for Patients with Primary Aldosteronism (FAIRY): A Multicenter, Randomized, Clinical Trial

Version Number: 1.0

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Synopsis

Title:

Finerenone for Patients with Primary Aldosteronism (FAIRY): A Multicenter, Randomized, Clinical Trial.

1.Objectives：

1.1 The primary objective is to evaluate the antihypertensive efficacy of finerenone compared to spironolactone in patients with PA after 12 weeks of treatment.

1.2 The secondary objective will include the followings:

1) To evaluate efficacy on hypokalemia of finerenone compared to spironolactone in patients with PA after 12 weeks of treatment.
2) To evaluate efficacy on plasma renin of finerenone compared to spironolactone in patients with PA after 12 weeks of treatment.
3) To evaluate safety of finerenone compared to spironolactone in patients with PA after 12 weeks of treatment.

2. Efficacy Endpoints:

2.1 The primary efficacy endpoint

The change from baseline in 24-hour systolic blood pressure (SBP) assessed by 24-hour ABPM compared to spironolactone after 12 weeks of finerenone therapy in patients with PA.

2.2 The secondary efficacy endpoints

The secondary efficacy endpoints include the followings:

- Change from baseline in 24-hour diastolic blood pressure (DBP) assessed by 24-hour ABPM;
- Blood pressure control rate at the end of the study;

Note: Blood pressure control rate is defined as the percentage of patients with mean seated office BP<140/90 mmHg.

- Change from baseline in daytime SBP assessed by 24-hour ABPM;
- Change from baseline in daytime DBP assessed by 24-hour ABPM;
- Change from baseline in nighttime SBP assessed by 24-hour ABPM;
- Change from baseline in nighttime DBP assessed by 24-hour ABPM;
- Change from baseline in office SBP;
- Change from baseline in office DBP;
- Change from baseline in serum potassium;
- Hypokalemia control rate at the end of the study

Note: Hypokalemia control rate is defined as the percentage of hypokalemic patients with serum potassium>3.5mmol/l at the end of the study.

- Change from baseline in plasma renin

2.3 The exploratory endpoints

The exploratory endpoints will include the followings:

- Change from baseline in urinary albumin-to-creatinine ratio (UACR);
- Change in the UACR in patients with baseline UACR more than 30 (mg/g Cr).

2.4 The safety endpoints

The safety endpoints will include the followings:

- Proportion of subjects with AEs;
- SAEs and AEs leading to discontinuation of treatment with study drug;
- Change in eGFR from baseline

3.Population:

3.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate:

- Aged between 18-75, male or female;
- With confirmed PA diagnosis (screening positive and at least one confirmatory test is positive);

NOTE: *Screening positive is defined as plasma aldosterone-to-renin ratio (ARR)≥ 20(pg/ml)/(μIU/ml) or ARRing positive is defined as plasma aldosteroconcentration (PAC) post captopril challenge test (CCT) ≥ 110 pg/ml or PAC post seated saline infusion test (SSIT) ≥ 80 pg/ml is considered positive. [ARR≥10(pg/ml)/(μIU/ml) or ARR≥150(pg/ml)/(ng/ml/hr) can be considered positive if the patients with hypokalemia (serum potassium < 3.5mmol/L) or adrenal nodules (diameter > 1cm)].*

- Not taking any antihypertensive drugs or on a stable regimen of antihypertensive agents (only α receptor blockers, dihydropyridines or non dihydropyridines calcium channel blockers are allowed) for more than four weeks before screening;
- With a mean seated office SBP ≥ 140 or DBP ≥ 90 mmHg;
- Able and willing to give informed consent for participation in the clinical study.

3.2 Exclusion Criteria

1) Planning to have subtyping examinations of PA (eg. adrenal vein sampling, PET-CT) within 3 months;
2) Planning to have adrenal surgery or other surgery within 3 months

3) With a mean seated office SBP ≥ 180mmHg or DBP ≥ 110mmHg before randomization;

Note: Mean seated BP is defined as the average of three seated BP measurements at any single clinical site visit. If the patient did not take their regularly scheduled antihypertensive medications prior to the visit, one BP re-test is allowed within two days after taking the medications.

4) Night shift worker;
5) Has a body mass index (BMI) ≥ 30 kg/m^2 at screening;
6) Has uncontrolled diabetes with fasting blood glucose (FBG) ≥13.3mmol/L at screening;
7) Has uncontrolled chronic diseases;
8) Has other known secondary hypertension (eg, renal artery stenosis, Cushing's syndrome, pheochromocytoma, or aortic coarctation);
9) Has known and documented heart failure (New York Heart Association [NYHA] class III or IV), liver transaminase levels are more than twice the upper limit of normal;
10) Has had CABG other major cardiac surgery (eg, valve replacement), peripheral arterial bypass surgery, or PCI within 6 months before screening;
11) Has had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months before screening;
12) Has poor compliance that can not fully participate in the study;
13) Has hyperkalemia with serum potassium > 5.0mmol/L without potassium supplementation;
14) Has a history of uncontrolled malignant tumor;
15) The office blood pressure measurements difference of more than 20mmHg in both arms
16) Unwilling or unable to stop taking medications might influence blood pressure, including sex hormones, glucocorticoids, non-steroidal anti-inflammatory drugs, cyclosporine, tacrolimus, or antidepressants;
17) Is pregnant, breastfeeding, or planning to become pregnant during the study;
18) Complicated with severe mental illness;
19) Has had prior organ transplant;
20) Has a history of allergy to finerenone or spironolactone;
21) Has typical consumption of ≥ 15 alcoholic drinks weekly;

Note: 1 drink of alcohol is equivalent to 360ml beer, 45ml spirits, or 150ml wine

22) Has participated in another clinical study involving any investigational drug within

30 days prior to screening；

23) Female of childbearing potential refusing to use non-hormonal methods of contraception during the study period;
24) Refuse to get rid of grapefruit or grapefruit juice while receiving finerenone treatment;
25) Other situations that the investigator assesses the subject as unable to complete the trial.

3.Study Design and Duration

3.1 Study Summery

The study is a multicenter, randomized controlled trial. The First Affiliated Hospital of Chongqing Medical University will be the responsible unit, and the Affiliated Hospital of Southwest Medical University, the Third Xiangya Hospital of Central South University, Fuling People's Hospital of Chongqing, Chongqing Wansheng Economic and Technological Development Zone People's Hospital, the First Affiliated Hospital of Kunming Medical University and Heping Hospital Affiliated to Changzhi Medical College will be the cooperating unit. This study is designed to evaluate the efficacy and safety of finerenone in patients with PA. Patients diagnosed with PA are randomly assigned to receive oral finerenone or spironolactone for 12 weeks, respectively. Blood pressure, renin, blood potassium and other indicators of the patients are observed, and the efficacy and safety of the two groups were compared.

Patients will be instructed to bring their study drug to all clinical site visits. Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical site visit. All clinical site visits will take place between 7:00 a.m. and 12:00 a.m.

3.2 Study Visit

This study will consist of 2 periods:

1. A Screening Period (Screening Visit [Visit 1]) of up to 2 weeks;
2. A Treatment Period (Visits 2 to 7) of 12 weeks;

Patients will complete at least 7 total visits over a period of approximately 3 months, including 5 Clinic Visits and 2 Telephone Visits. Additional Unscheduled Visits may occur at any time during the study.

<u>Screening Period (Visit 1, Week -2~0)</u>

Patients will provide informed consent at the Screening Visit (Visit 1) and undergo assessment for Inclusion/Exclusion Criteria. All patients will undergo 24-hour ABPM

at the first visit.

Patients with a confirmed diagnosis of PA who are willing to participate in the study are into the Screening Period. PA is defined as having a positive result of screening and confirmatory tests. Screening positive is defined as plasma aldosterone-to-renin ratio (ARR) ≥ 20(pg/ml)/(μIU/ml) or ARR≥300 pg/ml)/(ng/ml/hr) *[ARRs defined as having a positive(pg/ml)/(ng/ml/hr) can be considered positive if the patients with hypokalemia (serum potassium < 3.5mmol/L) or adrenal nodules (diameter > 1cm)]*. Plasma aldosterone concentration (PAC) post captopril challenge test (CCT) ≥ 110 pg/ml or PAC post seated saline infusion test (SSIT) ≥ 80 pg/ml is considered positive.

For the screening test and the confirmatory tests, antihypertensive medication is withheld or changed according to the guideline. Treatment with diuretics is withheld for at least 4 weeks. β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor blockers are stopped for at least 2 weeks. Only the non-dihydropyridine calcium channel blocker, terazosin, and doxazosin are allowed for uncontrolled hypertension.

Treatment Period (Visits 2 to 7, Week 0~12)

All patients who remain on a stable regimen of antihypertensive treatment, or who are not taking any antihypertensive medications through the Screening Period will be eligible for randomization. Eligible patients will be contacted via Clinic Visits (Visit 2) to be informed about the study qualification and to schedule their treatment period.
Eligible patients will be randomized 1:1 into one of the two treatment groups (finerenone and spironolactone).

Patients will complete at least 5 total visits over the treatment period of 12 weeks, including three Clinic Visits and two Telephone Visits. Clinical Visits (Visit 4, 6 and 7) are conducted on Week 4, Week 8 and Week 12 (the last day of the treatment period), and two Telephone Visits (Visit 3 and Visit 5) are conducted on Week 2 and Week 10. Additional Unscheduled Visits may occur at any time during the study period.

If the office blood pressure remains uncontrolled on Week 4 (ie, systolic blood pressure ⩾140mmHg or diastolic blood pressure ⩾90mmHg], finerenone and spironolactone will be increased to 40mg per day (the maximum dose). Patients will also be monitored for events of special interest associated with the study medication, including

hyperkalemia, hypotension, impotence, gynecomastia and menstrual abnormalities, in these instances, the dose is either maintained or decreased, as determined by the investigator. When the patient's blood pressure is up to target, if the patient's hypokalemia is not controlled (i.e., the potassium is <3.5mmol on the date of follow-up), thedose will also be increased to 40mg per day.

Study drug (finerenone or spironolactone) dispensing may occur at any time starting at Visit 2 and before Visit 7. On Clinical Visit days, patients will self-administer the morning dose of background antihypertensive medications at home and withhold the study drug. At the clinical site, patients will self-administer the morning dose of study drug under the supervision of site staff after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue taking their study drug once daily by mouth at approximately the same time each morning. The primary efficacy endpoint evaluation will take place at the End of Treatment (Visit 7).

Study visits will follow the Schedule of Procedures (Appendix A).

4. Dosage and Route of Administration:

Finerenone tablets and spironolactone tablets will be administered during the Treatment Period. Finerenone and spironolactone doses to be tested in this study are 20mg or 40 mg.

Patients will receive finerenone tablets of either their assigned dose or matching spironolactone tablets during the Treatment Period, starting at Visit 2 and concluding at Visit 7.

5. Statistical Analyses:

The following analysis populations are defined for the different types of data analysis:

- Intention-to-treat (ITT) Population

The ITT Population will include all patients randomized into the study. Treatment classification will be based on the randomized treatment;

- Modified intention-to-treat (mITT) Population

The mITT Population will include patients randomized and received at least 1 dose of the study drug. Treatment classification will be based on the randomized treatment. The mITT population will be used for the primary analysis of all efficacy endpoints;

- Per Protocol (PP) Population

The PP Population will include all patients in the mITT population and who did not

experience a major protocol deviation that potentially impacted the primary efficacy endpoint. The PP population, along with the reason for exclusion, will be finalized prior to study end.

- Safety Population;

The Safety Population will include all patients who receive at least 1 dose of any randomized study drug. Treatment classification will be based on the actual treatment received. The Safety Population will be the primary population used for the safety analyses.

Efficacy analysis

The primary efficacy analysis will compare the change in 24-hour SBP assessed by ABPM from baseline (Visit 2) to the End of Treatment (Visit 7) between finerenone and spironolactone. Statistical analyses will be primarily descriptive. Descriptive statistics (eg, mean, standard deviation, median, minimum and maximum) will be presented for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables.

Safety analysis

The safety will be assessed from the time of informed consent until the end of the Follow-up Period. The Safety Population will be the primary population for the safety analysis. All safety endpoints will be summarized descriptively.

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
PA	Primary Aldosteronism
ABPM	Ambulatory Blood Pressure Monitoring
AE	Adverse Event
SBP	Systolic Blood Pressure
TEAE	Treatment-Emergent Adverse Event
DBP	Diastolic Blood Pressure
ARR	Aldosterone-to-Renin Ratio
PAC	Plasma Aldosterone Concentration
CCT	Captopril Challenge Test
SSIT	Seated Saline Infusion Test
MRA	Mineralocorticoid Receptor Agonist
BMI	Body Mass Index
NYHA	New York Heart Association
CABG	Coronary Artery Bypass Grafting
PCI	Percutaneous Coronary Intervention
PRC	Plasma Renin Concentration
SAE	Serious Adverse Event
ITT	Intent-to-Treat
mITT	Modified Intention-to-treat
DMSB	Data Safety Monitoring Board
TAE	Treatment Adverse Event
PPS	Per Protocol Set
SS	Safety Set

PASS 11	Power Analysis and Sample Size Software 11
EH	Essential Hypertension
CVD	Cardiovascular Disease
CKD	Chronic Kidney Disease
MR	Mineralocorticoid Receptor
ARTS	Mineralocorticoid Receptor Antagonist Tolerability Study
HFrEF	Heart Failure with Reduced Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
T2DM	Type 2 Diabetes Mellitus
DKD	Diabetic Kidney Disease
ARTS-DN	Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy
CRF	Case Report Form

1. Introduction

Primary aldosteronism (PA) is one of the most common causes of secondary hypertension. Compared to patients with essential hypertension (EH), patients with PA have a higher risk of cardiovascular disease (CVD) and all-cause mortality[1-2]. Therefore, early treatment is important for PA prognosis. The treatment is different based on PA subtypes. Unilateral PA is recommended to be treated with surgery, while bilateral PA is mainly treated with an oral mineralocorticoid receptor antagonist (MRA)[3].

Spironolactone, a non-selective MRA, has traditionally been used in the management of PA[3]. But its use has been limited by adverse effects such as gynecomastia, mastodynia, and menstrual abnormalities due to a high-binding affinity for progesterone or androgen receptors, and it increases the risk of hyperkalemia in patients with stage 3 or higher chronic kidney disease (CKD) [4-5.]

Finerenone is a novel non-steroidal MRA, with higher selectivity towards the mineralocorticoid receptor (MR) compared to spironolactone and stronger MR-binding affinity than eplerenone. This combination of potency and selectivity towards the MR along with balanced tissue distribution in the heart and kidney compared with spironolactone or eplerenone may lead to more pronounced cardiorenal protection, particularly in high-risk patients with impaired kidney function. The FIDELIO-DKD study indicated that in patients with type 2 diabetes combined with chronic kidney disease, the overall adverse event rate of finerenone treatment was not significantly different compared with placebo (87.3% vs 87.5%, respectively)[6]. Further, the phase 2b ARTS-Diabetic Nephropathy trial confirmed the safety of finerenone in patients with diabetic kidney disease[7.] In addition, the phase 2a Mineralocorticoid Receptor antagonist Tolerability Study (ARTS) trial showed that finerenone had comparable efficacy to spironolactone in patients with HFrEF and mild CKD, with smaller increases in serum potassium level and smaller decreases in estimated glomerular filtration rate (eGFR)[8].

1.1 Rationale

It is well recognized that renal epithelial MRs modulate salt and volume handling and BP regulation by the kidney. MRs may also modulate BP through effects on endothelial and vascular function. Reductions in BP load on the vasculature can protect against target organ damage in patients with CKD associated with T2D. Therefore, the impact of MRAs including finerenone on pathways regulating BP load on the vasculature should be considered.

Previous trials have reported conflicting data about the antihypertensive effects of

finerenone. A study by Filippatos et al demonstrated that finerenone can reduce SBP by 3.31 mmHg in 1530 DKD patients with a history of CVD and 3.11 mmHg in 1303 patients without a history of CVD[9]. Bakris et al included 821 patients with diabetes and high or very high albuminuria, suggesting that the mean differences of SBP between the placebo and 7.5-, 10-, 15-, and 20-mg/d finerenone groups are -2.8mmHg, 0.1mmHg, −5.1mmHg and−4.7mmHg[7]. Agarwal et al included 823 patients with type 2 diabetes and CKD who were randomized into a placebo or finerenone group, they found the 10-, 15-, and 20-mg/d finerenone groups exhibit a change in 24-h SBP of -8.3mmHg, -11.2mmHg and -9.9mmHg, respectively[10]. They also evaluated the antihypertensive effect of finerenone in resistant hypertension of CKD, the results indicate that finerenone is associated with a lower SBP reduction compared with spironolactone[11].

We conducted a randomized pilot study to investigate the antihypertensive efficacy and safety of finerenone versus spironolactone in patients with PA. In this pilot study, a total of 60 patients underwent randomization. The mean change of daytime SBP in the finerenone group was -9.9±13.0 mmHg, which was not significantly different from that in the spironolactone group (-7.8±10.2 mmHg, P=0.49). Changes in daytime DBP (-4.9±7.9 mmHg for finerenone and -5.0±8.4 mmHg for spironolactone, P=0.96), 24-hour SBP (-10.9±12.5 mmHg for finerenone and -7.8±9.5 mmHg for spironolactone, P=0.29),24-hour DBP (-5.9±7.4 mmHg for finerenone and --4.7±6.7 mmHg for spironolactone, P=0.50), office SBP (-17.7±19.7 mmHg for finerenone and -17.1±19.0 mmHg for spironolactone, P=0.90), and office DBP (-9.1±8.3 mmHg for finerenone and -6.8±11.8 mmHg for spironolactone, P=0.40) were similar in the two groups. This study provides information for large-scale clinical studies. Therefore, we are planning a multicenter randomized clinical trial next.

1.2 Risk/Benefit

1.2.1 Potential Risks

Due to MRA's mode of action, hyperkalemia is an important identified risk which is also identified from previous studies. Patients with pre-existing renal impairment are at an increased risk of experiencing clinically significant hyperkalemia. However, considering that many patients with PA also have concurrent hypokalemia, the risk will be reduced. Moreover, Spironolactone is a non-selective MRA that can bind to and inhibit the androgen receptor, leading to potential anti-androgenic adverse effects with long-term use. These adverse effects may include gynecomastia, impotence, menstrual disorders, breast-distending pain, and the risk of hyperkalemia.

In our previous pilot study, we also evaluated the safety of hyperkalemia and renal

function injury. Adverse events were reported in six patients receiving spironolactone (20.7%), including one patient who reported hyperkalemia, compared to none in the finerenone group. No patients in either group discontinued treatment due to adverse events.

Like any antihypertensive therapy, there is a theoretical risk of hypotension from finerenone or spironolactone. If administered, any standard-of-care antihypertensives that may be given during the study as add-on treatments for high blood pressure also contribute to this risk. The onset of action of finerenone and spironolactone is predicted to be gradual and blood pressure will be monitored closely.

1.2.2 Potential Benefits

Finerenone or spironolactone will be administered to patients with PA. Following the administration of a therapeutically effective dose of Finerenone and spironolactone, patients may experience a reduction in blood pressure. This may potentially reduce the risk of target organ damage and cardiovascular events associated with hypertension and high aldosterone levels.

2. Study Objectives

2.1 The Primary Objective

To evaluate the antihypertensive efficacy of finerenone compared to spironolactone in patients with PA after 12 weeks of treatment.

2.2 The Secondary Objective

The secondary objective will include the followings:

1) To evaluate efficacy on hypokalemia of finerenone compared to spironolactone in patients with PA after 12 weeks of treatment.
2) To evaluate efficacy on renin of finerenone compared to spironolactone in patients with PA after 12 weeks of treatment.
3) To evaluate safety of finerenone compared to spironolactone in patients with PA after 12 weeks of treatment.

3 Study Description

3.1 Summary of Study Design

The study is a multicenter, randomized controlled trial. The First Affiliated Hospital of Chongqing Medical University will be the responsible unit, and the Affiliated Hospital of Southwest Medical University, the Third Xiangya Hospital of Central South

University, Fuling People's Hospital of Chongqing, Chongqing Wansheng Economic and Technological Development Zone People's Hospital, the First Affiliated Hospital of Kunming Medical University and Heping Hospital Affiliated to Changzhi Medical College will be the cooperating unit. Patients diagnosed with PA are randomly assigned to receive oral finerenone or spironolactone for 12 weeks, respectively. Blood pressure, renin, blood potassium and other indicators of the patients are observed, and the efficacy and safety of the two groups were compared.

Patients will be instructed to bring their study drug to all clinical site visits. Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to each clinical site visit. All clinical site visits will take place between 7:00 a.m. and 12:00 a.m.

3.2 Study visit

This study will consist of 2 periods:

1. A Screening Period (Screening Visit [Visit 1]) of up to 2 weeks;
2. A Treatment Period (Visits 2 to 7) of 12weeks;

Patients will complete at least 7 total visits over a period of approximately 3 months, including 5 Clinic Visits and 2 Telephone Visits. Additional Unscheduled Visits may occur at any time during the study.

Screening Period (Visit 1, Week -2~0)

Patients will provide informed consent at the Screening Visit (Visit 1) and undergo assessment for Inclusion/Exclusion Criteria. All patients will undergo 24-hour ABPM at the first visit.

Patients with a confirmed diagnosis of PA who are willing to participate in the study are into the Screening Period. PA is defined as having a positive result of screening and confirmatory tests[2,11-14]. Screening positive is defined as plasma aldosterone-to-renin ratio (ARR) ≥ 20(pg/ml)/(μIU/ml) or ARR≥300 pg/ml)/(ng/ml/hr). Plasma aldosterone concentration (PAC) post captopril challenge test (CCT) ≥ 110 pg/ml or PAC post seated saline infusion test (SSIT) ≥ 80 pg/ml is considered positive.

[Note: ARR≥10(pg/ml)/(μIU/ml) or ARR≥150(pg/ml)/(ng/ml/hr) can be considered positive if the patients with hypokalemia (serum potassium < 3.5mmol/L) or adrenal nodules (diameter > 1cm)].

For the screening test and the confirmatory tests, antihypertensive medication is withheld or changed according to the guideline. Treatment with diuretics is withheld

for at least 4 weeks[2,13]. β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor blockers are stopped for at least 2 weeks. Only the non-dihydropyridine calcium channel blocker, terazosin, and doxazosin are allowed for uncontrolled hypertension.

Treatment Period (Visits 2 to 7, Week 0~12)
All patients who remain on a stable regimen of antihypertensive treatment, or who are not taking any antihypertensive medications through the Screening Period will be eligible for randomization. Eligible patients will be contacted via Clinic Visits (Visit 2) to be informed about the study qualification and to schedule their treatment period.
Eligible patients will be randomized 1:1 into 1 of the 2 treatment groups (Finerenone and spironolactone).

Patients will complete at least 5 total visits over a period of approximately 12 weeks, including three Clinic Visits and two Telephone Visits. Clinical Visits (Visit 4 and Visit 5) are conducted on Week 4, Week 8 and Week 12 (the last day of the treatment period), and two Telephone Visits (Visit 3 and Visit 5) are conducted on Week 2 and Week 10. Additional Unscheduled Visits may occur at any time during the study period.

If the office blood pressure remains uncontrolled on Week 4 (ie, systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥90 mmHg), the dose of finerenone and spironolactone will be increased to 40mg per day (the maximum dose). Patients will also be monitored for events of special interest associated with the study medication, including hyperkalemia, hypotension, impotence, gynecomastia and menstrual abnormalities, in these instances, the dose is either maintained or decreased, as determined by the investigator. When the patient's blood pressure is up to standard, if the patient's hypokalemia is not controlled (i.e., the potassium is <3.5mmol on the date of follow-up), the patient will also be increased to 40mg per day.

Study drug (finerenone or spironolactone) dispensing may occur at any time starting at Visit 2 and before Visit 7. On Clinical Visit days, patients will self-administer the morning dose of background antihypertensive medications at home and withhold the study drug. At the clinical site, patients will self-administer the morning dose of study drug under the supervision of site staff after completion of pre-dose evaluations and laboratory sampling. Between clinical site visits, patients will continue taking their study drug once daily by mouth at approximately the same time each morning. The primary efficacy endpoint evaluation will take place at the End of Treatment (Visit 7).

Study visits will follow the Schedule of Procedures (Appendix A).

4 Selection and Withdrawal of Patients

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate:

1) Aged between 18-75, male or female;
2) With confirmed PA diagnosis (screening positive and at least one confirmatory test is positive);

NOTE: *Screening positive is defined as plasma aldosterone-to-renin ratio (ARR)≥ 20(pg/ml)/(μIU/ml) or ARR≥300(pg/ml)/(ng/ml/hr). Plasma aldosterone concentration (PAC) post captopril challenge test (CCT) ≥ 110 pg/ml or PAC post seated saline infusion test (SSIT) ≥ 80 pg/ml is considered positive. [ARR≥10(pg/ml)/(μIU/ml) or ARR≥150(pg/ml)/(ng/ml/hr) can be considered positive if the patients with hypokalemia (serum potassium < 3.5mmol/L) or adrenal nodules (diameter > 1cm)].*

3) Not taking any antihypertensive drugs or on a stable regimen of antihypertensive agents other than MRA for more than four weeks before screening;
4) With a mean seated office SBP ≥ 140 or DBP ≥ 90 mmHg;
5) Able and willing to give informed consent for participation in the clinical study.

4.2 Exclusion Criteria

1) Planning to have subtyping examinations of PA (eg. adrenal vein sampling, PET-CT) within 3 months;
2) Planning to have adrenal surgery or other surgery within 3 months
3) With a mean seated office SBP ≥ 180mmHg or DBP ≥ 110mmHg before randomization;

Note: Mean seated BP is defined as the average of 3 seated BP measurements at any single clinical site visit. If the patient did not take their regularly scheduled antihypertensive medications prior to the visit, 1 BP re-test is allowed within 2 days after taking the medications.

4) Night shift worker;
5) Has a body mass index (BMI) ≥ 30 kg/m^2 at screening;
6) Has uncontrolled diabetes with fasting blood glucose (FBG) ≥13.3mmol/L at screening;
7) Has uncontrolled chronic diseases;
8) Has other known secondary hypertension (eg, renal artery stenosis, Cushing's syndrome, pheochromocytoma, or aortic coarctation);

9) Has known and documented heart failure (New York Heart Association [NYHA] class III or IV), liver transaminase levels are more than twice the upper limit of normal;
10) Has had CABG other major cardiac surgery (eg, valve replacement), peripheral arterial bypass surgery, or PCI within 6 months before screening;
11) Has had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months before screening;
12) Has poor compliance that can not fully participate in the study;
13) Has hyperkalemia with serum potassium > 5.0mmol/L without potassium supplementation;
14) Has a history of uncontrolled malignant tumor;
15) The office blood pressure measurements difference of more than 20mmHg in both arms
16) Unwilling or unable to stop taking sex hormones, glucocorticoids, non-steroidal anti-inflammatory drugs, cyclosporine, tacrolimus, or antidepressants;
17) Is pregnant, breastfeeding, or planning to become pregnant during the study;
18) Complicated with severe mental illness;
19) Has had prior organ transplant;
20) Has a history of allergy to Finerenone or spironolactone;
21) Has typical consumption of ≥ 15 alcoholic drinks weekly;

Note: 1 drink of alcohol is equivalent to 360ml beer, 45ml spirits, or 150ml wine

22) Has participated in another clinical study involving any investigational drug within 30 days prior to screening；
23) Female of childbearing potential refusing to use non-hormonal methods of contraception during the study period;
24) Refuse to get rid of grapefruit or grapefruit juice while receiving finerenone treatment;
25) Other situations that the investigator assesses the subject as unable to complete the trial.

4.3 Withdrawal Criteria

Participation of patients in this clinical study will be discontinued for any of the following reasons:

1) The patient withdraws consent or requests discontinuation from the study for any reason;
2) Hypertensive emergencies[15], i.e., systolic blood pressure ≥180 or diastolic blood

pressure ≥110mmHg, accompanied by target organ damage, should be withdrawn from the study and treated according to medical routine; Patients with the above mentioned poor blood pressure control during treatment, but no discomfort, can wait for blood pressure retest on the second day, if the systolic blood pressure is still ≥180 or diastolic blood pressure ≥110mmHg, then withdraw from the study;

3) The patient used prohibited concomitant medications (refer to 5.5) for more than 1 week, and is still using them 2 weeks before the last visit of the study;

4) The patient has any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;

5) The patient fails to comply with protocol requirements or study-related procedures;

6) The patient becomes pregnant.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, they will be requested to undergo the Early Termination Procedures and site staff should make every effort to complete the full panel of assessments scheduled for the End of Treatment (Visit 7). The reason for patient withdrawal must be documented in the case report form (CRF). Patients should still attend study visits after Early Termination for safety monitoring.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records. Withdrawn patients will not be replaced.

4.4 Early Termination Procedures

The End of Treatment for patients completing the study is Visit 7. For patients who are withdrawn from the study prior to completion, all Visit 6 procedures will be performed at the Early Termination Visit.

4.5 Criteria for Temporary Suspension of Dosing

Dosing of patients in this clinical study will be suspended temporarily for any of the following reasons:

• Any SAE that is deemed related to the study drug;

• Withdrawal of a patient from the study for safety-related reasons;

•Mild to moderate AEs that is deemed related to the study drug and the patients could not tolerate continued treatment

• Potassium ≥5.5 mEq/L; the patient should stop study drug dosing and present to the

clinical site immediately for repeat testing.

5 Study Treatments

5.1 Treatment group

Eligible patients will be randomized in a 1:1 ratio to one of the following groups:

- 20mg finerenone; or
- 20mg spironolactone.

We will double the dose of finerenone or spironolactone (up to a maximum dose of 40 mg/d) every 4 weeks if mean office seated BP remains ≥140/90 mmHg or the hypokalemia is uncontrolled.

5.2 Randomization and Treatment Period

Patients who meet all eligible criteria will be randomized 1:1 into 1 of the 2 treatment groups (finerenone and spironolactone). The dose used in the assigned regimen will be doubled after 4 weeks if, at that time, the patient remains a mean office seated BP of 140 mm Hg or higher (systolic) or 90 mm Hg or higher (diastolic): at week 4, the dose will be doubled from 20 mg once daily to 40 mg once daily (maximum dose) in both finerenone and spironolactone group. The dose will not be increased if the patient has severe TAEs. In these instances, the dose is either maintained or decreased, as determined by the investigator.

5.3 Drug Supplies

After eligible patients randomized into treatment groups, an investigator will dispense the corresponding medication based on the group assignment of the patients.

5.4 Treatment Adherence

At Visits 2 to 7, treatment adherence will be calculated by site staff using pill counts. During the Treatment Period, site staff will collect information from the patient regarding any delays in taking the study drug and missed study drug doses and record them in source files and CRF.

For all protocol-specified doses when the patient is not at the clinical site, patients will self-administer study drug at home and continue taking their background antihypertensive medications. Each patient will be counseled by site staff at every visit on the importance of adhering to their background antihypertensive regimen, study drug, and bringing their medications to each clinical site visit.

5.5 Prior and Concomitant Medications and/or Procedures

5.5.1 Excluded Medications and/or Procedures

- Any antihypertensive medications other than the background treatment in the Screening Period;
- Nonsteroidal Anti-inflammatory Drugs;
- Licorice;
- Strong CYP3A inhibitors (eg. Clarithromycin);
- Strong or moderate CYP3A inducers (eg. Rifampin);
- Glucocorticoid
- Cyclosporine
- Tacrolimus
- Antidepressants
- Estrogenic contraceptives

For CYP3A inhibitors or inducers, see the online reference at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

5.5.2 Documentation of Prior and Concomitant Medication Use

All concomitant medications and concurrent therapies will be documented. Dose, route, unit frequency of administration, indication for administration, and dates of medication administration will also be captured in source documents and on the appropriate CRF.

5.6 Rescue therapy

If poor blood pressure control persists (SBP≥160mmHg or DPB≥100 mmHg) after adjusting spironolactone or finerenone to the maximum dose for 2 to 4 weeks, amlodipine can be treated remedial (5 to 10mg/ day)

5.7 Treatment for Hypokalemia

For patients with low potassium (serum potassium <3.5mmol), potassium supplementation will be given according to the severity of hypokalemia before randomization, and potassium supplementation is stopped 2 weeks after starting MRA treatment, and then the treatment plan is adjusted according to the blood potassium reexamination in V4 (4 weeks after starting MRA treatment): If the serum potassium is <3.5mmol/1, MRA should be supplemented with 20mg qd up to the maximum dose, and the serum potassium should be re-checked 4 weeks later (V5), and the treatment

regimen should be adjusted according to the above principles.

6 Study Procedures

6.1 Informed Consent

Written consent will be obtained from all patients before any protocol-specific procedures are performed.

Information about the study will be given to the patient both verbally and in writing. The written patient information will explain the objectives of the study, potential risks and benefits, and the impact of early withdrawal on the scientific validity of the study. The patient must have adequate time to read the information and to ask the Investigator any questions. The Investigator must ensure that the patient has understood the information provided before written consent is obtained. If there is any doubt as to whether the patient has understood the written or verbal information, the patient must not enter the study.

6.2 Screening Period (Visit 1, Week -2 ~0)

For the screening test and the confirmatory tests, antihypertensive medication is withheld or changed according to the guideline.

The following procedures will be performed at Visit 1:

• Obtain informed consent;
• Assess eligibility based on Inclusion/Exclusion Criteria;
• Perform 24-hour ABPM;
• Record demographics and medical/surgical history;
• Assess and record AEs;
• Record prior medications;
• Measure weight and height;
• Record vital signs;
• Measure seated BP and heart rate;
• ECG;
•Collect urine sample for urinalysis and blood samples for FPG, ALT, AST, creatinine, electrolyte, PAC and PRC,UACR

6.3 Treatment Period

6.3.1 Baseline and Randomization (Visit 2, Day 0)

The following procedures will be performed at Visit 2:

• Check inclusion and exclusion criteria;
• Randomization to finerenone or spironolactone once daily;
• Record pre-dose office seated BP;
• Dispense the study drug;
• Record concomitant medications;
• Record adverse events;
• First administration of study drug;
• Perform the following routine safety evaluations pre-dose;
• Record weight;
• Record vital signs;
• Perform physical examination (general appearance, skin, heart, lungs, and abdomen);

6.3.2 Telephone Call (Visit 3 and Visit 5, Week 2 and Week 10 respectively)

The following procedures will be performed at Visit 3 and Visit 5:

- Assess and record AEs;
- Record concomitant medications;
- Perform adherence counselling;
- Record home seated BP;
- Provide the following instructions for the next visit.

Patients should take their scheduled morning doses of background antihypertensive medications at home on the morning of their next visit; Patients must bring their background antihypertensive medications to the clinical site for their next visit; and Patients should not exercise, smoke, or consume caffeinated beverages or food for at least 2 hours prior to the next visit.

6.3.3 Visit 4, Week 4.

The dose used in the assigned regimen will be doubled after 4 weeks if, at that time, the patient remains a mean office seated BP of 140 mm Hg or higher (systolic) or 90 mm Hg or higher (diastolic): at week 4, the dose will be doubled from 20 mg once daily to 40 mg once daily (maximum dose) in both finerenone and spironolactone group.

The following procedures will be performed at Visit 4:

• Assess and record AEs;
• Record concomitant medications;
• Record office seated BP;
• Assess treatment adherence based on pill counts;
• Perform the following routine safety evaluations pre-dose;
• Record weight;

• Record vital signs;
• Perform physical examination (general appearance, skin, heart, lungs, and abdomen);
• Measure standing BP and heart rate
• Collect blood samples for the following:
    Serum potassium
    Serum creatinine

6.3.4 Visit 5, Week 8.

Same to the Visit 4

6.3.5 End of Treatment (Visit 7, Week 12)

The following procedures will be performed at Visit 6:
• Perform 24-hour ABPM
• Assess and record AEs;
• Record concomitant medications;
• Assess treatment adherence based on pill counts;
• Perform the following routine safety evaluations pre-dose;
• Record weight;
• Record vital signs;
• Perform physical examination (general appearance, skin, heart, lungs, and abdomen);
Measure standing BP and heart rate
• Collect urine sample for urinalysis; and
• Collect blood samples for the following:
    PAC
    PRC
    Serum potassium
    Serum creatinine
    UACR

Study visits will follow the Schedule of Procedures (Appendix A).

7 Efficacy Assessments

7.1 Primary Efficacy Endpoint

The change from baseline in 24-hour systolic blood pressure (SBP) assessed by 24-hour ABPM compared to spironolactone after 12 weeks of finerenone therapy in patients with PA.

7.2 Secondary Efficacy Endpoints

- Change from baseline in 24-hour diastolic blood pressure (DBP) assessed by 24-hour ABPM;
- Blood pressure control rate at the end of the study;

Note: Blood pressure control rate is defined as the percentage of patients with mean seated office BP<140/90 mmHg.

- Change from baseline in daytime SBP assessed by 24-hour ABPM;
- Change from baseline in daytime DBP assessed by 24-hour ABPM;
- Change from baseline in nighttime SBP assessed by 24-hour ABPM;
- Change from baseline in nighttime DBP assessed by 24-hour ABPM;
- Change from baseline in office SBP;
- Change from baseline in office DBP;
- Change from baseline in serum potassium;
- Hypokalemia control rate at the end of the study

Note: Hypokalemia control rate is defined as the percentage of hypokalemic patients with serum potassium>3.5mmol/l at the end of the study.

- Change from baseline in plasma renin.

7.3 Exploratory Endpoints

The exploratory endpoints will include the followings:

- Change from baseline in urinary albumin-to-creatinine ratio (UACR);
- Change in the UACR in patients with baseline UACR more than 30 (mg/g Cr).

8 Safety Assessments

8.1 Safety Endpoints

All safety endpoints will be summarized descriptively.

The safety endpoints will include the following:

- Proportion of subjects with AEs;
- SAEs and AEs leading to discontinuation of treatment with study drug;
- Change in eGFR from baseline.

8.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation that occurs to a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment.

8.2.1 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE according to its potential relationship to study drug using the categories of **YES** or **NO**.

Mild – *Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated.*

Moderate – *Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).*

Severe – *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an AE.*

8.2.2 Causality assessment

The relationship between an AE and the administration of the study drug is to be assessed according to the following definitions:

NO (not related, unlikely to be related) – *The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.*

YES (possibly, probably, or definitely related) – *The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.*

8.2.3 Adverse Events of Special Interest

For this study, AESIs include the following:

- Symptoms of decreased kidney function such as oliguria, swelling, and foamy urine;
- Gynecomastia, impotence, menstrual disorders, and breast-distending pain
- Side effects such as itching and dizziness;

8.3 Serious Adverse Events

An AE is considered serious if, in the view of either the Investigator, it results in any of the following outcomes:

- Death;

- A life-threatening AE;
- Requires hospitalization or prolongation of existing hospitalizations;
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.

8.4 Serious Adverse Event Reporting

All SAEs occurring from the time of informed consent until the end of the study must be reported to investigators within 24 hours of the knowledge of the occurrence. The Investigator must continue following the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

8.5 Management of Potassium Levels

Potassium will be monitored closely throughout this study, with assessments of potassium concentration scheduled at all visits.

For potassium≥5.5 mmol/L, the patient should present to the clinical site immediately for repeat testing, and the study drug dosing need not be stopped. According to the retest results one week later, the investigator will decide whether to continue the medication.. If the potassium is normal, the original dose is given in half, and the retest is conducted one week later.

8.6 Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety Follow-up Period defined in the protocol, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

9 Blood Pressure Measurement

BP will be measured at clinic visits using the following standardized procedures according to American Heart Association statement[15]:

- Seated office BP should be measured with the same validated arm electronic sphygmomanometer by trained clinicians or nurses at any clinical single site visit;
- Patients should not exercise, smoke, or consume caffeinated beverages or food 30 minutes prior to assessment of vital signs and BP measurement;
- Patients should be ensured that they have emptied their bladders;

- Patients should be seated for at least 5 minutes in the examination room with the back supported, feet flat on the floor, and the measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- An appropriately sized cuff should be used with the bladder centered over the brachial artery;
- The arm with the higher mean BP value at Screening should be used for Screening and subsequent BP measurements;
- All BP measurements should be obtained at approximately the same time of day (7:00am- 10:00am)
- Three seated BP measurements (each measurement 1 to 2 minutes apart) should be obtained
- Using the same arm and the Omron HBP-1320 for monitoring blood pressure at each clinical site visit. Mean seated BP is defined as the average of 3 seated BP measurements at any single clinical site visit;
- If the lowest and highest SBP measurements are >15 mmHg apart, additional readings should be performed; and average the last 3 consecutive measurements (measurements 2-4). If the measurements are still >15 mmHg apart, take one additional reading and average the last 3 consecutive measurements (measurements 3-5). If the measurements are still >15 mmHg apart, take one final measurement and average the last 3 consecutive measurements (measurements 4-6).
- Place cuff of 24-h ambulatory blood pressure on bare arm with tubing passing upwards around patient's neck to be connected to the monitor on the waist to avoid the impact of frequent activities.
- The 24-h ambulatory blood pressure is assessed every 15 min during waking hours and every 30 min during sleep. ABPM data will be summarized separately as 24-hour mean, daytime mean and nighttime mean. BP readings at or after 6:00 am and before 10:00 pm are daytime readings. Readings at or after 10:00 pm and before 6:00 am the next day are nighttime readings. ABPM data require a minimum of 20 valid awake and seven valid asleep BP readings, and 70% of the reading should be valid reading, if it is not up to this standard, the ABPM needs to be re-measured. Patients should be instructed to deal with what they are expected to do during a 24-h ABP recording. Patients should keep a diary card, reporting major events occurring during the recording time, and writing down the name, dose, and time of administration of each prescribed drug, the sleeping and awakening times, time of main meals, and also a short description of any unusual activity and of any symptoms that might occur. Patient should be also instructed to follow their usual daily activities, but to remain still and to keep the arm

hanging down along the body each time the cuff starts inflation during the measurements.

- Quality control: Special attention must be placed on assessment and maintenance of the instrument's accuracy as per the manual that accompanies the instrument.

10 Statistics

10.1 Analysis Populations

The following analysis populations are defined for the different types of data analysis:

- Intention-to-treat (ITT) Population

The ITT Population will include all patients randomized into the study. Treatment classification will be based on the randomized treatment;

- Modified intention-to-treat (mITT) Population

The mITT Population will include patients randomized and received at least 1 dose of any study drug. Treatment classification will be based on the randomized treatment. The mITT population will be used for the primary analysis of all efficacy endpoints;

- Per Protocol (PP) Population

The PP Population will include all patients in the mITT population and who did not experience a major protocol deviation that potentially impacted the primary efficacy endpoint. The PP population, along with the reason for exclusion, will be finalized prior to study end.

- Safety Population

The Safety Population will include all patients who receive at least 1 dose of any randomized study drug. Treatment classification will be based on the actual treatment received. The Safety Population will be the primary population used for the safety analyses.

10.2 Efficacy analysis

The primary efficacy analysis will compare the change in 24-hour SBP assessed by ABPM from baseline (Visit 2) to the End of Treatment (Visit 7) between finerenone and spironolactone. Statistical analyses will be primarily descriptive. No formal hypothesis testing will be conducted. Descriptive statistics (eg, mean, standard deviation, median, minimum and maximum) will be presented for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables.

10.3 Safety Analysis

The safety will be assessed from the time of informed consent until the end of the

Follow-up Period. The Safety Population will be the primary population for the safety analysis. All safety endpoints will be summarized descriptively.

10.4 Sample Size

The assumption of this study is that the antihypertensive effect of finerenone is non-inferior to spironolactone. The sample size was based on data from our pilot study to assess the efficacy and safety of finerenone versus spironolactone in PA. According to pilot study, the standard deviation of 24-hour SBP were12.5mmHg in the finerenone group and 9.5mmHg in the spironolactone group respectively. Previous studies on antihypertensive RCT mostly set blood pressure in the range of 2-6 mmHg as the non-inferior limit[17-19], while the European Society of Hypertension pointed out that a difference of less than 5mmHg is clinically acceptable[20]. Therefore, the non-inferior limit is set as 4 mmHg. Using 80% power to measure the antihypertensive effect between the two groups, a unilateral significance level α=0.025, a total sample size of 244, an estimated dropout rate of about 20%, and a final sample size of 244/0.8=306, with a target of 153 patients per group.

11 Data Management and Record Keeping

A Data Safety Monitoring Board (DSMB) will meet periodically to monitor the study. The primary function of this committee is safety monitoring, and the committee will not discontinue the study for a finding of positive efficacy for any of the doses being considered. As part of these reviews, the DSMB will receive summaries of study conduct measures as well as safety and efficacy data. The DSMB may recommend discontinuing enrollment for a dose for safety or lack of efficacy.

The DSMB Chair is an expert in PA who is well-versed in GCP management. The Chair's responsibilities include facilitating discussions, integrating different perspectives, and reaching consensus among the responsible centers. The Chair is also committed to participating in DSMB activities throughout the trial period. The DSMB will hold regular meetings to review the trial's progress and ensure the research's quality. Please see the attachment for the full membership list. The main members include:

Chairman: Yan Ren is an Associate Professor at West China School of Public Health, Sichuan University, Chengdu, Sichuan, People's Republic of China.. Her research focuses on adrenal disorders, particularly primary aldosteronism. She has rich clinical experience in the clinical diagnosis and treatment of adrenal diseases.

Bin Peng is a Professor with a PhD in Epidemiology and Health Statistics. He serves as the Deputy Director of the Department of Statistics at the School of Public Health, Chongqing Medical University. His research and teaching focus on epidemiological methods and health data analysis, contributing significantly to public health research and education.

Weiping Li is an Associate Professor Department of Information Engineering, First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China. He has been engaged in the clinical and basic research of endocrine and metabolic diseases for a long time, and is good at the clinical diagnosis and treatment of diabetes, hypertension, polycystic ovary syndrome, thyroid and adrenal diseases.

12 Data Collection and Handling

12.1 Case Report Form (CRF)

The CRF is completed by the investigator based on the original examination report, medical history collection, and physical examination results. The CRF should be completed timely and ensure that the data entered can be traced from the original record. When modifying data, you need to enter the reason and time for the modification and sign the name. Authorized personnel is required to confirm the authenticity, completeness, and timeliness of the CRF data and to sign it. Paper CRF will be made by the researchers into electronic data for analysis. Before the database is locked, the research team needs to complete the data cleaning and hold a DSMB meeting to determine the analysis population. Decisions made during the DSMB meeting should be documented. After the DSMB meeting is passed, the research team confirms that the research database in the electronic system is locked, and the data cannot be changed after the lock.

12.2 Data Quality Assurance

To ensure the data reliable, the following items are made:

- Guidance materials are provided to research centers;
- Provides training and guidance to researchers and research coordinators. This training will provide relevant research protocols, case report forms (CRF);
- Regular visits to the research centers;
- Receive consultation and contact with research center staff through email, phone, we-chat, etc., to review and verify the accuracy of reported data.

In addition, data will be checked periodically against source files located at the study

center. The investigator will keep all raw data (e.g. laboratory test results, medical records, etc.)

12.3 Data accuracy

Two researchers will independently input the data to generate two sets of databases. Subsequently, data analysis software was used for consistency checks to ensure the consistency of the two sets of databases. If any inconsistencies are found, the data will be corrected by re-examining the original case report form or laboratory report. This method can effectively reduce the possible errors in the process of data entry, and ensure the accuracy and reliability of data.

13 Investigator Requirements and Quality Control

13.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible. The ethics committee of The First Affiliated Hospital of Chongqing Medical University approved the protocol.

13.2 Informed Consent

The ICFs must be in compliance with local regulatory requirements, and legal requirements. The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any protocol-specific activity is performed and should document in the source documentation that consent is obtained prior to enrollment in the study. The original signed copy of the ICF(s) must be maintained by the Investigator. A copy of the signed ICF(s) will be given to the patient.

13.3 Publication policy and use of data

The investigator has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data, results, and all intellectual property rights in the data and results derived from

the study will be the property of the principal investigator(Qifu Li and Shumin Yang) who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the principal investigator before any study data are submitted for publication. The principal investigator reserves the right to deny publication rights until mutual agreement on the content, format, and interpretation of data in the manuscript, and journal selected for publication are achieved.

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Appendix A: schedule of procedures

Visit Week (Period window)	Screening and Randomization		Treatment				
	Visit 1 Week -2~0	Visit 2 Week 0 (+/-0)	Visit 3 Week 2 (+/-5 days)	Visit 4 Week 4 (+/-5 days)	Visit 5 Week 8 (+/-5 days)	Visit 6 Week 10 (+/-5 days)	Visit 7 Week 12 (+/-5 days)
In- and exclusion criteria	√	√					
Informed consent	√						
Randomization		√					
Office blood pressure and heart rate	√	√		√	√		√
Home blood pressure			√			√	
Ambulatory blood pressure	√						√
Medical history/Prior medication	√	√	√	√	√	√	√
AE assessment and Pregnancy	√	√	√	√	√	√	√
ECG	√			√	√		√
Laboratory examination							
ARR	√			√	√		√
Blood routine	√						
Urine routine	√						
Liver function	√						
Renal function	√			√	√		√
Potassium	√			√	√		√
UACR	√						√
Study drug dispense	√			√	√		√
Compliance assess	√	√	√	√	√	√	√
Guidance adherence	√	√	√	√	√	√	√
Provide instructions for next visit		√	√	√	√	√	