<No.: F506-CL-0912> Phase III Study Protocol

A phase III, randomized, open, parallel-controlled, multi-center study to compare the efficacy and safety of Tacrolimus capsules and Cyclophosphamide injection in treatment of lupus nephritis

NCT02457221

Sponsor: Astellas Pharma China Inc.

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I. SIGNATURES

1. AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This clinical study will be conducted in adherence to Good Clinical Practice (GCP), and applicable laws and regulatory requirements, as well as this study protocol. As the evidence of the agreement, the investigator and responsible person of the sponsor will sign the bipartite agreement.

2. SPONSOR'S SIGNATURE

A phase III, randomized, open, parallel-controlled, multi-center study to compare the efficacy and safety of tacrolimus capsules and cyclophosphamide injection in treatment of lupus nephritis

Sponsor's personnel:

3. INVESTIGATOR'S SIGNATURE

A phase III, randomized, open, parallel-controlled, multi-center study to compare the efficacy and safety of tacrolimus capsules and cyclophosphamide injection in treatment of lupus nephritis

ISN/Protocol No. F506-CL-0912, Date: December 25, 2018

I have read all pages of this clinical study protocol for which Astellas Pharma China Inc. is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) GCP and China GCP guidelines. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH-GCP and China GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: _____

Date (DD MM YYYY)

Printed Name: _____

Address: _____

_____

II. CONTACT INFORMATION OF THE STUDY

CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

SERIOUS ADVERSE EVENT REPORT

FAX: 010-88019165

III. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviation	Description of Abbreviation
95%CI	95% Confidence Interval
ACA	Anticardiolipin
ACEI	Angiotensin-Converting Enzyme Inhibitors
ACR	American College of Rheumatology
AE	Adverse Event
AI	Active Index
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ANA	Antinuclear Antibody
ARB	Angiotensin II Receptor Blocker
AST	Aspartate Aminotransferase (GOT)
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C3, C4	Complement C3, C4
CFDA	China Food and Drug Administration
CI	Chronic Index
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum Blood Concentration

Abbreviation	Description of Abbreviation
CMV	Cytomegalovirus
CRF	Case Report Form
CRO	Contract Research Organization
CTX	Cyclophosphamide
DILI	Drug-Induced Liver Injury
dsDNA	Anti-Double-Stranded DNA Antibodies
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ESR	Erythrocyte Sedimentation Rate
EULAR/ERA-EDTA	European League Against Rheumatism/European Renal Association–European Dialysis and Transplant Association
FAS	Full Analysis Set
FK506	Tacrolimus
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
γ-GTP	γ- Glutathione Transpeptidase (GGT)
HbA1c	Glycated hemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus

Abbreviation	Description of Abbreviation
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISN	International Study No.
KDIGO	Kidney Disease: Improving Global Outcomes
LN	Lupus Nephritis
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate Mofetil
MP	Methylprednisolone
MRL	Mixed Lymphocyte Reaction
NDA	New Drug Application
PFDA	Province Food and Drug Administration
PK	Pharmacokinetics
PPS	Per Protocol Set
RBC	Red Blood Cell
RCT	Randomized Controlled Trials

Abbreviation	Description of Abbreviation
SAE	Serious Adverse Event
SDV	Source Data Verification
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
Scr	Serum Creatinine
SLE	Systemic Lupus Erythematosus
SLE-DAI	Systemic Lupus Erythematosus - Disease Activity Index
SOP	Standard Operating Procedures
SAF	Safety Analysis Set
SUSAR	Suspected Unexpected Serious Adverse Reactions
TAC	Tacrolimus
TMA	Thrombotic Microangiopathy
ULN	Upper Limit of Normal
WBC	White Blood Cell

List of Key Study Terms

Terms	Definition of terms
Baseline	1) Observed values/findings which are regarded as calibrated zero status in the study. 2) Time when 'Baseline' is observed.
Discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a trial by an enrolled subject. Four categories of discontinuation are distinguished: 1) dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); 2) investigator-initiated discontinuation (e.g., out of a certain reason); 3) loss to follow-up: cessation of participation without notice or action by the subject; 4) sponsor initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject data from analysis. "Termination" has a history of synonymous use, but is now considered non-standard.
Enroll	To register or enter into a clinical trial; transitive and intransitive. Informed consent precedes enrollment, which precedes or is contemporaneous with randomization.
Investigational period	Period of time where major interests of protocol objectives are observed, and where the investigational drug or control drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the investigational drug or control drug.
Randomization	Action to allocate a subject to the treatment group or treatment cohort. Depending on the rules for handling study drugs, 'Randomization' is usually executed just before entering the 'investigational period'.
Screening	1) Process for selecting candidates for the study. 2) Process for checking the eligibility of subjects usually done during the "pre-investigational period".
Screening failure	The screened subject failed to fulfill protocol inclusion and/or exclusion criteria and thus cannot receive randomized or open label study treatment, or the subject decided not to

	participate anymore (withdrew consent) prior to completing pre-investigational period.
Study period	Period of time from start to end of the study.
Subject	An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Title of Study	A phase III, randomized, open, parallel-controlled, multi-center study to compare the efficacy and safety of Tacrolimus capsules and Cyclophosphamide injection in treatment of lupus nephritis
Planned Study Period	From August 2014 to June 2018
Study Objective(s)	The objective of this study is to evaluate the efficacy and safety of Tacrolimus capsules for induction remission in patients with lupus nephritis, and compare the efficacy and safety with Cyclophosphamide injections to indicate that Tacrolimus capsules are not inferior to Cyclophosphamide injection.
Planned Total Number of Site and Location	Approx. 25 sites, in China
Design and Methodology	This is a randomized, open, 1:1 parallel controlled, multi-center, non-inferiority clinical study. Study group: Tacrolimus capsules + steroid, 147 subjects Control group: Cyclophosphamide injections + steroid, 147 subjects
Number of Subjects Planned	294 cases of eligible subjects
Selection Criteria	Inclusion Criteria: 1. Chinese male or female aged 18-60 years, 18.5≤Body Mass Index (BMI) <27; 2. Diagnosed as systemic lupus erythematosus (based on American Rheumatism Association Diagnostic Criteria 1997, refer to appendix 3); 3. Diagnosed as III, IV, V, III + V, IV + V lupus nephritis (according to the LN classification in International Society of Nephrology and Renal Pathology Society (ISN/RPS) 2003) within 24 weeks before enrollment with renal biopsy; 4. 24-hour urine protein ≥ 1.5g, Scr<260umol/L (or 3mg/dL); 5. Subject or his/her witness or legal representative signed the informed consent form

	Exclusion Criteria: 1. Class II or VI lupus nephritis or with TMA; 2. Received immunosuppressants (mycophenolate mofetil (MMF), cyclosporine, methotrexate, mechlorethamine, chlorambucil, tripterygium preparations, leflunomide etc.) treatment with a duration of more than one week within 30 days prior to enrollment; 3. Received tacrolimus (except for topical use) or cyclophosphamide treatment within 30 days prior to enrollment; 4. Received a course of methylprednisolone (MP) pulse therapy or gamma globulin treatment or plasma exchange within 30 days prior to enrollment; 5. Patients with history of allergies to tacrolimus, cyclophosphamide or methylprednisolone; 6. Pregnancy, lactation or patient unwilling to take contraceptive measures; 7. Patients with estimated maintenance dialysis for more than eight weeks; or dialysis for more than two weeks prior to entering observation; 8. Patients received kidney transplantation or plan to have kidney transplantation recently; 9. Serum creatinine (Scr) ≥260umol/L (or 3mg/dL); 10. Patients suffering from liver dysfunction (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to 3 times the upper limit of normal lab value) or bilirubin greater than or equal to 3 times the upper limit of normal lab value; 11. Patients diagnosed with diabetes; 12. History of gastrointestinal bleeding or pancreatitis within 3 months; 13. Uncontrollable hyperkalemia after dietary therapy or reduction of potassium treatment (exceed the upper limit of normal lab value); 14. Patients suffering from lupus pneumonia or lung injury; 15. Patients with anemia (hemoglobin <7g/dl) or bone marrow suppression (WBC $<3.0\times10^9$/L, and/or neutrophils $<1.5\times10^9$/L, and/or platelets $<50\times10^9$/L) not secondary to systemic lupus erythematosus; 16. With congenital heart disease, arrhythmia, heart failure or

	other severe cardiovascular diseases; 17. With refractory hypertension (defined as blood pressure still exceeds 180/110 mmHg despite taking three different types of antihypertensive drugs [one of them is diuretic] simultaneously); 18. Patients with recurrent tumors within 5 years; 19. Severe infection that requires intravenous antibiotics within 2 weeks prior to randomization; 20. Patients with infection of hepatitis B virus or hepatitis C virus; patients with active tuberculosis; patients with severe immunodeficiency diseases (including active cytomegalovirus infection (positive CMV IgM antibody), or human immunodeficiency virus (HIV) infection, etc.); 21. Patients with lupus encephalopathy or other life-threatening complication of systemic lupus erythematosus; 22. Patients participated in other clinical trials within three months before enrollment; 23. Patients not suitable to participate in this study as determined by the investigators.
Discontinuation Criteria	1. Patients or their legal representatives volunteer to withdraw; 2. According to the patient's conditions, drugs that prohibited in the study or other immunosuppressive agents, or a second MP pulse therapy is needed; 3. Uncontrollable infection; 4. Adverse events lead to discontinuation of the study, for example, i. AST, ALT: ≥ 3 times of the upper limit of normal range; ii. Scr: ≥ 3 times of the upper limit of normal range; 5. Lupus exacerbations during treatment; or lupus disease recurrence; or lupus disease relapse. 6. Violate the inclusion/exclusion criteria; 7. Subjects fail to take the study drugs in accordance with the protocol for 14 consecutive days due to various reasons (such as infection, etc.); 8. The sponsor stops the trial for safety reasons; 9. Patients considered as not suitable to continue by the Ethics Committee for some reasons; 10. Patients considered as not suitable to continue by the

	investigator; 11. Tacrolimus capsules withdrawal > 14 consecutive days or cyclophosphamide injection pulse therapy of less than 4 doses; 12. Patients with WBC aplasia. 13. Subject becomes pregnant.
Study Drug Dose: **Mode of Administration:** **Duration of Treatment:**	• Dose: Starting dose as 4mg/day, begin to monitor the blood concentration 7 days after administration. Dose adjustment beginning from 14 days after first dose, the target blood concentration is 4-10ng/ml, the target dose is 0.08-0.1mg/kg/d. If blood drug concentration < 4ng/ml or > 10ng/ml, adjust the dose to the target blood concentration. If the blood concentration <4ng/ml with the target dose, increase the dose but with the maximum less than 0.15mg/kg/d, if with the maximum dose the blood concentration is still <4ng/ml, subjects can stay in the study only subjects can tolerate the treatment. If blood concentration > 10ng/ml, reduce the dose by 25% and test blood concentration one week later; if blood concentration ≥ 15ng/ml, reduce the dose by 50% or withdraw the drug (such as occurrence of severe AE) and drug concentration should be retested within 7 days of reduce or interruption. When there is conflict, prioritize tacrolimus target blood concentration rather than the target dose. • Administration method: administered after the end of MP pulse therapy, it is recommended that the oral daily dose be administered in two divided doses (e.g. morning and evening). Capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption. In order to get stable blood drug concentration result, please use even number of daily dose, within allowed target dose and equivalent dosage in the morning and evening. • Duration of treatment: 168 days (24 weeks)
Reference Therapy Dose: **Mode of**	• Dose: Starting dose as 0.75g/m^{2}BSA, thereafter, dose adjustment target is 0.5-1.0 g/m^{2}BSA, dose adjustment is 0.25 g/m² BSA each time. The hematology test (white blood cell count), patients' status and safety would be considered when adjust the dose, the investigators

Administration: **Duration of Treatment:**	should make the judgement based on both scientific and ethic aspects to make the best decision to protect the patients' health and benefit. *[DuBois formula BSA(m^2) = 0.007184 ×weight(kg)$^{0.425}$ × height(cm)$^{0.725}$]* • Administration method: administered after the end of MP pulse therapy, intravenous injection after dissolved in 250ml saline every 4 weeks for 6 consecutive times. • Mesna can be applied to prevent Cystitis and appropriate hydration therapy can be provided basing on edema of the patient. • Duration of treatment: 168 days (24 weeks)
Dose of Steroid: **Mode of Administration:** **Duration of Treatment:**	• Dose: MP, 0.5g/day. Mode of Administration: Intravenous pulse therapy for continuous 3 days. • Duration of treatment: 3 days. • Dose: Prednisone tablet, 5mg/tablet. • Mode of Administration: Oral administration. Starting dose as 0.8 mg/kg/day and the maximum dose of 45mg/day. Reduce the dose by 5mg 4 weeks later to 20mg/day every 2 weeks, then by 2.5mg to 10mg/day every 2 weeks and maintain it. • Duration of treatment: 168 days (24 weeks)
Concomitant Medication	Drugs excluded in inclusion/exclusion criteria are prohibited.

Efficacy Variables:	**Primary efficacy endpoints:** Remission rate in endpoint assessment (24 weeks) (complete remission + partial remission) (Patients of early withdrawal are included in endpoint assessment) **Secondary efficacy endpoints:** 1) 24-hour urine protein at all visits except visit 2, 4, 5 (Day1, Weeks 4, 8, 12, 16, 20, 24), and change from baseline; 2) Serum albumin at all visits except visit 2 (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24), and change from baseline; 3) Serum creatinine at all visits except visit 2 (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24), and change from baseline; eGFR at all other post-baseline visits (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24) comparing with baseline, based on CKD-EPI formula [26]: $141\times\min(Scr/k,1)^{\alpha}\times\max(Scr/k,1)^{-1.209}\times0.993^{Age}\times1.018$[if female] $\times1.159$[if black] (Scr [mg/dL], K= 0.9 for males or 0.7 for females, α= -0.411 for males or-0.329 for females, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1); 4) SLE-DAI and immune parameters (ESR, C3, C4, dsDNA) in Week 4, 12 and 24, and change of SLE-DAI and immune parameters in Week 4, 12 and 24 from baseline; 5) Renal biopsy AI (active index) and CI (chronic index) in Week 24, and change from baseline; 6) Percentage of patients converted to other immunosuppressive therapy in the study group and the control group during 24 weeks; 7) Percentage of patients with serum creatinine rise to two times of the baseline at 24 weeks, percentage of patients with dsDNA and ANA converting from positive to negative.
Safety Variables:	Adverse event, vital signs, lab tests
Statistical Methods	*Demographics and other baseline parameters*

	• The analysis will be conducted in the FAS, PPS and SAF. Appropriate statistical test methods will be adopted for intergroup comparison based on different data types (T test, chi-square test and Wilcoxon rank test, etc.). Significance test level is set as 5%. For factors showing imbalance between groups that may affect the efficacy assessment, subgroup analysis and calibration analysis will be adopted for the main variables to examine its influence. *Primary efficacy analysis* • CMH test analysis will be used. The 95% confidence interval of efficacy difference will be calculated and used for non-inferiority test. *Secondary efficacy analysis* • All secondary efficacy variables will be compared between groups. Secondary efficacy endpoints will be analyzed with appropriate statistical methods (T test, chi-square test or the Wilcoxon rank test) based on data type. Significance test level is set as 5%. *Safety analysis* • Safety set will be used for safety analysis. Adverse events, vital signs, and laboratory tests are safety analysis indicators. Significance test level is set as 5%. *Management of adverse event and serious adverse event* 1) Investigators are responsible for causality assessment of adverse events in clinical study. 2) Report time of serious adverse events: death or life-threatening cases: on same day of report; other serious cases: within 24 hours. 3) All adverse events/abnormal lab results should be recorded in the corresponding location in the CRF. 4) Investigators should ensure the follow-up of subjects with adverse events. Follow-up data should also be recorded in the corresponding location in the CRF. 5) Key observations of this study: incidence of infection; incidence of gastrointestinal reactions; incidence of bone

	marrow suppression; incidence of abnormal liver function; incidence of hyperglycemia; incidence of renal failure.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

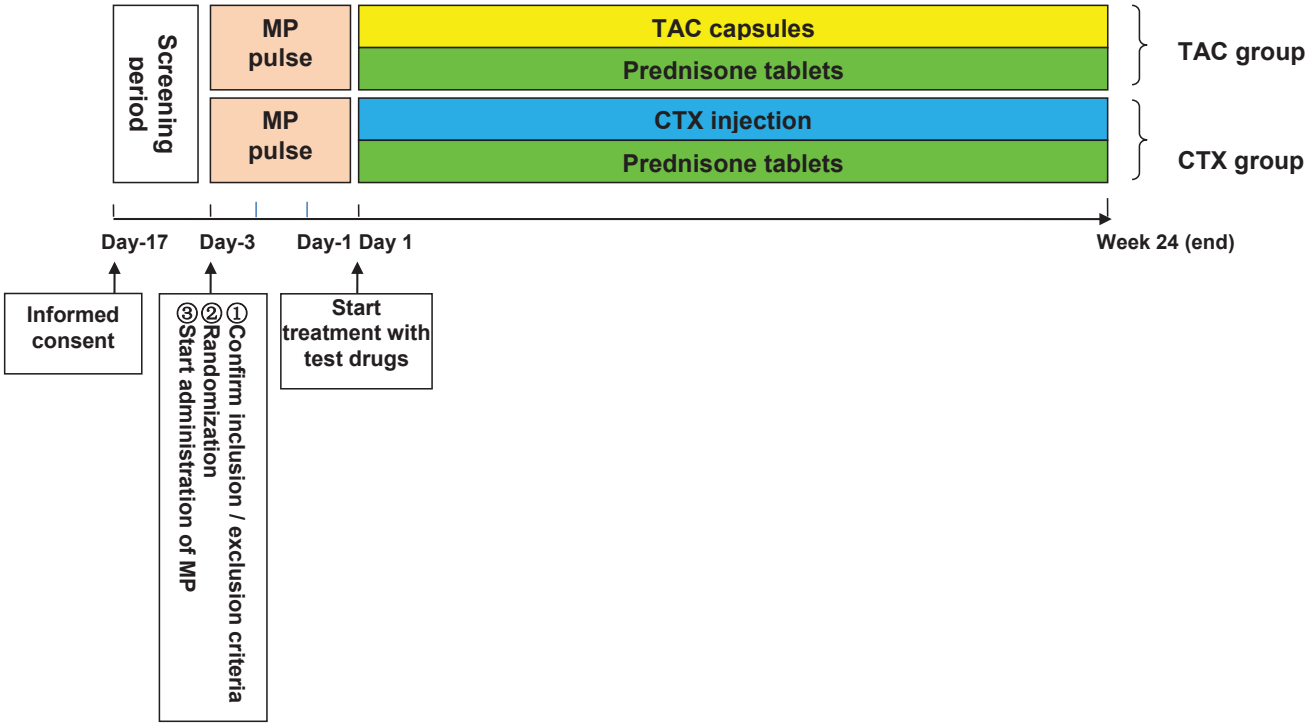

Table 1: Assessment Schedule

Test items	Screening	Induction remission stage									
	Visit 1[13]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11/Discontinuation [14]
	Screening (Day -17~-3)	Day -3,-2,-1	Day 1	Week 1 (Day 8±3)	Week 2 (Day 15±3)	Week 4 (Day 29±5)	Week 8 (Day 57±5)	Week 12 (Day 85±5)	Week 16 (Day 113±5)	Week 20 (Day 141±5)	Week 24 (Day 169±5)
Sign informed consent	X										
Urine HCG pregnancy test [1]	X				X	X	X	X	X	X	X
Demographics and Medical history	X										
Renal biopsy [2]	X										X
HBV/HCV/HIV/CMV [3]	X										
Physical examination, BMI	X		X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X	X	X
Blood routine, blood biochemistry, blood lipids [4]	X		X	X	X	X	X	X	X	X	X
HbA1c	X							X			X
Urine routine	X		X	X	X	X	X	X	X	X	X
24-hour urine protein	X		X			X	X	X	X	X	X
eGFR	X		X	X	X	X	X	X	X	X	X
ESR, A-dsDNA, ANA,C3, C4	X					X		X			X
A-Sm, ACA [5]	X										
ECG	X		X			X	X	X	X	X	X
Chest X-ray	X							X			X
SLE-DAI	X					X		X			X

Test items	Screening	Induction remission stage									
	Visit 1[13]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11/Discontinuation [14]
	Screening (Day -17~-3)	Day -3, -2, -1	Day 1	Week 1 (Day 8±3)	Week 2 (Day 15±3)	Week 4 (Day 29±5)	Week 8 (Day 57±5)	Week 12 (Day 85±5)	Week 16 (Day 113±5)	Week 20 (Day 141±5)	Week 24 (Day 169±5)
Inclusion/Exclusion criteria [6]	X	X									
Randomization [7]		X									
Corticosteroid dispensation and/or accountability [8]		X (MP)	X	X	X	X	X	X	X	X	X
TAC/CTX dispensation and accountability [9]			X	X	X	X	X	X	X	X	X
Patient Diary card dispensation [10]	X		X			X	X	X	X	X	
Drug blood concentration test [11]				X		X	X	X	X	X	X
Dose adjustment [12]					X		X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X	X	X	X	X

[1] Urine HCG pregnancy test is only applicable for female subjects. Dipstick test is used at all required visits except for Visit 1at which serum test is conducted (central lab). Study drugs should only be provided when the result of each test is negative.

[2] Patients had renal biopsy within 24 weeks and without significant change in the disease don't have to re-test in enrollment. The renal biopsy at the end of study observation is optional which is determined based on the patients' willingness.

[3] HIV is tested at site lab. Investigators are recommended to complete the CMV test at site lab for the purpose of shortening screening period. Should CMV test be not applicable at site lab, central lab will do it instead.

[4] Routine blood test: red blood cell count, hemoglobin, platelets, white blood cell count, white blood cell classification. Blood biochemistry: Na+, K+, Ca2+, Mg2+, glucose, serum creatinine, urea nitrogen, uric acid, total bilirubin, total protein, albumin, aspartate aminotransferase (SGOT/AST), alanine aminotransferase (SGPT/ALT), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP). Blood lipids: total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG). Fasting is required for blood sample collection. Urine routine: Protein, glucose, nitrite, pH, ketone body, blood cells and

urinary sediment.

[5] Investigators are recommended to complete A-Sm and ACA test at site lab for the purpose of shortening screening period. Should these tests be not applicable at site lab, central lab will do it instead.

[6] MP administration should be done after judgment of Inclusion/Exclusion criteria and randomization at Visit 2 on Day -3.

[7] Randomization is conducted at Visit 2 on Day -3, after re-confirmation of the Inclusion/exclusion criteria and before first dose of the MP administration.

[8] At only Visit 2, MP is dispensed, from Visit 3 (including Visit 3), only prednisone tablets are dispensed. At Visit 11, steroid should be returned and counted but not be dispensed any more.

[9] At Visit 11, study drugs should be returned and counted but not be dispensed any more. CTX only dispensed on V3, V6-V10.

[10] Patient diary card will be dispensed at the visits specified in this schedule. Except for Visit 1, the original copy of completed diary card should be returned to investigator and filed at site.

[11] After Visit 5, investigators adjust the dose of TAC based on the drug blood concentrations test result. For subjects whose TAC dose has been adjusted at Visit 5 or following visits, investigators may initiate an unscheduled visit around 7 days after this TAC dose adjustment visit for the purpose of collecting blood sample to test TAC blood concentration as needed. Blood sample in TAC group should be collected before dosing on the visit day and 12±2 hours after last dose in the last day.

[12] For patients that received the unscheduled visit after Visit 5, investigators may adjust TAC dose according to TAC blood concentration collected at the unscheduled visit.

[13] Screening period is no more than 14 days during Visit 1. (Day -17~ -3)

[14] Once early termination is determined, subject should complete the examinations for withdrawing visit as soon as possible.

1 Introduction

1.1 Background

Lupus nephritis (LN) is still the main manifestation of systemic lupus erythematosus (SLE), 60% of patients with systemic lupus erythematosus can develop into disease with involvement of end organs. According to the International Society of Nephrology/Renal Pathology Society (ISN / RPS) LN classification (2003), although the treatment for diffuse proliferative LN has made some progress, the treatment for Class III, IV and V LN is still unsatisfactory.

Cyclophosphamide (CTX) has been used for LN treatment for decades. Randomized controlled trials (RCTs) showed that CTX combined with steroid is the standard treatment for LN [1, 2 ,3, 4].

According to the published review recently, for severe LN, including Class III, IV and V LN, the best 24-week induction therapy seems to be CTX combined with steroid through intravenous injection [5].

In the SLE treatment recommendation of European League Against Rheumatism (EULAR), the recent Cochrane review showed that, comparing with monotherapy of steroid, CTX combined with steroid reduced the risk of doubling serum creatinine level, and in 2008, the EULAR recommended intravenous injection of CTX combined with MP as the treatment for severe LN [6].

In the KDIGO Clinical Practice Guideline for Glomerulonephritis released in June 2012, steroid combined CTX or mycophenolate mofetil (MMF) are recommended as the initial treatment for Class III and IV LN [7].

In the guidelines for diagnosis and treatment of severe SLE released by Chinese Rheumatology Association in 2010, the therapies for severe SLE (SLE complicated by significant organ damage) include steroids, CTX, MMF and cyclosporine A (CsA). So far, CTX combined with steroid is still the gold standard for the treatment of severe LN in U.S. National Institutes of Health programs and European programs [8].

In the guidelines for diagnosis and treatment of pediatrics kidney disease (draft) published in 2010, CTX was recommended as the primary treatment for LN [9].

Although CTX is the standard treatment for LN, we must also consider the toxicity of CTX, including ovarian toxicity, bone marrow suppression and other toxicities. Therefore, it is necessary to explore other alternative treatment options.

Tacrolimus (Prograf ®) is a lipophilic macrolide immunosuppressant, and its active ingredients were firstly extracted from fermentation broth of Streptomyces of Tsukuba soil in Japan in 1984. It is a calcineurin inhibitor, and similar to cyclosporine A(CsA), it can inhibit the production of IL-2 and T cell activation [10]. In addition, tacrolimus can

also significantly inhibit Th2 cells producing IL-10, thereby preventing the B cells from producing autoantibodies [11, 12]. Moreover, the unique immunosuppression mechanism of tacrolimus enables action through CsA-insensitive pathway. Tacrolimus can inhibit activation of initial T cell, and also inhibit activation and proliferation of sensitized T cell [13]. Its inhibitory effect on T cell activation is 10-100 times stronger than cyclosporine A [14]. Tacrolimus has been widely used to prevent postoperative graft rejection after liver or kidney transplantation and for the treatment of graft rejection after liver or kidney transplantation that other immunosuppressive drugs can't control.

Animal experiments showed that tacrolimus can significantly reduce urinary protein excretion and serum anti-dsDNA antibody levels in MRL/lpr lupus mice, inhibit glomerular cell proliferation and crescent formation, and reduce the deposition of immune complexes [15, 16]. It was found in the preliminary clinical observation that tacrolimus have significant efficacy in treatment of lupus nephritis, which is manifested as quickly reducing proteinuria, elevating serum albumin, reducing autoantibody levels, and significantly alleviating active lesions of renal tissue. The multi-center clinical observations with 63 cases of lupus nephritis in Japan showed: comparing tacrolimus combined with steroid (28 cases) and placebo combined with steroid (35 cases), LNDAI in tacrolimus group reduced 32.9 ± 31.0% [17].

In recent years, tacrolimus showed efficacy as treatment for severe LN in many randomized controlled studies [18-21], so tacrolimus combined with steroid is considered as the replacement therapy for severe LN in the future.

1.2 Non-clinical and Clinical Data

1.2.1 Non-clinical Data

1.2.1.1 Pharmacology

1) Effects based on pharmacodynamics

In vitro effects of FK506

- Strongly inhibit mixed lymphocyte reaction (MLR), production of IL-2 and IFN-γ in lymphocyte, and production of T-cell stimulating peripheral blood mononuclear cell inflammatory cytokines.
- Inhibit response of T cell-dependent antibody in human B cells. Furthermore, although it doesn't inhibit proliferative response to LPS stimulation in mice spleen cells, it can inhibit the proliferative response to anti-IgM antibodies stimulation.
- Partially inhibit human peripheral blood mononuclear cells and alveolar macrophages producing cytokines.

In vivo effects of FK506

- Strongly inhibit the antibody production in mice and delayed hypersensitivity.
- Inhibit the prolongation of survival days and the occurrence of proteinuria of natural incidence of SLE in mice.
- In the graft-versus-host (GVH) reaction induced nephritis model of mice, prophylactic medication suppresses the elevation of anti-double-stranded (ds) DNA antibodies and decrease of complement C3 in serum, also suppresses the deposition of immune complex in glomerular and incidence of glomerulonephritis. In addition, the medication after successful immune suppresses increase of albumin concentration in urine, pathological deterioration of glomerular nephritis, and deposition of immune complex in glomerulus.
- In anti-Thy1.1 antibody-induced nephritis model of rat, it inhibits the increase of urinary protein, and also the occurrence of messenger RNA (mRNA) of IL-2, IFN-γ in glomerular.

2) Safety pharmacology

In the intravenous administration of FK506 of more than 0.1mg/kg, anesthetized dogs were found to have increased respiratory rate, decreased blood pressure, pulse rate and thighs arterial blood flow, but in the intravenous administration of placebo without FK506 injection, equivalent changes were also found, these respiratory and circulatory system effects may be caused by polyoxyethylene hydrogenated castor oil 60 added in the injection as dissolving auxiliary agent. On the other hand, the effects on the respiratory and circulatory systems of anesthetized cats and anaesthetized rats were milder than the dog, while the effects on placebo were weak or with no effect. In the intravenous administration of FK506 of more than 0.32mg/kg, the spontaneous physical activities of mice were found to be reduced; when administered of more than 1mg/kg, pilocarpine-induced salivary hypersecretion in anesthetized rabbits and rat gastric secretion suppression were found; when administered of 3.2mg/kg, rats had tachypnea, diarrhea, prone position, licking, weight gain suppression, temperature decrease, conditioned avoidance response suppression and moisture storing in small intestine and hyperfunction.

In oral administration of FK506 of more than 3.2mg/kg, it was found that acetic acid writhing had abirritation in mice; when administered of more than 10mg/kg, the pulse rate of rats decreased; when it is 32mg/kg, blood pressure of rats decreased, urine output and Na^+ excretion increased.

In the in vitro experiments of removed organ, when FK506 was 3.2×10^{-5} g/mL, contraction increase and muscle tension and hyperfunction of removed pregnant

uterus and non-pregnant uterus (estrus) are found.

1.2.1.2 Toxicology

Oral LD50 of rats were 134 mg/kg (male) and 194 mg/kg (female), the minimum lethal dose was 100 mg/kg in both male and female. Intravenous LD50 were 57 mg/kg (males) and 23.6 mg/kg (females), the minimum lethal doses were 32 mg/kg (male) and 18 mg/kg (female). Single oral dose of 250 mg/kg in baboon only caused mild acute poisoning. After intravenous administration of 50 mg/kg, acute shock symptoms can be observed.

Chronic toxicity trials in rats and baboons showed that the oral doses of this drug were 1.5 and 10.0 mg/kg/day, intravenous doses were 0.32 and 1.0 mg/kg/day, and slight, reversible renal toxicity was observed. Moreover, it was observed that part of the pancreas endocrine was damaged. This change was also reversible.

The minimum oral toxic doses in rats and baboons were 1.5 and 10.0 mg/kg/day respectively, intravenous toxic doses were 0.1 and 0.5 mg/kg/day respectively. In rats with doses of more than 0.5mg/kg/day, mild eye and peripheral nerve toxicities were observed, and when the dose was more than 3.2 mg/kg/day, the central nervous system would be affected.

It was observed that rabbits were particularly sensitive to intravenous administration of this product. When the dose was more than 2 × 0.05 mg/kg/day, cardiotoxic effects were observed.

Relevant in vivo and in vitro trials showed that the product didn’t have any mutagenic potential.

In the 1-year chronic toxicity trials (rats and baboons), and long-term carcinogenicity trials (18 months in mice, 24 months in rats), the product didn’t show any direct carcinogenic risk.

In the rat trials, conception, development of embryos and pups, development before and after birth and perinatal were only be damaged after giving obvious toxic dose (3.2 mg/kg/day). The only exception is that when giving this product of 0.1mg/kg/day, birth weight of pups had reversible decrease. Further trials conducted in rabbits also showed toxicity in embryos and pups. But it was only limited to daily dose of 1.0mg/kg, and the matrix also had obvious toxic and side reactions.

1.2.2 Clinical Data

For details, please refer to the latest edition of “Investigator's Brochure for tacrolimus”.

1.2.2.1 Clinical Pharmacokinetics

Absorption

Tacrolimus can be absorbed through gastrointestinal tract in the male. In about 1-3 hours after orally taking tacrolimus capsules, maximum blood concentration (Cmax) can be reached. In some patients, tacrolimus showed long-term continuous absorption, and thus producing a relatively flat absorption curve. The average oral bioavailability of tacrolimus was 20% to 25%.

After oral administration in liver transplant patients (0.30 mg/kg/day), the steady state blood concentration was reached within 3 days in the majority of patients.

Studies in healthy volunteers showed that when given the same dose, tacrolimus capsules 0.5mg, 1mg, and 5mg were bioequivalent.

In fasting conditions, absorption rate and absorption extent of tacrolimus were the highest. The postprandial absorption rate and absorption extent of tacrolimus were lower, especially after high-fat diet. High carbohydrate diet had no significant effect on this.

In stable liver transplant patients, moderate fat (34% calories) postprandial oral bioavailability of tacrolimus reduced. The decrease of AUC (27%), Cmax (50%) and increase of tmax (173%) were the evidence.

In a study of stable renal transplant patients, patients took standard continental breakfast immediately after taking tacrolimus, and its effect on oral bioavailability was not significant. The decrease of whole blood AUC (2-12%) and Cmax (15-38%) and increase of tmax (38-80%) was the evidence.

Bile wouldn’t affect the absorption of tacrolimus.

AUC values of tacrolimus and whole blood trough concentrations at steady state had strong correlation, so monitoring of whole blood trough concentrations can make good assessment on systemic absorption.

Distribution and elimination

For the intravenous drip in males, distribution of tacrolimus can be described as a two-compartment model. In the systemic circulation, tacrolimus was highly bound to erythrocyte, so the distribution ratio of whole blood/plasma concentration was about 20:1. In plasma, tacrolimus was highly bound to plasma proteins (> 98.8%), mainly including serum albumin and α-1-acid glycoprotein.

Tacrolimus was widely distributed in the body. Based on blood concentration, volume of distribution at steady state was approximately 1300 L (healthy subjects). According to whole blood concentration, the mean volume of distribution was 47.6 L.

Tacrolimus was a drug with low clearance rate. According to whole blood

concentration, the average total body clearance (TBC) of healthy subjects was approximately 2.25 L/h, while in the adult liver, kidney and heart transplant patients, the TBC were 4.1 L/h, 6.7 L/h, and 3.9 L/h respectively. TBC of pediatric liver transplant patients was approximately 2 times of adult liver transplant patients. The factors, such as low hematocrit and protein levels, which can lead to increase of unbound part of tacrolimus, or increase of corticosteroid drug-induced metabolism were considered as causes for high clearance rate after transplantation.

Tacrolimus had long half-life with wide variation. The average half-life of healthy volunteers was approximately 43 hours. In adult and pediatric liver transplant patients, the average half-life was 11.7 hours and 12.4 hours respectively, while that for the adult liver transplant patients was 15.6 hours. Clearance rate increase was caused by the shortened half-life of transplant patients.

Metabolism and biotransformation

Tacrolimus were generally metabolized in the liver, and the main metabolic enzyme was P450-3A4. It was also considered that tacrolimus was metabolized on the intestinal wall. Tacrolimus had a variety of metabolites. Only one metabolite was demonstrated in in vitro trial to have similar immunosuppressive activity with tacrolimus. Other metabolites only had weak or had no immunosuppressive activity. In system cycle, only one non-active metabolite existed in low concentrations. Thus, the pharmacological activity of tacrolimus was irrelevant to its metabolites.

Excretion

After intravenous and oral administration of C^{14} labeled tacrolimus, most substances with radioactivity were excreted in the faeces. About 2% of substances with radioactivity were excreted in the urine. Less than 1% of the parent drug of tacrolimus was detected in the urine and faeces, indicating that tacrolimus was almost completely metabolized prior to excretion: bile is the major route of excretion.

1.2.2.2 Clinical Efficacy and Safety

Four clinical trials were conducted in Japan in total: Phase II clinical trial (medication for 28 weeks, continuous medication from 28 weeks to 104 weeks at most), Phase II clinical continuous trial (continuous medication from 104 weeks to 312 weeks at most), Phase III clinical trial (medication for 28 weeks), and Phase III continuous trial (continuous medication from 28 weeks to February 2007 (to approval) at most).

Phase II clinical trials were conducted since November 1998 (medication for 28 weeks, continuous medication from 28 weeks to 104 weeks at most) to study its efficacy and safety, while placebo-controlled double-blind Phase III clinical trials on comparison between groups were conducted in April 2003 (medication for 28 weeks).

Meanwhile, continuous study with patients participating in phase II and III clinical trials as the objects was conducted to study the long-term efficacy and safety.

1) **Medication for 28 weeks (results in the main assessment period)**

Twenty one LN subjects with insufficient treatment effect by usual dose of steroids, or treatment difficulties with steroids agent due to adverse reactions, nephritis without remission were enrolled as subjects and orally administered 3mg of tacrolimus (can be increased to 5mg) after dinner once daily for 28 weeks.

The improvement rates above moderate at last (after 28 weeks) of primary efficacy endpoints of 24-hour urine protein, creatinine clearance, urine red blood cell count were 4/16 cases (25.0%), 3/11 cases (27.3%), 1/7 cases (14.3%).

In the safety review at last (after 28 weeks), 16/21 cases (76.2%) are above “basically safe”. There were 5 serious adverse reactions in one case (abnormal glucose tolerance, blood sugar (BS) increase, HbA1c elevation, glycated albumin elevation, positive urine sugar). For other adverse reactions, there were10/21 (47.6%) cases visible complications and the main symptoms included diarrhea, gastritis and other digestive symptoms, as well as hair loss and insomnia and so on. Only 1/21 cases (4.8%) of infection occurred, upper respiratory tract infections and vaginal candidiasis appeared in the same case. 8/20 cases (40.0%) had abnormal changes of clinical examination values, as the main item, hematologic value changes (leukocytosis and lymphocyte decrease) and so on.

2) **Continuous medication from 28 weeks to 104 weeks at most**

For lupus nephritis, 21 patients from Phase II clinical trial of FK506 21 were enrolled to complete the medication during specified main assessment period of 28 weeks, and after 28 weeks, 13 cases continued medication, among which 11 cases completed 104 weeks of medication.

The improvement rates above moderate of primary efficacy endpoints of 24-hour urine protein and creatinine clearance, improvement rate of urine cell cylinder were 6/13 cases (46.2%), 2/8 cases (25.0%) and 3/7 cases (42.9%) respectively at last, especially 24-hour urinary protein quantification had trend of enhanced improvement effect with time relative to improvement rates above moderate of 4/12 cases (33.3%) after 28 weeks, 5/8 cases (62.5%) after 104 weeks.

The final summarized safety above “basically safe” accounted for 11/13 patients (84.6%). The adverse reactions from 28 weeks to 104 weeks included 1 serious adverse reaction in one case (enteritis); others were visible complications 6/13 cases (46.2%), and the main symptoms were diarrhea and other gastrointestinal symptoms, hypertension, dizziness, etc. There were 3/13 cases (23.1%) of visible infection, including colitis, urinary tract infections and fungal dermatitis. There were 5/13 cases (38.5%) of abnormal changes of clinical examination value, including γ-GTP

increase, urinary sediment abnormality (white blood cells), etc. In addition, comparing with adverse reactions at 28 weeks after treatment, the incidence of adverse reactions from 28 weeks after medication to 104 weeks increased.

3) **Phase II continuous trial in Japan**

Subjects participated in Phase II clinical trials and completed the 104 weeks of treatment were enrolled to study the safety and efficacy of long-term medication for more than 104 weeks. In 11 subjects participated in Phase II clinical trials and completed 104 weeks of treatment, 9 cases participated in this trial. From completion of Phase II clinical trials to the start of this trial, there is no interval of not using the study drug and all cases completed the treatment in Phase II clinical trials would start the continuous medication after 104 weeks immediately.

In February 28, 2005, based on preliminary analysis, 4 patients continued the treatment, while the other 5 stopped. At last, based on preliminary analysis, the improvement rates over moderate of 24-hour urine protein and creatinine clearance rate were 33.3% (3/9 cases) and 16.7% (1/6 cases) respectively. Likewise, from improvement over mild, the rates were 77.8% (7/9 cases) and 66.7% (4/6 cases) respectively. Serum creatinine did not change in all cases, and red blood count in the urine in normal cases was relatively more. At last, based on preliminary analysis, cases with moderate improvement/assessment case accounted for 1/3, and similarly, the cylindrical cell in urine was 60.0% (3/5).

4) **Phase III clinical trial in Japan**

A double-blind, placebo-controlled, multi-center clinical trial in LN patients to evaluate the efficacy and safety of tacrolimus. The 63 patients used steroid agents of 10mg/day or more, and with treatment difficulties were enrolled as subjects (28 cases in FK506 group, 35 cases in placebo group) to take 3 capsules of designated study drug orally after dinner for 28 weeks (FK506 capsules 1mg or FK506 placebo capsules).

There are 5 primary efficacy endpoints (24-hour urine protein, urine red blood count, serum creatinine, anti-dsDNA antibody and complement C3). The change rate on final total score was -32.9±31.0% in FK506 group, 2.3±38.2% in placebo group. Comparing with placebo group, the FK506 group showed significant change rate.

The incidence of adverse reaction (can’t deny the causality of adverse events) was 92.9% (26/28 cases) in FK506 group, 80.0% (28/35 cases) in placebo group, and there is no significant difference between the 2 groups.

1.3 Summary of Key Safety Information for Study Drugs

Refer to the latest version of “Investigator’s Brochure for tacrolimus” for the main safety information of Tacrolimus.

Refer to the package insert of cyclophosphamide for the main safety information of cyclophosphamide.

1.4 Risk-Benefit Assessment

Tacrolimus is a macrolide immunosuppressant which has been used to prevent graft rejection after liver or kidney transplantation and for the treatment of graft rejection that can’t be controlled by other immunosuppressive drugs after liver or kidney transplantation application.

Immunosuppressant agents are widely used for lupus nephritis (LN) treatments. Comparing with the current standard cyclophosphamide treatment for LN, tacrolimus is used as another immunosuppressant to be developed for LN treatment. Other non-clinical and clinical studies confirmed that tacrolimus can improve the symptoms of lupus nephritis (see the latest version of the “Investigator’s Brochure for tacrolimus”).

Since all subjects in this Phase III study will receive one of the two treatments for LN, it is reasonable to expect that all the subjects can benefit from participating in the study.

This study was carefully designed and all known risks of candidates were minimized; all subjects were screened before participating in this study to reduce the probability and impact of these risks. In addition, the periodic safety monitoring in treatment and safety follow-up will guarantee rapid detection and appropriate treatment of any unexpected effects during the study.

In addition, the study protocol also includes well-defined criteria for permanent withdrawal of subjects from the study (Section 3.4). Moreover, participants can withdraw from the study at any time without giving reasons.

Overall, based on the available non-clinical and clinical data, and minimizing strategies for the risks above, current risk-benefit characteristics of the study is considered as acceptable.

2 STUDY OBJECTIVE(S), DESIGN AND VARIABLES

2.1 Study Objectives

The objective of this study is to evaluate the efficacy and safety of tacrolimus capsules for induction remission in patients with lupus nephritis, and compare the efficacy and safety with cyclophosphamide injections to indicate that tacrolimus capsules are not inferior to cyclophosphamide injection.

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a randomized, open, 1:1 parallel controlled, multi-center, non-inferiority clinical study.

Study group: tacrolimus capsules + steroid 147 subjects

Control group: cyclophosphamide injections + steroid 147 subjects

2.2.2 Dose Rationale

According to the previous results of clinical studies in Japan, comprehensive results of clinical studies for outside indications in China [24, 25] and the investigators' opinion, the standard dose of tacrolimus in the study is determined as 0.08-0.1mg/kg/d, and target concentration as 4-10ng/ml.

0.5 -1.0 g/m² BSA cyclophosphamide injections were selected based on that the KDIGO, ACR, EULAR/ERA-EDTA and Rheumatology branch of the Chinese Medicine Association all recommended this dose in treatment of lupus nephritis.

2.3 Variables

2.3.1 Primary Variable

Remission rate in endpoint assessment (24 weeks) (complete remission + partial remission)

Patients of early withdrawal are included in endpoint assessment. For the definition of efficacy variables, please refer to section 5.3.1.

2.3.2 Secondary Variables

1) 24-hour urine protein at all visits except Visit 2, 4, 5 (Day1, Weeks 4, 8, 12, 16, 20, 24), and change from baseline;

2) Serum albumin at all visits except Visit 2 (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24), and change from baseline;

3) Serum creatinine at all visits except Visit 2 (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24), and change from baseline; eGFR at all other post-baseline visits (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24) comparing with baseline, based on CKD-EPI formula: $141\times\min(Scr/k,1)^{\alpha}\times\max(Scr/k,1)^{-1.209}\times0.993^{Age}\times1.018$[if female] ×1.159[if black] (Scr [mg/dL], K= 0.9 for males or 0.7 for females, α= -0.411 for males or-0.329 for females, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1);

4) SLE-DAI and immune parameters (ESR, C3, C4, dsDNA) in Week 4, 12 and 24, and change of SLE-DAI and immune parameters in Week 4, 12 and 24 from baseline;

5) Renal biopsy AI (active index) and CI (chronic index) in Week 24, and change from baseline;

6) Percentage of patients converted to other immunosuppressive therapy in the study group and the control group during 24 weeks;

7) Percentage of patients with serum creatinine rise to two times of the baseline at 24 weeks, percentage of patients with dsDNA and ANA converting from positive to negative.

3 STUDY POPULATION

3.1 Selection of Study Population

Class III, IV, V, III + V, IV + V lupus nephritis patients diagnosed by renal biopsy.

3.2 Inclusion Criteria

1) Chinese male or female patients aged 18-60 years, 18.5≤Body Mass Index (BMI) <27;

   Note: Aged from 18 to 60 years of age inclusive.

2) Diagnosed as systemic lupus erythematosus (based on American Rheumatism Association Diagnostic Criteria 1997, please refer to appendix 3);

3) Diagnosed as III, IV, V, III + V, IV + V lupus nephritis (according to the LN classification in International Society of Nephrology and Renal Pathology Society (ISN/RPS) 2003) within 24 weeks before enrollment by biopsy diagnosis;

4) 24-hour urine protein ≥ 1.5g, Scr<260umol/L (or 3mg/dL);

5) Subject or his/her witness or legal representative signed the informed consent form.

3.3 Exclusion Criteria

1) Class II or VI lupus nephritis or with TMA;

2) Received immunosuppressants (mycophenolate mofetil (MMF), cyclosporine, methotrexate, mechlorethamine, chlorambucil, tripterygium preparations, leflunomide etc.) treatment with a duration of more than one week within 30 days prior to enrollment;

3) Received tacrolimus (except for topical use) or cyclophosphamide treatment within 30 days prior to enrollment;

4) Received a course of methylprednisolone (MP) pulse therapy or gamma globulin treatment or plasma exchange within 30 days prior to enrollment;

5) Patients with allergic history of tacrolimus, cyclophosphamide or methylprednisolone;

6) Pregnancy, lactation women or patient unwilling to take contraceptive measures;

7) Patients with estimated maintenance dialysis of more than eight weeks; or dialysis for more than two weeks prior to entering observation;

8) Patients received kidney transplantation or plan to have kidney transplantation recently;

9) Serum creatinine (Scr) ≥ 260umol/L (or 3mg/dl);

10) Patients suffering from liver dysfunction (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to 3 times of the upper limit of normal lab value) or bilirubin greater than or equal to 3 times of the upper limit of normal range;

11) Patients diagnosed with diabetes;

12) History of gastrointestinal bleeding or pancreatitis within 3 months;

13) Uncontrollable hyperkalemia after dietary therapy or reduction of potassium treatment (exceed upper limit of normal lab value);

14) Patients suffering from lupus pneumonia or lung injury;

15) Patients with anemia (hemoglobin < 7g/dl) or bone marrow suppression (WBC $<3.0\times10^9$/L, and/or neutrophils $<1.5\times10^9$/L, and/or platelets $<50\times10^9$/L) not

secondary to systemic lupus erythematosus;

16) With congenital heart disease, arrhythmia, heart failure and other serious cardiovascular diseases;

17) With refractory hypertension (defined as blood pressure still higher than 180/110 mmHg while taking three different types of antihypertensive drugs [one of them is diuretic] simultaneously);

18) Patients with recurrent tumors within 5 years;

19) Severe infection that requires intravenous antibiotics within 2 weeks prior to randomization;

20) Patients with infection of hepatitis B virus or hepatitis C virus; patients with active tuberculosis; patients with severe immunodeficiency diseases (including active cytomegalovirus infection (positive CMV IgM antibody), or human immunodeficiency virus (HIV) infection, etc.);

21) Patients with lupus encephalopathy or other life-threatening complication of systemic lupus erythematosus;

22) Patients participated in other clinical trials within three months before enrollment;

23) Patients considered as not suitable to participate in this study by the investigator.

3.4 Discontinuation Criteria for Individual Subjects

A discontinuation is a subject who enrolled in the study and for whom study treatment is terminated prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

The investigator or the sub-investigator will discontinue the study when study continuation becomes difficult in the study period for the reasons given in the following. For subjects who withdraw after taking the drug for the treatment period, the examinations and evaluations scheduled for the last visit(Visit 11) in the treatment period will be conducted to the extent possible at the time of discontinuation will be conducted as far as possible (see "V. FLOW CHART AND SCHEDULE OF ASSESSMENTS"). Subjects who withdraw due to an adverse event will receive appropriate treatment according to necessity. Those who withdraw from the study will be handled as discontinuations and the investigator or the sub-investigator will enter the reason for discontinuation, etc. in the eCRF.

1) Patients or their legal representatives volunteer to withdraw;
2) According to the patient's conditions, drugs that prohibited in the study or other immunosuppressive agents, or a second MP pulse therapy is needed;
3) Uncontrollable infection;
4) Adverse events lead to discontinuation of study, for example,
   i. AST, ALT: ≥ 3 times of the upper limit of normal range;
   ii. Scr: ≥ 3 times of the upper limit of normal range;
5) Lupus exacerbations during treatment; or lupus disease recurrence; or lupus disease relapse.
6) Violate inclusion/exclusion criteria;
7) Subjects don't take the study drug in accordance with the protocol for 14 consecutive days due to various reasons (such as infection, etc.);
8) The sponsor stops the trial for safety reasons;
9) Patients considered as not suitable to continue by the Ethics Committee for some reasons;
10) Patients considered as not suitable to continue the study by the investigators;
11) Tacrolimus capsules withdrawal > 14 consecutive days or cyclophosphamide injections pulse therapy of less than 4 doses;
12) Patients with WBC aplasia;
13) Subject becomes pregnant.

4 STUDY DRUGS

4.1 Description of Study Drugs

The study drugs consist of the investigational drug tacrolimus capsules and the control drug cyclophosphamide injection, for the treatment period.

4.1.1 Study drug(s): Tacrolimus Capsules 1mg

Brand name	Tacrolimus (Prograf®)
Active ingredient	Tacrolimus
Chemical Name	[3S-[3R*[E(1S*,3S*,4S*)], 4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26a-VI-decyl hydrogen - 5,19-dihydroxy- 3-[2- (4- hydroxy-3- methoxy – cyclohexyl)-

	1-methylvinyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c] [1,4] oxa heterocyclic tricosene -1,7,20,21 (4H,23H)-tetraone, monohydrate
Molecular formula	$C_{44}H_{69}NO_{12}\cdot H_2O$
Molecular mass weight	822.03
Formulation and content	White hard capsules with contents of white powder
Manufacturer	Manufacturer: Astellas Ireland Co., Ltd. Sub-packing enterprise: Astellas Pharma (China), Inc.
Storage conditions	Open the foil package, store at room temperature under 25℃ in its original packaging
Shelf life	36 months. After opening the foil package, it should be used within 12 months.

4.1.2 Control Drug(s): Cyclophosphamide Injection

General name	Cyclophosphamide injection
Active ingredient	Cyclophosphamide
Chemical Name	P- [N, N-bis (β-chloroethyl)] -1-oxo-3-aza-2-phospha-cyclohexane -P-oxide monohydrate
Molecular formula	$C_7H_{15}Cl_2N_2O_2P\cdot H_2O$
Molecular mass weight	279.10
Formulation and content	0.2g white crystal or crystalline powder
Manufacturer	Baxter
Storage conditions	Store in a well-closed container, protected from light and under 25℃.
Shelf life	24 months

4.1.3 Basic treatment: Steroid

Note: Please refer to the latest package insert of the products for the basic treatment.

4.1.3.1 Methylprednisolone injection

General name	6 - methyl prednisolone; Methylprednisolone
Active ingredient	Methylprednisolone sodium succinate
Chemical Name	6α-methyl-11β,17,21-trihydroxy-1,4-pregnadiene-3,20-dione
Molecular formula	$C_{22}H_{30}O_5$
Molecular mass weight	374.48
Formulation and contents	For 40mg formulation, the upper chamber of each 1ml dual chamber bottle contains diluent (9mg benzyl alcohol dissolved in water for injection), with the lower chamber containing Methylprednisolone sodium succinate and excipients: sodium phosphate monohydrate, disodium phosphate (anhydrous), lactose, 10% sodium hydroxide solution and water for injection. For 125mg formulation, the upper chamber of each 2ml dual chamber bottle contains diluent (18mg benzyl alcohol dissolved in water for injection), with the lower chamber containing Methylprednisolone sodium succinate and excipients: sodium phosphate monohydrate, disodium phosphate (anhydrous), 10% sodium hydroxide solution and water for injection. For 500mg formulation, there is one bottle of sterile powder and one bottle contains diluent (7.8ml, with 70.2mg benzyl alcohol dissolved in water for injection), with sterile powder contains Methylprednisolone sodium succinate and excipients: sodium phosphate monohydrate, disodium phosphate (anhydrous), 10% sodium hydroxide solution and water for injection.
Manufacturer	Pfizer
Storage conditions	Drugs haven't been mixed: Stored at room temperature (15-25℃). Solution has been mixed: stored at room temperature (15-25℃) and use within 48 hours
Shelf life	60 Months

4.1.3.2 Glucocorticoids

General name	Prednisone Acetate Tablets
Active ingredient	Prednisone acetate
Chemical Name	17α, 21-dihydroxypregn-1,4-diene-3,11,20 -trione 21-acetate
Molecular formula	$C_{23}H_{28}O_6$
Molecular mass weight	400.47

Formulation and content	White tablet
Manufacturer	TianJin LiSheng
Storage conditions	Store in a well-closed container, protected from light and in a dry place
Shelf life	36 months

4.2 Packaging and Labeling

All medications used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person in accordance with Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH-GCP guidelines, and applicable local laws/regulations.

4.3 Study Drug Handling

Current ICH-GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (e.g. pharmacist), and

- that such deliveries are recorded
- that study drug is handled and stored safely and properly
- that study drug is dispensed to study subjects in accordance with the protocol
- that any unused study drug is returned to the sponsor upon end of study or expiration of administration

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines should be followed:

- The investigator agrees not to supply study drugs to any persons except the subjects in this study.
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- A study drug inventory will be maintained by the investigator/pharmacist. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory

on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and returned medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.

4.4 Blinding

Not applicable.

4.5 Assignment and Allocation

Once subject eligibility to enter the study is confirmed at Day -3 before 1st administration of MP, subjects will be randomized to one of the treatment groups in a 1:1 ratio using a IWRS randomization.

Stratified randomization will be adopted to randomize the subject to one of the treatment groups. Pathological type of renal biopsy will be employed as stratification factor. Pathological types of subjects categorized as: III, IV, V, III+V and IV+V.

To minimize the risks of randomized patients not receiving the study drug, randomization will be conducted when all assessments in Visit 2 are completed and subjects are found suitable for randomization.

Once a subject number was assigned, even though the subject didn't receive the study drug, the number shall not be used again.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drugs and Other Medications

5.1.1 Dose/Dose Regimen and Treatment Cycle

1) Tacrolimus capsules

- Dose: Starting dose as 4mg/day, begin to monitor the blood concentration 7 days after administration. Dose adjustment beginning from 14 days after first dose, the target blood concentration is 4-10ng/ml, the target dose is 0.08-0.1mg/kg/d.
- Administration method: administered after the end of MP pulse therapy, it is recommended that the oral daily dose be administered in two divided doses (e.g. morning and evening). Capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to

achieve maximal absorption. In order to get table blood drug concentration result, please use even number of daily dose, within allowed target dose and equivalent dosage in the morning and evening.

- Duration of treatment: 168 days (24 weeks)

2) Cyclophosphamide injection

- Dose: Starting dose as 0.75g/m^{2}BSA, thereafter, dose adjustment target is 0.5-1.0g/m^{2}BSA, dose adjustment is 0.25 g/m² BSA each time. The hematology test (white blood cell count), patients' status and safety would be considered when adjust the dose, the investigators should make the judgement based on both scientific and ethic aspects to make the best decision to protect the patients' health and benefit.

  [DuBois formula：$BSA(m^2) = 0.007184 \times weight(kg)^{0.425} \times height(cm)^{0.725}$]

- Administration method: administered after the end of MP pulse therapy, intravenous injection after dissolved in 250ml saline every 4 weeks for 6 consecutive times.
- Mesna can be applied to prevent Cystitis and appropriate hydration therapy can be provided basing on edema of the patient.
- Duration of treatment: 168 days (24 weeks)

3) Glucocorticoids

- Dose: Methylprednisolone 0.5g/day
- Administration method: methylprednisolone intravenous pulse.
- Duration of treatment: 3 consecutive days

4) Prednisone tablets

- Dose: starting dose as 0.8 mg/kg/day and the maximum dose of 45mg/day. Reduce dose 4 weeks later by 5mg to 20mg/day every 2 weeks, then by 2.5mg to 10mg/day every 2 weeks and maintain.
- Administration method: oral
- Duration of treatment: 168 days (24 weeks)

5.1.2 Increase or Reduction in Dose of the Study Drugs

1) Tacrolimus capsules

- Begin to monitor blood concentration in 7 days after administration. If blood

drug concentration < 4ng/ml or > 10ng/ml, adjust the dose to the target blood concentration. If the blood concentration <4ng/ml with the target dose, increase the dose but with the maximum less than 0.15mg/kg/d, if with the maximum dose the blood concentration is still <4ng/ml, subjects can stay in the study only subjects can tolerate the treatment. If blood concentration > 10ng/ml, reduce dose by 25% and test blood concentration one week later; if blood concentration ≥ 15ng/ml, reduce dose by 50% or withdraw drug (such as occurrence of severe AE) and drug concentration should be retested within 7 days of reduce or interruption. When there is conflict, prioritize tacrolimus target blood concentration rather than the target dose.

5.1.3 Previous and Concomitant Medication (Drugs and Therapies)

5.1.3.1 Previous Medication (Drugs and Therapies)

All the drugs (previous drugs) and therapies (previous therapies) taken by the subjects 3 months prior to the day of signing the ICF and all previous therapies for lupus nephritis prior to the day of signing the ICF will be entered in the eCRF as follows.

<table>
<tr><th>Previous medication</th><th>Study period</th><th>Items recorded on eCRF</th></tr>
<tr><td>Previous drugs (all drugs)</td><td rowspan="2">3 months prior to the day of signing the ICF</td><td>Drug name, daily dosage, route of administration, treatment period, reason for use, administration time</td></tr>
<tr><td>Previous therapies</td><td rowspan="2">Therapy name, treatment period, reason for treatment, time of treatment</td></tr>
<tr><td>Previous therapies for lupus nephritis</td><td>Prior to the day of signing the ICF</td></tr>
</table>

5.1.3.2 Concomitant Medication (Drugs and Therapies)

All the drugs (concomitant drugs) and therapies (concomitant therapies) taken by the subjects from the day of signing the ICF to completion of the study will be entered into the eCRF as follows. Anaesthetic and other operation related drugs are not needed to be recorded.

Concomitant medication	Study period	Items recorded on eCRF
Concomitant drugs	From the day of signing the ICF to	Drug name, daily dosage, route of administration, treatment

	completion of the study.	period, indication, administration time
Concomitant therapies		Therapy name, treatment period, indication, time of treatment

1. Prohibited concomitant medications

- Other immunosuppressive agents, such as mycophenolate mofetil, azathioprine, cyclosporine, methotrexate, rapamycin, mechlorethamine, chlorambucil, vincristine, procarbazine, leflunomide, tripterygium
- Plasmapheresis or immunoglobulin through intravenous infusion
- Biological agents (infliximab, adalimumab, etanercept, efalizumab, alefacept)
- Non-steroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors, high-dose or long-acting sedatives are prohibited in induction remission period
- Using of other drugs that may have an influence on blood-drug concentration (see Appendix 8 “Drug that possible interact with Tacrolimus”) should be avoided with efforts

2. Permitted concomitant medications

ACEI and ARB: can be continued during the study if administered before enrollment. But if high blood pressure occurs during the trial, ACEI/ARB should be replaced by CCB or other antihypertensive agents. Calcium, vitamin D and/or dimethyl phosphate can be used to prevent steroid-induced osteoporosis

- Symptomatic treatment can be used for minor gastrointestinal adverse events (e.g. nausea, vomiting, and diarrhea), (for example: loperamide for diarrhea, antiemetic metoclopramide or domperidone for nausea, vomiting). Proton pump inhibitors or ranitidine are allowed for indigestion, while magnesium or aluminum agents containing antacids are to protect the gastric mucosa, but it can’t be used with the study drugs at the same time, and can be taken one hour before or two hours after taking the study drugs.
- Amphotericin and nystatin are allowed to prevent fungal infection; low dose of sulfamethoxazole/trimethoprim are allowed for pneumocystis carinii pneumonia.
- Granulocyte colony stimulating factors are allowed for neutropenia of severe infections (infections require intravenous antibiotics)
- Erythropoietin can be used for severe anemia (Hb < 10g/dl)
- Low molecular heparin can be used as early stage anticoagulant to prevent

thrombus and myocardial infarction according to clinical needs

3. Concomitant drugs that investigators need to monitor the blood concentration closely in tacrolimus group when used.

- Drugs that possible interact with tacrolimus (see the Appendix 8 of the full protocol)

5.1.4 Treatment Compliance

The investigator or sub-investigator will confirm the drug compliance based on the information provided by the subjects or number of study drug returned in each visit. The subjects are required to return any unused drugs. From Visit 4 to the end of the trial, drug compliance need to be confirmed in each visit. The number of dispensed, returned and lost study drug will be recorded in eCRF. Investigator/pharmacist will record the study drug that can't be recovered as well as the reasons (if any) in the drug count table.

Even any subject stops the visit and it's hard to get drug compliance information, the investigator or sub-investigator should contact the subject by telephone, letters to confirm drug compliance and try to recover the unused drugs as possible.

If the study drugs can't be taken due to adverse events, it should be input in the specified portion of eCRF.

For subjects with poor compliance (defined as taking < 80% or > 120% of the required number of tablets or not take drugs according to the protocol for 7 consecutive days), they should be guided based on the importance of the study protocol and the dosing regimen.

5.1.5 Emergency Procedures and Management of Overdose

Tacrolimus

The experience in overdose is limited.

Early clinical experience suggested that overdose symptoms (initial dose is 2-3 times of the recommended dose) may include kidney, nerve and cardiac disease, impaired glucose tolerance, hypertension, and electrolyte imbalance (hyperkalemia). Excessive immunosuppression can increase the risk of serious infection. Liver function has significant effects on the pharmacokinetic parameters before and after surgery, so the patients with liver transplant failure and using this product after other immunosuppressive agents must be closely monitored to avoid overdose. Tacrolimus has no specific antidote yet. If overdose occurs, general supportive therapy and symptomatic treatment should be used.

Because of its poor water solubility, and extensive binding with plasma protein and erythrocyte, tacrolimus can't be cleared through blood dialysis. For patients with very high blood concentrations, it has been reported that penetration and dialysis can significantly reduce blood concentrations of tacrolimus, while for oral overdose, gastric lavage and the use of adsorbents (such as activated charcoal) may be helpful.

Cyclophosphamide injection

There is no antidote for cyclophosphamide yet, so cautions should be paid to the dose in using.

But dialysis can help cyclophosphamide excretion, so when treating cyclophosphamide suicide, overdose and poisoning, hemodialysis should be carried out as soon as possible. Based on the blood concentration of cyclophosphamide that does not metabolize, dialysis clearance rate can be calculated up to 75ml/min (the normal renal clearance rate is 5-11 ml/min). There is also a set of experiments reported the clearance rate of dialysis as 194 ml/min. After 6 hours of dialysis, the dose of cyclophosphamide in dialysis fluid can be tested as about 72% of drug dose.

Drug overdose can be complicated by bone marrow suppression and leukopenia. The severity and duration of myelosuppression depend on the dose. Blood counts and monitoring should be often conducted in patients in treatment. If there is neutropenia, treatment for infection prevention should be given or after infection, antibiotics should be used for treatment. If the platelet counts decrease, platelet replacement should be conducted as needed. Mesna can be applied to prevent cystitis so as to reduce urinary tract toxicity.

Note: intravenous infusion leakage of cyclophosphamide wouldn't cause damage to the tissues around the vein, because its cytostatic effect only shows after its metabolism by the liver. If there is a large area of drug leakage, infusion should be stopped to conduct partial treatment to drain fluid leakage, and wash with saline, at the same time, it is recommended to keep the infusion site physically immobile.

5.1.6 Criteria for Continuation of Treatment

Not applicable.

5.1.7 Restrictions During the Study

Not applicable.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

After obtaining written informed consent, the following subject backgrounds will be confirmed and entered in the eCRF with previous treatments.

- Birth year and date
- Sex
- Height
- Body weight
- History of smoking, and history of alcohol use
- Race

5.2.2 Medical History

During screening period, medical history will be recorded in eCRF.

1) Previous medical history

- Diseases resolved by the day of signing the ICF are included as previous history and will be entered into the eCRF including diagnostic name, onset time, and recovery time.
- As a rule, temporary diseases resulting in a complete recovery of the subject (such as common cold) as well as otorhinolaryngological, dental, dermatological, and ocular diseases will not be recorded.

2) Concomitant diseases

- Diseases not resolved by the day of signing the ICF will be defined as concomitant diseases.
- All concomitant diseases will be investigated and the diagnostic names and onset times will be entered into the eCRF.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

During screening period, the following items concerning lupus nephritis, which is the target disease in this clinical study, will be confirmed and entered into the eCRF.

1) Diagnosis: lupus nephritis

    - Systemic lupus erythematosus (diagnosis is based on diagnostic criteria of American Rheumatism Association 1997, refer to appendix 3)

2) Description of targeted disease: diagnosis time, severity, pathological class, duration and symptoms of lupus nephritis.

   - Diagnosed as Class III, IV, V, III + V, IV + V lupus nephritis in renal biopsy within 24 weeks before enrollment (according to LN classification of International Society of Nephrology and Renal Pathology Society (ISN/RPS) 2003)
   - SLE disease activity index (SLE-DAI)

5.3 Efficacy Assessment

Data obtained in Visit 1 will be used as baseline value to evaluate the efficacy.

All blood samples, urine samples, and pathology specimens should be collected to detect the following indicators in the planned specific visits. All blood and urine samples will be collected and prepared at the site. HIV will be tested at site lab; other samples will be transported to the central lab for analysis. Investigators are recommended to complete CMV, A-Sm, and ACA test at site lab for the purpose of shortening the screening period. Should these tests be not applicable at site lab, central lab will do it instead. Patients had renal biopsy within 24 weeks and without significant change in the disease conditions don't have to re-test in enrollment. The renal biopsy at the end of the study observation is optional which is determined based on the patients' willingness. Please refer to "V. flowchart and assessment schedule" for the specific timetable for test:

1) 24-hour urinary protein quantitation
2) Serum albumin
3) Serum creatinine
4) Immune parameters: ESR, complement C3, C4, dsDNA, Sm, ACA, ANA
5) SLE-DAI (For scoring criteria, refer to Appendix 4)
6) Renal biopsy pathological AI (active index), CI (chronic index); (For scoring criteria, refer to Appendix 6)
7) Urinary sediment

5.3.1 Primary Efficacy Endpoints: Remission Rate in Endpoint Assessment (24 weeks) (Complete Remission + Partial Remission)

Patients of early withdrawal are included in endpoint assessment

Definition of efficacy endpoints:

- Complete remission: urine protein < 0.5g/24hr, and serum albumin≥3.5g/dl, and stable renal function (Scr in the normal range or Scr increase ≤ 15% baseline value)
- Partial remission: urine protein < 3.5 g/24hr, and urine protein decreased by >50% comparing with the baseline, and serum albumin ≥ 3.0g/dl, and stable renal function (Scr in the normal range or Scr increase ≤ 15% baseline value)

5.3.2 Secondary Efficacy Endpoints

1) 24-hour urine protein at all visits except visit 2, 4, 5 (Day1, Weeks 4, 8, 12, 16, 20, 24), and change from baseline;

2) Serum albumin at all visits except visit 2 (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24), and change from baseline;

3) Serum creatinine at all visits except visit 2 (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24), and change from baseline; eGFR at all other post-baseline visits comparing with baseline, based on CKD-EPI formula: $141\times\min(Scr/k,1)^{\alpha}\times\max(Scr/k,1)^{-1.209}\times0.993^{Age}\times1.018$[if female] $\times1.159$[if black] (Scr [mg/dL], K= 0.9 for males or 0.7 for females, α= -0.411 for males or-0.329 for females, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1);

4) SLE-DAI and immune parameters (ESR, C3, C4, dsDNA) in Week 4, 12 and 24, and change of SLE-DAI and immune parameters in Week 4, 12 and 24 from baseline;

5) Renal biopsy AI (active index) and CI (chronic index) in Week 24, and change from baseline;

6) Percentage of patients converted to other immunosuppressive therapy in the study group and the control group during 24 weeks;

7) Percentage of patients with serum creatinine rising to two times of the baseline within 24 weeks, percentage of patients with dsDNA and ANA converting from positive to negative within 24 weeks.

5.4 Safety Assessment

The data obtained in Visit 1 will be used as the baseline of safety assessment. The following tests and observation should be conducted for safety assessment. HIV is tested at site lab; other lab tests are done at the central lab. Investigators are recommended to complete CMV, A-Sm, and ACA test at site lab for the purpose of shortening the screening period. Should these tests be not applicable at site lab, central lab will do it instead. Please refer to “V. flowchart and schedule of

assessment" for the timetable of tests.

5.4.1 Vital Signs

Blood pressure and pulse rate should be tested after sitting for 5 minutes. Blood pressure should be measured with the same method on the same arm for 2 consecutive times with interval of 1-2 minutes. The average value of two measurements of blood pressure will be taken as the value for blood pressure. For the measurement of pulse rate, if there are several measurements, the first measurement of each visit should be recorded on eCRF. Please refer to "V. flowchart and assessment schedule" for the timetable of tests.

5.4.2 Adverse Events

Adverse events after signing ICF should be collected (starting from Visit 1), till 15 days after the last visit. If adverse event occurred 15 days later after the last visit and investigator could not rule out the relationship between the event and study drugs, the event should also be collected. Adverse events or their changes will be obtained from the spontaneous report, physical examination, electrocardiogram (ECG), clinical lab test result and study related test of the subjects.

For adverse events, the following information should be obtained: name of the event, onset date, start time, end date, the results and severity (see "5.5.4 Criteria for severity definition of adverse events"), severity (see "5.5.2 Definition of serious adverse events (SAE)"), measures taken (giving the study drug and other treatments), and the causality with the study drug, as well as the reasons for the determination, if necessary, the details of measures taken and clinical process should also be specified.

If the disease name of a certain adverse event can be determined with the signs or symptoms, disease name served as the diagnosis should be preferred in record rather than the signs and symptoms. If the diagnosis can't be made based on the signs or symptoms, the investigators or sub-investigators can treat each sign or symptom as separate adverse event.

If adverse event (including abnormal laboratory values) reoccurs after brief disappearance, it should be treated as a new adverse event. If there are complications or worsening of adverse events, they should be treated as new adverse events.

In Visit 3 and the subsequent visits, investigators or sub-investigators assess various changes of lab test values. For the changes of lab test values in treatment and follow-up period, they should be compared with test values in Visit 1 (baseline) to

determine whether there is an abnormal condition. No matter whether the lab test values are within the normal range, abnormal changes with clinical significance will be considered as adverse events, but for symptoms, signs or diseases related abnormal changes have been recorded as adverse events will not be treated as separate adverse event.

Lack of efficacy/disease progression does not belong to AE.

Please refer to Section 5.5 “adverse events and other safety aspects” for AE details.

5.4.2.1 Adverse Events of Possible Hepatic Origin

Subjects with AEs of hepatic origin accompanied by liver function tests abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

The test should be conducted according to the terms listed in Appendix 2. Please refer to “V. flowchart and schedule of assessment” for the timetable of tests.

Once the AST or ALT values of subjects exceed 2 times of the upper limit of normal, or Scr values exceed 2 times of the upper limit of normal, retesting is strongly recommended within 2 weeks after the first test or as soon as possible.

All samples should be collected in fasting state and prior to giving the study drug. Subjects in non-fasting state when taking samples should return to the site for sampling within the specified period.

5.4.4 Physical Examination

The investigator or sub-investigators should confirm the conditions of subjects through inquiry, inspection and palpation and record the abnormal conditions on medical records or other source files.

5.4.5 Electrocardiogram (ECG)

The investigator or sub-investigators should be responsible for interpreting each 12-lead ECG, and assess it based on 3-level system (normal, abnormal without clinical significance, or abnormal with clinical significance). In addition, abnormal results should be specified. ECG copies or duplicates shall be submitted to the sponsor. For the timetable of tests, please refer to “V. flowchart and assessment

schedule".

5.4.6 Imaging

Since screening period (Visit 1), subjects should have bilateral chest X-ray examination regularly. For the timetable of tests, please refer to "V. flowchart and assessment schedule".

Diagnosis and treatment for cerebrovascular or cardiovascular events, if MRI or CT scan, ultrasound examination, angiography, X-ray, or other imaging tests are carried out, even conducted by other institution other than the site, relevant imaging results should be obtained as possible and submitted to the sponsor.

5.4.7 Key Observations

Key observations of this study: incidence of infection, gastrointestinal reactions, bone marrow suppression, abnormal liver function, hyperglycemia and renal failure.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG result, physical examination) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or examination value is clinically significant in the opinion of the investigator

5.5.2 Definition of Serious Adverse Events (SAEs)

A serious AE is any untoward medical occurrence at any dose which leads to following outcomes:

- Results in death
- Is life threatening (an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other major medical events

For hospitalization, when hospitalization is not associated with an AE and evidence supports this, the hospitalization itself is not considered to be an AE, providing that the cause (non-AE) of the hospitalization is mentioned in the report. For example: Admission for treatment of a pre-existing condition not associated with the development of a new AE or with an aggravation of the pre-existing condition or previously planned admissions (e.g. admission for routine checkups, patient education, planned medical procedures, etc.).

For significant medical events, medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate, such as those events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are as follows: intensive treatment in an emergency room or at home for allergic bronchospasm; blood crisis or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Additionally, Astellas requests that all medical events listed in Appendix <5> (EVENTS ALWAYS CONSIDERED TO BE SERIOUS) should be reported as SAE.

If a subject becomes pregnant during treatment, this should be reported as if it were a SAE. Refer to Section 5.5.7. Procedure in Case of Pregnancy

5.5.3 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "adverse events whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	**Criteria for casual relationship**

Not related	A clinical event, including laboratory test abnormality, without a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying diseases provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a clear time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

5.5.4 Criteria for Defining the Severity of an Adverse Event

The following standard with 3 grades is to be used to measure the severity of adverse events, including abnormal clinical laboratory values.

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator or sub-investigator must report to the sponsor / delegated CRO by telephone or fax immediately (within 24 hours of awareness or as soon as possible).

The investigator should complete and submit a SAE report form containing all information that is required by the Regulatory Authorities to CFDA, PFDA, IEC and sponsor / delegated CRO by fax or email within 24 hours of awareness

For specific contact information, please see chapter II contact information of key personnel of sponsor. Please fax SAE report form to:

- CFDA fax number: 010-88363228
- Pharmacovigilance Department of CRO fax number: 010-88019165

Full details of the SAE should also be recorded on the medical records and on the CRF.

The following minimum information is required:

- ISN/Study number
- Subject number, sex and age
- The date of report
- Signature of investigator who reported the SAE.
- Administration of study drugs
- A description of the SAE (event, seriousness of the event)
- Causal relationship with the study drug

The severity of the SAE will be graded as mild, moderate or severe and the investigator will make a judgment as to whether the SAE was related to study drug (see section 5.5.4 and 5.5.3 respectively).

The sponsor or delegated CRO will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission to their IRB/IEC within timelines set by CFDA. The investigator should provide written documentation of IRB/IEC notification for each report to the sponsor.

5.5.6 Follow-up to Adverse Events

Reporting procedures for follow-up reports is identical to that for initial reports.

All adverse events occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized. (all follow-up results should be reported to the sponsor or delegated CRO).

If during adverse event follow-up, the adverse event progresses to an *"*SAE*"*, or if a subject experiences a new SAE, and relation with the study drugs cannot be excluded, the investigator must immediately report the information to CFDA, PFDA, IEC, the sponsor or its delegated CRO in accordance with the procedures and timelines as specified in Section 5.5.5.

5.5.7 Procedure in Case of Pregnancy

Female subjects with childbearing potential must receive pregnancy test at screening, and the investigators should ensure that the pregnancy test result of each female subject with childbearing potential before drug administration is negative. Only those female subjects with postmenopausal for at least 2 years, or permanent

sterilization, for example by tubal ligation, hysterectomy or bilateral salpingectomy, are considered as infertile.

Subjects and their sexual partners must take acceptable and effective contraceptive methods during the study and within 30 days after the end of the study. Acceptable and effective contraceptive methods: IUD, condoms plus spermicide, contraceptive diaphragm plus spermicide and sterilization. Subjects should have pregnancy test again at the end of the study or withdrawal from the study.

After confirming the pregnancy of female subjects, the investigators should stop the study drug immediately, and perform withdrawal process of female subjects. If the female subjects or the sexual partners of the male subjects get pregnant during the study or within 30 days after stopping the study drug, investigators should report the information to sponsor or its delegated CRO within 24h after awareness of the event. Pregnant events should be recorded in Pregnancy Event Reporting Form, which should contain the following information: EDD (expected delivery date), expected termination of pregnancy date, LMP (last menstrual period), expected conception date, pregnancy outcome, data of neonate (s), etc. Follow-up information of pregnancy events should be also included in this form, where assessment concerning the potential causal relationship between the study drugs and any abnormal pregnancy outcome(s) should be provided. In case of any SAEs during the pregnancy, investigators should report the information following the procedures as specified in Section 5.5.5. The outcome of pregnancy should be followed up until fetal birth or 30 days after the end of pregnancy with other ways.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including deformity in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy is mentioned below.

- ″Spontaneous abortion″ includes abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.
- If an infant died more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator.
- In the case of a delivery of a living newborn, the ″normality″ of the infant is evaluated at the birth.
- ″Normality″ of the miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

5.5.8 Supply of New Information Affecting the Conduct of the Study

When new information become available, which is necessary for conducting the clinical study properly and also which will lead to a protocol amendment, the sponsor should inform regulatory authorities, as well as all investigators involved in the clinical study, who will then inform the IRB/IEC of such information, and when needed, should amend the subject information.

5.6 Study Drug Concentration

Based on the clinical data of tacrolimus in transplantation field, the absorption and metabolism of tacrolimus in human body have great individual differences. Therefore, the blood concentration of tacrolimus needs to be monitored during treatment, and the dose needs to be adjusted based on the blood concentration. The blood concentrations of tacrolimus in this trial are tested by Covance central lab.

5.6.1 Blood Sampling

Subjects in tacrolimus group need to take blood samples to test the blood concentration in each visit at Visit 4 and from Visit 6 to the last visit. An unscheduled visit may be initiated between visit 5 and Visit 6 if dose adjustment is necessary.

1) At each sampling time point, 4ml whole blood samples for detection of tacrolimus are collected in EDTA Vacutainer (K2EDTA anticoagulants in the tube with purple lid)
2) After sample collection, invert the blood collection tube for several times to mix the sample well.
3) Put the sample collection tube in ice bath or water bath. Centrifuge is not required.
4) Invert the blood collection tube for several times to mix the whole blood sample well, and spit the whole blood sample to two samples with substantially the same volume following standard experimental procedure, the storage tube for split charging need to be labeled.
5) The labels on the storage tube need to be pasted firmly. The contents of label include subject number, initials of subjects.
6) Within 90 minutes after sample collection, store the parallel split plasma samples in the refrigerator at -20℃.
7) Within 24 hours after samples collection, No.1 split whole blood samples are shipped to Covance central lab to the concentration of tacrolimus in whole blood.

No.2 split samples are kept in the center first, and then transported to Covance central lab if necessary. In each batch of shipping sample, sufficient dry ice should be filled to control the temperature of sample in delivery.

5.7 Total volume of blood sampling

Total volume of blood sampling for TAC group subjects is about 113.3mL, for CTX group is about 85.3mL. The following table lists the blood volume required for each visit.

Visit	V1	V3	V4	V5	V6	V7	V8	V9	V10	V11
Hematology, HbA1c	2mL	2mL	2mL	2mL	2mL	2mL	3mL	2mL	2mL	2mL
Blood biochemistry, blood lipids and electrode	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL
ESR	1.2 mL	--	--	--	1.2 mL	--	1.2 mL	--	--	1.2 mL
Other (Immunology, Virology)	20.5 mL	--	--	--	5mL	--	5mL	--	--	5mL
TAC blood concentration*	--	--	4mL	--	4mL	4mL	4mL	4mL	4mL	4mL
TAC Group Sampling volume in each visit	26.2 mL	4.5 mL	8.5 mL	4.5 mL	14.7 mL	8.5 mL	14.7 mL	8.5 mL	8.5 mL	14.7mL
CTX Group Sampling volume in each visit	26.2 mL	4.5mL	4.5mL	4.5mL	10.7mL	4.5mL	10.7mL	4.5mL	4.5mL	10.7mL

* Only collected for subjects in TAC group

Sampling time points are as follows:

- Routine blood test, blood biochemistry, blood lipids, immunology, ESR, HbA1c: fasting state is required for blood sample collection;
- Blood concentration of TAC: the sampling time of subjects in TAC group is before taking TAC in the day of visit and 12 ± 2 hours after the last dose;

The sampling volume may change in case of required retest or unscheduled visits.

6 TERMINATION OF THE CLINICAL STUDY

1) When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reasons to the investigator.
2) If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor of the discontinuation and the reason for it.

7 STATISTICAL METHODOLOGY

The primary variable, secondary variables, and other technical details concerning data analysis will be written in a separate statistical analysis plan (SAP), the data will be reviewed and the SAP will be finalized before database lock.

7.1 Sample Size

The determination of bound of non-inferiority test refers to the Phase III, randomized, double-blind, parallel-group, placebo-controlled study in Japan (Study No.: FJ-506-LN02). The complete plus partial remission rate in the placebo group and tacrolimus group of this study were 2.9% and 46.4% respectively. If assuming that cyclophosphamide has the same efficacy with tacrolimus, the efficacy value of cyclophosphamide is 43.5%, the bound of non-inferiority test should be set as 1/3 of the efficacy value as 15%. Assuming the complete plus partial remission rate in this study is between 70% and 100%, based on the information, the complete plus partial remission rate of tacrolimus and cyclophosphamide should be 80%. Based on the assumptions above, calculating as test efficacy of 80%, 125 patients are needed for each group to demonstrate that tacrolimus is non-inferior to cyclophosphamide. 294 patients are planned to be enrolled assuming 15% of lost to follow-up, dropout and

other conditions.

7.2 Analysis Set

7.2.1 Full Analysis Set (FAS)

Full analysis set (FAS) is defined as all subjects receiving at least one dose of the study drug, and with any efficacy data.

7.2.2 Per Protocol Set (PPS)

Per protocol set (PPS) includes subjects in the full analysis set that complete follow-up of 12 weeks (85±5 days) or more, and includes those withdraw early due to lack of efficacy; medication compliance is between 80% -120%; no major protocol violations. Major protocol violations will be clearly defined in the statistical analysis plan. These subjects are the main population for efficacy analysis.

7.2.3 Safety Analysis Set (SAF)

The safety population included all subjects receiving at least one dose of the study drug.

7.2.4 Pharmacokinetic Analysis Set (PKAS)

Not applicable.

7.3 Demographics and Other Baseline Characteristics

Baseline is defined as the last assessment before administration of the study drug (screening assessment). FAS, PPS and SAF are analyzed.

Two-sided significance level is set at 5%. Subgroup analysis and calibration analysis may affect the effect of malconformation factors between groups in efficacy assessment on the analysis of primary endpoints.

7.4 Analysis of Efficacy

This analysis will be conducted in PPS and FAS, and PPS will be the primary efficacy analysis set.

The statistical analysis will consist of:

- Descriptive statistics for the quantitative variables, including the mean, 95% CI on the mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, maximum, and the number of observations.
- Frequency distribution for the qualitative variables including the number and percentage for each of the scores or categories, and the number of observations.
- Non-inferiority testing for the primary efficacy variable.
- Statistical verification for the secondary efficacy variables.

All tests will be performed two-sided, at the 5% level of significance.

A SAP will be prepared prior database lock describing the data analysis in more detail. Deviations from the SAP will be justified in the study report.

7.4.1 Analysis of Primary Variable

7.4.1.1 Primary Analysis

Primary efficacy endpoints are evaluated though two-sided 95% CI. 95% CI of the difference between two treatment groups (tacrolimus group - cyclophosphamide group) is used to evaluate whether the remission rate after 24 weeks in tacrolimus group is non-inferior to cyclophosphamide group. Non-inferiority bound is set as 15%, if the lower limit of the 95% CI ≥ -15%, then the non-inferiority conclusion can be drawn. The primary analysis set of efficacy analysis is PPS population.

7.4.1.2 Sensitivity Analysis

Sensitivity analysis is to assess the robustness of the results of the primary analysis. Approaches of sensitivity analysis will be described in SAP.

7.4.1.3 Subgroup Analysis

To evaluate the consistency of primary endpoint over demographics and other baseline characteristics, subgroup analysis will be performed. Subgroups will be described in SAP.

7.4.2 Analysis of Secondary Variables

Secondary efficacy endpoints are mainly analyzed through comparing test. The statistical description of change from baseline in each required visit should be given. For the difference between the groups of change from baseline of two treatment

groups in each visit, the estimated value and 95% CI should be calculated.

7.4.3 Analysis of Other Variables

Not applicable.

7.5 Analysis of Safety

Safety endpoints include adverse event, vital signs and lab test.

This analysis will be conducted in SAF. The two-sided significance level of all statistical tests will be 5%.

All adverse events will be analyzed using preferred term and major system organ classification codes in MedDRA.

Analyses of adverse events appearing after treatment include:

- Summarize frequency distribution by category of subjects with adverse events, serious adverse events, and adverse events and serious adverse events leading to permanent discontinuation of the study drug;
- Summarize frequency distribution of subjects with adverse events according to major organ system classification codes and preferred term in MedDRA (according to the correlation with the study drug and severity).

Descriptive statistical analyses are conducted to vital signs and lab tests.

7.6 Analysis of Pharmacokinetics

Not applicable.

7.7 Other Analysis

Not applicable.

7.8 Interim Analysis (and Early Termination of Clinical Study)

Not applicable.

7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

When calculating the primary efficacy endpoints (remission rate in endpoint assessment), missing data will be filled by using last-observation-carried-forward method. Secondary efficacy endpoints analysis only includes subjects without missing data in baseline, and the intermediate missing data will be filled with last-observation-carried-forward method. Whether outliers and follow-up data outside the visit windows are included in the analysis will be discussed in the data auditing meeting and determined before database locking.

8 Operational and Administrative Considerations

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The investigator or designee will enter data collected using an Electronic Data Capture (EDC) system.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

For screening failures, informed consent date, screening date and reason for screening failure will be collected in screening failure log (SFL), if applicable. This information can be entered into the study database.

Central laboratory data will be transferred electronically to the Data Management Center at predefined intervals during the study.

The laboratory may provide the Data Manager with a complete and clean copy of the data, accompanied by a Quality Control statement.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, height and body weight)
- Inclusion and exclusion criteria details

- Randomization number
- Participation in study and signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- Adverse events (onset time, outcome, severity, seriousness, treatment, other measures taken, and causal relationship to the study drug) and concomitant medication (if applicable).
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)
- Other comments in the eCRF (the comments in the CRF for follow-up for cases in which follow-up investigation of adverse events is conducted)

8.1.3 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning CRA(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the site must accept monitoring and auditing by the sponsor as well as inspections from the IRB/IEC and CFDA. In these instances, they must provide all study-related records, such as source documents (refer to Section 8.1.2 "Specification of Source Documents") when they are requested by the sponsor CRAs and auditors, the IRB/IEC, or CFDA. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data management will be coordinated by the Data Science/Data Operations Department of the sponsor or delegated CRO in accordance with the SOPs for data management. All study specific processes and definitions will be documented by Data Management. Coding of medical and medicine terms will be performed using MedDRA and WHODDE.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

Prior to concluding the study contract, the IRB/IEC will review and approve the protocol, Investigator's Brochure (IB), and various documents used to obtain a subject's consent to secure the subject's human rights, safety, and welfare.

8.2.2 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to GCP, ICH Guidelines and the applicable laws and regulations.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent Form

Prior to execution of the clinical study, the investigator should prepare the written informed consent form and other written information in collaboration with the sponsor and revise the information whenever necessary. The written informed consent form and any other written information should be submitted to the sponsor and be subject to prior approval by the IRB/IEC.

- The investigator/sub-investigator is responsible for explaining the nature and purpose of the study as well as other study-related matters to subjects, using the written information, and for obtaining their full understanding and written consent to participate in the study of their own free will.
- The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the written information, or write down his/her name, and date the form.
- Informed consent must be obtained by the time that the first observations / examinations of the pre-investigational period are performed.
- The investigator or other responsible personnel must give a copy of the signed consent form to the subject and store the original appropriately in accordance

with the rules at the site concerned.

- The investigator or other responsible personnel should note the following when obtaining consent from subjects:
  - No subject may be subjected to undue influence, such as compulsory enrollment into a study.
  - The language and expressions used in the written information should be as plain and understandable as possible. Subjects should be given the opportunity to ask questions and receive satisfactory answers to the inquiry, and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or contents that causes the subject to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the site, the investigator/sub-investigator, collaborators, or the sponsor from liability for negligence.
- The signed consent forms will be retained by the investigator and made available (for review only) to the CRA and auditor upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1) The investigator/sub-investigator will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study (e.g., report of serious adverse drug reactions). The communication should be documented in the subject's medical records, and it should be confirmed whether the subject is willing to remain in the study or not.
2) If the investigator recognizes the necessity to revise the written information in the terms and conditions applicable to paragraph 1, the written information should be revised immediately based upon the newly available information, and be re-approved by the IRB/IEC.
3) The investigator/sub-investigator should obtain written informed consent to continue participation with the revised written information defined in paragraph 2, even if subjects are already informed of the relevant information orally. The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the informed consent form, or write down his/her name and date the form. The investigator or other responsible personnel should give a copy of the signed informed consent form to the subject who had given consent with

the written information and store the original appropriately as done for the previous informed consent.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

8.2.5 Administrative Matters

8.2.6 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the IB and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

The study will be considered for publication or presentation at (scientific) symposia and congresses. The investigator will be entitled to publish or disclose the data generated at their respective site only after allowing the sponsor to review all transcripts, texts of presentations, and abstracts related to the study at least 90 days prior to the intended submission for publication or any other disclosure. This is necessary to prevent premature disclosure of trade secrets or patent-protected information and is in no way intended to restrict publication of facts or opinions formulated by the investigator. The sponsor will inform the investigator in writing of any objection or question arising within 30 days of receipt of the proposed publication material. The manuscript can be published only after agreement between the investigator, etc. and the sponsor.

8.2.7 Documents and Records Related to the Clinical Study

The sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, as applicable)
- IB (and amendments, as applicable)
- eCRFs and SAE Report Worksheet
- Study drug with all necessary documentation
- Study contract
- Approval of regulatory authority

In order to start the study, the investigator and/or site is required to provide the following documentation to the sponsor:

- Signed Investigator's Statement in this protocol and CRF
- Current Curricula Vitae of all investigators and site staffs
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Executed study contract
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory head)

At the end of the study, the sponsor is responsible for the collection of:

- Unused study documentation
- Unused study drug

The investigator will archive all study data (e.g., Subject Identification Code List, source data, eCRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. It is recommended, however, that records be retained for at least five years in the event follow-up is necessary to help determine any potential hazards to subjects who took part in the study. The sponsor will notify the investigator if the New Drug Application (NDA) is approved or if the Investigational New Drug (IND) is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on eCRFs supplied for each subject.

The investigator and sponsor will mutually agree upon the storage format for the retention of electronic data.

8.2.8 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments. Depending on the nature of the amendment and/or administrative change, either IRB/IEC approval or notification is required. The changes will become effective only after the approval of the sponsor, the investigator, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the Sponsor and the Investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the assessment of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information.

If there are changes to the Informed Consent Form, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.2.9 Insurance of Subjects and Others

If a subject suffers any study-related injury, the sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the site, the sponsor will consult with the site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

1) If a subject incurs an injury as a result of participation in the clinical study, the site should provide medical treatment and other necessary measures. The sponsor should be notified of the injury.
2) When the subject claims compensation from the site for the above study-related injury, or such compensation may be claimed, the site should immediately communicate the fact to the sponsor. Both parties should work together towards compensation settlement.
3) The sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.

4) The sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

8.2.10 Investigator Signing the Clinical Study Report

A final study report should be signed by a Principal Investigator. The Principal Investigator will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study.

9 Quality Assurance

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to inspect/audit the clinical study at any or all investigational sites. The auditor is independent from the CRA and project management team at the Sponsor. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 Study Organization

10.1 Independent Data and Safety Monitoring Board (DSMB)

Sponsor will establish an Independent Data and Safety Monitoring Board (DSMB) to assess the study related safety information.

10.2 Other Assessment Committee(s)

Not applicable.

10.3 Other Study Organization

Not applicable.

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APPENDIX 1. LIST OF PROHIBITED CONCOMITANT MEDICATION AND THERAPY

Prohibited drugs and treatments in each period are listed in the following table. This table didn't list all prohibited drugs and treatment. If investigators have any concern, they should contact the CRA responsible for the site.

Drug/Treatment	Limiting period
Immunosuppressants (mycophenolate mofetil (MMF), cyclosporine, methotrexate, mechlorethamine, chlorambucil, tripterygium preparations, leflunomide, etc.) treatment with duration of more than one week	Within 30 days before enrollment to the end of treatment
Tacrolimus (except topical use) or cyclophosphamide	Within 30 days before enrollment
Methylprednisolone pulse therapy (0.5g/day for 3 days) or gamma globulin or plasma exchange	Within 30 days before enrollment
Maintenance dialysis for more than eight weeks; or dialysis for more than two weeks	Before enrollment to the end of treatment
Kidney transplantation	Before enrollment to the end of treatment
Antibody induction therapy	Before enrollment to the end of treatment
Immunoglobulin or plasmapheresis	Enrollment to the end of treatment
Other immunosuppressants other than study drug	Enrollment to the end of treatment
ACEI, ARB	If not taken before enrollment, then do not take from enrollment to the end of treatment

APPENDIX 2. LABORATORY TESTS

Items	Visit	Sampling tube	Parameter analysis
Hematology	Visit 1 Visit 3 Visit 4	Sampling tubes containing K2EDTA	Red blood cell count, hemoglobin, platelets, white blood cell count, white blood cell classification
Blood biochemistry	Visit 5 Visit 6 Visit 7 Visit 8 Visit 9 Visit 10 Visit 11	Sampling tube for serum separation	Na^+, K^+, Ca^{2+}, Mg^{2+}, blood glucose, serum creatinine, urea nitrogen, uric acid, total bilirubin, total protein, albumin, aspartate aminotransferase SGOT/AST, alanine aminotransferase SGPT/ALT, γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP)
Blood lipids		Sampling tube for serum separation	Total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG)
Immunology	Visit 1	Sampling tube for serum separation	A-Sm and ACA
	Visit 1 Visit 6 Visit 8 Visit 11	Sampling tube for serum separation	A-dsDNA, ANA, C3, C4
HbA1c	Visit 1 Visit 8 Visit 11	Sampling tubes containing K2EDTA	HbA1c
ESR	Visit 1 Visit 6 Visit 8 Visit 11	Vacuum sampling tube for ESR	ESR
Virology	Visit 1	Sampling tube for serum separation	HBV, HCV, HIV, CMV
Urine pregnancy	Visit 1 Visit 5~11	Sampling tube for serum separation Test paper	HCG

Urinalysis	Visit 1 Visit 3 Visit 4 Visit 5 Visit 6 Visit 7 Visit 8 Visit 9 Visit 10 Visit 11	Urine specimen container (10mL)	Protein, glucose, nitrite, pH, ketone body, blood cells, sediment
24-hour Urine protein	Visit 1 Visit 3 Visit 6 Visit 7 Visit 8 Visit 9 Visit 10 Visit 11	Urine specimen container (10mL)	24-hour Urine protein

APPENDIX 3. AMERICAN RHEUMATISM ASSOCIATION DIAGNOSTIC CRITERIA FOR SLE 1997

Those meet 4 or more of 11 items below can be diagnosed as SLE.

Criteria	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin allergies caused by sunlight
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
5. Nonerosive Arthritis	Non-erosive arthritisinvolving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Hydrohymenitis	(1) Pleuritis: pleuritic pain or rubbing heard or pleural effusion. Or (2) Pericarditis: abnormal electrocardigram or rubbing heard or pleural effusion
7. Renal Disorder	(1) Proteinuria > 0.5 grams or > + + + (2) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	(1) Seizures – non-drugs or metabolic disorder; e.g., uremia, ketoacidosis, or electrolyte imbalance (2) Psychosis -- non-drugs or metabolic disorder; e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	(1) Hemolytic anemia complicated by increased reticulocytes or (2) Leukopenia--< 4×10^9/L on ≥ 2 occasions or (3) Lyphopenia--< 1.5×10^9/L on ≥ 2 occasions or (4) Thrombocytopenia, < 100×10^9/L (except drug effects)
10. Immunologic Disorder	(1) Anti ds-DNA antibody (+), or (2) Anti Sm antibody (+), or (3) Anti-cardiolipin antibodies (+) (including anti-cardiolipin antibody, or lupus anticoagulant, or Syphilis false positive reactions for at least 6 months, one of three conditions)
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or other abnormal test titer equivalent to this method, and drug-induced “lupus syndrome” is excluded.

APPENDIX 4. SLE-DISEASE ACTIVITY INDEX (SLE-DAI) SCORE CRITERIA

Derivation of the SLE-DAI, Arthritis and Rheumatism 1992, 35(6): 630.

Systemic Lupus Erythematosus Disease Activity Index 2000, The Journal of Rheumatology 2002; 29; 288.

Score	Item	Definition
8	Seizure	Recent onset. Exclude metabolic, infectious or drug cause
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked illogical thinking, bizarre behavior. Exclude uremia and drug causes.
8	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroids or optic neuritis. Exclude hypertension, infection, or drug causes
8	Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	Arthritis	More than 2 joints with pain & signs of inflammation (i.e. tenderness, swelling or effusion).
4	Myositis	Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	Urinary casts	Heme-granular or red blood cell casts.
4	Hematuria	> 5 RBC/Hp. Exclude stone, infection, or other cause.
4	Proteinuria	>0.5 g/24hr.
4	Pyuria	>5 WBC/Hp, exclude infection.
2	Rash	New onset or recurrence of inflammatory type rash.
2	Alopecia	New onset or recurring abnormal, patchy or diffuse loss of hair.
2	Mucosal Ulcers	New onset or recurring oral or nasal ulcerations.
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion or pleural thickening.
2	Pericarditis	Pericardial pain with at least one of the following: rub, effusion or electrocardiogram confirmation.
2	Low Complement	C3, C4 lower than normal value
2	A-dsDNA	+

1	Fever	>38°C, exclude infectious cause.
1	Thrombocytopenia	<100,000/mm^3
1	Leukopenia	<3000/mm^3 exclude drug causes.

APPENDIX 5. EVENTS ALWAYS CONSIDERED TO BE SERIOUS

If any of the following adverse events occur during the study, they should be considered as serious adverse events and reported as described in Section 5.5.5.

- acute liver failure
- acute renal failure
- acute respiratory failure
- agranulocytosis
- anaphylaxis
- any malignancy
- aplastic anemia
- confirmed or suspected transmission of infectious agents by marketed product
- congenital anomalies
- hepatic necrosis
- malignant hypertension
- pulmonary hypertension
- convulsion
- torsades de pointe
- toxic epidermal necrolysis
- ventricular fibrillation
- haemolytic anaemia
- bone marrow failure
- myocardial infarction
- cardiac arrest
- deafness
- blindness
- pancreatitis acute
- acute graft versus host disease
- Septic shock
- Sepsis
- Rhabdomyolysis
- respiratory failure
- Stevens-Johnson syndrome

APPENDIX 6. LN Pathological Activity Score Criteria

Items	Score		
Active index (AI) Glomerular lesions	1	2	3
Cells increase/spherical	<25%	25-50%	>50%
Leukocyte infiltration/spherical (>2)	Mild	Moderate	Severe
* Loop necrosis/nuclear fragmentation	<25%	25-50%	>50%
Microthrombus	Mild	Moderate	Severe
*Cellular crescents	<25%	25-50%	>50%
Interstitial lesions			
Cell infiltration	Mild	Moderate	Severe
Total			
Chronicity index (CI) Glomerular lesions	1	2	3
Global sclerosis	<25%	25-50%	>50%
Fibrous crescent	<25%	25-50%	>50%
kidney tubules lesions			
Atrophy	Mild	Moderate	Severe
Interstitial fibrosis	Mild	Moderate	Severe
Total			

Note: * should score × 2, activity points up to 24 points, chronic points up to 12 points.

APPENDIX 7. TACROLIMUS BLOOD CONCENTRATIONS TEST SAMPLE COLLECTION, HANDLING, STORAGE, AND SHIPPING

1. At each sampling time point, 4ml whole blood samples for detection of tacrolimus are collected in EDTA Vacutainer (K2EDTA anticoagulants in the tube with **purple** lid)
2. After sample collection, invert the blood collection tube for several times to mix the sample.
3. Put the sample collection tube in ice bath or water bath. **No need to centrifuge.**
4. Invert the blood collection tube for several times to mix the whole blood sample, and spit the whole blood sample to two samples with substantially the same volume following standard experimental procedure, the storage tube for split charging need to be labeled.
5. The labels on the storage tube need to be pasted firmly. The contents of label include subject number, initials of subjects.
6. Within 90 minutes after sample collection, parallel split plasma samples must be stored in the refrigerator at -20 ℃.
7. Within 24 hours after samples collection, No.1 split whole blood samples are shipped to Covance central lab to the concentration of tacrolimus in whole blood. No.2 split samples are kept in the center first, and then transported to Covance central lab if necessary. In each batch of shipping sample, sufficient dry ice should be filled to control the temperature of sample in delivery.

APPENDIX 8. DRUG THAT POSSIBLE INTERACT WITH TACROLIMUS

During the study, trough level of tacrolimus should be monitored closely when the drugs in the following table were used that may interact with tacrolimus:

Increasing the concentration of Tacrolimus				
Drug name	Interaction	Mechanism of action	Measures *	Annotation
(Ⅰ) Increasing the assimilating of Tacrolimus				
Cisapride (prepulside) metoclopramide (paspertin)	May increase the blood trough concentration of Tacrolimus	Impulsion preparations of gastrointestinal tract	M	
(Ⅱ) Inhibiting the metabolism of Tacrolimus				
Bromocriptine	May increase the blood trough concentration of Tacrolimus	Confirmed inhibition on the metabolism of Tacrolimus in vitro	M	Unknown
Chloramphenicol	According to the report, the blood trough concentration of Tacrolimus is increased for 2 or 3 times in the next day after taking chloramphenicol, so it needs to lessen 83% of the Tacrolimus dose	Inh biting the metabolism of Tacrolimus	M	Monitor the blood trough concentration of Tacrolimus to minimize the toxicity, adjust the dose when Tacrolimus is taken with chloramphenicol or discontinued
Chloroquine	May increase the blood trough concentration of Tacrolimus	May inhibit the metabolism of Tacrolimus	M	Before entering the malaria affected area, monitor its action to the Tacrolimus
Cimetidine (Tagamet)	According to the report, the Tacrolimus blood concentration of the rat rises by 3 times	Inhibiting the metabolism of Tacrolimus	M	Unknown
CLA	According to the report, the Tacrolimus blood concentration rises by 4 times when combined with it, renal toxicity still occurs when reducing the dose of CLA	Macrolide antibiotic and the isoenzyme cytochrome P450IIIA forms into a composite which inhibits the drug metabolism	A	Reduce the dose of Tacrolimus by instructions during the drug combination
Clotrimazole	The Tacrolimus blood trough concentration rises by 2-3 times as combined with it, 2 times increase for AUC and accompanied with renal toxicity	Unknown for exact mechanism Possible mechanism (1) Clotrimazole may compete with Tacrolimus for intestinal juncture, which decreases the Tacrolimus metabolism. (2) Directly inhibit the Tacrolimus metabolism of hepatocyte cytochrome P450	A	Reduce the dose of Tacrolimus to avoid the renal toxicity
DNZ	The Tacrolimus blood concentration rises by 4 times 4 days after the usage of DNZ, which results in more tremor, and a higher serum creatinine	May inhibit the metabolism of Tacrolimus	A	Monitor the serum creatinine, reduce the dose of Tacrolimus to avoid the toxicity
Dapsone	May increase the blood trough concentration of Tacrolimus	May inhibit the metabolism of Tacrolimus	M	Minimum anticipated clinical affection

Diltiazem	Tacrolimus concentration rises by 3 times in an acute treatment of a rat case by this drug	Inh bit the metabolism of Tacrolimus of the rat In animal and in vitro cases, it inhibits the Tacrolimus metabolism through competing with Tacrolimus for cytochrome P450 isoenzyme.	M	Treatment outcome unknown
Ergotamine	May increase the blood trough concentration of Tacrolimus	Confirmed inhibition on metabolism of Tacrolimus in vitro	M	Treatment outcome unknown
Erythrocin	According to the report, blood concentration of Tacrolimus rises more than 6 times 4 days after the usage of this drug, and the clearing, decrease, renal toxicity of Tacrolimus are also reported.	Inh bit the metabolism of Tacrolimus by suppressing liver and/or intestines cytochrome (P450IIIA and P450IA2)	A	Monitor the renal function, adjust the dose by instructions to avoid the toxicity
Ethinylestradiol	Increase blood trough concentration of Tacrolimus	Confirmed decrease of metabolism of Tacrolimus in vitro	M	Monitor the renal function, and reduce the dose of Tacrolimus to avoid the renal toxicity
Fluconazole	Interaction based on dose: concentration of Tacrolimus rises by 1.4 times with a usage of 100mg/d of this drug, and 3.1 times for 200mg/d Renal toxicity and neurotoxicity is also reported	Inh bit the metabolism of Tacrolimus by suppressing the cytochrome P450	A	If this drug dose is 200mg/d, the dose of Tacrolimus should be decreased 50%; if it is over 200mg/d, the dose of Tacrolimus should be adjusted to avoid the renal toxicity.
Grapefruit juice (flavone)	Affection to metabolism unknown at present. May increase the blood trough concentration of Tacrolimus	A known certain ingredient in grapefruit juice (flavone) may inhibit cytochrome P450 IIIA enzyme	A	There is no statement on its clinical relations, patient should prevent from drinking grapefruit juice when using Tacrolimus
Indinavir	May increase the blood trough concentration of Tacrolimus	May inhibit the drug metabolism induced by cytochrome P450	M	No report about it. Its affection maybe less than that of Ritonavir Monitor the blood concentration when using protease inh bitor or changing the treatment
Itraconazole	Blood trough concentration of Tacrolimus rises by 3 times after its combined administration, with a concomitant rise of serum creatinine	Inh bit the metabolism of Tacrolimus by suppressing the cytochrome P450IIIA4	A	Monitor the serum creatinine, reduce the dose of Tacrolimus to avoid the toxicity

*:M=monitor the concentration of Tacrolimus; A=avoid the use with Tacrolimus as possible; S=separate taking for Tacrolimus and drugs

Concentration increase of Tacrolimus				
Drug name	Interaction	Mechanism of action	Measures *	Annotation
(Ⅱ) Inhibiting the metabolism of Tacrolimus (Continued)				
KCZ	Prograf concentration rises 152% by AUC, according to the report, 3 days after using KCZ, AUC rises 506% 7 days after the treatment	Inh bit the metabolism of Prograf by suppressing the cytochrome P450IIIA4	A	Reduce the dose of prograf to avoid the toxicity
Mefloquine	May increase the blood trough concentration of Prograf	May inhibit the metabolism of Prograf	M	Before entering the malaria affected area, monitor its affection to the concentration of Prograf
Midazolam (Dormicum)	May increase the blood trough concentration of Prograf	Confirmed decrease of metabolism of Prograf in vitro	M	Treatment unknown
Nefazodone	The blood trough concentration of Prograf rises over 2 times after using this drug, with a concomitant	May inhibit the metabolism of Prograf cytochrome P3A4 or intestine	M	Reduce the dose of prograf to avoid the toxicity, monitor the blood concentration and serum

	rising of serum creatinine, and neurotoxicity ever reported			creatinine of prograf
Nelfinavir	May increase the blood trough concentration of Prograf	May inhibit the drug metabolism involved by cytochrome enzyme	M	No report. Its estimation affection less than that of Ritonavir Monitor the serum creatinine when using protease inhibitor or changing the treatment
Nicardipine	May increase the blood trough concentration of Prograf	May inhibit the Prograf metabolism involved by cytochrome enzyme P450	M	Monitor its affection to the concentration of Prograf
Nifedipine	In a review on a DDLT using prograf and Nifedipine, it may increase the prograf blood concentration and reduce the accumulated dose	It is confirmed that CYP3 A strongly inhibits the Prograf metabolism in vitro	M	When combined with Nifedipine or Nifedipine treatment is suspended, properly adjust the dose of prograf
OME (Losec)	Increase the blood trough concentration of prograf (3 cases reported)	In vitro inhibits the Prograf metabolism, maybe OME is also a substrate of CYP3A	M	In these 3 cases, 2 cases have no side reaction, 1 case has a behavior change (non-specifity)
Quinindium	May increase the blood trough concentration of Prograf	In vitro inhibits the Prograf metabolism, maybe Quinindium is also a substrate of CYP3A	M	Treatment unknown
Ritonavir	May increase the blood trough concentration of Prograf	May inhibit the Prograf metabolism involved by cytochrome P450	A	No report. Monitor the serum creatinine when using protease inhibitor or changing the treatment
SQV	May increase the blood trough concentration of Prograf	May inhibit the Prograf metabolism involved by cytochrome P450	M	No report. Its estimation affection less than that of Ritonavir. Monitor the serum creatinine when using protease inhibitor or changing the treatment
Triacetyloleandomycin	Increase the blood concentration of Prograf	Inh bit the Prograf metabolism by an induction of suppressing the cytochrome (P450IIIA, P450IA2) of liver and intestine	A	Monitor the blood trough concentration of Prograf, adjust the dose based on the result to avoid the toxicity.
Verapamil	According to the report of a rat case, it increases the blood concentration of Prograf	Confirmed inhibition on the metabolism of Prograf in vitro	M	Treatment unknown
Concentration decrease of Tacrolimus				
Drug name	Interaction	Mechanism of action	Measures *	Annotation
(Ⅰ) Decrease the assimilating of Tacrolimus				
Antiacid such as hydroxide, sodium bicarbonate	According to the report, there is an instant 40% dose loss of prograf when using hydroxide in vitro But among the 9 healthy patients, there is no clear distinction between Cmax, Tmax and AUC of control group and antiacid group	The in vitro result shows that PH value is involved in the degradation and absorbing of prograf.	M	Treatment unknown
(Ⅱ) Inducing the metabolism of Tacrolimus				
Anticonvulsive drug such as phenobarbital (luminal), primidone (Mysoline), carbamazepine (Tegretol)	May decrease the circulating concentration of prograf which may result in a low treatment effect, and increase the rejection of an acute transplant	Intensify the enzyme induction of cytochrome P450	M	Adjust the dose when using with an anticonvulsive drug

Dexamethasone	May decrease the blood trough concentration of Prograf	Induce the metabolism of Prograf (a rat metabolism increase over 3 times)	M	No open data, clinical relation unknown
Nevirapine	May decrease the blood trough concentration of Prograf	May induce the Prograf metabolism involved by cytochrome P450	A	No report.
Phenytoin (Dilantin)	Decrease the blood trough concentration of prograf (1 case reported)	Phenytoin may induce the Prograf metabolism. Full blood concentration and free blood concentration of Phenytoin increases (1 case reported)	M	Monitor blood concentration, adjust the doses of both according to the result
Rifabutin	May decrease the blood trough concentration of Prograf	Induce the metabolism of cytochrome P450	M	No interaction report based on the known action mechanism of prograf till now, interaction may be possible
Rifampicin	The blood concentration of Prograf lower than the treatment concentration and acute rejection may be seen .	Induce the metabolism of Prograf by inducing the cytochrome P450	A	When combined with rifampicin or rifampicin treatment is suspended, properly adjust the dose of prograf

*:M=monitoring the blood concentration of Tacrolimus; A=avoid using with Tacrolimus as possible; S=separate taking for Tacrolimus and drugs

Renal toxicity increasing				
Drug name	Interaction	Mechanism of action	Measures *	Annotation
Aminoglycosides antibiotic (AMK, GEN, TOB etc.)	May increase the blood trough concentration of Prograf and blood concentration of aminoglycosides antibiotic	May increase renal toxicity	M	Monitor the daily blood concentration of serum creatinine and aminoglycosides ant biotic, adjust the dose based on the monitoring
Anphotericin B	May increase the blood trough concentration of Prograf	May increase renal toxicity	M	A fat-soluble anphotericin B has a less toxicity.
Cis-platinum	Increase the blood concentration of Prograf	May increase renal toxicity	A	Make a further monitoring on the renal function, and the increase possibility of renal toxicity of the prograf is unknown
CsA (Sandimmune and Sandimmune neoral)	May increase the CsA concentration of the circulation	There has been reports in vitro metabolism inh biting of CsA in liver macrosome The prograf concentration required for in vitro metabolism inhibiting of CsA is 100 times higher than the blood concentration of the patient using prograf.	M	In vitro clinical data unknown NDRD maybe caused when using both because of the coordination or increase of the renal toxicity and immune suppression Start another drug 24 hours later after a drug withdrawal
Foscarnet	May increase the renal toxicity of prograf	·Increase renal toxicity: Foscarnet has a renal toxicity.	M	Make a further monitoring on the renal function
Brufen, NSAIDS (profenid, Indometacin, naproxen etc.)	May decrease the prostaglandin secretion of the kidney, and facilitate the acute renal failure	Cooperativity for suppressing the prostaglandin if combined with prograf Some NSAIDS inhibiting cytochrome system The prograf may be replaced by other high-protein combination drugs (NSAIDS, etc.)	M	Its affection to the patient with poor liver function may increase. Care should be given when prograf is used with other drug with renal toxicity.
Pentamidine	Renal function failure often occurs when using this drug in vein	May increase renal toxicity	M	It has no interaction when using pentamidine aerosol, monitor the

				renal function when the vein preparation of pentamidine is used combined with prograf.
Vancomycin	Increases serum creatinine, decreases creatinine clearance rate	May increase renal toxicity	M	Adjust the dose of vancomycin if there is a renal damage
Drug interaction induced by Tacrolimus				
Drug name	Interaction	Mechanism of action	Measures *	Annotation
Increasing the concentration of other drug				
Phenytoin (Dilantin)	Increases the full plasma and free concentrations of phenytoin (1 case), blood concentration decrease of prograf reported	-Prograf may inhibit the metabolism of phenytoin -Phenytoin may be replaced from albumin by prograf	M	Make a frequent monitoring on the blood concentration of phenytoin, adjust the dose of both based on the blood concentration
Neurotoxicity				
Acyclovir (aciclovir)	For a patient who has a renal damage, neurotoxicity may occur if the dose of acyclovir is not decreased	Renal insufficiency caused by prograf	M	If using together, monitor the renal function (serum creatinine, creatinine clearance rate (50ml/min)), adjust the dose of acyclovir based on the instructions
Increasing the effect of antihistamine				
Astemizole (Hismanal) terfenadine	May have the effect of antihistamine, at same time possbly with an arrhythmia	Inhibit of prograf to cytochrome P450	A	Though no report is seen, interaction of both can't be excluded. No such possibility is reported as the patient changes to take the antihistamine
Cooperativity				
Mthyl prednisolone	Hormone affection of clinical treatment	Prograf may in vitro inhibit the metabolism of hormone cytochrome P450	M	Cooperativity effect is seen for most in vitro combined use, treatment result doesn't indicate any disulfiram like effect, including those with methyl-4-sulfydryl side chain.
Disulfiram-l ke effect				
Including cephalosporin of mthyl-4-sulfydryl side chain, Cefamandole, cefoperazone (Cefobid), cefotetan, and metronidazole	Hemangiectasis, hypotension, nausea and vomiting, chest pain, weakness and insanity	There may be a disulfiram-like effect if it is combined with the alcohol in the vein preparation of prograf	M	Not popular, no critical clinical significance
Other effects				
Mycophenolate mofetil	According to the report, the mycophenolic acid concentration increases obviously in the patient who gets a kidney transplant, and in vitro immunodepression effect increases too	Prograf inh bits the metabolism of mycophenolic acid	M/S	Monitoring is needed because of the MMF side reaction

*:M=monitoring the blood concentration of Tacrolimus; A=avoid using with Tacrolimus as possible; S=separate taking for Tacrolimus and drugs

Drug interaction induced by Tacrolimus (continued)				
Drug name	Interaction	Mechanism of action	Measures *	Annotation
Other effects (continued)				
Potassium-sparing diuretics (Amipramizide, spironolactone, Triamterene and its compound combining with Hydrochlorothiazide	Hyperpotassaemia related with prograf has been reported	Renal damage is caused by prograf	A	
Attenuated vaccine	Vaccine efficacy may decrease	·Immunodepression effect of prograf	A	Monitor the efficacy of the vaccine
Live vaccine (typhoid, oral trivalent poliomyelitis vaccine, BCG, yellow fever vaccine, measles-parotitis-rubella vaccine)	Spread by infection	·Immunodepression effect of prograf	A	Forbidden to be used for patient who has a prograf treatment, severe side reaction may occur if using the vaccine

*: M=monitoring the blood concentration of Tacrolimus; A=avoid using with Tacrolimus as possible; S=separate taking for Tacrolimus and drugs

APPENDIX 9. OTHER CONTACTS

CONTRACT RESEARCH ORGANIZATION (PPD)

PPD

CENTRAL LABORATORY PPD

PPD

INTERACTIVE VOICE/NETWORK RESPONSE SYSTEM PPD

Toll Free Number:

PPD

ELECTRONIC DATA COLLECTION SYSTEM (PPD)

PPD

DRUG SHIPPING LOGISTICS (PPD

PPD

Statistical Analysis Plan

A phase III, randomized, open, parallel-controlled, multi-center study to compare the efficacy and safety of Tacrolimus capsules and Cyclophosphamide injection in treatment of lupus nephritis

Prepared by:

R&G PharmaStudies Co., Ltd.

NCT02457221

Sponsor: Astellas Pharma China Inc.

Version: 6.0

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PPD

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LIST OF ABBREVIATIONS AND KEY TERMS

Abbreviation	Description of Abbreviation
AE	Adverse Event
AI	Active Index
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ANA	Antinuclear Antibody
AST	Aspartate Aminotransferase (GOT)
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body Surface Area
C3, C4	Complement C3, C4
CI	Chronic Index
95% CI	95% Confidence Interval
CMV	Cytomegalovirus
CRF	Case Report Form
DILI	Drug-Induced Liver Injury
dsDNA	Anti-Double-Stranded DNA Antibodies
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ESR	Erythrocyte Sedimentation Rate
FAS	Full Analysis Set
GGT	γ-Glutamyl Transpeptidase
HbA1c	Glycated hemoglobin
HBV	Hepatitis B Virus

Abbreviation	Description of Abbreviation
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IWRS	Interactive Web Response Systems
MedDRA	Medical Dictionary for Regulatory Activities
MP	Methylprednisolone
PPS	Per Protocol Set
PT	Preferred term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
Scr	Serum Creatinine
SLE-DAI	Systemic Lupus Erythematosus – Disease Activity Index
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
WHODDE	WHO Drug Dictionary Enhanced

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures to be used for analyzing and reporting the efficacy and safety for study F506-CL-0912. It should be used in conjunction with the following documents: study protocol, case report form, analysis dataset specifications and shells for tables, listings and graphs. This SAP is based on the final protocol (Version 6.0, DEC 25nd, 2018) and eCRF (Version 4.1, NOV 27th, 2015). The SAP is finalized and signed prior to database hard lock.

2. STUDY OBJECTIVE AND ENDPOINTS

The objective of this study is to evaluate the efficacy and safety of Tacrolimus capsules for induction remission in patients with lupus nephritis, and compare the efficacy and safety with Cyclophosphamide injections to indicate that Tacrolimus capsules are not inferior to Cyclophosphamide injection.

Objectives	Endpoints
Primary	
To evaluate the efficacy of Tacrolimus capsules versus Cyclophosphamide in terms of remission rate (24 weeks) in patients with lupus nephritis.	Remission rate at 24 weeks
Secondary	
To summarize 24-hour urine protein at all visits except visit 2, 4, 5 (Day1, Weeks 4, 8, 12, 16, 20, 24), and compare change from baseline between two treatment groups at each visit	24-hour urine protein concentration and change from baseline

To summarize Serum albumin at all visits except visit 2 (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24), and compare change from baseline between two treatment groups at each visit	Serum albumin concentration and change from baseline
To summarize Serum creatinine at all visits except visit 2 (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24), and compare change from baseline at each visit ; To summarize and compare eGFR at all other post-baseline visits (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24) comparing with baseline between two treatment groups	Serum creatinine concentration and change from baseline; eGFR and change from baseline
To summarize SLE-DAI and immune parameters (ESR, C3, C4, dsDNA) in Week 4, 12 and 24, and compare change of SLE-DAI and immune parameters in Week 4, 12 and 24 from baseline between two treatment groups	SLE-DAI and immune parameters (ESR, C3, C4, dsDNA) and change from baseline
To summarize Renal biopsy AI (active index) and CI (chronic index) in Week 24, and compare change from baseline between two treatment groups;	Renal biopsy AI (active index) and CI (chronic index) and change from baseline
To compare Percentage of patients converted to other immunosuppressive therapy in the study group and the control group during 24 weeks between two treatment groups;	Percentage of patients converted to other immunosuppressive therapy

To compare Percentage of patients with serum creatinine rise to two times of the baseline at 24 weeks, percentage of patients with dsDNA and ANA converting from positive to negative between two treatment groups.	Percentage of patients with serum creatinine rise to two times of the baseline at 24 weeks, percentage of patients with dsDNA and ANA converting from positive to negative.

2.1 Statistical Hypotheses

The primary analysis will compare the remission rate at 24 weeks in study group (P_s) to the remission rate in control group (P_c) and demonstrate whether the treatment effect in study group is non-inferior to that in control group. The hypotheses used to assess the non-inferiority are:

- Null hypothesis (H_0): $P_s - P_c \leq -15\%$
- Alternative hypothesis (H_1): $P_s - P_c > -15\%$

3. STUDY DESIGN

This is a randomized, open-label, parallel group, active-controlled, multi-center phase III study of tacrolimus capsules in combination with steroid in subjects with lupus nephritis

Study group: tacrolimus capsules + steroid 147 subjects

Control group: cyclophosphamide injections + steroid 147 subjects

Once subject eligibility to enter the study is confirmed at Day -3 before 1st administration of MP, subjects will be randomized to one of the treatment groups in a 1:1 ratio using an IWRS randomization.

Stratified randomization will be adopted to randomize the subject to one of the

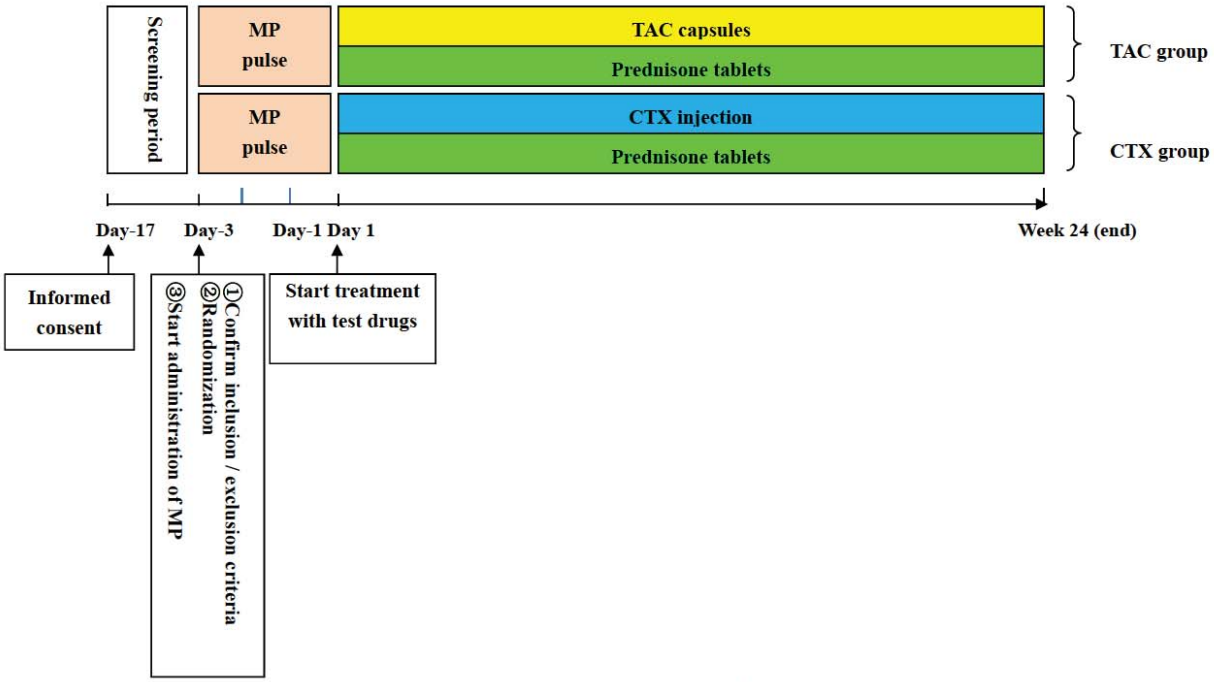
treatment groups. Pathological type of renal biopsy will be employed as stratification factor. Pathological types of subjects categorized as: III, IV, V, III+V and IV+V.

To minimize the risks of randomized patients not receiving the study drug, randomization will be conducted when all assessments in Visit 2 are completed and subjects are found suitable for randomization.

Once a subject number was assigned, even though the subject didn’t receive the study drug, the number shall not be used again.

Flow Chart and Schedule of Assessments

Flow Chart



Assessment Schedule

Test items	Screening	Induction remission stage									
	Visit 1[13]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11/Discontinuation [14]
	Screening (Day -17~-4)	Day -3,-2,-1	Day 1	Week 1 (Day 8±3)	Week 2 (Day 15±3)	Week 4 (Day 29±5)	Week 8 (Day 57±5)	Week 12 (Day 85±5)	Week 16 (Day 113±5)	Week 20 (Day 141±5)	Week 24 (Day 169±5)
Sign informed consent	X										
Urine HCG pregnancy test [1]	X				X	X	X	X	X	X	X
Demographics and Medical history	X										
Renal biopsy [2]	X										X
HBV/HCV/HIV/CMV [3]	X										
Physical examination, BMI	X		X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X	X	X
Blood routine, blood biochemistry, blood lipids [4]	X		X	X	X	X	X	X	X	X	X
HbA1c	X							X			X
Urine routine	X		X	X	X	X	X	X	X	X	X
24-hour urine protein	X		X			X	X	X	X	X	X

Test items	Screening	Induction remission stage									
	Visit 1[13]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11/Discontinuation [14]
	Screening (Day -17~-4)	Day -3,-2,-1	Day 1	Week 1 (Day 8±3)	Week 2 (Day 15±3)	Week 4 (Day 29±5)	Week 8 (Day 57±5)	Week 12 (Day 85±5)	Week 16 (Day 113±5)	Week 20 (Day 141±5)	Week 24 (Day 169±5)
eGFR	X		X	X	X	X	X	X	X	X	X
ESR, A-dsDNA, ANA,C3, C4	X					X		X			X
A-Sm, ACA [5]	X										
ECG	X		X			X	X	X	X	X	X
Chest X-ray	X							X			X
SLE-DAI	X					X		X			X
Inclusion/Exclusion criteria [6]	X	X									
Randomization [7]		X									
Corticosteroid dispensation and/or accountability [8]		X (MP)	X	X	X	X	X	X	X	X	X
TAC/CTX dispensation and accountability [9]			X	X	X	X	X	X	X	X	X
Patient Diary card dispensation [10]	X		X			X	X	X	X	X	

Test items	Screening	Induction remission stage									
	Visit 1[13]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11/Discontinuation [14]
	Screening (Day -17~-4)	Day -3,-2,-1	Day 1	Week 1 (Day 8±3)	Week 2 (Day 15±3)	Week 4 (Day 29±5)	Week 8 (Day 57±5)	Week 12 (Day 85±5)	Week 16 (Day 113±5)	Week 20 (Day 141±5)	Week 24 (Day 169±5)
Drug blood concentration test [11]				X		X	X	X	X	X	X
Dose adjustment [12]					X		X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X	X	X	X	X

[1] Urine HCG pregnancy test is only applicable for female subjects. Dipstick test is used at all required visits except for Visit 1at which serum test is conducted (central lab). Study drugs should only be provided when the result of each test is negative.

[2] Patients had renal biopsy within 24 weeks and without significant change in the disease don't have to re-test in enrollment. The renal biopsy at the end of study observation is optional which is determined based on the patients' willingness.

[3] HIV is tested at site lab. Investigators are recommended to complete the CMV test at site lab for the purpose of shortening screening period. Should CMV test be not applicable at site lab, central lab will do it instead.

[4] Routine blood test: red blood cell count, hemoglobin, platelets, white blood cell count, white blood cell classification. Blood biochemistry: Na+, K+, Ca2+, Mg2+, glucose, serum creatinine, urea nitrogen, uric acid, total bilirubin, total protein, albumin, aspartate aminotransferase (SGOT/AST), alanine aminotransferase (SGPT/ALT), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP). Blood lipids: total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG). Fasting is required for blood sample collection.

Urine routine: Protein, glucose, nitrite, pH, ketone body, blood cells and urinary sediment.

[5] Investigators are recommended to complete A-Sm and ACA test at site lab for the purpose of shortening screening period. Should these tests be not applicable at site lab, central lab will do it instead.

[6] MP administration should be done after judgment of Inclusion/Exclusion criteria and randomization at Visit 2 on Day -3.

[7] Randomization is conducted at Visit 2 on Day -3, after re-confirmation of the Inclusion/exclusion criteria and before first dose of the MP administration.

[8] At only Visit 2, MP is dispensed, from Visit 3 (including Visit 3), only prednisone tablets are dispensed. At Visit 11, steroid should be returned and counted but not be dispensed any more.

[9] At Visit 11, study drugs should be returned and counted but not be dispensed any more. CTX only dispensed on V3, V6-V10.

[10] Patient diary card will be dispensed at the visits specified in this schedule. Except for Visit 1, the original copy of completed diary card should be returned to investigator and filed at site.

[11] After Visit 5, investigators adjust the dose of TAC based on the drug blood concentrations test result. For subjects whose TAC dose has been adjusted at Visit 5 or following visits, investigators may initiate an unscheduled visit around 7 days after this TAC dose adjustment visit for the purpose of collecting blood sample to test TAC blood concentration as needed. Blood sample in TAC group should be collected before dosing on the visit day and 12±2 hours after last dose in the last day.

[12] For patients that received the unscheduled visit after Visit 5, investigators may adjust TAC dose according to TAC blood concentration collected at the unscheduled visit.

[13] Screening period is no more than 14 days during Visit 1. (Day -17~ -4)

[14] Once early termination is determined, subject should complete the examinations for withdrawing visit as soon as possible.

4. SAMPLE SIZE

The determination of bound of non-inferiority test refers to the Phase III, randomized, double-blind, parallel-group, placebo-controlled study in Japan (Study No.: FJ-506-LN02). The complete plus partial remission rate in the placebo group and tacrolimus group of this study were 2.9% and 46.4% respectively. If assuming that cyclophosphamide has the same efficacy with tacrolimus, the efficacy value of cyclophosphamide is 43.5%, the bound of non-inferiority test should be set as 1/3 of the efficacy value as 15%. Assuming the complete plus partial remission rate in this study is between 70% and 100%, based on the information, the complete plus partial remission rate of tacrolimus and cyclophosphamide should be 80%. Based on the assumptions above, calculating as test efficacy of 80%, 125 patients are needed for each group to demonstrate that tacrolimus is non-inferior to cyclophosphamide. 294 patients are planned to be enrolled assuming 15% of lost to follow-up, dropout and other conditions.

5. ANALYSIS SET

All Randomized Subjects：All randomized subjects will include all subjects who are randomized to the study.

Full Analysis Set (FAS)：Full analysis set is defined as all subjects receiving at least one dose of the study drug, and with any efficacy data post baseline.

Per Protocol Set (PPS): Per protocol set includes subjects in the full analysis set that complete follow-up of 12 weeks (85±5 days) or more, and includes those withdraw early due to lack of efficacy; medication compliance is between 80% -120%; no major protocol violations. It will be finally determined at the Data Review Meeting (DRM) prior to Database Lock. These subjects are the main population for efficacy analysis.

Safety Analysis Set (SAF): The safety population included all subjects receiving

at least one dose of the study drug.

Efficacy analyses will be conducted based on FAS and PPS. And safety data summaries and analyses will be produced based on SAF.

Analysis set will be decided during the Data Review Meeting; explanation should be provided for any violation against definition of each analysis data set.

6. STUDY VARIABLE

6.1 Efficacy variables

6.1.1 Primary efficacy variable

The primary efficacy variable is remission rate in endpoint assessment (24 weeks) (complete remission + partial remission). Patients of early withdrawal are included in endpoint assessment.

Definition of efficacy endpoints:

- Complete remission: urine protein < 0.5g/24hr, and serum albumin≥3.5g/dl, and stable renal function (Scr in the normal range or Scr increase ≤ 15% baseline value)
- Partial remission: urine protein < 3.5 g/24hr, and urine protein decreased by >50% comparing with the baseline, and serum albumin ⩾ 3.0g/dl, and stable renal function (Scr in the normal range or Scr increase ⩽ 15% baseline value)

6.1.2 Secondary efficacy variable

1. 24-hour urine protein at all visits except visit 2, 4, 5 (Day1, Weeks 4, 8, 12, 16, 20, 24), and change from baseline;

2. Serum albumin at all visits except visit 2 (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24), and change from baseline;

3. Serum creatinine at all visits except visit 2 (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24), and change from baseline; eGFR at all other post-baseline visits (Day1, Weeks 1, 2, 4, 8, 12, 16, 20, 24) comparing with baseline, based on CKD-EPI formula:

   $141\times\min(Scr/k,1)^{\alpha}\times\max(Scr/k,1)^{-1.209}\times0.993^{Age}\times1.018$[if female] $\times1.159$[if black] (Scr [mg/dL], K= 0.9 for males or 0.7 for females,α= -0.411 for males or-0.329 for females, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1);

4. SLE-DAI and immune parameters (ESR, C3, C4, dsDNA) in Week 4, 12 and 24, and change of SLE-DAI and immune parameters in Week 4, 12 and 24 from baseline;

5. Renal biopsy AI (active index) and CI (chronic index) in Week 24, and change from baseline;

6. Percentage of patients converted to other immunosuppressive therapy in the study group and the control group during 24 weeks;

7. Percentage of patients with serum creatinine rise to two times of the baseline at 24 weeks, percentage of patients with dsDNA and ANA converting from positive to negative.

6.2 Safety variable

The safety variables include adverse events, vital signs, laboratory assessments, physical examination, ECG and imaging.

6.2.1 Adverse Event (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

A Treatment Emergent Adverse Event (TEAE) is defined as an AE with an onset date on or after starting administration of the study drug or any ongoing AE on the date of first dose that has worsened in severity after administration of the study drug. All adverse events collected that begin within 30 days of taking the last administration of study drug will also be counted as TEAE.

A Serious Adverse Event (SAE) is defined as any AE which leads to following outcomes:

- Results in death
- Is life threatening (an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other major medical events

6.2.2 Laboratory variables

The test should be conducted according to the terms listed in the following table. Please refer to “flowchart and schedule of assessment” for the timetable of tests.

Items	Visit	Sampling tube	Parameter analysis
Hematology	Visit 1 Visit 3 Visit 4	Sampling tubes containing K2EDTA	Red blood cell count, hemoglobin, platelets, white blood cell count, white blood cell classification
Blood biochemistry	Visit 5 Visit 6 Visit 7 Visit 8 Visit 9 Visit 10 Visit 11	Sampling tube for serum separation	Na^+, K^+, Ca^{2+}, Mg^{2+}, blood glucose, serum creatinine, urea nitrogen, uric acid, total bilirubin, total protein, albumin, aspartate aminotransferase SGOT/AST, alanine aminotransferase SGPT/ALT, γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP)
Blood lipids		Sampling tube for serum separation	Total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG)
Immunology	Visit 1	Sampling tube for serum separation	A-Sm and ACA
	Visit 1 Visit 6 Visit 8 Visit 11	Sampling tube for serum separation	A-dsDNA, ANA, C3, C4
HbA1c	Visit 1 Visit 8 Visit 11	Sampling tubes containing K2EDTA	HbA1c
ESR	Visit 1 Visit 6 Visit 8 Visit 11	Vacuum sampling tube for ESR	ESR
Virology	Visit 1	Sampling tube for serum separation	HBV, HCV, HIV, CMV
Urine pregnancy	Visit 1 Visit 5~11	Sampling tube for serum separation Test paper	HCG

Items	Visit	Sampling tube	Parameter analysis
Urinalysis	Visit 1 Visit 3 Visit 4 Visit 5 Visit 6 Visit 7 Visit 8 Visit 9 Visit 10 Visit 11	Urine specimen container (10mL)	Protein, glucose, nitrite, pH, ketone body, blood cells, sediment
24-hour Urine protein	Visit 1 Visit 3 Visit 6 Visit 7 Visit 8 Visit 9 Visit 10 Visit 11	Urine specimen container (10mL)	24-hour Urine protein

6.2.3 Vital signs

Vitals signs will include systolic blood pressure, diastolic blood pressure, and pulse.

6.2.4 Electrocardiogram

Each 12-lead ECG will be assessed and recorded based on 3-level system (normal, abnormal without clinical significance, or abnormal with clinical significance).

6.2.5 Physical Examination

Physical examination results will be presented as Normal or Abnormal.

6.2.6 Exposure

Total exposure time (days) will be calculated from the first dose to the last dose:

Total exposure = (last dose date - first dose date) + 1

Actual exposure time (days) will be calculated from first dose to the last dose, taking account of dose interruptions.

Actual exposure = ((last dose date - first dose date) + 1)
- total duration of dose interruption (i.e. number of days without dose)

6.2.7 Concomitant medications

Concomitant medications are defined as all the drugs (concomitant drugs) and therapies (concomitant therapies) taken by the subjects from the day of signing the ICF to completion of the study.

7. STATISTICAL CONSIDERATIONS

7.1 General rule

All analysis will be conducted using SAS® Version 9.4 or higher (SAS Institute, Cary, NC).For quantitative variables, descriptive statistics will be presented as the mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, maximum, and the number of observations. For qualitative variables, the number and percentage for each of the scores or categories will be presented. Counts that are zero will be displayed as "0". Unless otherwise specified, the denominator for all percentages will be based on the number of subjects in the analysis set of that treatment group. The rule of decimal is specified as follow:

Description	Characteristic	Number of decimal places
Count	N	0
Mean	Mean	As in source + 1

Description	Characteristic	Number of decimal places
Standard deviation	Std	As in source + 2
Minimum	Min	As in source
Median	Median	As in source + 1
Maximum	Max	As in source
Q1/Q3	Q1/Q3	As in source + 1
Percentage	%	1 *

* Number of decimal places can be two, if necessary.

Statistical analysis will be conducted using two-sided hypothesis tests at the 0.05 level of significance unless otherwise specified. p-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999, it will be reported as ">0.999."

7.2 Multiple Comparisons/Multiplicity

Primary variable has been defined for this study for one critical treatment contrast (tacrolimus plus steroid versus cyclophosphamide injections plus steroid). The secondary variables defined are intended to provide supportive evidence relating to the primary objective. No interim analyses are planned. Hence efficacy variables will be assessed without adjustment for multiple comparisons.

7.3 Data handling conventions

7.3.1 Missing data

Missing efficacy data will be handled using imputation approach. For the primary analysis, missing data for remission at week 24 will be imputed by last observation carried forward (LOCF) for each subject. Secondary efficacy endpoints analysis only includes subjects without missing data in baseline, and the intermediate missing data will be filled with last-observation-carried-forward method. LOCF will also be used for efficacy endpoints of subjects with early withdrawal.

Two imputation ways will be applied to missing SLE-DAI items. One is to impute as 0 and the other one is LOCF.

7.3.1.1 Imputation of Partial Dates

Missing data occurs when any protocol required data is not provided, leading to blank fields on the collection instrument. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Incomplete AE and medication start and stop dates will be imputed as below. Note that the rules defined below are used for sorting and slotting purposes only. All reported data in listings will report the partial or missing dates. Imputed dates will not be used to calculate study day or duration.

Adverse Events

If the start date is completely missing, the start date is set to the date of first dose.

If the year is present and the month and day are missing or the year and day are present and the month is missing:

If year = year of first dose, then set month and day to month and day of first dose.

If year < year of first dose, then set month and day to December 31st.

If year > year of first dose, then set month and day to January 1st.

If the month and year are present and the day is missing:

If year = year of first dose and

If month = month of first dose then set day to day of first dose date

If month < month of first dose then set day to last day of month

If month > month of first dose then set day to 1st day of month

If year < year of first dose then set day to last day of month

If year > year of first dose then set day to 1st day of month

For all other cases, set the start date to the date of first dose.

Concomitant Medications

If the start date is completely missing, then the start date will not be imputed.

If the year is present and the month and day are missing or the year and day are present and the month is missing:

Set month and day to January 1st.

If the year and month are present and the day is missing:

Set day to 1st day of month.

If the end date is completely missing, then the end date will not be imputed.

If the year is present and the month and day are missing or the year and day are present and the month is missing:

Set month and day to December 31.

If the year and month are present and the day is missing:

Set day to last day of the month.

Imputation Rules for Lab Values Outside of Quantification Range

Lab values below the lower limit of quantification (LLoQ) that are reported as "<LLoQ" or "≤LLoQ" in the database will be imputed by LLoQ × 0.99 for analysis purposes. The original value will be listed.

Lab values above the upper level of quantification (ULoQ) that are reported as ">ULoQ" or "≥ULoQ" in the database will be imputed by ULoQ × 1.01 for analysis purposes. The original value will be listed.

7.3.2 Multiple assessments

Where there are multiple assessments at a given time point (planned, repeated and unscheduled), the first non-missing planned result will be used in the summary tables for that time point. If the result from planned assessments are missing, then the first non-missing result from unscheduled assessment will be used. However, all results will be included in the listings.7.3.4 Laboratory assessments.

If results for clinical laboratory evaluations are recorded as “less than” or “greater than” the value (e.g. <x，≤x，>x，≥x), x will be listed as the same of CRF recorded in the listing. However, the value for the descriptive statistical summary is listed as follow:

Case Description	**Value for Descriptive Summary**
<x	subtract one significant digit unit from original result
≤x	X
>x	add one significant digit unit from original result
≥x	X

7.3.3 Derived and Transformed data

7.3.3.1 Reference dates

Both of efficacy reference date and safety reference date will be the date of first dose of investigational product (Tacrolimus capsules or Cyclophosphamide Injections).

7.3.3.2 Study day

If the date of interest occurs on or after reference date, then the study day will be calculated as (date of interest - reference date) + 1. If the date of interest occurs before reference date, then the study day will be calculated as (date of interest –reference date). There is no study day 0. Study Day 1 is the day of the first dose of study drug.

7.3.3.3 Duration

Durations (e.g., the duration of an adverse event, duration of exposure, etc.) are calculated as the stop date minus the start date plus one.

For converting durations (e.g., duration of adverse events, duration of exposure, age to weeks, months or years), use the following:

- To report the duration in weeks divide the number of days by 7.
- To report the duration in months use:

(YEAR(stopdate + 1) - YEAR(startdate)) * 12 + (MONTH(stopdate + 1) - month(startdate) - 1) + (DAY(stopdate + 1) > = DAY(startdate))

- To report the duration in years use:

intck('year', startdate, stopdate + 1) - (month(stopdate + 1) < month(startdate) or (month(stopdate + 1) = month(startdate) and day(stopdate + 1) < day(startdate)))

The algorithms above for age and duration return whole numbers for months and years, accurately accounting for the actual numbers of days in the months or years between the start date and the stop date.

7.3.3.4 Baseline definition

Baseline is defined as the last non-missing assessment before Methylprednisolone pulse therapy (screening assessment). The logic step is as below:

a. If single measurement is recorded, this one will be baseline
b. Otherwise, if multiple measurements are recorded and we can distinguish the date/time order, the last non-missing one will be baseline
c. Otherwise, if multiple measurements are recorded on the same day and we can not distinguish the time order, the scheduled one will be baseline

d. Otherwise, baseline will be missing

7.3.3.5 Change from baseline

All changes from baseline will be calculated with respect to the baseline value defined as in previous section, using the following:

Change from baseline= post baseline value- baseline value

Percent change from baseline= Change from baseline/ baseline value× 100

7.3.4 Analysis Visit Window

For assessments need to be summarized by visit, assessment results will be assigned to calculated analysis visit windows (using study day), according to table below:

CRF	Nominal Day/ Time (Study Day)	Visit Window	Actual Assessment Day	Analysis Visit
Visit 1		**-17 to -4**	**-17 to -4**	Baseline
Visit 2		**-3 to -1**	**-3 to -1**	Baseline
Visit 3	1	1	1	Day 1
Visit 4	8	5 to 11	2 to 11	Week 1
Visit 5	15	12 to 18	12 to 22	Week 2
Visit 6	29	24 to 34	23 to 43	Week 4
Visit 7	57	52 to 62	44 to 71	Week 8
Visit 8	85	80 to 90	72 to 99	Week 12
Visit 9	113	108 to 118	100 to 127	Week 16
Visit 10	141	136 to 146	128 to 155	Week 20
Visit 11 or Discontinuation	169	164 to 174	≥156	Week 24

For visit-based summaries, if there is more than one value per subject within a visit window, value from planned visit should be used. If it's not available then the closest to the planned study day value should be summarized. The visit will be missing if no assessment was reported within the specified visit window around the planned study day.

8. STATISTICAL ANALYSIS

8.1 Subject disposition

The disposition of subjects will be summarized, including the numbers and percentages of subjects for the following categories: all randomized subjects, subjects who provide ICF, screen failure subjects, subjects completed the study, subjects early discontinued from the study, subjects in the full analysis set, subjects in the per protocol set, and subjects in the safety analysis set. All percentages are based on the number of all randomized subjects. Also randomized subjects will be summarized by center.

The primary reason for subject discontinuation from study will also be summarized. The reasons for discontinuation will include randomized/registered but never received/dispensed study drug, adverse event, death, lack of efficacy, lost to follow-up, progressive disease, protocol violation, withdrawal by subject, study terminated by sponsor, non-compliance with study drug, recovery, pregnancy, other.

8.2 Demographics and other baseline characteristics

The analysis will be based on FAS, PPS and SAF separately.

8.2.1 Demographics

The following demographic and baseline characteristics will be summarized:

- Age at time of informed consent (in years, as a continuous variable)
- Age group (<65,>=65)
- Sex (Male, Female, Unknown)
- Race ((ASIAN/OTHER)
- Weight
- Height
- BSA
- BMI
- Tobacco history (NEVER USED TOBACCO /CURRENT TOBACCO USER/FORMER TOBACCO USER)
- Alcohol History (NEVER USED ALCOHOL/CURRENT ALCOHOL USER/FORMER ALCOHOL USER)

Age will be calculated as the difference of the date of informed consent and date of birth in years with the decimals truncated. Percentages for qualitative data will be calculated based on the number of subjects in the analysis set of that treatment group. Descriptive statistics will be used for quantitative data.

8.2.2 Medical history

Medical history includes previous and current medical conditions. Medical history will be summarized by system organ class and preferred term. The incidence is only one occurrence of a preferred term/system organ class per subject. If a subject reports multiple medical histories under the same preferred term, then the count of incidences for that preferred term will only be incremented by one. If a subject reports multiple medical histories under the same system organ class, then the count of incidences for that system organ class will also only be incremented by one. System organ class and preferred term coded in MedDRA 17.0 will be presented in descending order of total frequency of occurrences. Previous medical history and current medical history will be presented separately.

8.2.3 Diagnosis of the target disease, severity, and duration of disease

The target disease in this clinical study is lupus nephritis. The number and percentage for each of the pathological class will be presented. The duration in years of lupus nephritis from the time of diagnosis to the time of signed informed consent and SLE-DAI will be summarized by descriptive statistics. The diagnosis time (year and month), Pathological Type and duration will be presented in the listing.

Duration of lupus nephritis (years) = (time of signed informed consent (year/month) – time of diagnosis (year/month)) / 12

For diagnosis dates with partial information, the below rules will be used.

Case Label	Description of Cases	Derivation Rule
1a	'Diagnosis Date' is complete	= Diagnosis Date
1b	'Year' is missing or 'Diagnosis Date' is completely missing	= missing
1c	'Year' is not missing but 'Month' is missing	= January (Year as reported on CRF)

8.2.4 Inclusion and exclusion criteria

Subjects must meet all specified inclusion and none of the exclusion criteria in order to be eligible to participate in the study. Inclusion and exclusion criteria information will be presented in the listing.

8.3 Previous and concomitant medication

Previous medication: all the drugs taken by the subjects 3 months prior to the date of signing the ICF.

Concomitant medication: all drugs except those specified for the study taken by the subjects from the date of signing the ICF to completion of the study. Anaesthetic and other operation related drugs are not needed to be recorded.

If medication start date is at or after informed consent date, then medication will be summarized as concomitant medication regardless of whether medication end date is missing or not. If medication end date is before informed consent date, then medication will be summarized as previous medication regardless of whether medication start date is missing or not. Note that medication that started prior to informed consent date and continued after dosing will be summarized as previous medication and separately as concomitant medication.

Previous and concomitant medications will be summarized by medication class and medication name for the safety analysis set, respectively. All medications will be coded according to WHO drug dictionary (Version: WHODDE(B2) V2014MAR) and Anatomical Therapeutic Chemical (ATC) coding. The number of subjects who took each previous and concomitant medication will be counted in the tables. Within the summary for previous and concomitant medications respectively, subjects who took a medication multiple times will be counted only once for that medication at the coding level. Medications will be presented in decreasing order of frequency based on the total number of subjects who took each medication.

Medication class, medication name, verbal term total daily dose, dose units, frequency, route, start date, stop date, and reason for use will be presented in the listing.

8.4 Non-medication therapy

For subjects who receive any non-medication therapy will be recorded on eCRF. Non-medication therapy information including therapy details, start and stop date, and the indication for which the therapy was administered will be presented in the listing.

8.5 Investigational product compliance

Compliance will be summarized by treatment groups for Tacrolimus Capsules and Cyclophosphamide Injections.

Dosing compliance, defined as actual dose taken divided by planned dose per protocol times 100%, will be summarized for FAS, PPS and SAF. The formulas for calculating the overall dosing compliance are as follows:

Dosing Compliance (%) = Actual dose taken × 100% / Planned dose taken per protocol

8.6 Protocol deviations

Protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. Protocol deviations will be captured by the clinical monitoring team on an ongoing basis throughout the study. These deviations will be discussed on a case by case basis and classified into major and minor deviations before database lock (DBL). Major protocol deviations will be used when determining the PPS and will be summarized by treatment group. A by-subject listing of major protocol deviations will be provided.

Subject counts and percentages will be displayed by the following violation categories:

- Informed Consent Form
- Eligibility Criteria
- Withdrawal Criteria
- Treatment Compliance
- Site Visit
- SAE
- Concomitant Medications/treatments
- Safety Variables and Pregnancy Test
- Study Procedure

8.7 Efficacy analysis

This analysis will be conducted in PPS and FAS, and PPS will be the primary efficacy analysis set.

CMH test analysis will be used for the primary efficacy analysis. All secondary efficacy variables will be compared between two treatment groups. Secondary efficacy endpoints will be analyzed with appropriate statistical methods (ANCOVA or CMH, adjusted for stratification factor) based on data type.

8.7.1 Analysis of primary variable: Remission Rate

8.7.1.1 Primary analysis on remission rate

The primary analysis will be based on the evaluation from investigator.

The primary efficacy endpoint for this study is remission rate in endpoint assessment (24 weeks) (complete remission + partial remission). Primary efficacy endpoints are evaluated through two-sided 95% CI. 95% CI of the difference between two treatment groups (tacrolimus group - cyclophosphamide group) is used to evaluate whether the remission rate at 24 weeks in tacrolimus group is non-inferior to cyclophosphamide group. Non-inferiority bound is set as 15%, if the lower limit of the 95% CI $\geq$ -15%, then the non-inferiority conclusion can be drawn. The primary analysis set of efficacy analysis is PPS population.

CMH test analysis with adjustment factor (pathological type) will be used for the primary efficacy analysis. The 95% confidence interval of efficacy difference will be calculated and used for non-inferiority test.

The stratified newcombe confidence interval will be applied and the core sample code is as following: *table I*treat*avalc / riskdiff(common column=1 cl=newcombe) cmh nocol nopercent plots=none*.

8.7.1.2 Sensitivity analysis on remission rate

Following sensitivity analysis will be performed in order to show the robustness of the primary analysis result:

a) CMH (LOCF, PPS)

Analysis of remission rate with CMH method will be based on derived response from laboratory test data on PPS.

b) CMH (LOCF, FAS)

The primary analysis of remission rate with CMH method will be repeated on FAS.

c) CMH (Completer, FAS)

The primary analysis of remission rate with CMH method will be repeated only on those in FAS who complete week 24 remission assessment, without LOCF.

8.7.1.3 Subgroup analysis on remission rate

In order to assess the consistence of the primary efficacy outcome among different sub-populations, following subgroup analysis will be performed:

a) Sex (Male, Female)
b) BSA (< Median BSA at Baseline, >= Median BSA at Baseline)
c) Pathological types (Type III, Type IV, Type V, Type III+V, Type IV+V)
d) Duration of Lupus Nephritis (<= 6 months, > 6 months)
e) SLE-DAI (>= 10, < 10)
f) SLE-DAI (>= 4, < 4)

8.7.2 Analysis of secondary variable

Analysis for secondary variables including 24-hour urine protein, Serum albumin, Serum creatinine, eGFR, SLE-DAI, ESR, C3, C4, dsDNA, AI and CI will be conducted

at various visits as specified in the Study Schedule of the protocol. The results and change from baseline in each required visit should be summarized by descriptive statistics. For the difference of change from baseline between two treatment groups in each visit, the estimated value and 95% CI should be calculated. Also, p-value will be provided based on ANCOVA for the group comparison, adjusted with stratification factor. To assess the impact of missing data on the analysis result, an MMRM model with stratification factor as a covariate will also be applied.

The number and percentage will be presented respectively for secondary variables including percentage of patients converted to other immunosuppressive therapy in the study group and the control group during 24 weeks, percentage of patients with serum creatinine rising to two times of the baseline at 24 weeks, and percentage of patients with dsDNA and ANA converting from positive to negative at 24 weeks. Group comparison should be conducted by CMH test adjust for stratification factor.

For SLE-DAI, primary analysis will base on subject who had no missing items. And sensitivity analysis will base on both 0 and LOCF imputation.

8.8 Safety analysis

Safety endpoints include exposure, adverse events, vital signs, laboratory test, physical examination, ECG, and imaging. This analysis will be conducted in SAF.

8.8.1 Extent of exposure

Duration of Drug Exposure:

The duration of drug exposure will be summarized for Tacrolimus Capsules, Cyclophosphamide Injections, Prednisone and MP.

Interruptions or dose incompliance between first dose date and last dose date will be included in the duration of drug exposure.

Dose Summary:

Total dose summary by visit for Tacrolimus Capsules (mg), Cyclophosphamide Injections (g), prednisone (mg) and MP (g) is summarized by descriptive statistics.

Tacrolimus blood concentration and dose adjustments:

Tacrolimus blood concentration will be summarized by scheduled visits.

Percentages for category of Tacrolimus blood concentration (< 4 ng/ml, 4-10 ng/ml, > 10 ng/ml) by visit will be calculated based on the number of subjects in the analysis set of that treatment group. The percentage for number of dose adjustment due to Trough Level Control will also be calculated.

Cyclophosphamide Dose per BSA:

Descriptive statistics will be used to summarize Cyclophosphamide dose per BSA (g/m^2) by visit.

Cyclophosphamide dose per BSA (g/m^2) = Actual dose taken (g)/BSA (m^2)

BSA will be calculated using the following formula:

DuBois formula $BSA(m^2) = 0.007184 \times weight(kg)^{0.425} \times height(cm)^{0.725}$

8.8.2 Adverse events

AEs will be classified into standardized medical terminology from the verbatim description (investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA).Verbatim description and MedDRA level terms, including the system organ class and preferred term for all AEs will be presented in the data listings. In table summaries, the denominator for percentages will be the number of subjects in the treatment group within the safety analysis set. AEs are coded according to (MedDRA) version 17.0.

AEs will be presented by system organ class and preferred term. The subject level incidence is only one occurrence of a preferred term/system organ class per subject. If a subject reports multiple AEs under the same preferred term, then the count of subject level incidences for that preferred term will only be incremented by one. If a subject reports multiple AEs under the same system organ class, then the count of subject level incidences for that system organ class will also only be incremented by one. System organ classes will be presented in descending order of total frequency of subject level occurrences. Within each system organ class, preferred terms are presented in the same descending order of total frequency of subject level occurrences.

Adverse Drug Reactions (ADR) is defined as adverse event that is related to study drug (Relationship to Study Drug was categorized as “Possible” or “Probable” in eCRF). TEAE is defined as the adverse event that happens after the treatment of study drug (Tacrolimus or Cyclophosphamide). The summary for TEAE will include:

- Summarize frequency distribution by category of subjects with adverse events, serious adverse events, adverse events and serious adverse events leading to permanent discontinuation of the study drug, serious TEAE related to study drug, and serious TEAE related to study drug leading to early withdrawn from study.

- Summarize frequency distribution of subjects with adverse events according to major system organ classification codes and preferred term in MedDRA (according to the correlation with the study drug and severity).

8.8.3 Vital signs

Vital signs and weight will be descriptively summarized by treatment group and clinic visit. Changes from Baseline to each individual post-Baseline visit will also be presented.

8.8.4 Laboratory tests

Results for clinical laboratory evaluations including: hematology, blood biochemistry, blood lipids, HbA1c, virology, immunology, serum/urine pregnancy and urinalysis will be conducted at various visits as specified in the Study Schedule of the protocol. Descriptive statistics will be used for quantitative variables. For qualitative variables, the number and percentage for each parameter in both treatment groups will be presented. Summary tables summarizing within normal range, high (above upper limit of normal range) and low (below lower limit of normal range) results for each parameter, by visit and treatment group, will be provided. Shift tables, by treatment group, showing the shift in normal range assessment from baseline to end of treatment will also be provided for each parameter.

8.8.5 Physical examination

The investigator or sub-investigators should confirm the conditions of subjects through inquiry, inspection and palpation and record the abnormal conditions on medical records or other source files. The result of physical examination will be categorized as “Normal” or “Abnormal”. The number and percentage for each category will be presented at various visits as specified in the Study Schedule of the protocol.

8.8.6 Electrocardiogram (ECG)/X-ray

The investigator or sub-investigators should be responsible for interpreting each 12-lead ECG, and assess it based on 3-level system (normal, abnormal without clinical significance, or abnormal with clinical significance).Shift from baseline to each post-baseline visit for the clinical significance assessment will be summarized. All ECG data will be presented in the listing. The same method will be used for the analysis of X-ray examination.

8.8.7 Liver events

Incidence of patients with liver function test results satisfying the drug-induced liver injury (DILI) criterion defined as (> 3x upper limit of normal [ULN] for ALT/AST, >2xULN for total bilirubin and > 2xULN for alkaline phosphatase at the

same time-point) will be presented by visit.

In addition, incidence of elevated liver function test results will be presented at each visit by elevation criterion. Elevation criteria are given as follows:

- ALT (ULN - ≤ 3xULN, > 3xULN - ≤ 5xULN, > 5xULN)
- AST (ULN - ≤ 3xULN, > 3xULN - ≤ 5xULN, > 5xULN)
- Total Bilirubin (ULN - ≤ 2xULN, > 2xULN)
- Alkaline Phosphatase (ULN - ≤ 2xULN, > 2xULN)

9. MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

Mock TLGs will be provided in a separate document.