

Informed Consent Form

Study Title: A Safety and Efficacy Study of a Chronopharmacokinetic Model-Guided Individualized Tacrolimus Dosing Regimen in Kidney Transplant Recipients

Informed Consent Form Version: V1.2, 2024-09-28

Research Institution: The First Affiliated Hospital of Guangzhou Medical University

Principal Investigator: Liu Xiaoyou

Patient Name: _____ Patient Name Abbreviation (Initials): _____

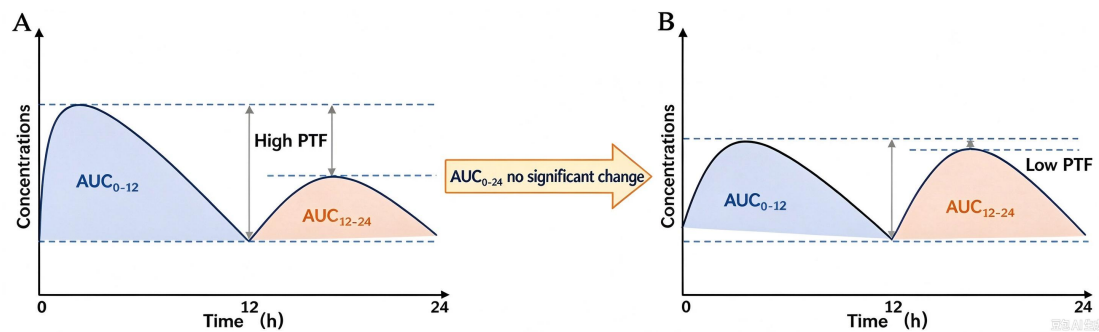
Dear Prospective Participant (Subject):

We are inviting you to take part in a clinical research study as a subject. This informed consent form provides you with information to help you decide whether to participate in this study. Please take the time to read the following information carefully. If you have any questions or do not understand any terms, you are welcome to discuss them with the study doctor.

Your participation in this study is entirely voluntary. This study has been reviewed and approved by the Research Project Review Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University.

1. Study Background

Kidney transplantation is the optimal treatment for patients with end-stage kidney disease. Calcineurin inhibitors, of which tacrolimus is representative, serve as first-line antirejection drugs after organ transplantation and have enabled long-term survival of kidney transplant recipients. However, tacrolimus has a narrow therapeutic window, and the high inpatient variability caused by factors such as metabolic enzyme activity and the type and state of food intake directly affects graft survival. In addition, the *in vivo* pharmacokinetics of tacrolimus exhibit typical chronopharmacological phenomena: under a twice-daily equal-dose regimen, the concentration-time curve is characterized by high morning and evening peaks, large peak-to-trough fluctuations, and marked differences between morning and evening exposure (Figure 1A). This fluctuation in exposure and the out-of-window concentrations are closely associated with the renal and pancreatic (islet) toxicity of tacrolimus and are also key factors limiting the long-term survival of grafts maintained on tacrolimus in kidney transplant recipients. Currently, routine monitoring of the tacrolimus steady-state trough concentration (C_{trough}) cannot reflect the degree of intra-day fluctuation, and, as a post-hoc measurement, it is associated with a certain delay. We therefore proposed the research concept of improving the tacrolimus daily dosing regimen by exploiting this chronopharmacological phenomenon (Figure 1B) and attempted to establish a tacrolimus chrono-population pharmacokinetic model using data from 18 kidney transplant recipients at our center. On the premise of not reducing total exposure (AUC₀₋₂₄), the tacrolimus "low in the morning, high in the evening" dosing regimen simulated by the chronopharmacokinetic model reduces morning-evening fluctuation while also achieving a saving in daily dose, and at the same time preserves room for dose individualization. This is expected to provide an effective, feasible, safer, and more economical long-term tacrolimus regimen for kidney transplant recipients.



2. Purpose of the Study

This study aims to address the limitations of the chronopharmacological fluctuation inherent in the current conventional tacrolimus twice-daily equal-dose regimen used in kidney transplant recipients, as well as the lack of corresponding monitoring tools. Using model-informed precision dosing (MIPD), we will propose an individualized dosing regimen that reduces intra-day chronopharmacological fluctuation of tacrolimus, and will verify the efficacy and safety of the tacrolimus chrono-individualized dosing regimen in stable-phase kidney transplant recipients through a multicenter, randomized controlled study. The long-term pharmaco-economic value of this dosing regimen and the biomarkers for individualized tacrolimus dosing will also be explored.

3. Study Procedures

This study is designed as a multicenter clinical study conducted in two parts. Part 1 is a multicenter observational study, and Part 2 is a multicenter randomized controlled study. The study is open-label (unblinded).

Step 1 uses a multicenter observational cohort design and plans to enroll 50 participants. After the patients agree, sign the informed consent form, and complete screening, intensive blood sampling will be performed (blood sampling at 13 time points). Using the 0–12-hour and 12–24-hour post-dose periods, MIPD modeling, machine learning, and PPK methods will be used to screen for significant covariates affecting the in vivo pharmacokinetic behavior of tacrolimus and to establish a tacrolimus chronopharmacokinetic model.

Step 2 uses a multicenter, randomized, controlled design and plans to enroll 105 participants. Among these, 5 participants are sentinel patients who, after achieving steady state on the tacrolimus chrono-individualized dosing regimen, will undergo intensive blood sampling to verify AUC₀₋₁₂, AUC₁₂₋₂₄, AUC₀₋₂₄, changes in calcineurin activity, and the applicability of the limited sampling strategy (LSS), thereby demonstrating the preliminary efficacy of the tacrolimus chrono-individualized dosing regimen and the feasibility of the monitoring strategy. The subsequent 100 participants, after completing screening, will be randomized at a 1:1 ratio into the experimental group (individualized dosing regimen based on the tacrolimus chronopharmacokinetic model) or the control group (conventional clinical dosing regimen) to receive tacrolimus treatment. The observation period is 1 year. During the study, participants will undergo safety and efficacy assessments at the times and in the manner specified in the study flow table.

Part 2 of the clinical study uses randomized grouping. "Randomization" means that you will be allocated by chance to one of the treatment groups, to reduce bias. You have a 1 in 2 chance of

receiving the tacrolimus chrono-model–guided individualized dosing regimen, and a 1 in 2 chance of receiving the original conventional clinical dosing regimen. The specific assignment will be determined at random by a computer program. Neither you nor your doctor can choose which dosing regimen you receive. This ensures that the different dosing regimens are evaluated in a fair manner.

4. What We Ask You to Do

To ensure that this study runs smoothly and successfully, we ask you to cooperate with the following:

Take your medication and undergo examinations as arranged by the investigator.

You must not change your current treatment or start any new treatment on your own without first confirming with the study doctor.

You are required to inform the study doctor about any health problems, even those you consider unimportant.

You are required to tell the study doctor about all other medications you are taking (including herbal medicines) before and during the study, apart from the study medication.

If study treatment is terminated early for any reason, we hope you will complete the final evaluation with the study doctor.

You are required to undergo examinations according to the standard post-kidney-transplantation follow-up plan to ensure stable graft function.

In addition to the standard follow-up plan, you are required to attend additional study visits as scheduled by the study plan, to ensure your safety.

Please record your medication diary card, blood glucose monitoring results, and blood pressure records truthfully and as required, and hand them to your study doctor at the next visit.

5. Risks and Discomfort of Participation

The adverse reactions that [tacrolimus] may cause are as follows:

As a commonly used immunosuppressive drug, tacrolimus has good immunosuppressive efficacy but is also accompanied by some side effects common to such drugs. Common side effects include liver and kidney toxicity; pancreatic (islet) toxicity; and tremor.

Risks of blood sampling

For Part 1 patients, intensive blood sampling will be used, with blood drawn at 12–13 time points for drug concentration measurement. Approximately 2–3 mL of blood will be drawn at each time point. At the first blood draw, an indwelling cannula (intravenous line) will be placed to reduce the pain and discomfort of repeated needle insertion. Risks of drawing blood from an arm vein include transient discomfort and/or bruising. Although very unlikely, infection, bleeding, blood clotting (coagulation), or fainting (syncope) may also occur.

6. Benefits of Participation

If you agree to participate in this study, you may potentially receive direct medical benefits, but you may also receive no benefit. All recipients enrolled in the study will receive professional and timely guidance from the kidney transplant team before, during, and after surgery and throughout follow-up; all examination parameters will be closely monitored, and abnormal findings will be

actively tracked and managed. If the results of this study confirm that the individualized dosing regimen based on the tacrolimus chronopharmacokinetic model is safe and effective, subjects may be able to reduce their tacrolimus dose, achieve more stable drug concentrations, experience fewer ADRs, and save on medical costs—and may even experience improved short-term graft function and prolonged long-term graft survival. We hope that the information obtained from your participation in this study will, in the future, improve the short-term and long-term kidney transplant outcomes for you and for other patients who undergo kidney transplantation.

7. Alternative Treatments

If I do not participate in this study, are there any other treatment options available to me?

If you do not participate in this study, you may continue to take your original immunosuppressive regimen. We will continue to follow you up regularly according to the standard post-kidney-transplantation follow-up plan to safeguard your health.

8. Costs Related to Participation

Participation in this study involves only intensive blood sampling to measure tacrolimus AUC concentrations, or the use of a modified tacrolimus dosing regimen. The modified tacrolimus regimen adjusts the morning/evening dose ratio without changing the total daily dose; therefore, no additional drug dose will be involved, and our preliminary results suggest that tacrolimus use may actually be reduced. In addition, no extra therapeutic drugs or examinations will be added. Accordingly, this study does not provide free medication (no study drug supply). The observation and follow-up work of this study is performed by adding study visits on the basis of the standard post-kidney-transplantation follow-up plan, to ensure your health. The costs of the standard post-kidney-transplantation follow-up plan are borne by the patient. The costs of the additional unscheduled visits, the additional tacrolimus concentration measurements, and the treatment of adverse events genuinely arising from the modified regimen will be provided free of charge, to ensure your safety.

9. Compensation

For your participation, apart from the standard post-kidney-transplantation follow-up plan, when additional sample collection is required, you will receive compensation of ¥300 for intensive blood sampling (12–13 time points) and ¥150 for limited sampling strategy (LSS, 4–5 time points) blood sampling; in addition, a nutritional allowance of ¥100 and a transportation allowance of ¥100 will be provided. Compensation will be paid on a per-participation basis according to the number of visits.

10. Compensation for Injury (Indemnification)

During your participation in this clinical study, if any study-related injury occurs or a serious adverse event arises, the study sponsor will bear the treatment costs and provide corresponding compensation in accordance with Chinese law.

However, study-related injuries do not include injuries arising from the following circumstances:

The natural course or progression of your underlying disease or medical condition;

Your negligence or willful misconduct (for example, failure to strictly follow this consent form,

the study protocol, or the instructions given by the study doctor or study staff).

11. Insurance

No insurance will be purchased for this study.

12. Right to Refuse Participation or Withdraw from the Study

You may choose not to participate in this study, and you have the right to withdraw at any stage of the study without giving any reason. Your medical care and rights will not be affected in any way by such a decision. However, the processing of your data by the investigator before withdrawal is lawful; if data obtained before withdrawal have already been integrated into the study project and cannot, for practical reasons such as cost, be removed, the data may continue to be used in this study while protecting your privacy. Once you decide to participate in this study, please sign this informed consent form to indicate your consent. Before entering the study, the study doctor will perform screening to confirm whether you are a suitable candidate.

13. Privacy and Confidentiality

During the study, your personally identifiable information, such as your name and sex, will be replaced by a code or number and kept strictly confidential. Only the relevant doctors will know your personal information, and your right to privacy will be well protected. The results of the study may be published in journals, but no personally identifiable information about you will be disclosed.

If you agree to participate in this study, all of your medical records may be reviewed by the relevant personnel of the institution sponsoring this study, by the relevant regulatory authorities, or by an independent ethics committee, to check whether the study is being conducted appropriately. By signing the informed consent form, you agree to such review by the aforementioned parties.

14. Collection of Biological Samples

In this study, according to the intensive blood sampling schedule (12–13 time points), approximately 2–3 mL of peripheral blood will be collected at each time point using EDTA tubes, for measurement of tacrolimus AUC concentrations. For the remaining biological samples, you ☐ consent / ☐ do not consent to the investigator's disposal and their possible use for other exploratory indicator studies. If you choose not to consent, the samples will be disposed of as medical waste in strict accordance with national laws and regulations.

17. How to Obtain Help During the Study

You may learn about the study-related information and progress at any time. If you have any questions related to this study, please contact 18922217771 and contact Liu Xiaoyou.

If, during the study, you have questions about your rights as a research participant, you may contact the Research Project Review Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University at 020-81566265.

If you fully understand the content of this research project and agree to participate in this study, you will sign this informed consent form. The form is made in duplicate, with one copy retained by the investigator and one copy retained by the subject or the subject's legal representative.

Signed by the subject or his/her legal representative:

Statement of Consent:

I confirm that I have read and understood the informed consent form for this study, that the possible problems during the study and their solutions have been explained to me, and that I have had the opportunity to raise my own questions.

I understand that participation in this study is entirely voluntary and that refusing to participate will not prejudice any benefit to which I am entitled.

I have been informed that the members of the research team for this study and the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University all have the right to review the study records and case data, and I agree that the aforementioned persons may have direct access to my study records, and I understand that such information will be kept confidential. I agree to participate in this study.

Subject's signature: _____ Date: _____

Guardian's signature: _____ Date: _____

Relationship to the subject: _____

The following is to be completed by the study doctor who performs the informed consent process:

Investigator's Statement: I confirm that I have explained and discussed with the patient the nature, purpose, requirements, and possible risks of this study, and have also discussed the alternative treatment options. I confirm that a copy of this informed consent form has been given to the subject for retention.

Investigator's signature: _____ Date: _____