Instructions for Subjects/Informed Consent

Name of the Research Project: Testing of HIV Protease Inhibitors to suppress inflammation and improve cardio pulmonary hemodynamics in subjects with pulmonary Arterial hypertension

Clinical research unit: Center of Clinical Pharmacology, the Third Xiangya Hospital, Central South University; Department of Cardiology, Xiangya Hospital, Central South University

Principal Investigators: Professor Hong Yuan and Professor Zaixin Yu

1. Invitation on participating in this clinical study

We sincerely invite you to participate in a clinical study implemented by the Center of Clinical Pharmacology, the Third Xiangya Hospital, Central South University and Department of Cardiology, Xiangya Hospital, Central South University.

To help you decide whether to participate in this study, it is very important to understand a detailed the reason for this study and the content of the study. Please carefully read the following information, and you can also discuss with your family, friends and doctors. If you have any that you do not understand or you want to know more about the information of the study, please ask the doctors at any time.

The informed consent will also inform you of how your medical information will be used and who will see the information.

If you are willing to participate in the study after your understanding of this study, we will ask you to sign the agreement, and we will also provide you a signed copy of the consent form so that you can feel free to browse or seek opinions of others.

2. What is this kind of research?

This study uses the idiopathic pulmonary arterial hypertension patients as the research subjects. In the study, the safety of saquinavir (SQV) combined with ritonavir (RIT) in the treatment of the idiopathic pulmonary arterial hypertension patients will be observed, and the treatment will decrease the inflammatory biomarker levels of the idiopathic pulmonary arterial hypertension patients and improve the symptoms of the patients will be evaluated. Safety of saquinavir combined with ritonavir has been confirmed in a large number of foreign researches,

and the therapy has obtained the audit of the State Food and drug administration ad it can be used in China.

This research has been approved by the medical ethics committee of the Third Xiangya Hospital of Central South University and Xiangya Hospital of Central South University. This study was conducted in the Xiangya Hospital of Central South University, and a total of about 20 cases of patients with idiopathic pulmonary arterial hypertension participated in this study. These patients may be divided into three dose groups of saquinavir combined with ritonavir:

Micro dose group	SQV combined with RIT（0.3mg/kg +0.03mg/kg, twice a day）
Low dose group	SQV combined with RIT（3mg/kg +0.3mg/kg, twice a day）
Standard dose group	SQV combined with RIT（15mg/kg +1.5mg/kg, twice a day）

3. What is the drug of the study?

The pathogenesis of Idiopathic pulmonary arterial hypertension is still unclear and inflammation and immunity alteration are increasingly recognized features of PAH. A drug combination that was developed to target human immunodeficiency virus (HIV) Protease to treat HIV infection has been shown to block inflammation and prevents pulmonary artery hypertension in well-established animal models. The combination of Saquinavir/ritonavir will be used in a clinical trial to determine if this drug combination has beneficial effects in the setting of your disease.

SQV was the first HIV-PI approved by the Food and Drug Administration (FDA). SQV has been shown to be safe even when give chronically in humans. SQV is typically administered with ritonavir which increases the bioavailability of SQV. The FDA approved dosage of SQV+ RIT for HIV infection is SQV1000-mg twice daily (5 x 200-mg capsules or 2 x 500-mg tablets) in combination with RIT 100-mg twice daily. RIT should be taken at the same time as SQV and within 2 hours after a meal. Abundant of clinical studies have demonstrated this regimen was well tolerated and safe in HIV-infected participants and other patients.

If you want to get more information about these drugs, please ask the doctors.

4. Why am I selected?

Because your disease condition conforms to the related manifestations and symptoms of research of idiopathic pulmonary arterial hypertension, and you are suitable for the participation condition of this study.

5. Will I have to attend?

No. If you participate in this study not completely voluntarily, you can choose not to participate in the study. If you decide not to participate in, this will not affect the relationship between you and your doctor. Your doctor will discuss other treatment options with you, including the risks and benefits of these treatments.

You can withdraw from the study at any time for any reason and request, please contact with your doctor. In order to ensure your safety, please complete the last visit, so that the doctor can finish all the examination items and find the possible adverse reactions required in the last examination. Whether you attend or refuse to participate in the study, or withdraw from the study halfway, the decisions are not affect your any rights and interests.

6. What is the alternative treatment?

If you choose not to participate in the study, you can use other drugs to reduce pulmonary arterial hypertension.

7. If I join in, which group will I be arranged into?

All the participating patients may be divided into different dose groups, which is the same to you. Which group you will be arranged is determined by your visiting sequence. You and your doctor cannot decide in advance which group you will be in.

8. What will you do during the study period?

During the whole study period, you need to live in the wards of the Department of cardiology, Xiangya Hospital of Central South University in 2 weeks (14 days). The doctors of the hospitals will visit and interview on the 28th day after giving drugs. The specific method and time are shown in the table below.

On the first visit, you will be screened for eligibility for you. If you meet all the inclusion conditions, you will be selected to participate in the study.

During the study period, you will conduct the relevant examinations or inspections based on the research projects. The specific times of various examinations will be determined by the doctors according to your illness development circumstances. About 20ml or less blood will be drawn every time (as the case may be).

Study Phase	Screening	Pre-Treatment	Treatment	

Visit Type	Outpatient Clinic	Inpatient assessment					Outpatient Clinic
Days on Intervention							Day 28
Study Procedures		Baseline (Day -1 & 0)	Day 1	Day 2	Day 13	Day 14	
Informed Consent	x						
Medical History and Demographics	x						
I/E Criteria	x						
Physical Exam	x	x				x	x
6MWD		x				x	x
Vital Signs	x	x	x	x	x	x	x
Oxygen Saturation	x	x	x	x	x	x	x
Laboratory Tests	x	x				x	x
NT-proBNP、ANP		x				x	x
Inflammatory Biomarker		x	x	x	x	x	x
ECG	x	x	x	x		x	
Echocardiogram	x	x				x	x
NYHA/WHO functional class assessment	x	x		x		x	x
Compliance evaluations		x	x	x	x	x	
AE Assessment		x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x

9. What do I need to do?

You must tell your doctor of all the past and present diseases suffering and the scheduled treatment schemes, and which drugs you allergic to, and all the drugs you are currently using.

To better evaluate the efficacy of drugs, during the study period, you need to strictly follow the doctor's orders to take a prescribed amount of drugs in fixed time every day, and some drugs are prohibited to be used. Please inform the doctor all the drugs you used since the last interview in each visit and interview, including the drugs in other prescription of other doctors and purchased in pharmacies, and return all the research drugs not taken and residual drug packing after taking drugs. It is recommended that you bring together all drugs taking at every visit.

Please inform your doctor any change of health condition in every visit. You can ask your doctor any time if there is any change of health condition during the study period. If there is an emergency or be hospitalized, you or your family please inform your doctor immediately.

10. What are the known side effects of the study drugs?

Generally speaking, all the treatment drugs will usually have side effects. No matter what kind of treatment you take, you will be accompanied by other risks. If you have any discomfort, please tell your doctor promptly.

Previous clinical studies showed that very few patients might have rare, unforeseen allergic reactions, and extension of electrocardiogram QT or PR interval. Prolongation of the QT interval can increase the risk of arrhythmia such as severe torsades de pointes arrhythmias. Prolonged PR interval leads to abnormal ECG signal, slowing down of heart rate or even stopping of heartbeat, heart conduction block. However, under normal conditions, the adverse reaction of SQV+ RIT is usually lighter, and commonly adverse reactions are fatigue, headache, gastrointestinal discomfort, nausea, diarrhea, drowsiness, rash, abnormal taste, dizziness, insomnia, allergies, dry mouth, odynuria and so on. After stopping the medicine, it usually can be improved without needing of special treatment.

11. How will be if there is new information during the study period?

If there is any important new information about the study drug during the study period, and it may affect your willingness in participation in the research continuously, we will inform you and discuss with you whether we should continue to study. If you decide to withdraw, the doctor will arrange follow-up treatment for you.

12. How will be if there are adverse events?

In addition to the known side effects of drugs, we can't deny that you may not appear unpredicted adverse events in the study.

If you have side effect in the course of the study, please inform your doctor promptly, and he will have to judge and deal with.

13. What may be benefit if you participate in the research?

At present, there is still no specific drug for the pulmonary hypertension, and the existed drugs mainly play roles of anapetia so as to reduce pulmonary artery pressure. Our recent studies showed that *in vivo* inflammation indexes were increased significantly in patients with idiopathic pulmonary arterial hypertension. According to the existing research results, it is

suggested that SQV+ RIT can reduce the pulmonary arterial pressure and improve symptoms by decreasing the inflammation in patients. SQV+ RIT are the marketed drugs, and you will likely benefit from drugs on the treatment of your disease. In addition, we will provide the study drug freely, and pay the designed laboratory examination cost in the research. The results of laboratory examinations done in the study will also help you to the judgment of your health condition. During the study period, we will subsidize all your transportation expenses during the study period, and provide treatment of pulmonary arterial hypertension medication a month freely according to your previous medication. In addition, we will provide follow-up 2 consecutive years hospital examinations including ultrasonography electrocardiogram, blood biochemical examination etc..

In addition, the society will largely benefit from the study results obtained from the study: there may be a new therapeutic method for the treatment of pulmonary arterial hypertension patients in the future. Your participation in this project will provide a positive medical support for the treatment of the majority of patients with pulmonary arterial hypertension including you.

14. How to do if damage occurs?

During the study period, the doctor will give you treatment in accordance with the study plan to prevent side effects and your health damage.

During the study, please follow the doctor's instructions. In normal circumstances complying with the provisions of the study, if there is related bodily injury in this study, you will get timely and positive treatment and compensation. If there is uncommon symptom of emergence of drug adverse reactions, please contact the doctors immediately. However, if you have an intent case or negligence, sometimes you are not possibly to obtain compensation.

15. Confidentiality -- who will see my information?

The research data will be saved in the Third Xiangya Hospital of Central South University, although the test results may be published, it will not disclose any information about your identity.

16. Contact information -- if I have any worry?

The doctor information is as follows. If you have any concerns or any questions about the study, or the occurrence of any emergency, please contact your doctor. Please keep this information.

Name (regular script): _____

Contact phone: _____

Informed consent

I have confirmed the following items:

1. The purpose of this study is to observe the safety of saquinavir combined with ritonavir in the treatment of the patients with idiopathic pulmonary arterial hypertension and evaluate whether it can reduce the inflammatory biomarker levels and improve the symptoms of the patients with idiopathic pulmonary arterial hypertension;
2. Safety of saquinavir combined with ritonavir has been confirmed in a large number of foreign researches, and the therapy has obtained the audit of the State Food and drug administration ad it can be used in China.
3. I will carry out the experiment according to the research procedures and related requirements under the guidance of experienced clinicians;
4. I will be classified into either group of 3 dose groups and receive different doses of saquinavir treatment combined with ritonavir.
5. Taking saquinavir combined with ritonavir may occur adverse reactions that have been reported or unknown, and I should cooperate with the doctor during treatment;
6. I can withdraw from the research at any time voluntarily and it will not affect the future relationship between doctors and patients and treatment;
7. During the study, if I have any questions for study, or any discomfort, I can contact with the doctor;

At the same time, I declare the following items:

1. The doctor has explained to me the medical terms used, and all the problems on the study pointed out by me have been answered satisfactorily and I have cleared this;
2. I am willing to comply with the study medication method;
3. During the study, I am willing to cooperate with the doctor within the prescribed period of time for treatment, and do the appropriate checks;
4. Have received the informed consent;

Name (Regular script): _____Contact telephone number:_____

Signature of subject: _____Date_____Year_____Month_____Day

The legal guardian (relationship):_____Contact telephone number:_____

Signature: _____Date_____Year_____Month_____Day

I have explained the details of the study to the volunteers participated in the study, and offered him/her a signed copy of the informed consent.

Researcher signature:_____Date_____Year_____Month_____ Day