Informed Consent Form

Proposal name： Effect of Canagliflozin on cardiac microcirculation function in patients with type 2 diabetes mellitus complicated with cardiovascular risk factors

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Introduction

We are doing research on effect of canagliflozin on cardiac microcirculation function in patients with type 2 diabetes mellitus (T2D) and at high risks of cardiovascular disease in Fudan Zhongshan hospital. We are going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.

Purpose of the research

T2D can cause macrovascular and microvascular complications. Numerous clinical trials have suggested that sodium-glucose cotransporter 2 (SGLT2) inhibitors could reduce risks of adverse cardiovascular events in patients with or without T2D. The reason we are doing this research is to find out if the drug canagliflozin, one of SGLT2 inhibitors could improve the cardiac microcirculation function in patients with type 2 diabetes mellitus (T2D) complicated with cardiovascular risk factors.

Type of Research Intervention

If you agree to participate in this study, please sign this informed consent form. The research will last 28-30 weeks and involve in five follow-up visits to the clinic.

Participant selection

We are inviting all adults with T2D complicated with cardiovascular risk factors in Fudan Zhongshan hospital to participate in the research on the effects of of canagliflozin on cardiac microcirculation function.

- *Do you know why we are asking you to take part in this study? Do you know what the study is about?*

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to

participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will offered the treatment that is routinely offered in this hospital for disease T2D, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.

- *If you decide not to take part in this research study, do you know what your options are? Do you know that you do not have to take part in this research study, if you do not wish to? Do you have any questions?*

Information on the Trial Drug

The drug we are testing in this research is called canagliflozin, one of SGLT2 inhibitors. The beneficial effects of SGLT2 inhibitors on cardiovascular events and cardiac structures and functions have been proven, however, little is known about the effects of SGLT2 inhibitors on cardiac microcirculation function. We now want to test the drug on patients with T2D and at high risks of cardiovascular diseases. This research is called a "phase 4" trial.

The drug canagliflozin is made by Company Xian-Janssen Pharmaceutical Ltd. You should know that it has a few side effects. For example, it can cause hypotension Hypotension, urinary and reproductive system infections, acute kidney injury, ketoacidosis, lower limb amputation, etc. Lower limb infections, gangrene, and diabetic foot ulcers are common causes of amputation. Patients with a history of amputation, peripheral vascular disease, and neuropathy have an increased risk of amputation.

Some participants in the research will not be given the drug which we are testing. Instead, they will be given the drug Sitagliptin, the drug which is most commonly used in this region to treat T2D. It may cause pancreatitis, vascular edema, peeling skin damage and other hypersensitive reactions, etc.

Procedures and Protocol

Because we do not know if the canagliflozin drug is better than the Sitagliptin drug for improve cardiac microcirculation function, we need to compare the two. To do this, we will put people taking part in this research into two groups. The groups are selected

by chance, as if by tossing a coin.

Participants in one group will be given the test drug canagliflozin, while participants in the other group will be given the drug Sitagliptin, and all of them will remain on metformin stable therapy. Considering the large differences in appearance and characters of the two drugs, both of us will know which drug you will take. We will then compare which of the two has the best results.

The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the drug is doing, we will find out which drug you are getting and make changes. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers.

We will take blood from your arm using a syringe and needle. For the first and last visit, we will take about 20 ml blood (show vial container with a small amount of water in it), and for the three follow-up visits, well will take about 10 ml blood. Each time visit, we will also take about 5 ml urine. At the end of the research, in 1.5 years, any left blood or urine sample the first and last visit will be reserved for five years and then will be totally destroyed.

Procedures and Protocol

During the research you make five visits to the clinic.

- In the first visit, a small amount of blood, equal to about a vial, will be taken from your arm with a syringe. About 5 ml urine will also be taken from you. This blood and urine will used for routine and biochemical tests. We will also ask you a few questions about your general health and measure how tall you are and how much you weigh. Moreover, we will provide you with cardiac magnetic resonance examination free of charge.
- At the next visit, which will be two to four weeks later, you will again be asked some questions about your health and then you will be given either the test drug

canagliflozin or the drug Sitagliptin.

- During the 26 weeks of intervention, you will be followed up for four times after four weeks, eight weeks, 13 weeks, and 26 weeks. At each visit time, you will come back to the clinic for a blood test and take physical examination. Moreover, at the last visit (26 weeks), we will provide you with cardiac magnetic resonance examination free of charge one more time.

Duration

The research takes place over 28 to 30 weeks in total. During that time, it will be necessary for you to come to the hospital 5 days , for four hours each day. We would like to meet with you three months after your last clinic visit for a final check-up.

In total, you will be asked to come 5 times to the clinic in 6 months. At the end of six months, the research will be finished

- *Can you tell me if you remember the number of times that we are asking you to come to the hospital to complete the treatment? The research project? How many injections will you be given? How many tablets? How much blood will be taken from your veins, using a syringe and needle? Over how many weeks? Etc. Do you have any other questions? Do you want me to go through the procedures again?*

Side Effects

As already mentioned, this drug can have some unwanted effects. it can cause hypotension Hypotension, urinary and reproductive system infections, acute kidney injury, ketoacidosis, lower limb amputation, etc. Lower limb infections, gangrene, and diabetic foot ulcers are common causes of amputation. It is possible that it may also cause some problems that we are not aware of. However, we will follow you closely and keep track of any unwanted effects or any problems. We may use some other medicines to decrease the symptoms of the side effects or reactions. Or we may stop the use of one or more drugs. If this is necessary we will discuss it together with you and you will always be consulted before we move to the next step.

Risks

Blood collection: This study will collect blood samples. The collection of blood samples

may cause temporary discomfort and/or bruising. If you experience any discomfort, new changes in your condition, or any unexpected situation during the study period, whether it is related to the study or not, you should notify your doctor in time , a doctor will make a judgment on this and give appropriate medical treatments.

Lead-in period: This trial requires 2-4 weeks to suspend the previous treatment with hypoglycemic drugs other than metformin. This period is called the “lead-in period” or “washout period”. If you have used other hypoglycemic drugs in the past, your disease may have an impact on blood sugar during the introduction period. You can consult your research doctor about related risks and monitoring measures.

CMR: During a CMRI scan, an allergic reaction to the contrast agent may occur. The treatment conditions are as follows: mild allergic reaction, which the subject can tolerate, no special treatment is required, and has no effect on the subject’s recovery; moderate allergic reaction, which is unbearable by the subject, requires special treatment, and has no effect on the subject’s recovery. Direct impact: Severe allergic reaction, endangering the life of the subject, causing death or disability, requires immediate emergency treatment. We will arrange for a qualified clinician to accompany each patient for a magnetic resonance examination, prepare anti-allergic and other rescue drugs in advance, and provide immediate treatment if there is an emergency to ensure patient safety.

Benefits

If you agree to participate in this study, you will receive 26 weeks of drugs, canagliflozin or sitagliptin for free. You will get free guidance from professional doctors, and you will get free physical and vital signs tests such as blood pressure and heart rate, routine and biochemical tests of blood and urine, as well as 12-lead ECG, echocardiography, fundus examination, and cardiac magnetic resonance. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit.

Reimbursements

We will give you 100 RMB to pay for your travel to the hospital and we will give you 50 RMB for blood drawing. You will not be given any other money or gifts to take part in

this research.

- *Can you tell me if you have understood correctly the benefits that you will have if you take part in the study? Do you know if the study will pay for your travel costs and time lost, and do you know how much you will be re-imbursed? Do you have any other questions?*

Confidentiality

With this research, something out of the ordinary is being done in your community. It is possible that if others in the community are aware that you are participating, they may ask you questions. We will not be sharing the identity of those participating in the research.

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, DSMB board, your clinician, etc.

Sharing the Results

The knowledge that we get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential information will not be shared. There will be small meetings in the community, and these will be announced. After these meetings, we will publish the results in order that other interested people may learn from our research.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Alternatives to Participating

If you do not wish to take part in the research, you will be provided with the established standard treatment available at the hospital. People who have malaria are given

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: Hongmei Yan; Shanghai Zhongshan Hospital; 180 Fenglin Rd, Shanghai, 200031, PR China; 13761666976.

- *Do you know that you do not have to take part in this study if you do not wish to? You can say No if you wish to? Do you know that you can ask me questions later, if you wish to? Do you know that I have given the contact details of the person who can give you more information about the study? Etc.*

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____
Day/month/year

If illiterate

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print

of participant

Signature of witness _____

Date _____
Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1.
2.
3.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year