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A 24-week, Multi-center, Randomized, Open-Label Clinical Trial to Compare the Impact of Xuezhikang and Atorvastatin on Glucose Metabolism in Dyslipidemia Patients with Prediabetes (XTREME Study)

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Sponsor：Ruyang Rural Health Institute(RRHI)

STUDY PROTOCOL SUMMARY

Study Title	A 24-week, Multi-center, Randomized, Open-Label Clinical Trial to Compare the Impact of Xuezhikang and Atorvastatin on Glucose Metabolism in Dyslipidemia Patients with Prediabetes
Objectives	**Primary objective** To determine whether XZK 1200mg/d, compared to atorvastatin 20mg/d, has a favorable impact on HbA1c levels from baseline to 24 weeks in dyslipidemia patients with prediabetes. **Secondary objective** （1） To evaluate the impact of XZK 1200mg/d on fasting plasma glucose (FPG), post prandial glucose (PPG) 2h and insulin production index levels compared with atorvastatin 20mg/d after 24 weeks of treatment in dyslipidemia patients with prediabetes. （2）To evaluate change in LDL-C levels after 24 weekds of treatment with XZK 1200mg/d as assessed by percentage change from baseline.
Study design	This study is a prospective, randomized, open-label, multi-center trial. The primary objective of the study is to assess whether XZK 1200mg/d, compared to atorvastatin 20mg/d, has a favorable impact on HbA1c levels at 24 weeks of treatment in dyslipidemia patients with prediabetes
Treatment / Interventions	Experimental group: Xuezhikang Capsule, 1200mg / day, twice a day, 2 capsules each time, after meals in the morning and evening. Control group: Atorvastatin Calcium Tablets, 20mg/day, once a day, one tablet each time, before bedtime; Continuous treatment for 24 weeks.
Investigational product	Experimental drug: Xuezhikang Capsule, specification: 300mg / capsule.

	Control drug: Atorvastatin Calcium Tablets, specification: 20mg / tablet.
Study Centre	This study will include approximately 20 sites in China
Number of subjects planned	392 subjects
Planed Study period	Estimated date of the first subject enrolled Jul 2022 Estimated date of the last subject completed Jul 2023
Inclusion Criteria	(1) Written informed consent provided (2) Age ≥40 years (3) Diagnosed Prediabetes, meeting one of the following conditions: ✓ Impaired fasting glucose (IFG): 5.6 mmol/L ≤ FPG <7.0 mmol/L ; ✓ Impaired glucose tolerance (IGT): 7.8mmol/L ≤ 2h PPG during 75g OGTT <11.0 mmol/L; ✓ HbA1c 5.7-6.4% (39-47 mmol/mol) (4) Dyslipidemia meets one of the following conditions: ✓ Fasting LDL-C ≥3.4mmol/L and＜4.9mmol/L，and TG≤5.6 mmol/L ✓ Fasting non-HDL-C ≥4.1mmol/L and < 5.7 mmol/L, and TG≤5.6 mmol/L (5) Completed one-week Patient diary, recorded at least 5 days in a week.
Exclusion criteria	(1) Patient with proven or documented atherosclerotic cardiovascular disease (ASCVD), including acute coronary syndrome (ACS), history of myocardial infarction (MI), stable or unstable angina pectoris, coronary or other revascularization, ischemic stroke, transient ischemic attack and peripheral vascular disease (PAD), etc. (2) Diagnosed diabetes According to 2021 the American Diabetes Association (ADA) “Standards of

Medical Care in Diabetes"

- ✓ FPG ≥126 mg/dL (7.0 mmol/L).
- ✓ 2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT.
- ✓ A1C ≥6.5% (48 mmol/mol).
- ✓ In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

(3) Patients with any lipid lowering drugs in the previous 3 months, including but not limited to statins, bile acid sequestrants, cholesterol absorption inhibitors, PCSK9 inhibitors, nicotinic acid, fibric acid derivatives, fibrates, other traditional Chinese medicine and n-3 fatty acids.

(4) Patients with any antidiabetic drugs.

(5) Contraindications to XZK or Atorvastatin:

- ✓ Allergic to XZK or Atorvastatin.
- ✓ Pregnancy or breastfeeding

(6) Uncontrolled hypertension (systolic blood pressure ≥180 mm Hg and/ or diastolic blood pressure ≥110 mm Hg) at screening.

(7) Active liver disease or hepatic dysfunction, including continuously elevated liver transaminase due to unknown causes. Abnormal liver function test at baseline (ALT or AST >3×ULN).

(8) Known renal dysfunction or elevated serum creatinine levels at baseline (with an eGFR≤60 mL/min/1.73 m^2).

(9) Other endocrine diseases that might influence the levels of lipid or lipoprotein, such as hypothyroidism.

(10) Patient has participated in clinical trials of other drugs in the past three months.

(11) Previous statin treatment causes creatine kinase (CK) increased 10 times, or myalgia myopathy (muscle pain or muscle weakness, accompanied by

	Creatine phosphokinase (CK) exceeds 10 times the ULN) (12)Estimated life expectancy < 6 months at the time of enrollment (13)Abuse of alcohol, or history of alcohol abuse. (14)Close affiliation with the investigators, e.g., a close relative for the investigator, dependent person (e.g., employee or student of the investigators)
Visit plan	5 visits: including enrollment period, baseline period, 4 weeks, 12 weeks and 24 weeks after randomization
Statistical Analyses	Analyses will be performed by SAS 9.4 statistical software. Descriptive statistics will be calculated, including n, means, standard deviations, medians, and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables. Percentage will be calculated based on non-missing data unless otherwise specified. Data will be examined for skewness, outliers. Transformations will be undertaken as needed. Missing data will be assumed missing completely at random. In general, no imputation will be applied unless otherwise specified.The primary and secondary endpoint will be analyzed using covariance(ANCOVA) model with treatment (XZK, atorvastatin) use the baseline HbA1c as the covariate.
Data collection	Case report form (CRF)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
AKI	Acute kidney injury
BUN	Blood urea nitrogen
CCC	Clinical Coordination Center
CCSPS	China coronary secondary prevention study
CHD	Coronary heart disease
CK	Creatine kinase
CRF	Case report form
CRO	Contract Research Organization
DILI	Drug-Induced Liver Injury
DKI	drug-induced kidney injury
ECG	Electrocardiograph
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
ITT	Intention-To-Treat
LDL-C	Low density lipoprotein cholesterol

MI	Myocardial infarction
OGTT	Oral glucose tolerance test
PPG	Post prandial glucose
PG	Prandial glucose
non-HDL-C	Non high density lipoprotein cholesterol
SAE	Serious adverse events
SCR	Serum creatinine
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin
TC	Total cholesterol
TG	Triglyceride
UADR	Unexpected adverse drug reaction
ULN	Upper Limit of Normal
XZK	Xuezhikang

1 INTRODUCTION

1.1 Background

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and accounts for 41% of all cause death in China[1]. Management of dyslipidemia is the main strategy to reduce the risk of ASCVD. To lower lipids, statins should be the first-line treatment in clinical practice. However, patients on statin treatment have been shown to exhibit an increased risk of dys-glycaemia and development of type 2 diabetes mellitus (T2DM)[2]. Dyslipidemia and diabetes mellitus are major risk factors of ASCVD, and the prevalence has been reached 40.4%[3] and 10.9%[4] among Chinese adults. China has the largest number of diabetes mellitus with 109.6 million Chinese adults suffering from the disease[5]. Genetic susceptibility may play an important role as Asians have a 60% increased risk of diabetes compared with Caucasians after adjusting for age, sex, and BMI[6]. Therefore, the management of patients with dyslipidemia in Prediabetes poses a challenging dilemma that requires balancing the benefit of reducing serum cholesterol against the risk of dys-glycaemia and development of T2DM, especially for Chinese even Asians.

Xuezhikang (XZK), a traditional Chinese medicine that contains natural lovastatin and multiple components for hyperlipidemia treatment, may have a lower risk of incident diabetes compared with the statin cohort. However, limited information was available to demonstrate XZK does not adversely affect glucose metabolism or incident diabetes. Therefore, we hypothesize that XZK 1200mg/d, compared to atorvastatin 20mg/d, has a favorable impact on the HbA1c levels in dyslipidemia patients with Prediabetes .

The Xtreme study is a 24-week, multi-center, randomized, open-label clinical trial that will compare the impact of XZK and Atorvastatin on glucose metabolism in dyslipidemia patients with Prediabetes. Prediabetes, including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or A1C 5.7–6.4% . Recruitment will occur at approximately 20 centers, where 392 adult participants in Prediabetes with dyslipidemia will be randomly assigned to receive XZK 1200mg/d or Atorvastatin 20mg/d. Randomized participants will be followed to a common study period.

1.2 Rationale for study design

Up to now, there is no published RCTs to compare the impact of XZK and statins on glucose metabolism in Prediabetes with dyslipidemia. However, systematic reviews of several large observational studies have recently

found statin treatment is associated with a modest increase in HbA1c in patients with T2DM. In these patients, the mean difference of HbA1c increased by 0.17% (95% CI 0.07, 0.27) compared with the blanking control group[7]. For instance, Atorvastatin 20mg is widely used medium intensity statin in clinical practice, but a cohort study based on a database of Korea populations reported that the use of low dose Atorvastatin 10-20mg tended to be a risk factor for onset diabetes (NODM) in Asians[8]. Meanwhile, a small RCT reported that HbA1c level was increased from 6.1% to 6.5% after Atorvastatin 20mg/d treatment for 2 months[9]. The long-term administration of statins might increase the risk of NODM approximately 10%-12%[10]. In short, a diabetogenic role of statins has been demonstrated both from randomized trials and meta-analyses, and risk factors include high dose, prolonged exposure, old age, prediabetic state and metabolic syndrome[11, 12]. In consideration of prediabetes, including IFG, IGT, or A1C 5.7–6.4%, will be further increased the risk of development diabetes mellitus, and the prevalence was 35.7% in China, we choose the patients in Prediabetes with dyslipidemia in our study[4].

XZK, a partially purified red yeast rice (RYR) under controlled pharmaceutical manufacturing conditions, contains a family of naturally occurring statins (monacolins)-most prominently monacolin K, which is identical to the lipid-lowering therapy lovastatin (Mevacor)[13]. In a meta-analysis, after compared the XZK treatment group showed significant lowering LDL-C effect compared with basic therapy groups. [14] Xuezhikang in the China Coronary Secondary Prevention Study trial(CCSPS) has shown that XZK significantly reduced the levels of TC, TG and LDL-C and increased that of HDL-C in patients with hyperlipidemia after 1200mg/d treatment for 8 weeks, among which TC decreased by 23.0%[15]. Furthermore, a retrospective cohort study that used Taiwan's National Health Insurance data on 34,504 persons with a RYR prescription in 2010-2014, found that a lower risk of incident diabetes when compared to lovastatin cohort (HR:0.46, 95% CI 0.43-0.50)[16]. Why XZK can lower the risk of incident diabetes compared to other statins? A variety of mechanisms have been elucidated. As main components in XZK, n-3 polyunsaturated fatty acid（PUFAs） can regulate the activity of key transcription factors to regulate gene expression in lipid metabolism and improve insulin sensitivity of type 2 diabetes mellitus to prevent diabetic complications. Six weeks of supplementation with n-3 PUFAs reduced the postprandial decrease in macrovascular function and meanwhile improved postprandial microvascular function[17]. Moreover, it was reported that magnesium deficiency can lead to the reduction of insulin sensitivity and affect the stability of glucose metabolism. Thus, increasing the intake of magnesium plays an important role in the prevention of noninsulin-dependent diabetes mellitus and its complications. Moreover, selenium reduces the production of oxygen free radicals in the body by glutathione peroxidase to prevent further oxidative damage in the body and the insulin A, B between the two peptide chains for ensuring the complete molecule structure and function of insulin to play a role

in lowering blood glucose. In addition, selenium also has inhibitory effects on complications of diabetes such as osteoporosis and retinopathy.

In addition, XZK has been proved to contain multiple active ingredients which leads to unique MOA and multiple benefits[13]. It is composed of 13 kinds of natural statins, unsaturated fatty acids, ergosterol, amino acids, flavonoids, alkaloid, trace elements, and other substances, and thus could be regarded as a natural lipid lowering polypill[14]. All the above-mentioned components might be involved in the mechanism of XZK to multiple benefits such as antiatherosclerosis, liver protection, anticancer, neural regulation and protection, and kidney protection effects[13]. Previous animal and cell experiments have shown that XZK can also activate the PPARα pathway and up-regulate apolipoprotein A5 (apolipoprotein A5 is the key regulator of TG metabolism) to achieve higher TG reduction when it reduces LDL-C by the same extent as simvastatin[18]. It is speculated that non-statin elements within XZK may play a synergistic role in regulating blood lipids and inhibiting the synthesis of triglycerides. The China Coronary Secondary Prevention Study (CCSPS) and other clinical studies confirmed that XZK capsules reduce lipid and significantly reduce the overall mortality of patients with coronary heart disease, the incidence of cardiovascular events. According to Chinese guidelines for the management of dyslipidemia in adults of 2016 revision, XZK amongst other statins are recommended for the first-line treatment of cholesterol controlling. Meanwhile, XZK 1200mg/d and Atorvastatin 20mg/d are medium intensity statins recommended in guideline[3]. therefore, we choose Atorvastatin 20mg/d as control drug in our research.

Physicians faced with a dyslipidemia patient with prediabetes often use statins therapy due to perceived efficacy. However, XZK is a promising option in this patient group due to their significantly lower risk of dys-glycaemia without compromising efficacy for lowering lipids in hyperlipidemia. Establishing comparable recurrent NODM rates in individuals with previous Prediabetes state would result in superior DM prevention for these patients.

1.3 Benefit/risk and ethical assessment

Benefit:

Evidence showed that XZK treatment by reducing LDL-C levels and TG levels significantly reduces the risk of CHD events by 45%. Therefore, for the clinical benefit of dyslipidemia patients with prediabetes , they will get expert advice and guidance of lipid management from physicians.

Potential risk:

Risk associated with Study Drug：

XZK capsule is a modernized proprietary Chinese medicine product with modern pharmaceutical technology and strict Good management practices (GMP)production management. A few mild or moderate gastrointestinal (GI) effects may occur when taking XZK, but a large number of clinical application results show that XZK capsule is safe and with few side effects [1].

Atorvastatin decrease cholesterol production in the liver by preventing the conversion of HMG-CoA to mevalonate. Common side effects to Atorvastatin include gastrointestinal (GI) effects, headache, and mild muscle pain. Rare side effect include rhabdomyolysis, dark urine, jaundice, etc.

Participants with high potential risk (meet one of the Exclusion Criteria) will not be eligible for enrollment . Moreover, we will minimize this risk by mandating adequate follow-up visit to ensure clinical assessment(e.g.CK and liver enzymes (ALT, AST)) during study participation . Local Investigator and the sponsor will also collect and report serious adverse events according to regulations. The study drug will be discontinued immediately, if any ADR occurs during the study.

Risk associated with Study Procedure：

In view of the few patients with prediabetes receive drug treatment and Statins are the most effective and acceptable drugs to treat dyslipidemia, patients may be initially hesitant to participant in this study. Previous studies have reported that XZK is effective in blood lipid reduction. We will provide the patients with pre-study education on dyslipidemia medication therapy.

Loss to follow up is another risk factor which can affect the incident rate in statistical analysis and outcome. However, this study is designed for 24 weeks short intervention and contains 5 visits with the assistance of local investigators and experienced CRO team. Therefore, we are confident to limit the loss to follow up rate.

1.4 Study Design

1.4.1Overall design

Xtreme study is a prospective, randomized, open-label, multi-center trial. The primary objective of the study is To determine whether XZK 1200mg/d, compared to atorvastatin 20mg/d, has a favorable impact on HbA1c levels from baseline to 24 weeks in dyslipidemia patients with prediabetes.

1.4.2. Randomization

Randomization of participants that meet all inclusion criteria and do not have any exclusion criteria will be randomly allocated in a 1:1 ratio to XZK group (xuezhikang [1200mg/d]) or ATV group (atorvastatin [20mg/d]) stratified by center and age(≥60 years old, <60 years old) Randomization will be done using a central, automated, web-based electronic randomization software. Randomization will occur within 3 days after the Laboratory result of randomization visit reported .

1.4.3. Minimizing Sources of Bias

Because treatment will be open-label, blindly tested of outcomes will be conducted by adjudicators who are unaware of treatment allocation.

1.4.4 Number of Centers

This study will include approximately 20 sites in China.

1.4.5 Number of Participants

There will be approximately 392 subjects randomized in this study. Justification for the sample size can be found in 8.1Sample size estimate.

1.4.6 Estimated Study Duration

Enrollment period will last from July 2022 to July 2023.

1.4.7 Study Duration for Participants

After signing the informed consent, subjects should be randomized within 7 days.

The follow-up duration of study participants will be 24 weeks after randomization.

1.4.8 End of Study

A subject is considered to have completed the study if he/she has completed all phases of the study including the last subject's last Follow-up or Early Discontinuation Visit.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of Xtreme is:

To determine whether XZK 1200mg/d, compared to atorvastatin 20mg/d, has a favorable impact on HbA1c levels from baseline to 24 weeks in dyslipidemia patients with prediabetes

2.2 Secondary Objective

Secondary objectives include:

（1） To evaluate the impact of XZK 1200mg/d on fasting plasma glucose (FPG), post prandial glucose (PPG) 2h and insulin production index levels compared with atorvastatin 20mg/d after 24 weeks of treatment in dyslipidemia patients with prediabetes.

（2）To evaluate change in LDL-C levels and non HDL-C after 24 weeks of treatment with XZK 1200mg/d as assessed by percentage change from baseline.

2.3 Safety

According to the routine procedure, adverse events, abnormal physical examination and abnormal laboratory data (ALT, CK, etc.) will be observed after randomization

3 STUDY POPULATION

Multiple strategies will be used to identify potentially eligible participants for this study. Only subjects that meet all of the inclusion criteria and none of the exclusion criteria listed below will be randomized into the study.

The Investigators are expected to maintain a patient log (Appendix I) of all potential study candidates that include limited information about the potential candidate (eg, date of screening). Before any study-specific procedure, the appropriate written informed consent must be obtained.

3.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Written informed consent provided
2. Age ≥40 years

(5) Diagnosed Prediabetes, meeting one of the following conditions:

- ✓ Impaired fasting glucose (IFG): 5.6 mmol/L ≤ FPG <7.0 mmol/L ;
- ✓ Impaired glucose tolerance (IGT): 7.8mmol/L ≤ 2h PPG during 75g OGTT <11.0 mmol/L;
- ✓ HbA1c 5.7-6.4% (39-47 mmol/mol)

3. Dyslipidemia meets one of the following conditions:

- ✓ Fasting LDL-C ≥3.4mmol/L and＜4.9mmol/L，and TG≤5.6 mmol/L
- ✓ Fasting non-HDL-C ≥4.1mmol/L and < 5.7 mmol/L , and TG≤5.6 mmol/L

4. Completed one-week Patient diary, recorded at least 5 days in a week.

3.2 Exclusion Criteria

1. Patient with proven or documented atherosclerotic cardiovascular disease (ASCVD) including Acute coronary syndrome (ACS), history of myocardial infarction (MI), stable or unstable angina pectoris, coronary or other revascularization, ischemic stroke, transient ischemic attack and peripheral vascular disease (PAD),etc.
2. Diagnosed diabetes

   According to 2021 the American Diabetes Association (ADA) "Standards of Medical Care in Diabetes"

   - ✓ FPG ⩾126 mg/dL (7.0 mmol/L).
   - ✓ 2-h PG ⩾200 mg/dL (11.1 mmol/L) during OGTT.
   - ✓ A1C ⩾6.5% (48 mmol/mol).
   - ✓ In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ⩾ 200 mg/dL (11.1 mmol/L).
3. Patients with any lipid lowering drugs in the previous 3 months, including but not limited to statins, bile acid sequestrants, cholesterol absorption inhibitors, PCSK9 inhibitors, nicotinic acid, fibric acid derivatives, fibrates, other traditional Chinese medicine and n-3 fatty acids.
4. Patients with any antidiabetic drugs.
5. Contraindications to XZK or Atorvastatin:
   - ✓ Allergic to XZK or Atorvastatin.
   - ✓ Pregnancy or breastfeeding
6. Uncontrolled hypertension (systolic blood pressure ⩾180 mm Hg and/ or diastolic blood pressure ⩾110 mm Hg) at screening.
7. Active liver disease or hepatic dysfunction, including continuously elevated liver transaminase due to unknown causes. Abnormal liver function test at baseline (ALT or AST >3×ULN).
8. Known renal dysfunction or elevated serum creatinine levels at baseline (with an eGFR⩽60 mL/min/1.73 m2).
9. Other endocrine diseases that might influence the levels of lipid or lipoprotein, such as hypothyroidism.
10. Patient has participated in clinical trials of other drugs in the past three months.

11. Previous statin treatment causes creatine kinase (CK) increased 10 times, or myalgia myopathy (muscle pain or muscle weakness, accompanied by Creatine phosphokinase (CK) exceeds 10 times the ULN)
12. Estimated life expectancy < 6 months at the time of enrollment
13. Abuse of alcohol, or history of alcohol abuse.
14. Close affiliation with the investigators, e.g., a close relative for the investigator, dependent person (e.g., employee or student of the investigators)

3.3 Subject enrolment and randomization

3.3.1 Number of Centers

This study will include approximately 20 sites in China.

3.3.2 Number of Participants

There will be approximately 392 subjects randomized in this study. Justification for the sample size can be found in 8.1 Sample Size estimate.

3.3.3 Randomization

Participants will be randomized using Interavtive Web Response System(IWRS), which is an online, central randomisation service. Allocation concealment will be ensured, as the service will not release the randomization code until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed.

All patients who give consent for participation and who fulfill the eligibility criteria will be randomized. Randomization will be requested by the investigator. In return, IWRS will send an answer form to the investigator who is not involved in assessing outcome of the study. The investigator will find the treatment condition to be conducted in this patient. The therapist then gives the information about treatment allocation to the patient. Staff responsible for outcome adjudication is not allowed to receive information about the group allocation.

The assessor regarding clinical outcomes will go through a profound assessment training program. The laboratory assessments will be marked by subject ID and performed by blinded. Randomization will occur within 3 days after the Laboratory result of randomization visit reported .

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the inclusion/meet exclusion criteria should not, under any circumstances, be enrolled or received study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must be withdrawn from the study. This has to be documented.

3.5 Methods for assigning treatment groups

The research center number must be marked before subject ID with two digitals. Subject ID will be consecutively numbered by the enrollment order. If a subject withdraws from the study during the study, the subject ID can no longer be used, and the withdrawn subject can no longer participate in the study.

3.6 study restriction

During the course of this study, any lipid-lowering medication other than the study drugs , antidiabetic agents, herbal medication, and weight-losing drugs are prohibited. All other drugs should be maintained as a stable dosage if possible.

3.7. Discontinuation of Study Drug

3.7.1. Permanent Discontinuation of Study Drug

For all participants who permanently discontinue study medication, the participants will still be part of the study, and outcome events and vital status must be reported until the common study end date. Discontinuing an investigational drug is usually the only available therapy to treat suspected Drug-Induced Liver Injury (DILI) , drug-induced kidney injury(DKI),and may not result in an immediate improvement as test values and symptoms can last (sometimes even progress) for days or weeks after the drug has been discontinued. Once discontinued, patients should not be re-exposed

to the suspected drug.

The study drugs should be discontinued in case

1) Meeting the criteria of possible Drug-Induced Liver Injury(FDA guidance)

- ALT or AST >8 ULN
- ALT or AST >5 ULN for more than 2 weeks
- ALT or AST >3 ULN and (TBL >2 ULN or INR >1.5)
- ALT or AST >3 ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

2) Diagnosis of rhabdomyolysis

● The clinical manifestations of rhabdomyolysis include myalgias, weakness, red to brown urine due to myoglobinuria, and elevated serum muscle enzymes. An acute elevation in the CK and other muscle enzymes and a decline in these values within three to five days of cessation of muscle injury. the CK is typically at least five times the upper limit of normal and is frequently greater than 5000 international units/L. The degree of myalgias and other symptoms varies widely, and some patients are asymptomatic. Fever, malaise, tachycardia, and gastrointestinal symptoms may be present.

●Other manifestations include fluid and electrolyte abnormalities, many of which precede or occur in the absence of acute kidney injury, and hepatic injury. Hypovolemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and metabolic acidoses may be seen. Hyperkalemia may result in cardiac dysrhythmias. Later complications include acute kidney injury (AKI), hypercalcemia, compartment syndrome, and, rarely, disseminated intravascular coagulation.

3) Pregnancy；

4) The investigator considers that study drug is harmful to the safety or health of the participants;

5)Participants request to stop using the test drug;

6) Sponsor requires participants to permanently stop taking study drug

3.7.2. Temporary Discontinuation of Study Drug

Adherence to the study drug will be evaluated and reinforced at every study visit. Participants who temporarily discontinued study drug should be re-challenged when applicable. Study drug should only be withdrawn if a clinically important adverse event related to the study medication occurs or the participant develops a contraindication.

The following conditions may lead to Temporary Discontinuation of Study Drug:

1）Predefined security thresholds are met (abnormal laboratory test findings , see detail in Section 3.7.1)

2）In case of AE/SAE or other causes, the investigator should consider temporarily discontinuing the drug

If the safety threshold is reached and the drug is temporarily discontinued, treatment will resume after approximately 2-4 weeks and be restarted at a lower dose

If the study drug is discontinued due to AE/SAE and there are no safety concerns any more (i.e., no causality in medical judgment； other transient symptoms) the investigator should try his/her best efforts to resume the clinical drug trail .

Other causes are defined as events that lead to study drug discontinuation and are not considered an AE/SAE, such as elective hospitalization without emergencies.

All temporary discontinuations should be recorded in the eCRF.

3.7.3. Rechallenge

If a study drug is stopped due to concomitant illness or other considerations, every attempt will be made to restart it, whenever possible.， Generally, rechallenge of subjects with significant AT elevations (>5xULN) should not be attempted..To maximize the adherence to the assigned therapy, any participant who decides to withdraw will initially be asked to attend follow-up visits, and at a later time to consider going back on his or her allocated therapy. Regardless of whether or not a participant has discontinued study drug every attempt will be made to ensure that he/she attends all follow-up visits and that all events are reported.

3.8. Participant Discontinuation from the study treatment

An excessive rate of participant discontinuations from either treatment or “drop-outs” from the study may render the trial non-interpretable. In this study, HbA1C data are crucial to the primary analysis and must be collected until the end of the study, even if participants are no longer taking study medication. Therefore, all efforts will be taken to

motivate participants to comply with all study procedures and to continue to be followed until the end of the trial.

Participants should be specifically asked about any possible AE or other reasons that led to their decision to withdraw from the study, and all AE information obtained should be recorded. Participants may withdraw their informed consent orally or in writing, and they are advised to withdraw informed consent in writing

The investigator and participant must discuss and determine further follow-up options. Options for follow-up are listed below, in descending order of preference:

1. Participant continues the regular study clinic visits at the investigator's site as outlined in

the protocol.

2. Participant will be contacted by phone at the regular follow-up intervals.

3. Participant allows his/her general practitioner or a family relative to be contacted at the regular follow-up interval.

4. Participant will be contacted once at the end of the study.

5. Participant withdraws consent. This will be the last option and means that the participant does not agree to any kind of follow-up and specifically refuses any further contact with the investigator. This should happen only in exceptional cases. If possible by local regulations, this decision will be provided in writing. Vital status will be obtained at study end through public information according to local guidelines and as allowed by local regulations. For participants who do not agree to attend regular study visits, the investigator will encourage the participant to return to the clinic for at least one final visit in order to perform all assessments as outlined for the end of Study(EOS) visit.

3.9 Lost to Follow up

We define loss to follow-up as incomplete ascertainment of the primary outcome for participants randomized in the trial.

All attempts will be made to find all participants.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

• The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel

the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

• Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

• If all attempts fail, depending on local legislation, death or other registries may be accessed or private investigation to locate a participant may be initiated.

• All randomly enrolled cases, no matter whether they fall off or not, should be recorded and retained, which can be kept as a file. It can also be used as the original record of Intention-To-Treat (ITT) analysis data.

4 STUDY PLAN AND TIMING OF PROCEDURES

4.1 Study Plan

Table 1 Study plan

		Screening	Randomisation	Treatment Phase		
Visits		**Visit** 0	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Timelines(week)		**-1**	**0**	**4**	**12**	**24**
Treatment Days		**7 +3**	**0**	**29 ±7**	**85 ±7**	**169 ±7**
Informed Consent signed		×				
Eligibility criteria		×	×			
General information	**Demographics**		×			
	Medical History		×			
	Physical examination		×	×	×	×

Medications	Concomitant medications		×	×	×	×
Clinical assessment	Serum lipids (TG/non HDL-C/TC/LDL-C)		×	×	×	×
	HbA1c		×		×	×
	Plasma Glucose (PG), insulin, C-peptide levels at fasting and 2 h after drinking glucose solution(75g glucose)		×	×	×	×
	Hepatic function (Bilirubin, albumin, liver enzymes)		×	×		×
	Creatine kinase (CK)		×	×		×
	Renal function (Serum creatinine, BUN ,eGFR)		×	×		×
	Routine blood test		×			×
	Pregnancy test (HCG test for women of childbearing potential only)		×			
	ECG		×			×
	Adverse events		×	×	×	×
Questionairre	IPAQ		×	×	×	×
Other work	Distributing study drugs		×	×	×	
	Patient medication guidance		×	×	×	
	Patient lifestyle guidance	×	×	×	×	×
	Patient diary dispendance	×	×	×	×	×
	Drug accountability log cards		×	×	×	×
	Retrieving drugs			×	×	×

4.2 Study procedure

This study consisted 2 periods: Screening and Open-label treatment

4.2.1 Screening period (Visit 0):

1. Informed Consent signed : participants should be fully notified before signing informed consent form. Investigator should also sign the informed consent form, copy of informed consent will give patient

2.Patient diary: Patients with eligible laboratory test results will record their daily diet, physical activity, and concomitant medication on the patient diary for one week. The patient records the regime 5 days per week, will be defined as good patient compliance and candidate subject.

4.2.2 Randomization and treatment period (Visit1-Visit4)

Subjects won't be able to eat or drink anything for eight hours before visit 1, visit 2, visit 3 and visit 4.
Visit 1（Randomization）

1.Before randomization, the investigator should complete the following actions and collect the relevant data:

- Collect general information:

  Demographics data: gender, date of birth, education, insurance
- Retrieving and reviewing the Patient Diary
- Collect the information of clinical assessment such as Serum lipids (TG/non HDL-C/TC/LDL-C), HbA1c , Plasma Glucose (PG), PPG, insulin and C-peptide at fasting and 2h after glucose solution（75g glucose） . Hepatic function (Bilirubin, albumin, liver enzymes), Creatine kinase (CK), Renal function (Serum creatinine, BUN ,eGFR), Routine blood test, Pregnancy test (HCG test for women of childbearing potential only),and ECG. According to the results of the above tests, screen the patients again.
- Eligibility criteria: To verify the participants satisfy all the inclusion criteria and without any exclusion criteria.

2. Randomization.

3. Medical history: Including previous medical history, treatment before screening and other comorbidities.

4. Physical examination: blood pressure, pulse rate, weight, height.

5. Collect the information of Concomitant medications.

6. Collect the information of history of adverse events with statins.

7. Collect physical activity information: Physical activity level by for Measurement of a Person's Habitual Physical Activity (IPAQ)

8. Patients should be guided for medication.

9. Distribute study drugs by groups, patients should start the treatment after the day of randomization

Visit 2（4 weeks after treatment phase）

1. Collect the information of Concomitant medications.

2. Collect the information of adverse events. If any AE is reported, relevant laboratory test should be collected.

3. Collect the information of clinical assessment such as Serum lipids (TG/non HDL-C/TC/LDL-C),Plasma Glucose (PG), PPG, insulin and C-peptide at fasting and 2h after drinking glucose solution（75g glucose）. Hepatic function (Bilirubin, albumin, liver enzymes), Creatine kinase (CK), Renal function (Serum creatinine, BUN ,eGFR).

4. Collect physical activity information: Physical activity level by for Measurement of a Person's Habitual Physical Activity (IPAQ)

5. Patients should be guided for medication and lifestyle

6. Review of the patient’s diary, compliance to study medication

7. Distribute study drugs by groups.

8. Retrieving drugs and log cards

Visit 3（12 weeks after randomization）

1. Collect the information of Concomitant medications.

2. Collect the information of adverse events. If any AE is reported, relevant laboratory test should be collected.

3. Collect the information of clinical assessment such as Serum lipids (TG/non HDL-C/TC/LDL-C), HbA1c, Plasma Glucose (PG), insulin and C-peptide at fasting and 2 h after drinking glucose solution（75g glucose）.

4. Collect physical activity information: Physical activity level by for Measurement of a Person's Habitual Physical Activity (IPAQ)

5. Patients should be guided for medication and lifestyle

6. Review of the patient’s diary, compliance to study medication

7. Distribute study drugs by groups.

8. Retrieving drugs and log cards

Visit 4（24 weeks after randomization）

1. Collect the information of Concomitant medications.

2. Collect the information of adverse events. If any AE is reported, relevant laboratory test should be collected.

3. Collect the information of clinical assessment such as Serum lipids (TG/non HDL-C/TC/LDL-C), HbA1c , Plasma Glucose (PG), PPG, insulin and C-peptide at fasting and 2h after glucose solution（75g glucose）,Hepatic

function (Bilirubin, albumin, liver enzymes), Creatine kinase (CK), Renal function(Serum creatinine, BUN ,eGFR), Routine blood test, and ECG.

4. Collect physical activity information: Physical activity level by for Measurement of a Person's Habitual Physical Activity (IPAQ)

5. Patients should be guided for medication and lifestyle

6. Review of the patient’s diary, compliance to study medication

7. Retrieving drugs and log cards

4.3 lifestyle modification

Throughout the study, investigators should emphasis the importance of adequate supportive care, such as diet, weight maintenance and physical activity. As guideline recommended, each participant should consume a dietary pattern that emphasizes intake of vegetables, fruits, whole grains, legumes, healthy protein sources(low-fat diary products, low-fat poultry (without the skin), fish/seafood, and nuts), and non tropical vegetable oils; and limits intake of sweets, sugar-sweetened beverages, and red meats. This dietary pattern should be adjusted to appropriate calorie requirements, personal and cultural food preferences, and nutritional therapy for other medical conditions including diabetes. Caloric intake should be adjusted to avoid weight gain, or in overweight/obese patients, to promote weight loss. In general, adults should be advised to engage in aerobic physical activity 3-4 sessions per week, lasting on average 40 minutes per session and involving moderate-to vigorous-intensity physical activity.

4.4 Patient diary

Patient diary will be used to evaluate subject compliance. Patient diary has to be completed by the subject every day in the last one week before the study visit. The diary includes date, dose of medication, time of dosage, daily diet, daily physical activity . (Appendix II)

5 STUDY ASSESSMENTS

5.1 Efficacy Assessments

5.1.1 Primary endpoint

The change value of HbA1c levels from baseline to 24 Weeks or before antidiabetic therapy initiation within 24 weeks.

5.1.2 Secondary endpoints

The change value of FBG, PPG 2h and HOMA-IR from baseline to 24 Weeks or before antidiabetic therapy initiation within 24 weeks.

The percentage change of LDL-C levels from baseline to 24 Weeks or before antidiabetic therapy initiation within 24 weeks.

The percentage change of non HDL-C levels from baseline to 24 Weeks or before antidiabetic therapy initiation within 24 weeks.

The change value of HbA1c levels from baseline to 12 Weeks or before antidiabetic therapy initiation within 12 weeks.

The change value of FBG, PPG 2h and HOMA-IR from baseline to 12 Weeks or before antidiabetic therapy initiation within 12 weeks.

The percentage change of LDL-C levels from baseline to 12 weeks or before antidiabetic therapy initiation within 12 weeks.

The percentage change of non HDL-C levels from baseline to 24 Weeks or before antidiabetic therapy initiation within 12 weeks.

5.2 Safety Assessments

5.2.1 Clinical Assessment

Baseline clinical and demographic characteristics will be measured at study enrollment. Variables of interest will include gender, age, weight, height, waistline, medical history, family history, smoking status, alcohol intake.

Physical examination:

Blood pressure, heart rate and ECG are measures of various physiological statistics, in order to assess the most basic body functions. Vital signs are also an essential part of a case when the subjects appear SAEs. The act of taking vital signs normally entails recording pulse rate (or heart rate) and blood pressure , but may also include other measurements.

New onset medical conditions:

ASCVD, hypertension, cancer, etc.

5.2.2 Laboratory assessments:

Blood samples for determination of clinical chemistry and urinalysis will be taken at the times indicated in the Study Plan and Time Schedule (see table 1).

The following laboratory efficacy variables will be measured:

Serum lipids (TG/non HDL-C/TC/LDL-C),HbA1c (%), Plasma Glucose (PG), insulin, C-peptide levels at fasting and 2 h after drinking glucose solution(75g glucose)

The following laboratory safety variables will be measured:

Hepatic function (Bilirubin, albumin, liver enzymes), Creatine kinase (CK), Renal function (Serum creatinine, BUN ,eGFR), Routine blood test, Pregnancy test (HCG test for women of childbearing potential only)

Notes：Male eGFR= 170x(Scr)-1.234x(Age)-0.179

Female eGFR= 170x(Scr)-1.234x(Age)-0.179x0.79

6 SAFETY

6.1 Definition of adverse events and adverse drug reaction

Adverse Events (AE), Adverse drug reaction (ADR), and unexpected adverse drug reaction (UADR) events are all considered as AEs.

6.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject’s medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates the pre-existing medical condition has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study, and involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

Overdose should also be considered as an AE.

6.1.2 Adverse Drug Reaction

An ADR is a response to a drug which is noxious and unintended and which occurs at doses normally used for the diagnosis, therapy or treatment of disease or for modification of physiological function. As opposed to an adverse event, is characterized by the fact that a causal relationship between the product and the occurrence is suspected.

An unexpected adverse drug reaction (UADR) is an ADR, the nature or severity of which is not consistent with the applicable product information

6.2 Serious adverse event

An AE is considered a serious AE (SAE) if it fulfills one or more of the following criteria:

- Results in death
- Is life-threatening
- Requires or prolongs hospitalization
- Is a congenital anomaly or birth defect
- Is a persistent or significant disability/incapacity
- Is another important medical event in the opinion of the investigator

The requirement or extension of hospitalization is not considered a SAE if it fulfills one or more of the criteria(see Appendix 2):

SAEs or non-serious AEs that are not study outcomes and are not expected as part of normal treatment and progression of the disease or expected with the treatment with Xuezhikang and atorvastatin, must be reported. All SAEs, all non-serious AEs leading to permanent discontinuation of study-drug treatment and non-serious AEs which the investigator considers of particular concern will be recorded on the Adverse Event Report form.

6.3 Adverse events requiring additional data collection

Adverse events requiring additional data collection are events which, in the evaluation of safety, have a special focus (e.g. required by the health authorities). The AEs requiring additional data collection are:

- Drug-Induced Liver Injury:

  ALT or AST >8 ULN

  ALT or AST >5 ULN for more than 2 weeks

  ALT or AST >3 ULN and (TBL >2 ULN or INR >1.5)

  ALT or AST >3 ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Rhabdomyolysis
- ASCVD
- Cerebrovascular event (stroke or TIA)
- Heart failure requiring hospitalization
- Pancreatitis
- Renal event
- Hypersensitivity reactions
- Acute gallstone disease
- Medication error (concerning trial products):

  Administration of wrong drug.

  Note: Use of wrong DUN is not considered a medication error.

- Wrong route of administration.

  Administration of an overdose with the intention to cause harm (e.g. suicide attempt).

- Accidental administration of a higher dose than intended. A higher dose is a dose of at least one tablet/capsule more than the intended dose; however the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

6.4 Collecting and Reporting Serious Adverse Events

6.4.1 Collection period

AE assessment will be conducted from the informed consent signed to the entire study.

6.4.2 Reporting Serious Adverse Events

SAEs should be reported to sponsor within 24h of learning of their occurrence.

The investigator is responsible for continuing to follow all SAE reports (whether related to study drug) until resolution or until the event is considered chronic and/or stable by the investigator and/or other physician who has the responsibility for the patient's medical care. Follow-up SAE reports will be reported according to the same timelines as initial reports, as soon as new significant information becomes available.

If any SAE occurs in patients who took Xuezhikang, investigators or other site personnel should also inform the Sponsor, whether considered causally related to the Xuezhikang.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately.

In keeping with regulatory guidance, outcome events and expected SAEs are not subject to expedited regulatory reporting will be reported in aggregate. Suspected Unexpected Serious Adverse Reactions [SUSARs] will undergo expedited reporting to relevant regulatory authorities (e.g., research ethics committees, National Medical Products Administration, and National Health Commission of the People's Republic of China). Investigators must report all SUSARs to sponsor as soon as possible and 24h of learning of the event. These SUSARs will be centrally reviewed and reported by the sponsor as soon as possible:

- For fatal or life-threatening SUSARs, sponsor must report as soon as possible and within 7 days of learning of the events. Active follow-up must be completed within the following 8 days (The first day of learning of the event is considered 0 day).

- For fatal or life-threatening SUSARs, sponsor must report as soon as possible and within 15 days of learning of the events.

  Send SAE reports to_Luye Pharma Group Co., Ltd_, via Email:__Beijing@luye.com__;

6.4.3 Reporting of non-serious ADR

Any non-serious ADR occurs in the course of the study must be reported per the China regulation.

If any non-serious ADR occurs in the course of the study, then investigators or other site personnel should inform Luye **within 7 calendar days** when he or she becomes aware of it.

All collected adverse events will be summarised in the final study report.

Send ADR reports to_Luye Pharma Group Co., Ltd_, via Email:__Beijing@luye.com__;

6.5 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

6.6 Overdose

There are no specific antidotes to xuezhikang and atorvastatin; Current experience with drug overuse is limited; a few cases of simvastatin overdose have been reported. In all conditions, there are no sequelae. Monitoring of CK and liver enzymes (ALT, AST) is recommended. Appropriate clinical testing and general supportive treatment should be given.

6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to _Luye Pharma Group Co., Ltd_, via Email:__Beijing@luye.com_.

6.7.1 Maternal exposure

If a subject becomes pregnant during the study, the investigational product should be discontinued immediately.

6.7.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and 4 weeks following the last dose of the investigational drug.

6.8 Adverse events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.9 Adverse events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated including laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s). Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Investigational product

	Investigational product	**Dosage form and strength**	**Manufacturer**
Experimental drug	Xuezhikang Capsule	300mg capsule	WBL Peking University Biotech Co
Control drug	Atorvastatin Calcium Tablets	20mg tablet	Pfizer Inc

7.2 Dose and treatment regimens

Experimental group: Xuezhikang Capsule, 1200mg / day, twice a day, 2 capsules each time, after meals in the morning and evening;

Control group: Atorvastatin Calcium Tablets, 20mg/day， once a day, one tablet each time, before bedtime;

Patients should start the treatment after the day of randomization, and Continuous treatment for 24 weeks.

7.3 Labelling

The packaging label of each drug will include at least the following information: name of Sponsor, Investigational product/study drug dosage form, route of administration, and quantity of dosage units, study code, medication instructions, expiration date, "for clinical trial use only", batch number, storage conditions, and " keep out of reach of children ".

7.4 Storage

Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

7.5 Compliance

Participants in both arms will self-administer the study the study drug at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets and patient diary during the site visits and documented in the source documents and CRF.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the subject.

Study site personnel, if applicable, or the monitor will account for all received study drugs and return all unused study drugs to sponsor.

Certificates of delivery and return should be signed.

7.7 Concomitant and other treatments

7.7.1 Prohibited combination treatment

Any drug that may affect glucose metabolism, such as metformin , steroids, etc.

7.7.2 Permitted combination treatment

In addition to the drugs listed above, other drugs are permitted to combine therapy, and the Investigators determine whether it is necessary to give patients a stable dose of combination treatment if possible.

Any treatment performed during the study should be recorded in the CRF.

8 STATISTICAL ANALYSES

8.1 Sample size estimate

The primary endpoint of the study is the change value of HbA1c levels from baseline to 24 Weeks or before antidiabetic therapy initiation within 24 weeks.

We assume that the HbA1c level doesn't change in XZK group, and an increase of HbA1c level by 0.3% in atorvastatin 20mg group based on findings from Koh K et al. The SD of change of HbA1c level is 1.0% for both treatment.

The sample size of each group of 176 will provide 80% power at a 5% significance level. Considering 10% drop out rate, the total sample size is 392.

8.2 General consideration

Analyses will be performed by SAS 9.4 statistical software. Descriptive statistics will be calculated, including n, means, standard deviations, medians, and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables. Percentage will be calculated based on non-missing data unless otherwise specified. Data will be examined for skewness, outliers. Transformations will be undertaken as needed.

Missing data will be assumed missing at random or missing completely at random. In general, no imputation will be applied unless otherwise specified.

8.3 Definitions of analysis sets

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP (investigational product) and have a non-missing HbA1c value at week 24. This analysis set will be used in both efficacy and safety analyses.

The Completer Analysis Set (CAS) includes subjects in FAS who completed IP and have a non-missing HbA1c value at week 24.

In all analysis sets, unless specified otherwise, subjects will be analyzed according to the ITT principle.

8.4 Efficacy analysis

8.4.1 The primary endpoints

The change value of HbA1c levels from baseline to 24 Weeks or before antidiabetic therapy initiation within 24 weeks will be analyzed using covariance(ANCOVA) model use the treatment group(XZK, atorvastatin) as the group and the baseline HbA1c as the covariate. The results will be presented as least squares means (lsmeans) with 95% confidence intervals and p-values. Model assumptions will be explored and, if necessary, appropriate transformations or non-parametric analysis techniques will be used. The primary analysis set for this analysis is the full analysis set (FAS).

8.4.2 Secondary endpoints

For each secondary endpoint, an ANCOVA model will be used that is similar to the one described for the primary analysis above.

8.4.3 Safety Endpoints Analyses

Adverse events are coded by using standard terminology. Subject incidences of treatment-emergent adverse events, serious adverse events, treatment-related adverse events and adverse events leading to discontinuation will be tabulated by system organ class and preferred term for each treatment group.

Subgroup analysis of AE tables by the stratification factor, gender, and age will be performed.

8.5 Subgroup analyses

In addition to the analysis described above, a set of analyses will be reported to explore whether intervention effects on the primary and secondary outcomes are consistent across subgroups of interest. These subgroups are:

a) male vs. female,

b) senior vs. non-senior (aged ≥60 at randomization vs. aged <60),

c) BMI ≥ 28kg/m2 vs. BMI < 28kg/m2

For each subgroup analysis, an ANCOVA model will be used that is similar to the one described for the primary analysis above, but with additional terms identifying subgroup membership and the intervention by subgroup interaction. We will report the Hommel adjusted p-values for the interaction effects.

9 STUDY AND DATA MANAGEMENT

9.1 Site selection

Sites that do not enroll subjects within 3 months of site initiation may be closed.

9.2 Training of study site personnel

The Principal Investigator should have the professional expertise, qualifications and abilities of clinical trials, and the staff should be relatively fixed after qualification.

The investigational staff should be uniformly trained to enable researchers to fully understand the specific connotation of the clinical trial protocols and their indicators.

9.3 Monitoring of the study

9.3.1 Source data

Source data include medical record, laboratory test report and instrumental examination report. Source documents storage refers to the Clinical Study Agreement for location of source data.

9.3.2 Research Agreement

The principal investigator at each center must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this study agreement shall prevail.

9.3.3 Archiving of study documents

The monitoring will identify the following:
Ensure each patient enrolled in the study has a complete folder;
Ensure informed consent of participating subjects is recorded in the folder and the process of informed consent is correct;
During the monitoring visit, the research process should be discussed with the researcher to confirm that all the procedures and operations in the protocol are performed as required;
Ensure that data are being accurately and timely recorded in the CRFs, and study drug accountability checks are being performed;

9.3.4 Deviation from the clinical study protocol

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol must be notified to or approved by each IEC or IRB
If a protocol amendment requires a change to a particular center's Written Informed Consent Form, then principal investigator and the center's IEC or IRB must be notified. Approval of the revised Written Informed Consent Form by the IEC or IRB is required before the revised form is used.
Sponsor will distribute amendments and new versions of the protocol to investigators, who in turn is responsible for the distribution of these documents to his or her IEC or IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

9.4 Study timetable and end of study

The study is expected to start in November 2021 and to end by Jul 2024.

First Subject Inclusion (FSI): July 2022

Last Subject Inclusion (LSI): July 2023

Last Subject Last Visit (LSLV): Jan 2024

Clinical study report: July 2024

9.5 Data management

9.5.1 Data from Clinical Sites

Participant Randomization: this study will use an internet-based, web browser randomization procedure. Clinical Sites access the randomization application through the study web site. Access to this application is password protected and its communications are encrypted. Once security requirements are satisfied, a series of questions identify and verify the eligibility of the participant prior to allowing randomization of the participant.

Participant Tracking: The Participant Tracking System (PTS) is a fully integrated tracking and notification system that advises clinic staff about participant follow-up windows, and projects clinic and laboratory workload for a week at a time (longer if necessary). Tracking a participant begins at screening and continues automatically throughout the project by integrating participant follow-up data with predetermined follow-up "windows". When a participant is enrolled into the study, a schedule of target dates for each of the visits is automatically generated. The report details the recommended "windows" that each visit should fall into and a case file is created for the participant.

Data Entry: The images on the data entry screens mirror the data collection forms for ease and accuracy of entry. Typically, as participant visits are completed, and hard copy forms are filled out, the clinic coordinator reviews each form for accuracy and completeness, including laboratory reports and any supporting documentation (hospital records, etc.). Once any data problems have been resolved, data are entered by clinic staff into the computer via the web-based browser application. During data entry, a variety of programmed edit checks are performed for key variables. When the edit checks fail, data may be flagged for further review or prevented from becoming part of the study database. Also, a sample of key forms may be double-keyed for additional quality control.

9.5.2 Central Database Edits

At regular intervals, data queries will be carried out on the computerized databases at the sites to perform consistency checks on key variables and forms, as a quality control check.

9.5.3 Feedback to Clinical Sites

Data edit reports will be generated to help ensure that data are entered in timely and complete manner. These reports will include both the assessment for each Clinical Site of the time between data collection and entry, and the report of

generation of missing items. These reports will be provided to the Clinical Sites, and study committees on a regular basis so that data collection items that are troublesome can be identified and Clinical Sites not meeting study standards can be notified.

9.5.4 Confidentiality

The confidentiality of all participant information must be protected at the Clinical Sites, and the CCC. Paper records and computer files must be appropriately safeguarded from unauthorized access.

Paper and/or electronic records for study participants will be stored at the Clinical Sites. Copies of records identified by participant identification number pertaining to SAEs and study-defined clinical events, including necessary medical records, will be stored at the sites. These records will receive the same care as would ordinary medical records. They will be stored in locked filing cabinets and/or filing rooms within secure office space or, if uploaded through the study website, they are stored in a non-url accessible area that can be accessed only through the website. Only study personnel who have completed training in data handling will have access to study forms.

Similar care will be used in the handling of the computer records of study data stored at each Clinical Site. Access to the data in any local database will be controlled by a system of user identification names and passwords. Each Clinical Site staff member must complete the data handling training program before being given an ID and password to use the data system. The privileges allowed to each ID can be individually specified by the local CCN Coordinator. All passwords stored within the system will be encrypted using SSL encryption.

10 REGULATORY，ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from Declaration of Helsinki and are consistent Chinese clinical trial research management norms and regulations.
- Applicable International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) Guidelines

10.2 Ethics and regulatory review

- The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to IRB/IEC and other applicable regulations

10.3 Informed Consent Process

The Principal Investigator(s) at each centre must explain to the human subject the following clinical trial matters in detail:

- Participation by the human subject is voluntary. The human subject has the right to withdraw from the trial at any time during any phase and shall not be subject to discrimination or retaliation. The human subject's medical treatment and rights and interests shall not be affected;
- The human subject shall be informed that his participation and personal trial data are confidential;
- The human subject shall be informed of the nature, purpose of the trial, the predicted possible benefits and risks that the human subject may suffer, and different groups in the trial in which the human subject may be placed, Other treatment options and subjects' rights and obligations in accordance with the declaration of Helsinki, the subjects must be given sufficient time to consider whether they are willing to participate in the trial, each subject should provide signed and dated informed consent before conducting the study
- The original, signed Informed Consent Form(s) will be stored in the Investigator's Study File

10.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities

The researchers will closely preserve information of the subject until it is eventually destroyed and will not continue to use or disclose it during this period. However, in some rare circumstances, researchers will continue to use or disclose information about subjects, even if the subjects have withdrawn from the study or the study has been completed. Including the following circumstances: removing the subject's information will affect the scientific nature of the study or the evaluation of data security; providing limited information for research, teaching or other activities (information does not include names, id card numbers, or other personal information that identifies them); and when government regulators need to monitor the study, they will require to see all the research information, including information about the subject's participation in the study.

10.5 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF;
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.6 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

10.7 Audit and inspection

- To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.
- In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.
- The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

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Appendix 1 Patient log

Patient name	Sex	Age	Screening Date	Dyslipidemia	Prediabetes	Exclusion Cretria	Screening outcome:	Date of Patient Diary feedback	Patient diary compliance	randomized ?	If Randomized, provide Subject ID
				Y/N	Y/N	Y/N	①recruited ②declined		Good/Poor/NA	Y/N	

Appendix 2 Patient diary

Diary drug usage
Please record your daily drug usage. If you take the drug as prescribed, drawn '√' in the box. If the drug dosage changes temporarily, please record the relevant dosage in the box.

Date of record: _____/____/____ - _____/____/____

Drug name	Time	Dosage	D1	D2	D3	D4	D5	D6	D7
Investigation product									
PI choose the investigation product，dwarn "√" in the box.									
□Xuezhikang	Morning	2 capsules							
	Evening	2 capsules							
□Atorvastatin	Evening	1 tablet							
Concomitant medications									
Please record other daily concomitant medication									
Drug name :	Morning								
	Noon								
	Evening								
Drug name :	Morning								
	Noon								
	Evening								
Drug name :	Morning								
	Noon								
	Evening								
Drug name :	Morning								
	Noon								
	Evening								
Drug name :	Morning								

	Noon								
	Evening								
Drug name :	Morning								
	Noon								
	Evening								
Drug name :	Morning								
	Noon								
	Evening								
Drug name :	Morning								
	Noon								
	Evening								
Drug name :	Morning								
	Noon								
	Evening								

Exercise Diary Log					
Date of record： __ __ __ __/__ __ /__ __ - __ __ __ __/__ __/__ __					
D1					
Morning		Afternoon		Evening	
Activity category	Activity duration（eg. 0.5h）	Activity category	Activity duration	Activity category	Activity duration
D2					
Morning		Afternoon		Evening	
Activity category	Activity duration	Activity category	Activity duration	Activity category	Activity duration
D3					
Morning		Afternoon		Evening	
Activity category	Activity duration	Activity category	Activity duration	Activity category	Activity duration
D4					
Morning		Afternoon		Evening	
Activity category	Activity duration	Activity category	Activity duration	Activity category	Activity duration
D5					
Morning		Afternoon		Evening	
Activity category	Activity duration	Activity category	Activity duration	Activity category	Activity duration
D6					

Morning		Afternoon		Evening	
Activity category	Activity duration	Activity category	Activity duration	Activity category	Activity duration
D7					
Morning		Afternoon		Evening	
Activity category	Activity duration	Activity category	Activity duration	Activity category	Activity duration

Diet Diary Log						
Date of record： __ __ __ __/__ __ /__ __ - __ __ __ __/__ __/__ __						
			breakfast	Lunch	Dinner	Snacks：
Carbohydrates	eg. Rice, steamed bun, steamed twisted roll, steamed stuffed bun, dumplings, pancake,corn, noodle, porridge, potato	Unit of weights can be measured in ge, bowl, ge, etc.				eg：melon seeds, peanuts, chips, etc.
Meat	eg. Pork, beef, lamb, chicken, duck, sausage, preserved ham	Unit of weights can be measured in jin, bowl, liang, etc.				
Seafood	eg. fish, shrimp, crab,etc	Unit of weights can be measured in tiao, ge, zhi, etc				
Vegetable	Tomato, cabbage, broccoli	Unit of weights can be measured in jin, plate, ge, etc.				

Fruit	eg. Apple, pear, grapes	Unit of weights can be measured in jin, plate, ge, etc.				
Dairy products	eg.yogurt, cheese	Unit of weights can be measured in bottle, jin, ge, etc.				
Beans or soy product	eg. tofu	Unit of weights can be measured in bowl, jin, etc.				
Eggs	eg. eggs, duck eggs	Unit of weights can be measured in ge.				
Sugar sweetened drinks	Coke, soda water, coffee, tea beverages	Unit of weights can be measured in bottle, bowl, jin, etc.				

Protein drinks	eg. Milk, soy milk	Unit of weights can be measured in milliliter, etc.				

Appendix 3 Serious Adverse Event Report (SAE)

Approval Number of the new drug clinical research： No.：

<table>
<tr><td colspan="2">The Report Type</td><td colspan="3">□The First-time Report
□The Follow-up Report
□The Summary Report</td><td>Report Date：</td></tr>
<tr><td colspan="2">Name of Medical Institution and Profession</td><td colspan="3"></td><td>Tel:</td></tr>
<tr><td colspan="2">Name of the Application Unit</td><td colspan="3"></td><td>Tel:</td></tr>
<tr><td colspan="2">Name of the Experimental Drug</td><td colspan="4">Chinese Name: English Name:</td></tr>
<tr><td colspan="2">Drugs Registry Classification and Dosage Form</td><td colspan="4">□Chinese Medicine □Chemical Medicine □ Biological Products For Treatment □Biological Products for Prophylaxis □Other: _____
RegistryClassification: _____ DosageForm: _____</td></tr>
<tr><td colspan="2">Classification of the clinical Research</td><td colspan="3">□Stage Ⅰ □Stage Ⅱ □Stage Ⅲ □Stage Ⅳ
□Bioequivalence test
□Clinical verification</td><td>Indications of the Clinical Research:
_____</td></tr>
<tr><td rowspan="2">Information of the Subjects</td><td>Name Initials(Pinyin):</td><td>Date of Birth:</td><td>Sex: □M □F</td><td>Height(cm)：</td><td>Weight(Kg)：</td></tr>
<tr><td colspan="5">Any comorbidities with treatment：□Yes □No
1. Disease：_____Drug Treatment：_____Dosage and Usage：_____
2. Disease：_____ Drug Treatment：_____ Dosage and Usage：_____
3. Disease：_____ Drug Treatment：_____ Dosage and Usage：_____</td></tr>
<tr><td colspan="2">Medical terms of the SAE(Diagnosis)</td><td colspan="4"></td></tr>
<tr><td colspan="2">Outcome of the SAE</td><td colspan="4">□Death Date: _____
□hospitalization-initial or prolonged □disability □incapacity
□congenital anomaly □life-threatening □Other</td></tr>
<tr><td colspan="3">Occurrence Date of the SAE: _____</td><td colspan="3">When do the Researcher find out the SAE:
_____</td></tr>
<tr><td colspan="2">Corresponding Steps to SAE</td><td colspan="4">□no action required □reduce dose □restore after symptoms pause □terminate or suspend the drug research</td></tr>
<tr><td colspan="2">Return of SAE</td><td colspan="4">□Disappearance of Symptoms（Sequelae □Yes □No）
□Persistence of Symptoms</td></tr>
</table>

Relationship of SAE to Research	□definite (clearly related to the research) □probable (likely related to the research) □unlikely (doubtfully related to the research) □unrelated (clearly not related to the research) □Unable to judge
Reported cased of similar SAE	Domestic: □Yes □No □Unknown Foreign: □Yes □No □Unknown
Detailed Description of the occurrence and treatment of the SAE:	

Report Institution: Position Title of the Reporter: Reporter's Signature:

Exclusions of Serious Adverse Event (SAE)

The requirement or extention of hospitalization is not considered a SAE if it fulfills one or more of the following criteria:

- Rehabilitation institutions, hospice care institutions, short-stay hospital admission of patients, care institutions, nursing homes, routine emergency admissions, same-day surgery (such as outpatient/ambulatory surgery).
- Hospitalization is not related to emergencies, or prolongation hospitalization is not related with a serious adverse event (e.g., admission to the hospital due to pre-existing disease, no exacerbation of the existing disease).
- Hospitalizations is associated with social factors (e.g., homeless patients).
- Hospitalizations is related to health management reasons (e.g., annual routine physical examinations).
- Hospitalizations required in clinical trials.
- Elective hospitalization without emergencies (e.g., elective cosmetic surgery), scheduled treatment or surgery should be recorded in the baseline.
- Invasive or non-invasive procedures that is diagnostic (or therapeutic), such as surgery, should not be reported as adverse events. However, if the disease condition that requires the surgery meets the definition of an adverse event, it should be reported (e.g., acute appendicitis that occurred during the reporting period of the adverse event should be reported as an adverse event, and the appendectomy performed accordingly should be recorded as the treatment method for the adverse event).