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CLINICAL TRIAL PROTOCOL

A Multi-center, Randomized, Controlled, Open-label Clinical Study to Evaluate the Efficacy and Safety of Mizoribine in Comparison with Cyclophosphamide in the Treatment of Lupus Nephritis

Protocol Number: HE-69-C-Lu-301

Version: Version 1.3

Date: 30 August 2016

Modification record:

Sponsor: Asahi Kasei Pharma Corporation

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National Principal Investigator: Xiangmei Chen, Academician

Investigational Institute: General Hospital of Chinese PLA

CRO: Hangzhou Tigermed Consulting Co., Ltd

PROTOCOL SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, China good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Asahi Kasei Pharma Corporation in confidential and, when this information is submitted to an Institutional Review Board (IRB) or Independent Ethics Committee (IEC), it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Yoshikazu Aoki		
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Xiangmei Chen		
Principal Investigator of Leading Site Printed Name	Signature	Date

Signature Page of Investigators in Each Site

I agree to conduct the study outlined above according to the terms and conditions of the protocol, China GCP guidelines and with applicable laws and regulations. All information pertaining to the study will be treated in a confidential manner.

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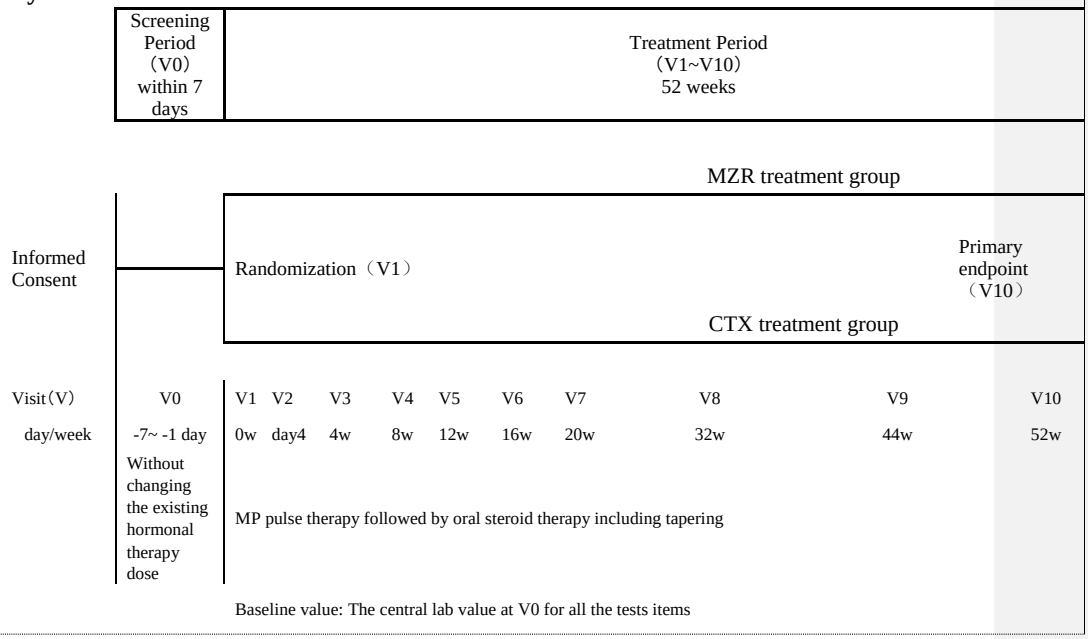
58

59 # PROTOCOL SYNOPSIS

Protocol Number	HE-69-C-Lu-301		
Study Title	A Multi-center, Randomized, Controlled, Open-label Clinical Study to Evaluate the Efficacy and Safety of Mizoribine in Comparison with Cyclophosphamide in the Treatment of Lupus Nephritis		
Version Number	Version 1.3	**Date**	30 Aug 2016
Sponsor	Asahi Kasei Pharma Corporation		
Clinical Phase	Phase III		
Indication	Lupus nephritis		
Overall study purpose and Primary objective	**Overall study purpose** To evaluate MZR treatment in comparison with CTX treatment, observe their efficacy and safety, obtain data from lupus nephritis patients treated with MZR, thus supporting the additional indications of MZR in China. **Primary objective:** To demonstrate that the treatment effect in lupus nephritis of MZR is non-inferior to that of standard therapy CTX through analyzing overall remission rate after treatment. *Total Remission Rate (TR(%)) = Complete remission rate (CR(%))＋Partial remission rate (PR(%))		
Study Design	A multi-center, randomized, controlled, open-label clinical study.		

Study outline



60

61

Number of subjects	In total, 250 subjects with LN will be randomized into MZR group or CTX group in a 1:1 ratio. MZR group: n=125 CTX group: n=125
Number of sites	Approximately 40 sites
Planed enrollment period	29 months
Inclusion and Exclusion Criteria	**I. Inclusion criteria:** 1. Patient has been diagnosed with SLE according to American College of Rheumatology (ACR) criteria in 1997; 2. Patient who has had a kidney biopsy within 365 days prior to screening which was confirmed as class III, III+V, IV, IV+V, or V according to the pathologic classification of International Society of Nephrology/Renal Pathology Society (ISN/RPS) in 2003; 3. Patient with 24hr-urine protein ≥ 1.0g; 4. SLE-DAI ≥ 8 ; 5. Male or female patient between 18 and 70 years (inclusive) at informed consent obtained date; 6. Patient with body weight between 40kg and 80kg (inclusive) at screening; 7. Patients who sign the informed consent form; **II. Exclusion criteria:** 1. Patient who had history of allergy to any investigational product (MZR, CTX) or hormone; 2. Patient who had received accumulated dosage of CTX >3g within one year prior to screening. 3. Patient who had received immunosuppressant or Chinese traditional medicine with immunosuppressive effect within 30 days prior to screening; 4. Patient who had received prednisone>1.0mg/kg/day or equivalent dose of other oral glucocorticoid therapies within 30 days prior to screening; 5. Patient who received other investigational drugs within 30 days prior to screening; 6. Patient who have received plasma exchange therapy or immunoadsorption therapy within 30 days prior to screening; 7. Patient who require pentostatin or live vaccine (not including flu vaccine); 8. Patient who is undergoing renal replacement therapy; 9. Patient who received kidney transplantation; 10. Patient with malignancy; 11. Patient with severe hypertension (SBP > 160mmHg or DBP > 100mmHg) which has not been effectively controlled; 12. Patient with white blood cell count ≤3×10^9/L /L(=3.0 GI/L); 13. Patient with SCr ≥ 176.8μmol/L;

	14. Patient who has a value that is > 3 times of the upper limit of normal range for AST or ALT; 15. Patient with hepatitis B, hepatitis C or HIV infection; 16. Patient with other suspected infections based on chest CT and/or laboratory findings; 17. Patient who is unsuitable for participating in this study in the opinion of investigators (e.g. uncontrolled diabetes, central nervous system lupus , lupus encephalopathy, active psychosis,osteonecrosis of the femoral head, fulminant hepatitis, peptic ulcer, etc.); 18. Female patient who is pregnant, currently breast feeding or willing to become pregnant; 19. Patient with any other diseases that would affect the evaluation of efficacy or safety.
Investigational Product	● Mizoribine tablets (MZR) − 50mg/tablet (oral) ● Cyclophosphamide (CTX) [positive comparator] − 0.2 g/ vial (i.v.)
Dosage and Administration	● MZR − Oral administration, daily dose of 150mg (50mg/tablet, t.i.d), starting from Visit 2 through this study ● CTX − Intravenous injection with between 0.5 to 1.0 g/m^2 body surface area each time (the maximum dose is 1.0 g/day each time). Single administration will be given each at V2-V7 (every 4 weeks); single administration at V8, V9 (every 12 weeks); Cyclophosphamide should be used once per visit.
Study Procedures	**Screening period (Visit 0)** The patients receive all assessments by the investigator, and those patients with lupus nephritis who satisfy the screening criteria will enter to visit 1. The original hormone therapies remain unchanged during screening period. If the patients received no hormone therapy prior to screening, no new hormone therapy is allowed. **Treatment Period (Visit 1 to Visit 10)** After all assessments by the investigator, the subjects who satisfy all inclusion criteria will be randomized at 1:1 ratio either to MZR treatment group or CTX treatment group (V1). All subjects will be treated with methylprednisolone (MP) pulse therapy (0.5g/day) for 3 days. After that, those subjects will be treated with study drug (MZR or CTX) and oral hormone therapy. During the treatment period, the subjects must return to the study center every 4 weeks (V2~V7), every 12 weeks (V8, V9) and 8 weeks after V9 (V10) to receive assessments of each parameter and collect blood and urine samples until the end of the study. During each visit, concomitant medication and adverse events/serious adverse events will be recorded in detail. Subjects are required to return

	remaining drugs including empty vials or packs.
Efficacy Variables	**Primary Efficacy Variable** To compare the total remission rate of MZR and CTX after treatment period (at Visit 10) • Total Remission Rate (TR(%))=Complete Remission Rate (CR(%))＋Partial Remission Rate (PR(%)) − CR: must meet ALL of the following criteria: • 24 hour urine protein < 0.3g; • Serum albumin ≥ 35g/L; • SCr value is within normal range or the elevation of SCr level is not more than 25% of baseline value (V 0) or the SCr level decreased from the baseline value (V 0); − PR: must meet ALL of the following criteria: • 24 hour urine protein decreases by ≥ 50% of baseline value (V0), and 24 hour urine protein < 3.5g; • Serum albumin ≥ 30g/L; • The elevation of sCr level is not more than 25% of baseline value (V 0) or SCr level decreased from the baseline value; • Not achieving complete remission. **Secondary Efficacy Variables:** • **Complete Remission Rate, Partial Remission Rate** − Assessment of the **Complete Remission rate** in MZR and CTX groups at the end of study (Visit 10); − Assessment of the **Partial Remission rate** in MZR and CTX groups at the end of study (Visit 10); − Assessment of the changes of **Overall Remission Rate** in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10); − Assessment of the changes of **Complete Remission rate** in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10); − Assessment of the changes of **Partial Remission rate** in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10); • **Treatment failure (Not achieving complete remission or partial remission)** − Assessment of the Treatment failure rate in MZR and CTX groups at the end of study (V 10); • **24 hours urine protein, Serum albumin** − Assessment of the changes and percentage change of **24**

	hours urine protein from the baseline in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10); – Assessment of the changes of and percentage change of **serum albumin** from the baseline in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10); • **SCr, eGFR (CKD-EPI formula), BUN** – Assessment of the changes of and percentage change of **SCr** from the baseline in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10); – Assessment of the changes of and percentage change of **eGFR** from the baseline in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10); – Assessment of the changes of and percentage change of **BUN** from the baseline in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10); • **C3, Anti-DNA antibody, ANA, Anti-Sm antibody, Anti-phospholipid antibody** – Assessment of the changes of immunological test (**C3**) from baseline in MZR and CTX groups during the treatment period (V7, V10); – Assessment of the changes of immunological test (**Anti-DNA antibody**) from baseline in MZR and CTX groups during the treatment period (V7, V10); – Assessment of the changes of immunological test (**ANA**) from baseline in MZR and CTX groups during the treatment period (V7, V10); – Assessment of the changes of immunological test (**Anti-Sm antibody**) from baseline in MZR and CTX groups during the treatment period (V7, V10); – Assessment of the changes of immunological test (**Anti-phospholipid antibody**) from baseline in MZR and CTX groups during the treatment period (V7, V10); • **SLE-DAI Score** – Assessment of the changes of **SLE-DAI score** from baseline in MZR and CTX groups during the treatment period (V7, V10); • **Endpoint event** – Progression to End-Stage Renal Disease or Doubling of SCr through the study.
Safety Variables	The following variables are needed to be recorded to assess safety of the

	investigational product: • Any reported adverse events [including SAE, pregnancy, important treatment-related adverse events, and adverse events leading to study discontinuation] • Laboratory test results: routine blood, blood biochemistry, routine urine and IgG • Body weight • Vital signs (blood pressure, pulse and body temperature) • 12-Lead ECG (resting state) • Chest CT
Statistical Analysis	**Selection of Data Set:** Efficacy analysis is based on FAS and PPS. Safety analysis is based on SS. • Full analysis set (FAS) will include all subjects who are randomized and receive at least one dose of study treatment and had at least one post-treatment efficacy assessment. • Per-Protocol Set (PPS) will include all subjects without any other major protocol violation in FAS. • Safety set (SS) will include all randomized subjects who receive at least one dose of study treatment and had at least one subsequent safety assessment after randomization. Non-inferiority testing will be applied for primary efficacy variable. Relative risk ratio between treatment groups and its 95% two-sided confidence intervals will be calculated for PPS population. Other variables including baseline variables and secondary efficacy variables will be based on descriptive statistics. Continuous variables will be analyzed by using descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum), while frequency and percentage calculation for categorical variable analysis.

62
63

Content

148

LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
ALB	Serum albumin
ALT	Alanine Transaminase
ANA	Anti-nuclear antibody
ARB	Angiotensin Receptor Blocker
AST	Aspartate Transaminase
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CFDA	China Food and Drug Administration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CR	Complete Remission
CRO	Contract Research Organization
CSR	Clinical Study Report
CTX	Cyclophosphamide
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
ESRD	End-stage Renal Disease
FAS	Full Analysis Set
FASD	First Administration of Study drug
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLU	Glucose

GMP	Guanine nucleotide
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HCV Ab	Hepatitis C virus antibody
HIV	Human Immunodeficiency Virus
hs-CRP	High sensitivity C-reactive protein
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IMP	Inosine Monophosphate
IMP-DH	Inosine 5-Monophosphate Dehydrogenase
IRB	Institutional Review Board
ISN	International Society of Nephrology
IWRS	Interactive Web Response System
JPMA	Japanese Pharmaceutical Manufacturers Association
KDIGO	Kidney Disease: Improving Global Outcomes
LN	Lupus nephritis
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
MP	Methyprednisolone
MZR	Mizoribine
PhRMA	Pharmaceutical Research and Manufacturers of America
PPS	Per Protocol Set
PR	Partial Remission
QA	Quality Assurance
RAS	Renin Angiotensin System
RND	Randomization
RPS	Renal Pathology Society
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SCr	Serum Creatinine
SLE	Systemic Lupus Erythematosus
SLE-DAI	Systemic Lupus Erythematosus Disease Activity Index
SOP	Standard Operating Procedures
SS	Safety Set
T-BIL	Total bilirubin
TC	Total cholesterol
TG	Triglycerides
TP	Total protein
TR	Total Remission
UA	Uric acid
UNS	Unscheduled visits

149

150

1. Study Background

1.1 Disease Description

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by the production of auto-antibodies. Antibodies against nucleosomes and double-stranded DNA have a central role in the pathogenesis of the disease [1].

SLE may involve all kinds of systems and organs [2]. Kidney involvement, that is, lupus nephritis, accounts for the most morbidity and mortality among all complications of each organ in SLE patients [3,4,5]. The young female patients have an increased long-term risk for end-stage renal disease (ESRD), on average, 20% require dialysis or renal transplantation within 10 year after diagnosis. Furthermore, renal survival has been seen in 50% of their patients with lupus nephritis at 20 years. Cardiovascular and cerebrovascular events account for approximately 25 to 50 % of deaths among patients who have lupus nehpritis [6,7,8,9].

In Europe, the incidence of SLE is estimated at 3.3 to 5.0 per 100,000 persons and the prevalence at 25.4 to 91.0 per 100,000 persons [10]. Most patients are women of childbearing potential [2,10]. Lupus nephritis occurs in up to 50 to 75% of SLE patients during the course of the disease [4,11,12]. The incidence of kidney involvement differs with ethnicity: a higher incidence of lupus nephritis has been reported among Black, Hispanic and Asian patients compared with Caucasian patients [13]. Progression into ESRD despite aggressive immunosuppressive therapy does occur [14,15,**Error! Reference source not found.**~~16~~].

Diagnosed patients with Lupus nephritis is usually performed the renal biopsy and classified. Generally, Class I and II do not require the immunosuppressive treatment. Advanced sclerosed Class VI is thought to be unexpected for this treatment [2]. The distribution of classification based on landmark trial of mycophenolate mofetil “The Aspreva Lupus Management Study Trial (ALMS) [17]” was III / III+V (15.7%), IV / IV+V (68.1%), and V only (16.2%).

As a standard treatment regimen for remission induction of proliferative lupus nephritis, intravenous cyclophosphamide (IVCY) and glucocorticoids has been widely accepted. Induction treatment for lupus nephritis with monthly intravenous cyclophosphamide (0.5~lg/m^2) has been accepted as standard clinical practice, as this regimen balances duration of time to achieve renal remission with risk of gonadal and other toxicity. Even so, cyclophosphamide is associated with sever adverse effects, such as infection, ovarian failure, malignancies, bladder cancer [18,19]. Thus more effective and safety alternative immunosuppressive drugs such as mycophenolate mofetil, tacrolimus and mizoribine have

been sought. Many studies have proven that mycophenolate mofetil is as effective as cyclophosphamide and has a better safety profile for lupus nephritis than cyclophosphamide [2,20,21].

1.2 Investigational Product(s) Description

Mizoribine (MZR) is originally isolated as an antibiotic agent with an activity against Candida albicans, and subsequently it was found to have strong immunosuppressive activity in various animal experimental models [22]. Mizoribine is an imidazole nucleoside and the metabolites, MZ-5-P, exerts its activity through selective inhibition of inosine monophosphate (IMP) synthetase and guanosine monophosphate synthetase, resulting in the complete inhibition of guanine nucleotide synthesis without incorporation into nucleotides. Mizoribine (MZR) is an immunosuppressant drug having selective inhibitory effects on inosine 5-monophosphate dehydrogenase (IMP-DH), an enzyme in the de-novo purine nucleotide synthesis system. MZR exerts a suppressive effect on cell-mediated and humoral immune responses by suppressing T- and B lymphocyte proliferation via the inhibition of guanosine monophosphate synthesis [23,24].

The clinical efficacy of MZR as an immunosuppressant for renal transplantation was investigated in various Japanese institutions during the period from 1978 to 1982, and in 1984, MZR has been firstly approved by the Japanese Ministry of Health, Labour and Welfare as a drug indicated for the prevention of rejection in renal transplantation in 1984 [25].

In addition, mizoribine (MZR) has been approved in Japan for the treatment of lupus nephritis (1990), rheumatoid arthritis (1992), and primary nephrotic syndrome (1995) [25], and in these diseases, it has often been used in combination with corticosteroids and/or anti-inflammatory drugs.

The clinical trials and post-marketing surveillance study involved a total of more than 4,000 cases receiving mizoribine therapy for kidney transplantation and three diseases (lupus nephritis, rheumatoid arthritis and nephrotic syndrome) showed that mizoribine was well-tolerated and had a good safety profile.

Presently, the combination of glucocorticoids with cyclophosphamide is an effective treatment for patients with lupus nephritis in Chinese market. However, the treatment regimen has its own disadvantages. E.g. multi-target therapy of mycophenolate mofetil and tacrolimus is more effective than intravenous cyclophosphamide for inducing complete remission in patients with class V+ IV lupus nephritis [26], which is thought to be unsatisfactory. Kagawa H reported that mizoribine and tacrolimus treatment with corticosteroids were well tolerated and

proved to be an optimal alternative including multi-target therapy remission - inducing regimen for lupus nephritis[Error! Reference source not found.27].

Mizoribine has been registered and marketed for the treatment of lupus nephritis in Japan. Although mizoribine for the prevention of rejection after renal transplantation has been approved in 1999 by China Food and Drug Administration (CFDA), and as an immunosuppressant with high safety, mizoribine has been used in Chinese clinical treatment for more than ten years, lupus nephritis as indication has not been authorized.

This study aims to compare the efficacy and safety of mizoribine and cyclophosphamide in patients with lupus nephritis, and obtain approval from CFDA of registration of mizoribine for treating lupus nephritis in China. According to the classification of registration regulations of CFDA, mizoribine belong to the Category 3 of imported chemical medicine. CFDA approval numbers are 2013L01477 and 2013L01478. This clinical study is designed based on the regulations of imported drug registration of CFDA.

2. Study Objective

2.1 Overall objective

To evaluate MZR treatment in comparison with CTX treatment, observe their efficacy and safety, obtain data from lupus nephritis patients treated with MZR, thus supporting the additional indications of MZR in China.

2.2 Primary objective

To demonstrate that the treatment effect in lupus nephritis of MZR is non-inferior to that of standard therapy CTX through analyzing total remission rate after treatment.

*Total Remission Rate (Total Remission Rate, TR(%)) = Complete remission rate (CR(%))＋Partial remission rate (PR(%))

2.3 Secondary objectives

Secondary objective of this study is to evaluate the efficacy (*see below*) and safety profile of MZR compared with CTX in the treatment of lupus nephritis.

- CR (%), PR (%);
- Treatment failure (not achieving complete remission or partial remission) (%)
- 24 hours urine protein, serum albumin;
- SCr, eGFR, BUN;
- C3, anti-DNA antibody, ANA, anti-Sm antibody, anti-phospholipid antibody
- SLE-DAI;
- Endpoint event;

2.4 Exploratory objectives

Exploratory objective of this study is to evaluate the changes of hs-CRP of MZR compared with CTX in the treatment of patients with lupus nephritis.

3. Selection and withdrawal of subjects

3.1 Inclusion criteria

Patients who participate in this study must meet the following criteria:

1. Patient has been previously diagnosed with systemic lupus erythematosus (SLE) according to American College of Rheumatology (ACR) criteria in 1997;
2. Patient who has had a kidney biopsy within 1 year prior to screening which was confirmed as class III, III+V, IV, IV+V, or V according to the pathologic classification of International Society of Nephrology/Renal Pathology Society (ISN/RPS) in 2003;
3. Patient with 24hr-urine protein ≥ 1.0g;
4. SLE-DAI≥8;
5. Male or female patient between 18 and 70 years (inclusive) when signing the informed consent;
6. Patient with body weight between 40kg and 80kg (inclusive) at screening;
7. Patients who sign the informed consent form;

3.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from this study:

1.Patient who had history of allergy to any investigational product (MZR, CTX) or hormone;
2.Patient who had received accumulated dosage of CTX >3g within one year prior to screening .
3.Patient who had received immunosuppressant or Chinese traditional medicine with immunosuppressive effect within 30 days prior to screening;
4.Patient who had received prednisone>1.0mg/kg/day or equivalent dose of other oral glucocorticoid therapies within 30 days prior to screening;
5.Patient who received other investigational drugs within 30 days prior to screening;
6.Patient who have received plasma exchange therapy or immunoadsorption therapy within 30 days prior to screening;
7.Patient who require pentostatin or live vaccine (not including flu vaccine);
8.Patient who is undergoing renal replacement therapy;
9.Patient who received kidney transplantation;
10.Patient with malignancy;
11.Patient with severe hypertension (SBP > 160mmHg or DBP > 100mmHg) which has not been effectively controlled;
12.Patient with white blood cell count $\leq 3\times10^9$/L /L(=3.0 GI/L);
13.Patient with SCr ≥ 176.8μmol/L;
14.Patient who has a value that is > 3 times of the upper limit of normal range for AST or ALT;
15.Patient with hepatitis B, hepatitis C or HIV infection;
16. Patient with other suspected infections based on chest CT and/or laboratory findings;

17.Patient who is unsuitable for participating in this study in the opinion of investigators (e.g. uncontrolled diabetes, central nervous system lupus , lupus encephalopathy, active psychosis，osteonecrosis of the femoral head, fulminant hepatitis, peptic ulcer, etc.);
18.Female patient who is pregnant, currently breast feeding or willing to become pregnant;
19.Patient with any other diseases that would affect the evaluation of efficacy or safety.

3.3 Premature withdrawal criteria for subjects

Definition of "subject premature withdrawal from the study": any subject who signed the informed consent form and accepted any study procedure of the study withdrew from the study prior to the last visit on any reason.

1. Withdrawal by subject: a subject decides to withdraw from the study (including both screening period and treatment period;
2. Screen failure: A subject does not satisfy the inclusion criteria or satisfy exclusion criteria at Visit 0 or Visit 1.
3. Protocol violation: any serious violation against inclusion or exclusion criteria found after the first dose of the investigational drug; A subject takes prohibited medications or prohibited therapy before the last planned visit. Other major violation.
4. Pregnancy: A subject becomes pregnant;
5. Subject's poor compliance with study drug: subject's poor compliance with the protocol, including refusal of continue treatment or observation;

   Note: see protocol section 6.3 Treatment compliance for details.
6. Investigator's decision: any medical condition, including those listed under the exclusion criteria of the protocol, or personal circumstances, which in the opinion of the investigator, exposes the subject to substantial risk by continuing in the study or does not allow the subject to adhere to the requirements of the study protocol.
7. Adverse event: the occurrence of any clinically significant adverse event or serious adverse event, which in the opinion of the investigator warrants subject's premature withdrawal. If an adverse event is considered by the investigator as not clinically related to the study drug or if the benefits of continued study treatment are considered to outweigh the importance of the adverse event, the treatment may be continued at the discretion of the investigator.

   Note: The subject who has shown the 1) WBC count: $\leq 3x10^9$/L (=3.0 GI/L) or 2) AST or ALT > 5 times of the upper limit of normal range will be discontinued from this study
8. Lost to follow-up: A subject does not come to a site for any reason before the planned last visit or the end of study visit.
9. Achieving endpoint event (progression to End-Stage Renal Disease" or "Doubling of SCr" through the study)

Note: see section 7.2 second efficacy variable for details.

10. Others: it's difficult for subject to continue study judged by principal investigator or co-investigators;

3.4 Early study termination

The study can be prematurely terminated at any time for any reason by sponsor. If it is necessary, the subject should be assessed at the end of study.

4. Overall study design

4.1 Type of the study

This is a multi-center, randomized, controlled, open-label clinical study including screening period (within 7 days) and treatment period (52 weeks), aiming to confirm the non-inferiority of MZR to CTX in the treatment of patients with lupus nephritis.

All qualified subjects after the screening period will be randomized into either MZR treatment group or CTX treatment group at the 1:1 ratio at Visit 1.

After randomization, subjects will be treated with methylprednisolone (MP) pulse therapy (0.5g/day) for 3 days. After that, subjects will receive study drug (MZR or CTX) and oral hormone therapy from Visit2 (day 4).

During the course of study, subjects will also be requried to receive hormone therapy as conventional therapy (see section 5.2 hormone therapy)

Note: Interval days from MP pulse therapy completion date to study drug treatment should be within 3 days (Interval from randomization date to study drug treatment date should be within 7 days)

The study outline:

	Screening period (V0) within 7 days	Treatment period (V1~V10) 52 weeks								
		MZR treatment group								
Informed consent		Randomization (V1)								Primary efficacy variables (V10)
		CTX treatment group								
Visits (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Day /week	-7~ -1 day	0w	day4	4w	8w	12w	16w	20w	32w	44w	52w
	Without changing the original hormone therapies	MP pulse therapy followed by oral hormone therapy with tapering (V1 to V10)									

Baseline value: The central lab value at V0 for all the tests;
Day1: randomization date (=V1)

The study flowchart is illustrated as below:

360

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Study Flow Chart

Category	Items for assessment	Screening period	Treatment period											
Visit schedule	Visit (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	UNS[19]	EOS[20]
	Days / Week (1 week=7days)	-7d~-1d	0w 1d	day4 4d	4w 29d	8w 57d	12w 85d	16w 113d	20w 141d	32w 225d	44w 309d	52w 365d		
	Visit Window		Randomization	+3d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	-	-
Screening criteria	Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-
	Inclusion criteria / exclusion criteria [1]	X	X	-	-	-	-	-	-	-	-	-	-	-
Medical history	Demographic/medical history [2]	X	-	-	-	-	-	-	-	-	-	-	-	-
	Medical history of SLE and Lupus nephritis [3]	X	-	-	-	-	-	-	-	-	-	-	-	-
	Renal biopsy and pathological classification [4]	X	-	-	-	-	-	-	-	-	-	-	-	-
Patient management	IWRS log in	X	X	X	X	X	X	X	X	X	X	-	X	-
	Randomization	-	X	-	-	-	-	-	-	-	-	-	-	-
Medication and therapy	Study drug dispense (CTX)	-	-	X	X	X	X	X	X	X	X	-	-	-
	Study drug dispense (MZR)	-	-	X	X	X	X	X	X	X	X	-	-	-
	Return of study drug [6]	-	-	X	X	X	X	X	X	X	X	X	-	X
	Compliance of study drug	-	-	X	X	X	X	X	X	X	X	X	-	X
	Hormone therapy (MP pulse)	-	X[5]	-	-	-	-	-	-	-	-	-	-	-
	Hormone therapy (oral) [7]	X[8]	-	X	X	X	X	X	X	X	X	X	X	X
	Concomitant medication and therapy [9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease activity	SLE-DAI	X	-	-	-	-	-	-	X	-	-	X	-	X
Adverse	AE[10]	X	X	X	X	X	X	X	X	X	X	X	X	X

event	SAE, Pregnancy,	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory	Biochemistry, eGFR[11]	X	-	-	X	X	X	X	X	X	X	X	X	X
	Routine blood [12]	X	-	-	X	X	X	X	X	X	X	X	X	X
	Routine urine [13]	X	-	-	X	X	X	X	X	X	X	X	X	X
	24 hours urinary protein1[14]	X	-	-	X	X	X	X	X	X	X	X	X	X
	Immunological test (C3,Anti-DNA antibody, ANA, Anti-Sm antibody, Anti-phospholipid antibody) [15]	X	-	-	-	-	-	-	X	-	-	X	-	X
	hs-CRP[16]	X	-	-	X	X	X	X	X	X	X	X	-	X
	Pregnancy test (female) [17]	X	-	-	-	-	-	-	X	-	-	X	X[21]	X
	HBsAg, HCVAb，HIV[18]	X	-	-	-	-	-	-	-	-	-	-	-	-
	IgG [22]	X	-	-	X	X	X	X	X	X	X	X	X	X
Vital signs	Height	X	-	-	-	-	-	-	-	-	-	-	-	-
	Body weight	X	-	X	X	X	X	X	X	X	X	X	X	X
	Vital signs (Blood pressure, Pulse, Temperature)	X	-	X	X	X	X	X	X	X	X	X	X	X
ECG	12-Lead resting electrocardiogram	X	-	-	-		-	-	-	-	-	X	X	X
CT	胸部 CT	X				X							X	X

1. Lab data at Visit 0 will be used for inclusion/exclusion screening (see the section 3.1, 3.2)
2. Race, Gender, Birth date. Medical history
3. Medical history of SLE (time since diagnosis of SLE), medical history of Lupus nephritis (time and age at diagnosis of Lupus nephritis)
4. The renal biopsy and pathological classification within 1 year prior to V0.
5. At visit 1, subjects will receive methylprednisolone (MP) pulse therapy (0.5g/day) for 3 days. After MP pulse therapy, at visit 2, study drug (MZR or CTX) with oral hormone therapy will be started (As buffer-days from MP therapy completion date to oral-hormone therapy starting date, maximum three (3) days will be allowed (e.g. national holidays)
6. Used CTX vials should be destroyed at the site.
7. Oral hormone therapy (see section 5.2 Hormone therapy for details)

8. The original hormone treatment regimen remains unchanged during the screening period. During the screening period, no new hormone therapy is allowed for subjects who never received hormone therapies.
9. Concomitant medication and therapy include ACEI , ARB and hydroxychloroquine sulfate treatment. Prohibited medications and treatment (immunosuppressive agents and Chinese traditional medicine with immunosuppressive effect other than study drug, Live vaccine (not including flu vaccine), Pentostatin, Other investigational drug, Plasma exchange therapy, Immunoadsorption therapy, hormone pulse therapy (excluding hormone pulse therapies specified in the protocol)).
10. AE and protocol defined important AE
11. Biochemistry, eGFR: tested at central lab (ALT, AST, Total Bilirubin, Total Protein, Albumin, Uric Acid, TC, TG, GLU,SCr, BUN, eGFR)
12. Routine blood: tested at central lab (Hemoglobin, Hematocrit, White blood cells, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, Red blood cells, Platelet count)
13. Routine urine: tested at central lab (dipstick test: urine protein, urine glucose; Urine duct type, Red blood cells /HP and White blood cells /HP were detected in V0/V7/V10/EOS)
14. 24 hours urinary protein: tested at central lab (whether patients are allowed to be hospitalized to collect urine for consecutive 24 hours so as to determine urinary protein should be judged by the investigator; If the patient has started collecting urine for 24 hours continuously in accordance with clinical routine procedures before informed consent, and the specimen meets the test requirements, the specimen can be used for V0.).
15. Immunological test: to be tested at central lab.
16. hs-CRP: to be tested at central lab.
17. Pregnancy tests should be performed for women of childbearing potential at central lab.
18. HBsAg, HCVAb and HIV are tested at central lab.
19. UNS(Unscheduled Visit): Unscheduled Visits. If an adverse event (such as infection) is suspected to occur between visits, the investigator should arrange unscheduled visits for examination and treatment of the subject as necessary.
20. EOS(End of Study): Final examination when subjects discontinue or drop
21. Pregnancy test should be performed for women of childbearing potential as needed.
22. IgG: Testing at the central laboratory.

4.2 Randomization

All eligible subjects are randomized to MZR group or CTX group at 1:1 ratio using IWRS system. Unique subject number will be assigned to subjects. The pathological classification will be regarded as a stratified factor. Please refer to IWRS site manual for operation in details.

- Re-screening

If a patient is not eligible to enter into the screening period and be screen failed, investigator could reconsider to re-screen the subject only if investigator consider that the patient could be potentially eligible when his/her condition changed.

In this case, a completely new subject number would be allocated and the patient would be needed to re-perform all Visit 0 assessments with new informed consent. Once a subject is randomized, this subject will not be allowed to be re-screened in this study.

4.3 Study Procedures and Treatment Phases

4.3.1 Screening period (visit 0)

The investigator will obtain written informed consent from the subjects prior to the performing any study-related procedures. During the screening period, subjects must be screened by the investigators according to the following procedures:

- Eligibility criteria (inclusion/exclusion criteria);

  Note: Lab data at Visit 0 will be used for inclusion/exclusion screening (see the section 3.1, 3.2)

- Login to IWRS system to register subjects;
- Medical history (Demographic/medical history, medical history of SLE and Lupus nephritis, renal biopsy and pathological classification)
- Medication and therapy (hormone therapies, concomitant medication and treatment).

  Hormone therapies: the original hormone therapies remain unchanged during screening period. If patients use no hormone therapies during screening period, use of new hormone therapy is not allowed. The type of hormone therapies used before screening is not limited. Those used during screening period are limited to prednisone or equivalent dose of methylprednisolone (refer to section 5.2 for hormone therapies).

- Disease activity (SLE-DAI score);
- Adverse event (AE, SAE, Pregnancy);
- Laboratory (routine blood, biochemistry, eGFR, routine urine, pregnancy test for

women of child bearing potential <HCG>, HBsAg, HCV Ab, HIV);

Note: please see flow chart and section 8.1.1 of the protocol Laboratory Tests for details.

- 24 hours urinary protein;
- Laboratory (immunological tests: C3, anti-DNA antibody, ANA, anti-Sm antibody, anti-phospholipid antibody);
- Laboratory (biomarker: hs-CRP);
- Laboratory (IgG);
- Height, body weight;
- Recording vital signs (blood pressure, pulse, temperature);
- 12-Lead resting electrocardiogram
- Chest CT

Baseline value: the central lab value at V0 for all the test items.

4.3.2 Treatment Period (Visit 1~10)

- **Visit 1(Randomization visit)**

Subject's inclusion eligibility will be evaluated, focusing on the following assessment items.

- Verify inclusion/exclusion criteria;

Note: lab data at V0 are used for inclusion/exclusion screening (see sections 3.1 and 3.2)

- Login IWRS system to manage and randomize subjects;

Methylprednisolone (MP) pulse therapy start date must be same as Randomization date (Randomization date = MP therapy start date= Day 1)

- Methylprednisolone (MP) pulse therapy (0.5g/day for 3 days)

Hormone therapy: methylprednisolone (MP) pulse therapy at V1 followed by oral hormone treatment at V2 (see Section 5.2 for Hormone Therapy for details)

- Records of concomitant medication and therapies
- Adverse event (AE, SAE, pregnancy)

Any female patient of child bearing potential who is suspicious of being pregnant during the treatment period will be required to return to the study center for pregnancy test.

- **Visit 2 (Day4: First administration of study drug)**

- Login IWRS system to conduct subject management;
- First study drug treatment (study drug dispense, compliance of study drug);

- Oral hormone treatment (see section 5.2 Hormone Therapy for details);
- Records of concomitant medication and treatment;
- Adverse event (Adverse event, SAE, pregnancy);
- Body weight;
- Recording vital signs (blood pressure, pulse, temperature).

- **Visit 3~10**

- Login IWRS system to conduct subject management;
- Medication and therapy (study drug dispense, return the investigational drug to the site, compliance of study drug, hormone therapy, concomitant medication and therapy);
- Disease activity (SLE-DAI score: V7, V10);
- Adverse event (Adverse event, SAE, pregnancy)
- Laboratory (biochemistry, routine blood, eGFR, routine urine, pregnancy test for women of child bearing potential (V7, V10));

Any female patient of child bearing potential who is suspicious of being pregnant during the treatment period will be required to return to the study center for pregnancy test.

- 24 hours urinary protein;
- Laboratory (immunological test: C3, Anti-DNA antibody, ANA, Anti-Sm antibody, Anti-phospholipid antibody (V7, V10);
- Laboratory (biomarker: hs-CRP);
- Laboratory (IgG)
- Body weight;
- Recording vital signs (blood pressure, pulse, temperature);
- 12-Lead resting electrocardiogram (V10);
- Chest CT (V3).

- **Unscheduled visit (UNS)**

- Login IWRS system to conduct subject management;
- Medication and therapy (hormone therapy, concomitant medication and therapy);
- Adverse event (Adverse event, SAE, pregnancy);
- Laboratory (biochemistry, routine blood, eGFR, routine urine, pregnancy test for women of child bearing potential);

Any female patient of child bearing potential who is suspicious of being pregnant during the treatment period will be required to return to the study center for

pregnancy test.

Note: see flow chart and section 8.1.1 of the protocol Laboratory Test for details.

- 24 hours urinary protein;
- Laboratory (IgG)
- Body weight;
- Recording vital signs (blood pressure, pulse, temperature);
- 12-Lead resting electrocardiogram;
- Chest CT.

Note: only essential tests and evaluation are performed at unscheduled visits. If an adverse event (such as infection) is suspected to occur between visits, the investigator should arrange unscheduled visits for examination and treatment of the subject as necessary.

4.3.3 Premature withdrawal from study visits (EOS)

Any subject who prematurely withdraws from the study must undergo the following procedures within 1 week from the withdrawal date, and record this information on the EOS visit in eCRF.

If the subject does not attend the study visit, follow-up should be continued according to the specified schedule by telephone except in the case that subject specifically refuses such follow-up and withdraws his/her consent.

- **The following items should be performed if subject prematurely withdraw from the study visits:**

- Login IWRS system to conduct subject management;

Note: Investigator will record the information of discontinuation to the Cerf.

- Medication and therapy (return the investigational drug to the site, compliance of study drug, hormone therapies, concomitant medication and therapy);
- Disease activity (SLE-DAI score);
- Adverse event (Adverse event, SAE, pregnancy);
- Laboratory (biochemistry, routine blood, eGFR, routine urine, pregnancy tests for women of child bearing potential);

Note: see flow chart and section 8.1.1 of the protocol Laboratory Test for details.

- 24 hours urinary protein;
- Laboratory (immunological test: C3, Anti-DNA antibody, ANA, Anti-Sm antibody, Anti-phospholipid antibody;

518 – Laboratory (biomarker: hs-CRP)
519 – Laboratory (IgG)
520 – Body weight;
521 – Recording vital signs (blood pressure, pulse, temperature);
522 – 12-Lead resting electrocardiogram;
523 – Chest CT.
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5. Investigational Drug

5.1 Drug Name and Dosage Form

The following are study drugs:

Investigational drug

Generic Name:	Mizoribine
Formulation:	50mg tablet (p.o.)
Pack Size(s):	110 tablets / pack
Storage:	Store at room temperature (not exceeding 30℃)
Expiry date:	36 months
Supplier:	Asahi Kasei Pharma Corporation
Manufacturer	Asahi Kasei Pharma Corporation

Control drug

Generic Name:	Cyclophosphamide
Formulation::	0.2g/vial (i.v.)
Pack Size(s):	5 vials/pack
Storage:	Store at temperature not exceeding 25℃
Expiry date:	24 months
Supplier:	Asahi Kasei Pharma Corporation
Manufacturer	Baxter Oncology GmbH

5.2 Instructions for Use

Investigational drug (MZR, CTX)

- **Mizoribine (MZR)**
  - Oral administration
  - 150mg daily starting from V2 (50mg/tablet, 1 tablet each time, t.i.d.)
- **Cyclophosphamide (CTX)**
  - Intravenous administration
  - Each administration will be given at V2-V7 (every 4 weeks), at V8 and V9 (every 12 weeks);
  - The dosage for each administration is 0.5~1.0g/m^2 body surface area (Dubois & Dubois formula), the maximum dosage is 1.0g/day for each administration. Cyclophosphamide should be used once per visit.

    Dubois & Dubois'formular：

- BSA (m^2) = 0.007184 × Height(cm)$^{0.725}$ × Weight(kg)$^{0.425}$

Dosing schedule

	Screening period	Treatment period									
Visit	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Day/week	-	0 RND	Day4 FASD	4w	8w	12w	16w	20w	32w	44w	52w
MZR	-	-	X	X	X	X	X	X	X	X	-
CTX	-	-	X	X	X	X	X	X	X	X	-

At Visit 1, Methylprednisolone (MP) pulse therapy (0.5g/day for 3 days) will be treated.
Subsequently, at Visit 2, study drug (MZR or CTX) will be administrated

After completion of all assessments at Visit 10, the trial is concluded except that adverse events needed to be followed. The investigators should provide proper treatment to subjects according to subject's disease condition. The treatment is excluded from this clinical trial.

V: Visit, RND: Randomization, FASD: First Administration of Study drug.

Study drug management (e.g. Study drug dispense at the protocol defined Visit, study drugs are dispensed and received by local depots) will be conducted using IWRS. Please see the IWRS site manual for operation in details.

Hormone therapies

Starts in V0,only prednisone and methylprednisolone are used in this study.

Methylprednisolone 4mg= prednisone 5mg

Dose conversion table of hormone therapies is as follows:

Corticosteroid	Equivalent dose (mg)
Prednisone	5
Methylprednisolone	4
Prednisolone	5
Hydrocortisone	20
Triamcinolone	4
Betamethasone	0.75
Dexamethasone	0.75

- **Screening period (V0)**

The original hormone therapies remain unchanged. During the screening period, if the patients never received hormone therapy, no new hormone therapy is allowed.

Note: patients who had received prednisone >1.0mg/Kg/day or equivalent dose of other glucocorticoids within 30 days period to screening are not allowed to be enrolled (refer to Section 3.1 Exclusion Criteria).

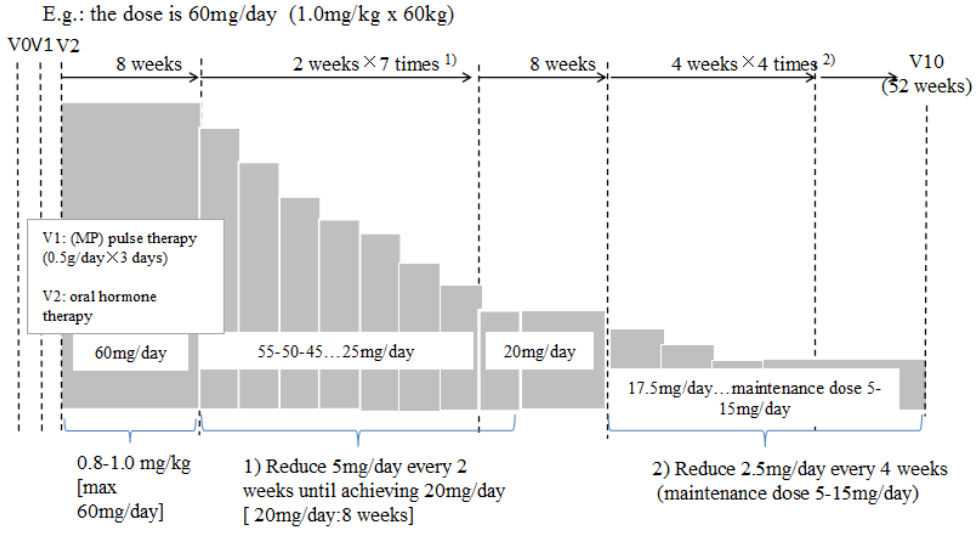
- **Treatment period (V1~V10)**

After randomization, Methylprednisolone (MP) pulse therapy (0.5g/day for 3 days) should be treated (V1). After MP pulse therapy, oral hormone treatment will be started on following oral hormone therapy guidance, Oral hormone dose adjustment is permitted within a clinically acceptable time window, while the investigator should adjust the hormone usage method as necessary according to the specific conditions of the subjects, and the dosage of hormones used during the study should be recorded in the original document and eCRF.

Oral hormone therapy guidance (V2 to V10): oral hormone therapy (0.8 to 1.0 mg/kg/day prednisone or equivalent dose of methylprednisolone) will be given for eight weeks (V2 to V4). The daily oral steroid dosage should not exceed 60mg/day (a patient with 80kg will be given 60 mg/day).

After 8 weeks (V4), steroid-tapering will be started. Dose reduction of 5mg/day (e.g. 55mg/day, 50mg/day…) will be performed every 2 weeks until 20mg/day. Dosing with 20mg/day will be continued for eight (8) weeks.

After that, dose reduction by 2.5mg/day (17.5mg/day, 15.0mg/day…) will be performed every 4 weeks. The dose should be maintained between 5mg/day and 15mg/day to the 52 weeks (V10).



Hormone therapies will be prescribed by study sites and will not be supplied by the Sponsor. Hormone therapies are not defined as an investigational product in this study. However, "hormone therapy" will be recorded in both source document and eCRF

- **Hormone therapies during deterioration**

When subject condition faces the deterioration 8 weeks after randomization (V4), the original dosage of hormone therapies (at most) can maintain 4 weeks. After the end of adjusted hormone treatment, investigator will assess the subject condition again. If the subject condition still meets the definition of deterioration, the subjects will be advised to withdraw from the study.

Deterioration defines as 24 hour urine protein level greater than 150% of the baseline value or worsening the SLEDAI score in comparison with baseline.

E.g.: If subject condition deteriorates at Visit 4, the dose of hormone therapies should be continued for 2 weeks to 4 weeks.

Standard case: hormone dose will be tapered by expected.				Deterioration case: doses of hormone therapies continue for 2 weeks to 4 weeks.			
Visit	V4		V5	Visit	V4		V5
Week	2 weeks	2 weeks	2 weeks	Week	2 weeks	2 weeks	2 weeks
Hormone	60			Hormone	60	60	60
		55					
			50				

5.3 Storage Condition

The investigational product must be transported to the study site before trial start in site. Then sufficient medication will be supplied regularly according to actual number of enrolled patients and amount for drug during the study course. The investigational products should be stored in a safe and secure place out of reach of the child.

5.4 Drug Dispensation and Check

The investigator must keep an accurate accounting of the number of investigational boxes/sachets. The study medication must be dispensed only by an appropriately qualified person to subjects in the study. The medication is to be used in accordance with the protocol by subjects who are under the direct supervision of an investigator.

5.5 Drug Return and destruction

The investigator must document all the dispensation information of the study drugs, including date, amount and subject number. The used and unused MZR and unused CTX should be returned according to the related regulations and procedures, while used CTX can be destroyed at local site according to the local regulation.

6. Treatment of Subjects

6.1 Study drug

Please refer to section 5.2 for details.

6.2 Concomitant Medication

The investigator should assess whether other drugs are allowed in consideration of the safety and health of patients, provided that it does not conflict with the exclusion criteria (section 3.2) or the concomitant medications prohibited in section 6.2.1 are not used.

RAS medication (ACE-inhibitor, ARB, Eplerenone, Renin inhibitor)

- RAS medication is recommended for the management of blood pressure by KDIGO guideline
- Newly treatment after screening period is not allowed. Continuous administration of the drug which has been given prior to screening period is allowed. It is strongly recommended that the drug and its original dose should be remained unchanged during the study.

Hydroxychloroquine sulfate

- Continuous administration of the Hydroxychloroquine sulfate which has been given prior to screening period is allowed with its original dose during the study.
- Newly treatment of hydroxychloroquine sulfate after screening period is not allowed.

6.2.1 Prohibited Concomitant Medications and Therapies

During this study, the use of the following medications or therapies may interfere with the interpretation of investigators and affect the evaluation of study results. They are therefore recognized as prohibited concomitant medication and therapy.

1) Immunosuppressive drugs and traditional Chinese medicine with immunosuppressive effect other than study drug;
2) Live vaccine(not including flu vaccine)
3) Pentostatin
4) Other investigational drugs
5) Plasma exchange therapy,immunoadsorption therapy

6) Hormone pulse therapy (except for protocol defined hormone pulse therapy)

6.3 Treatment Compliance

- **Compliance of Investigational Drug**

Compliance with the investigational product will be recorded throughout the study by the investigator. The returned packs or ampoules of study drug must be calculated.

A subject's compliance should be calculated at each visit from Visit 2. Once it has been evaluated that a subject's compliance will be less than 70% or more than 130% at Visit 10, the subject will be deemed to be in poor compliance and will be discarded from the PPS analysis but evaluated within the FAS and SS analysis.

$$\text{Treatment compliance} = \frac{\text{Actual medication of subjects}}{\text{planned medication of subjects}} \times 100\%$$

Note: CTX group: a total of eight (8) times of administration, less than six (6) administration or two continuous unuse of CTX will be recognized as poor compliance.

- **Suspension of Study Drug**

The subjects should strictly follow the dosing regimen. However, suspension of study drug is allowed for the consideration of subject’s safety (e.g. serious infection, SAE) according to investigator’s judgment based on local laboratory test results (MZR: the maximum duration of drug suspension is not more than 2 weeks, CTX: two continuous suspension are not allowed).

7. Efficacy Assessment

7.1 Primary Efficacy Variable

To compare the total remission rate of MZR and CTX groups after treatment period (at Visit 10);

Total Remission Rate (TR(%))=Complete Remission Rate (CR(%))＋Partial Remission Rate (PR(%));

The definition of **Complete Remission**: must meet ALL of the following criteria:

- 24 hour urine protein < 0.3g;
- Serum albumin ≥ 35g/L;
- SCr value is within normal range or the elevation of SCr level is not more than 25% of baseline value (V 0) or SCr level decreased from the baseline value (V 0);

The definition of **Partial Remission:** must meet ALL of the following criteria:

- 24 hour urine protein decreases by ≥ 50% of baseline value (V0), and 24 hour urine protein < 3.5g;
- Serum albumin≥30g/L;
- The elevation of SCr level is not more than 25% of baseline value (V 0) or the SCr level decreased from the baseline value;

- Not achieving complete remission.

7.2 Secondary Efficacy Variables

- **Complete Remission Rate and Partial Remission Rate**
  - Assessment of the **Complete Remission rate** in MZR and CTX groups at the end of study (Visit 10);
  - Assessment of the **Partial Remission rate** in MZR and CTX groups at the end of study (Visit 10);
  - Assessment of the changes of **Overall Remission Rate** in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10);
  - Assessment of the changes of **Complete Remission rate** in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10);
  - Assessment of the changes of **Partial Remission rate** in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10);

- **Treatment failure (Not achieving complete remission or partial remission)**

  - Assessment of the **Treatment failure rate** in MZR and CTX groups at the end of study (V 10);

- **24 hours urine protein, Serum albumin**

  - Assessment of the changes and percentage change of **24 hours urine protein** from the baseline in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10);

  - Assessment of the changes of and percentage change of **serum albumin** from the baseline in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10)

- **SCr, eGFR (CKD-EPI formula), BUN**

  - Assessment of the changes of and percentage change of **SCr** from the baseline in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10);

  - Assessment of the changes of and percentage change of **eGFR** (CKD-EPI formula) fromthe baseline in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10);

  - Assessment of the changes of and percentage change of **BUN** from the baseline in MZR and CTX groups during the treatment period (V4,V7, V8, V9 and V10);

- **C3, Anti-DNA antibody, ANA, Anti-Sm antibody, Anti-phospholipid antibody**

  - Assessment of the changes of immunological test (**C3**) from baseline in MZR and CTX groups during the treatment period (V7, V10);

  - Assessment of the changes of immunological test (**Anti-DNA antibody**) from baseline in MZR and CTX groups during the treatment period (V7, V10);

  - Assessment of the changes of immunological test (**ANA**) from baseline in MZR and CTX groups during the treatment period (V7, V10);

  - Assessment of the changes of immunological test (**Anti-Sm antibody**) from baseline in MZR and CTX groups during the treatment period (V7, V10);

  - Assessment of the changes of immunological test (**Anti-phospholipid antibody**) from baseline in MZR and CTX groups during the treatment period (V7, V10);

- **SLE-DAI Score**

  - Assessment of the changes of **SLE-DAI score** from baseline in MZR and CTX groups during the treatment period (V7, V10);

- **Endpoint event**

  - Endpoint event is defined as progression to end-stage renal disease or doubling of SCr through the study.

    - Progression to end-stage renal disease (ESRD) is defined as the need for chronic dialysis or renal transplantation;

    - Doubling of SCr is defined as the SCr value attains a level double that of the baseline value.

7.3 Exploratory Variables

- Assessment of the changes of biomarker test (**hs-CRP**) from baseline in MZR and CTX groups during treatment period of **hs-CRP** assessment (V4, V7, V8, V9 and V10);

8. Assessment of Safety

8.1 Safety Variable

The following variables are needed to be recorded to assess safety of the investigational drug:

- Any reported adverse events (including SAE, pregnancy, important treatment-related adverse events, and adverse events leading to study discontinuation);
- Laboratory test results: routine blood, blood biochemistry, routine urine and IgG;
- Body weight;
- Vital signs (blood pressure, pulse and body temperature);
- 12-Lead ECG (resting state);
- Chest CT

8.1.1 Laboratory tests

The following laboratory parameters will be tested:

- Routine blood: hemoglobin, hematocrit, white blood cell, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, platelet count, red blood cell;
- Biochemistry: ALT, AST, T-BIL, TP, ALB, UA, TC, TG, GLU, SCr, eGFR(CKD-EPI formula [27~~28~~]), BUN;

  *CKD-EPI公式：

  $eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female]

  SCr：unit of mg/dL，1mg/dL=88.4μmol/L；

  κ：female=0.7，male=0.9；

  α：female=-0.329，male=-0.411；

  min：stands for SCr/κ or1，use the smaller one；

  max：stands for SCr/κ or1，use the larger one；

- Routine urine (dipstick): urine protein, urine glucose; urine duct type, red blood cell /HP and white blood cell /HP were detected in V0/V7/V10/EOS
- 24 hours urinary protein;
- Immunological test : C3, anti-DNA antibody, ANA, Anti-Sm antibody, Anti-phospholipid antibody

- Biomarker test: hs-CRP;
- IgG;
- Serology: HBsAg, HCVAb, HIV;
- Pregnancy test (Female subjects of child bearing potential will undergo a serum pregnancy test <HCG>)

Laboratory test will be performed by a central laboratory. The investigator will evaluate the clinical significance of each laboratory value outside the reference range. The results of the local laboratory will nevertheless not be reconciled with the results of central laboratory, but the results of central laboratory will overrule the results of local laboratory. Please refer to Lab site manual for operation in details

8.2.1 Definition of AE

Adverse event (AE) is any untoward medical occurrence experienced by subjects after the informed consent form is signed, including clinical significant abnormal laboratory values compared with baseline (Visit 0) and intercurrent diseases which appears during the treatment period, regardless of its relationship to investigational drugs. Intermittent events caused by this study disease and/or concomitant diseases (diseases existing at the time of signing the informed consent) are not recorded as AEs. Worsening or exacerbation of this study disease and associated symptoms, laboratory tests, etc. are not recorded as AEs, but only if the worsening or exacerbation of the concomitant disease (disease existing at the time of signing the informed consent form) is more than expected, and the investigator should ensure that events are recorded. The event terms may reflect changes in the condition (e.g. "worsening of").

Investigators should strengthen the contact with subjects between the visit, timely detect the occurrence of adverse events in subjects, and ensure that subjects receive appropriate treatment when adverse events occur during the trial.

All adverse events that occurred must be reported in the eCRF by the investigators.

8.2.1.1 Definition of Important Adverse Event

Following investigational drug related adverse events are defined as important treatment related Adverse Events [2,29,30,3231].

- Granulocytopenia
- If white blood cell count is less than $3X10^9$/L, it is recommended to monitor every two days; daily monitoring is recommended in some special cases. If any bone marrow suppression is observed, monitoring of red blood cell and platelet counts is recommended. It is recommended to test urine sediments to count urine red blood cells routinely. It is the doctor in charge who decides whether some patients with neutropenia should use antibiotics or not. The patients with febrile neutropenia must use antibiotics and/or antifungal agents.
- Infection

  The infection may be associated with immunosuppressive effect of investigational drug and even be life-threatening sometimes. Sepsis and septic shock are also reported. Infections related to cyclophosphamide include pneumonia and recurrent infection with other bacteria, fungi, viruses, protozoans and parasites. Appropriate treatment must be given to treat infection. Sometimes, mizoribine may cause pneumonia, meningitis, sepsis, worsening of viral hepatitis, herpes zoster etc. The condition of patients should be observed, the drug withdrawal and appropriate treatment should be given if any abnormality is found.
- Hemorrhagic cystitis

  Sufficient mesna and enhanced rehydration are used to promote diuresis, thus significantly reducing the frequency and severity of bladder toxicity. It is important to ensure that patients will regularly empty the bladder. If cystitis associated with microscopic hematuria or gross hematuria is observed during the course of treatment, the drug should be withdrawn immediately until it returns to normal.
- Liver function impairment

  The condition of patients should be observed. Drug withdrawal and appropriate treatment should be given if necessary.
- Hyperuricemia
- Hyperuricemia should be controlled through the use of sufficient hydroation and/or allopurinol.
- Malignancy
- Amenorrhoea
- Alopecia

- Nausea, vomiting

8.2.2.1 Assessment of Intensity

The intensity of adverse events occurred during the entire course of the study will be assessed according to the table below:

Intensity grading	**Description of Intensity grading**
Mild	Be aware of a symptom, signs or event, but it can be easily tolerated
Moderate	Causes discomfort or interference with usual daily activities; necessary intervention may be needed;
Severe	Be unable to perform usual daily activities or seriously affect clinical condition; necessary intervention may be needed;

8.2.2.2 Assessment of Causality

The investigators should assess the possible relevance between adverse events and study drug according to the following criteria:

1) Definite: a clinical event follows a reasonable temporal sequence from the time of administration, is the known reaction of investigational drug, alleviates upon tapering or discontinuation of administration and reappears when the investigational product is used again.

2) Possible: a clinical event follows a reasonable temporal sequence from the time of administration, is the known reaction of investigational drug and may be caused by patient's clinical state or other therapies administered to the subject.

3) Unlikely: a clinical event does not follow a reasonable temporal sequence from the time of administration, does not meet the known reaction of investigational drug and may be caused by patient's clinical state or other therapies administered to the subject.

4) Not related: a clinical event which does not follow a reasonable temporal sequence from administration of the investigational product, meet the known reaction of non-investigational drug and could be reasonable explained by the subject's clinical state or other therapies administered to the subject. The disease improves or resolves upon discontinuation of administration of other therapies administered to subjects. It does

reappear when other therapies are administered.

5) Not Assessable: there is no definite relationship between the onset time of a clinical event and administration time of investigational drug. The event is similar to the known reaction of investigational drug and may be caused by the use of other drugs.

If the assessment is Definite, Possible, Unlikely or Not Assessable, then it will be considered as adverse reaction related to investigational drug and will be further determined whether it is a serious adverse event based on its severity degree.

8.2.2.3 Assessment of Outcome

The outcome of the adverse event will be described in terms of:

- Recovered/resolved: "(Serious) AE stop date" should be provided
- Recovering/Resolving: Can be used in cases where subject is known to be clearly recovering from an event. Event is, however, not resolved yet. Follow-up is required.
- Not recovered/not resolved: Event is ongoing
- Recovered/Resolved with sequelae: Used only with persistent incapacity/life-long sequelae, e.g. like blindness after diabetes mellitus, hemiparesis after stroke. "(Serious)AE stop date" should be provided
- Fatal: "(Serious) AE stop date" should be provided. Date of death should be provided only for events leading to death
- Unknown: Unknown to Investigator, e.g. subject lost to follow-up

If the outcome is "not recovered/not resolved" or "recovering/resolving" or "unknown", the AE stop date can be left blank.

If the outcome is "recovered/resolved" or "recovered with sequelae/resolved with sequelae" or "fatal", the AE stop date must be entered.

All adverse events and serious adverse events must be followed up to determine the final outcome.

Once a subject has completed the study, the investigator should follow up for outcomes of all adverse events until it is resolved or stable, patients lose to follow-up or other explanation can be made for this event.

8.2.3 Reporting of AEs

All adverse events occur in the study (Including both “Screening Period” and “Treatment Period”) will be graded as described in section 8.2.2.1 and reported in forms of eCRF. Causality between adverse event and the investigational product will be assessed.

The report of adverse event should contain classification, grade, relationship to the investigational drug except for adverse events in Screening Period, treatment and outcome. All adverse events should be followed until it is resolved or in a stable condition. The duration of each adverse event (start date and end date) will be recorded. The monitor will check the records in eCRF at any time.

8.3 Serious Adverse Events (SAE)

Any SAE (planned hospitalizations at the time of evaluation and treatment at each study visit, hospitalizations or extended hospitalizations occurring after the end of the study due to study disease and/or continuing treatment for that disease (which present at the time of signing the informed consent form) are excluded) occurred during the period from the signing date of informed consent to the 30th day after the last dose of investigational drug or last visit (whichever period is longer) should be expeditiously reported to sponsor (Medical Representative of Tigermed) within 24 hours recorded tin eCRF after it is acquainted by the investigators. SAE should also be reported using SAE Report Form.

8.3.1 Definition of SAE

A serious adverse event (SAE) is any untoward medical event occurred at any dose of study drug and met the following criteria:

- Resulting in death [a]
- Is life-threatening [b]
- Requires inpatient hospitalisation or prolongation of existing hospitalisation [c]
- Resulting in persistent or significant disability/incapacity [d]

- Is a congenital anomaly/birth defect [e]
- Requires medical or surgical intervention to prevent permanent impairment or damage [f]

Other medical situations, such as important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above instead of be immediately life-threatening or resulting in death or hospitalisation, which rapid scientific and medical judgment for whether it is required to be reported rapidly. These should also be considered to be serious adverse events.

A serious adverse event is further explained as follows:

a. Any death resulting from an adverse event occurring during the study period or within 30 days after the last dose of the investigational drug or the last visit, including deaths that appear to be completely unrelated to investigational drug.

b. The subject must have been at an immediate risk of dying from the adverse event as it occurred. This does not include events that might have caused death if they had occurred in a more serious form, ie. drug-induced hepatitis without hepatic failure.

c. Any adverse event resulting in hospital admission and prolongation of hospitalization (prolongs hospitalization means delayed planned or anticipated discharge date, again usually by at least 1 overnight stay), which does not include elective surgery for a condition that was present before trial entry and whose clinical course has not changed after exposure to the investigational drug.

d. Any adverse event resulting in impairment, damage, or disruption in the subject's body function, structure, or both, physical activities, or quality of life.

e. If there are suspicions that exposure of either parent to the investigational drug resulted in an adverse outcome in the offspring.

f. Any adverse event resulting in a condition which requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure of the subject (Examples of this can include procedures such as blood transfusion or catheterization. However, discontinuation of the investigational drug, or

routine administration of prescription medications or changes in their dosages, should not be considered as medical intervention.)

- Planned hospitalization for the study assessments at each Visit is not recognized as SAE in this study.
- Hospitalizations or prolonged hospitalizations that occurred after the end of the study as a result of continued treatment for the study disease and/or concomitant disease (disease present at the time the informed consent was signed) were not recorded as SAE.
- The deterioration or aggravation of diseases and related symptoms and laboratory tests in this study should be recorded as SAE if they meet the definition of SAE.

8.3.2 Pregnancy

If a female subject becomes pregnant during the course of the study (from informed consent to the 30th day after the last dose of investigator drug or the last visit, whichever period is longer), the pregnancy should be completed in a “Pregnancy Report Form” as per the same time frame of SAE, expeditiously reported to the sponsor (medical representative of Tigermed) and recorded in eCRF to follow its outcomes.

Any abortion, whether it is accidental, therapeutic or spontaneous, should also be reported using a Pregnancy Report Form.

Female subjects who become pregnant during the study should immediately discontinue the investigational product and inform the Investigator. The Investigator should give counsel to the subject, discuss the risks of continuing pregnancy and the possible effects on the foetus. The subject must withdraw from the study. Monitoring of the subject should continue until conclusion of the pregnancy.

8.3.3 Death

All deaths occur during the study period or within 30 days after a withdrawal (last visit) must be reported to the sponsor (medical representative of Tigermed) within 24 hours according to the SAE reporting procedure.

If a subject withdraws from the study due to death, this event may be reported as either progression of disease or an adverse event. If the death is a combination outcome of progression of disease and any other condition, the investigator must decide what the primary cause of death is and assign reasons for withdrawal to an appropriate category.

The report should contain information regarding of progression of disease, primary and secondary causes of death, if appropriate

8.3.4 Reporting of SAEs

Any serious adverse event related or unrelated to the investigational product occurs during the course of the trial (from the date obtaining informed consent to the 30th day after the last dose of investigational drug or the last visit, whichever period is longer) must be reported to the sponsor (medical representative of Tigermed), EC, CFDA, provincial Drug Administration and National Health Planning Commission within 24 hours after first knowledge by the Investigator.

In special cases, the Study Responsible Leader/Clinical Project Manager or monitors of the clinical trial can be contacted. She/he will then be responsible to transmit the information to safety service of sponsor.

The following information is the minimum that must be provided to sponsor (medical representative of Tigermed) within 24 hours for each serious adverse event:

- trial protocol number
- Site number
- investigator name
- subject number
- subject initials
- adverse event
- date of onset

– SAEs or not

– causality assessment

The following additional information must be provided to the sponsor (medical representative of Tigermed) as soon as available:

- event intensity
- outcome (plus date of resolution if available)
- withdrawal statement (yes or no)
- concurrent therapy (identify treatment for adverse event)
- date of birth and sex
- other current illnesses
- relevant medical history
- date and cause of death (if applicable)

The investigator is required to submit follow-up reports to the sponsor until the SAE has been resolved or, in the case of permanent impairment, until the SAE is considered to be stable.

CRO: the address of Hangzhou Tigermed Consulting Co. Ltd.

Room 813, Huawen International Building, No. 999, Zhongshanxi Road
Shanghai, China, 200051
Tel: (021)3250 3700
Fax: (021)3327 5864
Email: PV@tigermed.net

9. Data Management

9.1 Source Data, eCRF Filling and Transferring

Tigermed Data Management Department will be responsible for this study data management, to ensure clinical trial data validity, integrity, privacy and traceability.

Data will be entered into the eCRFs by the investigator, or authorized site staff. Only medically-qualified (sub) investigators can sign data on clinical assessments/safety. Any correction(s) made by the investigator, or authorized site staff, to the eCRF after original entry will be recorded in the system automatically.

9.2 Database Designing

Database will be set up by Tigermed Data Management Department, and will follow the standard of CDISC and ICH GCP in a validated system in compliance with FDA 21 CFR Part 11. System logging, data enrolling, data revision or delete will be managed.

9.3 Data Entry

The data will be entered by an authorized person into an EDC database. All data entered into the database will be checked for accuracy and completeness using a group of trial specific logical check which will be programmed in EDC system.

9.4 Query Handling

After data are entered and saved in EDC system, pre-programmed edit checks will run and system queries will be kicked which require the investigator to review and respond. Data management staff will review answered queries and close the queries if the responses are acceptable. Data management staff will also conduct manual review on the entered data to ensure the logic, consistency, and accuracy of the data.

Subject data listings/reports will be programmed to support manual data review during the study progress. Manual queries will be added in the EDC system when there is a need for the site staff to clarify/verify/confirm the data. Data Management staff should make sure that all queries are resolved before the lock of database.

10. Statistical Analysis

The statistical analysis will be performed by Tigermed.

The statistical analysis mentioned below is a prediction analysis made during the time of planning the trial. A detailed statistical analysis plan will be described in a separate document to be completed after having finalized the protocol.

The statistical analysis will be performed periodically on the available data extracted from the main database and the final results will be discussed in the final CSR.

10.1 Sample Size Determination

The sample size calculation is based on a noninferiority comparison between MZR and CTX groups with respect to the TR (%) after treatment. In the study of lupus nephritis, we assumed that the TR (%) in each group will be 73% [31,32] , therefore the Risk Ratio (RR) of MZR to CTX would be 1.0.

According to historical trials and a meta-analysis [33,34 ,35], the RR between the two treatment groups is about 2.2. Based on these results and recent studies [36], we can set the non-inferiority difference is 0.726 in accordance with FDA Guidance for Industry Non-inferiority Clinical trials in 2010.

The sample size is calculated based on the condition: TR(%) of 73% for both groups of treatment, non-inferiority difference of 0.726, power of 90% and one-sided significance level of 2.5%, assuming a drop-out rate of 20%, we plan to enroll 125 patients per group (total 250 patients). As this study intends to increase the indications of MZR, the sample size also meet the requirement of CFDA for minimum sample size (for the two indications added, 60 patients per group are needed).

SAS is used for sample size calculation.

10.2 Statistical Analysis Populations

- Full analysis Set (FAS) will include all subjects who are randomized and treated with at lease one dose of study drug with at least one post-treatment efficacy assessment.
- Per-Protocol Set (PPS) will include all FAS subjects without any other major protocol violation.

- Safety Set (SS) will include all randomized subjects who receive at least one dose of study drug and have at least one subsequent safety assessment.

All efficacy variables will be assessed in FAS and PPS population. All safety variables will be performed in SS population. Incidence of AEs will be compared between two groups. Safety analysis is based on the actually assigned treatments.

10.3 Demographic / Baseline Information

The demographic information and baseline indicators will be analyzed in FAS population. All demographic variables and baseline characteristics will be summarized by randomized treatment group (e.g. gender, birth date, body weight, time since diagnosis, disease classification, 24hours urinary protein, serum albumin, SCr, eGFR, SBP/DBP, RAS medication).

Continuous variables will be analyzed by using descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum, while frequency and percentage calculation for categorical variable analysis.

Detailed description will be included in SAP

10.4 Analysis for Primary Efficacy Variable

10.4.1 Primary analysis for Primary Efficacy Variable

Primary efficacy variable is TR (%) obtained at the time of 12-month treatment (52 weeks). The noninferiortity test of TR (%) will be performed in PPS population between MZR group and CTX group at Visit 10. Relative Risk Ratio and its two-sided 95% confidence intervals will be calculated.

10.4.2 Secondary analysis for Primary Efficacy Variable

- Relative Risk for TR (%) of between treatment groups at Visit 10 of study and its two-sided 95% confidence intervals will be calculated in FAS population.
- Number of subjects who achieved TR will be calculated in each group at each Visit in PPS population.

10.5 Analysis for Secondary Efficacy Variables

Secondary efficacy variables (see Section 7.2) will be analyzed as follows.

- Continuous variables: summarize data obtained at each visit before and after treatment in each group and calculate mean, SD, median, max and min;
- Categorical variables: summarize the numbers of subjects in each group at each Visit before and after treatment
- Response rate: calculate the number of responder and response rate after treatment at each visit in each group.

  Note: if other analysis is conducted, it will be pre-specified in the SAP before the lock of database.

10.6 Subgroup analysis

To assess the beneficial effects in subgroup, subgroup analysis will be performed as necessary. The following subgroup analyses are planned: pathologic classification, eGFR, C3, anti-DNA antibodies. Additional subgroup analyses will be pre-specified in the SAP before the lock of database.

10.7 Safety Analyses

The general physical examinations, vital signs, laboratory tests, adverse events, serious adverse events of the subjects should be carefully recorded for safety analyses.

The adverse events will be coded based on MedDRA and should be submitted by “preferred term and system organ class”.

The number of subjects who experienced any types of adverse events (by preferred term and system organ class in MedDRA) will be coded by treatment group, regardless of the number of adverse events reported in each subject. The number of the subjects who experienced AEs, number of AEs, the number of the subjects who experienced SAEs, the number of the subjects who were discontinued due to AEs, the number of important AEs, severity of all AEs, severity of AEs related to study drug and relationship to study drug will be tabulated by treatment group. Additional tabulation will be summarized by severity of AEs, severity of AEs related to the study drug, and onset time of AE. The proportion of subjects who experienced AEs in the two groups will be compared.

The changes of laboratory parameters will be reported in tables. Other safety data will be summarized as appropriate.

11. Clinical Trial Management

11.1 Announcement

This clinical trial will be carried out in accordance with the principles stated in the latest version of *Declaration of Helsinki*, China GCP and applicable clinical trial regulations.

11.2 Ethical Considerations

The investigator will submit the trial-related documents to the Ethics Committee(s) according to the regulatory requirements of the country.

A copy of the letter of approval from the Ethics Committee, which contains a list of the names and occupations of the members of the Ethics Committee participating in the discussion, as well as listing of documents reviewed, must be submitted to the sponsor prior to shipment of drug supplies to the investigator.

When the study protocol is approved by Ethics Committee, the sponsor/Tigermed should submit this clinical study protocol to CFDA for archiving.

This clinical trial must be approved by Ethics Committee and Drug Administration Department prior to implementation.

All subsequent protocol amendments must be submitted to the Ethics Committee for approval.

The investigator must inform the Ethics Committee of any serious adverse events occurring during the trial, which are likely to affect the safety of the patients or the conduct of the trial.

11.3 Source Data Verification

Investigators must properly handle all data obtained from this clinical study to ensure the rights and confidentiality of subjects who participate in this clinical study. The investigator must give the monitor/ inspector/ auditor access to review and verify all necessary clinical study data to confirm the accuracy of source data and to know the study progress. If any study data cannot be traced from source documents, investigators should help monitor / inspector/auditor/ to further confirm quality control of the data.

11.4 Quality Assurance / audit

Quality audits of this trial will be conducted by the sponsor, CRO's QA department or an authorized auditor. China GCP audits can also be performed by Drug Approval Authorities in China. The quality auditor should have access to all medical records, the trial related files and correspondence, and the informed consent documentation that is relevant to this clinical trial.

11.5 Informed Consent

The investigators have the responsibility of explaining the objectives, methods, benefits and potential risks of this clinical trial to each subject. The informed consent form signed by the subjects must be obtained prior to the initiation of any clinical trial-related operation procedures. The informed consent form should be given both orally and in a written form. Sponsor or CRO will provide to investigator proposed informed consent form which is complied with China GCP. The consent form must be signed and dated personally by the subject (or legal representative / witness, if applicable), before any study related procedure is performed. A copy of the signed consent form and information sheet should be given to the subject.

By signing the informed consent, the subject will accept that the available source data related to clinical study may be checked by the sponsor, the drug regulatory authorities, an auditor and/or the study monitor. The personnel who check the data must follow the statement of confidentiality.

11.6 Modification of Clinical Protocol

Once the final version of study protocol has been issued, the detailed protocol modification record must be made for any change to the protocol. The updated protocol must be signed by the investigators and sponsor, with version No. and date indicated.

All protocol amendments must be approved by the Ethics Committee in written form and submitted to the Drug Evaluation Authorities, if required. Administrative amendments can

be sent to the ECs for information only. The written review records of all documents must be submitted to the sponsor.

11.7 Case Report Forms (eCRF)

eCRFs will be setup in the EDC system by Tigermed Data Management staff. Patients are identified on the eCRF only by appropriate coded identification (e.g. subject number) and subject initials. eCRFs are used to record clinical trial data and are an integral part of the trial and subsequent reports. The entries, therefore, must be accurate and complete. The eCRF will be completed by the investigator or authorized persons (mentioned in the center study Authorization form) in EDC system. All required data fields must be completed and saved. The investigators are required to declare the accuracy of all data recorded in the eCRF via electronic signature.

eCRFs must be completed after each visit to reflect subject status during the course of the trial.

Documented medical histories and narrative statements relative to the subject's disease progress during the trial will be maintained by the investigator. These records should also include the following: originals, copies of laboratory data and other medical test results (e.g. ECGs), which must be kept at the site along with the subject’s medical file.

In this trial, no data are to be reported directly on the eCRF. All data should be documented in the individual patient’s medical file, considered as being source data, and then entered into the eCRF.

11.8 Monitoring

The sponsor assigns monitors for on-site monitoring. These monitors are either working directly for the sponsor or for a CRO company authorized by the sponsor. Monitors have to work according to Standard Operating Procedures (SOPs) and related procedures. These SOPs may be also from the authorized CRO Company. Monitoring visits will be performed between initiation visit and post-study visit at regular intervals.

Monitors should be allowed to have access to the source data related to clinical study and ensure the completeness and correctness of the entered data as well as consistency with source data by reviewing the eCRF entries according to SOPs.

eCRFs, copies of laboratory data, medical test results, work sheet for this study, and China GCP related essential documents must be available at all times for inspection by the clinical trial monitor, auditors and health authorities. The monitor will review all eCRFs and informed consent form.

11.9 Secrecy Agreement and Patient Privacy

The investigator commits himself/herself to keep secret from third parties any confidential information obtained from and concerning Asahi Kasei Pharma Corporation or this company's products, which in connection with the present contractual relationship are made available or disclosed, respectively, and to use this knowledge only as agreed upon.

If the sponsor has reasonable and just reasons to request investigators to maintain this Confidentiality Agreement, this Agreement shall be independent and valid during the existence of contractual relationship of two parties.

The investigator also commits himself/herself to protect the test subjects' privacy. In all documents submitted to the sponsor, the identity of a test subject can only be determined with the subject number, rather than with test subject's name and inpatient number. The investigator must take good care of the names and addresses of test subjects and enrollment lists corresponding to test subjects' number. These enrollment lists should be strictly kept confidential by the investigator, and cannot be submitted to the sponsor.

12. Publication

To promote openness and transparency concerning clinical trials conducted by Asahi Kasei Pharma Corporation, as well as sharing of valuable information with the scientific community, Asahi Kasei Pharma Corporation has decided that basic information on all clinical trials, sponsored by Asahi Kasei Pharma Corporation, will be posted on the publicly accessible website. If it is registered on the website, information on how to enroll in the trial may be obtained. Trial information will be published before the first patient enters into the clinical trial

This decision is in accordance with the recommendations of the International Committee of Medical Journal Editors (ICMJE) and Joint Position on the disclosure of clinical trial information via clinical trial registries and databases, as issued by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA).

A draft manuscript for joint publication will be prepared in collaboration between Asahi Kasei Pharma Corporation and the investigators. The company acknowledges the investigators' right to publish the results of the trial, irrespective of clinical trial results. Individual publications or presentations of data by one or more investigator(s) shall not be made before the results of the joint publication have been made public. The company retains the right to have any publication submitted to the company for review at least 30 days prior to the same paper being submitted for publication or presentation. Investigators should not to submit any part of their individual data for publication without the prior consent of Asahi Kasei Pharma Corporation. It is intended that this study will be published as a whole by the principal investigator while mentioning the investigators as co-authors.

13. Archiving of Trial Documents

According to the requirements of relevant regulations, the investigator must properly store the essential documents related to the clinical trial, including the Investigator Trial File. All essential documents should be retained until at least 5 years after the end of this study. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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36. RITUXILUP Trial, Plenary talk, The 10th INTERNATIONAL CONGRESS ON THE LUPUS, 2013

15. Attachment

15.1 Study medication lable（Sample）

For Clinical Trial Purpose Clinical Trial Permission Number:2013L01478
Mizoribine Clinical Trial Study Medication(Mizoribine) Protocol:HE-69-C-Lu-301
Batch number: XXXXX-A1 Expiration date: XX 201X
Specification:50mg/tablet Pack size:110tablets/box
Dosage: P.O, 50mg (or one tablet), Tid(detailed information please refer protocol or ICF)
Storage condition: Store at room temperature (not exceeding 30℃), prevent moisture
Please keep reach out of children
Sponsor: Asahi Kasei Pharma Corporation
Please return unused medication and (empty) cartoon to investigator

For Clinical Trial Purpose Clinical Trial Permission Number:2013L01478
Mizoribine Clinical Trial Study Medication(CTX) Protocol:HE-69-C-Lu-301
Batch number: XXXXX-A1 Expiration date: XXX 201X
Specification:0.2g/vial Pack size:5vials/box
Dosage: Intravenous administration (detailed information please refer protocol or ICF)
Storage condition: Store at temperature not exceeding 25℃
Please keep reach out of children
Sponsor: Asahi Kasei Pharma Corporation
Please return unused or partially used medication and cartoon to investigator

15.2 SLEDAI (Systemic Lupus Erythematosus Disease Activity Index)

Weighter	SLEDAI	Discriptor	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 perceptionof reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic 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 consciousnesswith 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. Excludemetabolic, infectious, or drug causes.
8		Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate 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, periungual infarction, 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 red blood cells/high power field. Exclude stone, infection, or other cause.
4		Proteinuria	> 0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4		Pyuria	> 5 white blood cells/high power field. 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	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2		Increased DNA Binding	> 25% binding by Farr assay or above normal range for testing laboratory.
1		Fever	> 38° C. Exclude infectious cause.
1		Thrombocytopenia	< 100,000 platelets/mm3.
1		Leukopenia	< 3,000 white blood cells/mm3. Exclude drug causes.
Total		Check box if descriptor is present at the time of visit or in the preceding 10 days: (Sum of weights next to descriptors marked present)	

Claire Bombardier, etal, Derivation of the SLEDAI, A disease activity index for Lupus patients. Arthritis and Rheumatism, Vol. 35, No.6 (June 1992), 630-640

15.3 1997 Update American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Criteria are cumulative and need not be present concurrently. SLE can be diagnosed by satisfying 4 of 11 criteria

Criterion	**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 rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *OR* 2. Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed *OR* 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance 1. *OR* 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia--with reticulocytosis *OR* 2. Leukopenia--< 4,000/mm3 on ≥ 2 occasions *OR* 3. Lyphopenia--< 1,500/ mm3 on ≥ 2 occasions *OR* 4. Thrombocytopenia--<100,000/ mm3 in the absence of offending drugs
10. Immunologic Disorder	Anti-DNA: antibody to native DNA in abnormal titer *OR* 2. Anti-Sm: presence of antibody to Sm nuclear antigen

	OR 3. Positive finding of antiphospholipid antibodies on: 1. 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. 2. a positive test result for lupus anticoagulant using a standard method, or 3. 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

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