Supplemental Material

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JSKDC Japanese Study Group of Kidney Disease in Children

Multicenter, randomized, double-blind, placebo-controlled, parallel group trial of mycophenolate mofetil after rituximab for childhood-onset complicated frequently relapsing or steroid-dependent nephrotic syndrome (JSKDC07)

Study Protocol

Japanese Study Group of Kidney Disease in Children
Study director: Kazumoto Iijima
Department of Pediatrics, Kobe University Hospital
7-5-2, Kusunokicho, Chuo-ku, Kobe, Hyogo, 650-0017 Japan
TEL: 078-382-6080 FAX: 078-382-6098
e-mail: iijima@med.kobe-u.ac.jp

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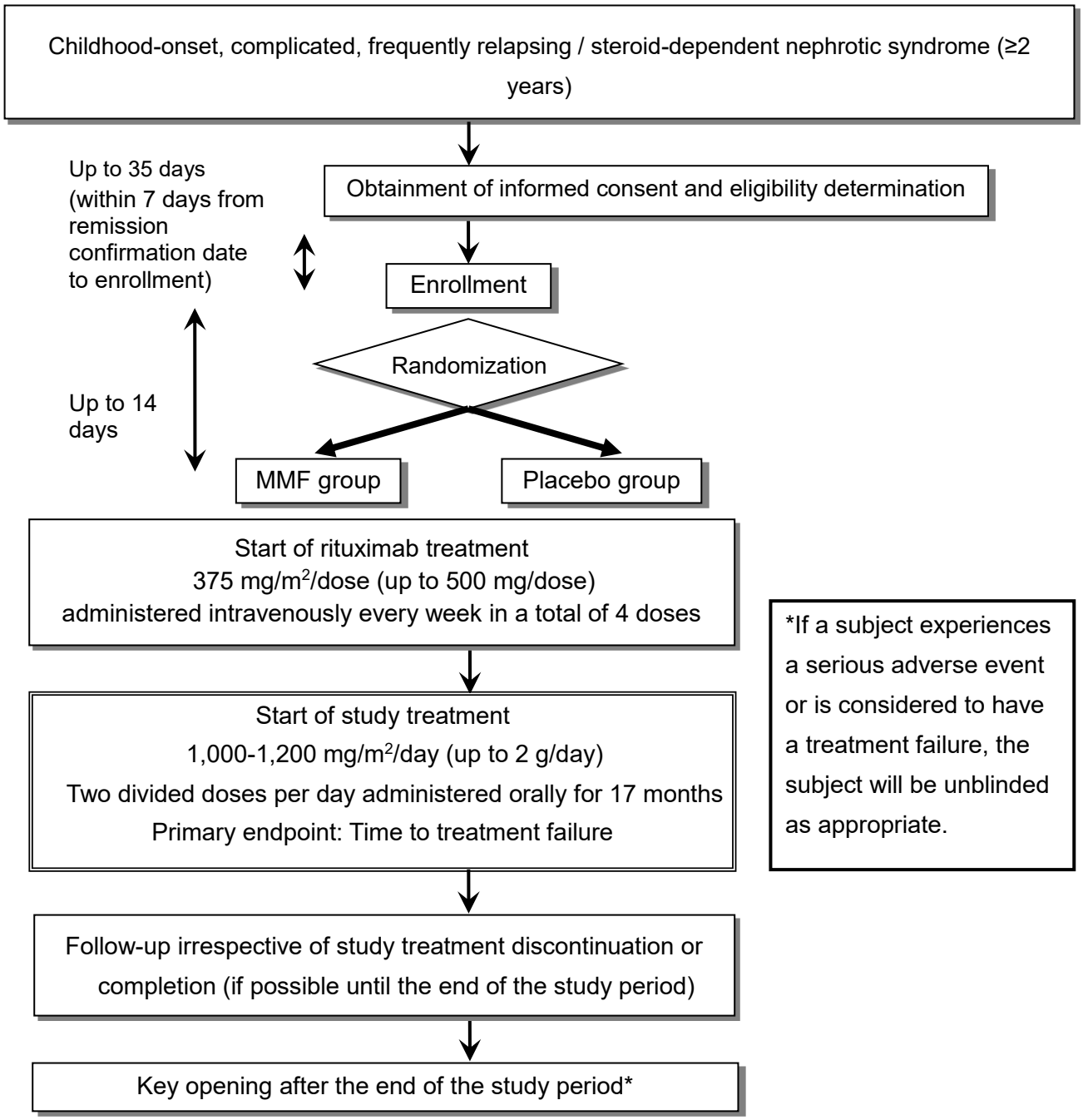
0 Outline

0.1 Study title

Multicenter Randomized Double-blind Placebo-controlled Parallel Group Trial of Mycophenolate Mofetil after Rituximab for Childhood-onset Complicated Frequently Relapsing or Steroid-dependent Nephrotic Syndrome

0.2 Study design (scheme)

This is a multicenter randomized double-blind placebo-controlled pararel group trial.



0.3 Objective

To evaluate the efficacy and safety of mycophenolate mofetil (MMF) as a remission maintenance therapy following rituximab treatment in patients with childhood-onset complicated frequently relapsing/steroid-dependent nephrotic syndrome. This study will demonstrate that MMF administered orally after rituximab treatment is superior to placebo in maintaining remission in a randomized controlled trial in patients with childhood-onset complicated frequently relapsing/steroid-dependent nephrotic syndrome.

Primary endpoint

Time to treatment failure (time to event)

Time from the enrollment date to the earliest of the dates of onset of the following events I) to III):

I) Frequent relapse, II) steroid dependence, III) steroid resistance

Secondary endpoints

Time to relapse, relapse rate (relapses/observed person-year), time to frequent relapse, time to steroid dependence, time to steroid resistance, daily steroid dose (mg/m^2/day), and duration of peripheral B-cell depletion

Safety endpoint

Proportion of patients with adverse events

0.4 Subjects (inclusion and exclusion criteria)

Patients whose legal guardians have provided consent to participate in the study or patients aged 20 years or older who themselves have provided consent, selected from among the patients who meet the definition of childhood-onset complicated frequently relapsing/steroid-dependent nephrotic syndrome specified in this study. However, patients diagnosed with secondary nephrotic syndrome, patients whose condition may be aggravated by the study treatment, and women who are pregnant or wish to become pregnant will be excluded.

0.5 Study treatment

Enrolled subjects will receive intravenous drip infusions of rituximab and either investigational drug (MMF, placebo) administered orally. The observation period will last for 18 months. If any relapse is observed, the specified treatment for relapses will be performed.

0.6 Target sample size and scheduled period

Target sample size: 80 patients (40 in the MMF group and 40 in the placebo group)

Scheduled registration period: February 1, 2015 to July 31, 2018

Scheduled observation and follow-up period: February 1, 2015 to January 31, 2020

Scheduled analysis period: February 1, 2020 to January 31, 2021

Scheduled publication date for clinical study report: March 31, 2021

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[Revision chronology]

Version 2.0 April 10, 2014
Version 2.1 September 4, 2014
Version 2.2 November 5, 2014
Version 2.3 January 21, 2015
Version 2.4 March 27, 2015
Version 2.5 December 16, 2015
Version 2.6 September 26, 2016
Version 2.7 June 13, 2017
Version 2.8 October 20, 2017
Version 2.9 August 20, 2018

Version 3.0	October 24, 2018
Version 3.1	July 29, 2019

Appendices

1 Background

1.1 Idiopathic nephrotic syndrome in children and its treatment

Nephrotic syndrome is a pathologic condition with heavy proteinuria, hypoproteinemia, and systemic edema, characterized by protein leakage into the urine due to glomerular capillary damage of the kidney.

Nephrotic syndrome in children develops commonly in their infancy or young childhood at 2 to 6 years of age, and is often discovered with eyelid and crus edema at the time of onset. About 90% of cases of nephrotic syndrome in children are idiopathic, often identified as the minimal-change type with almost no glomerular changes found on light microscopy.[1)]

The first-choice drug for idiopathic nephrotic syndrome in children is an oral corticosteroid (hereinafter referred to as a steroid drug). Response to steroid drug is an important prognostic factor,[2)] and the disease will be classified into a type according to this responsiveness, and the treatment strategy will be determined.

A clinical course of idiopathic nephrotic syndrome in children is shown in Figure 1.[3)] Eighty percent to 90% of patients with idiopathic nephrotic syndrome in children have steroid-sensitive nephrotic syndrome, which remits rapidly with steroid drug, and the remaining 10% to 20% have steroid-resistant nephrotic syndrome, which does not remit with steroid drug.[4)]

About 30% to 40% of cases of steroid-sensitive nephrotic syndrome develop frequently relapsing nephrotic syndrome, which relapses repeatedly in a relatively short time, or steroid-dependent nephrotic syndrome, which relapses with steroid drug tapering or discontinuation.[5,6)] In the case of frequently relapsing and steroid-dependent nephrotic syndrome, administration of high-dose steroids is required for each relapse, inducing steroid-specific adverse events. To avoid this problem, treatment with immunosuppressive drugs will be performed for the purposes of withdrawal from steroid drug and dose reduction. The KDIGO Guideline recommends alkylating agents (cyclophosphamide, chlorambutyl), levamisole, and calcineurin inhibitors (cyclosporine, tacrolimus) as immunosuppressive drug treatments for the frequently relapsing and steroid-dependent nephrotic syndrome.[7)] In Japan, cyclosporine, cyclophosphamide, and mizoribine are recommended in the Clinical Practice Guideline for Pediatric Idiopathic Nephrotic Syndrome 2013.[8)] The immunosuppressive drug cyclosporine is highly effective in suppressing relapses and withdrawing from steroid drug; however, most patients become frequently relapsing or steroid-dependent nephrotic syndrome again after discontinuation of cyclosporine. In addition, about 20% of patients do not respond to cyclosporine. Long-term administration and re-administration of cyclosporine are difficult, because the frequency of chronic renal toxicity increases when cyclosporine is administered at an intermediate dose (about 100 ng/mL as the trough level) for 2 years or more. The immunosuppressive drug cyclophosphamide is recommended to be administered at 2 to 2.5 mg/kg/day for 8 to 12 weeks, and it should be administered only in one course of treatment at a cumulative dose not exceeding 300 mg/kg.[8)] Cyclophosphamide causes gonadal toxicity as an adverse drug reaction (particularly azoospermia in boys: a meta-analysis reported that a cumulative dose exceeding 300 mg/kg increases the risk of gonadal toxicity, including azoospermia), whose risk is known to be high in patients in and after puberty. In addition, cyclophosphamide has been reported to be low in remission maintenance effect for patients with steroid-dependent nephrotic syndrome. Although the immunosuppressive drug mizoribine has been shown to be highly safe, no sufficient relapse-suppressing effect has been noted.

While patients with steroid-resistant nephrotic syndrome are treated with immunosuppressive drugs, most patients develop end-stage kidney disease if the immunosuppressive drugs are not effective. The aforementioned guideline recommends cyclosporine used alone or in combination with methylprednisolone pulse therapy.[8)] Although more than 80% of steroid-resistant nephrotic syndrome patients achieve complete remission with those therapies, some of those patients develop frequently relapsing or steroid-dependent nephrotic syndrome during treatment or after discontinuation of treatment.

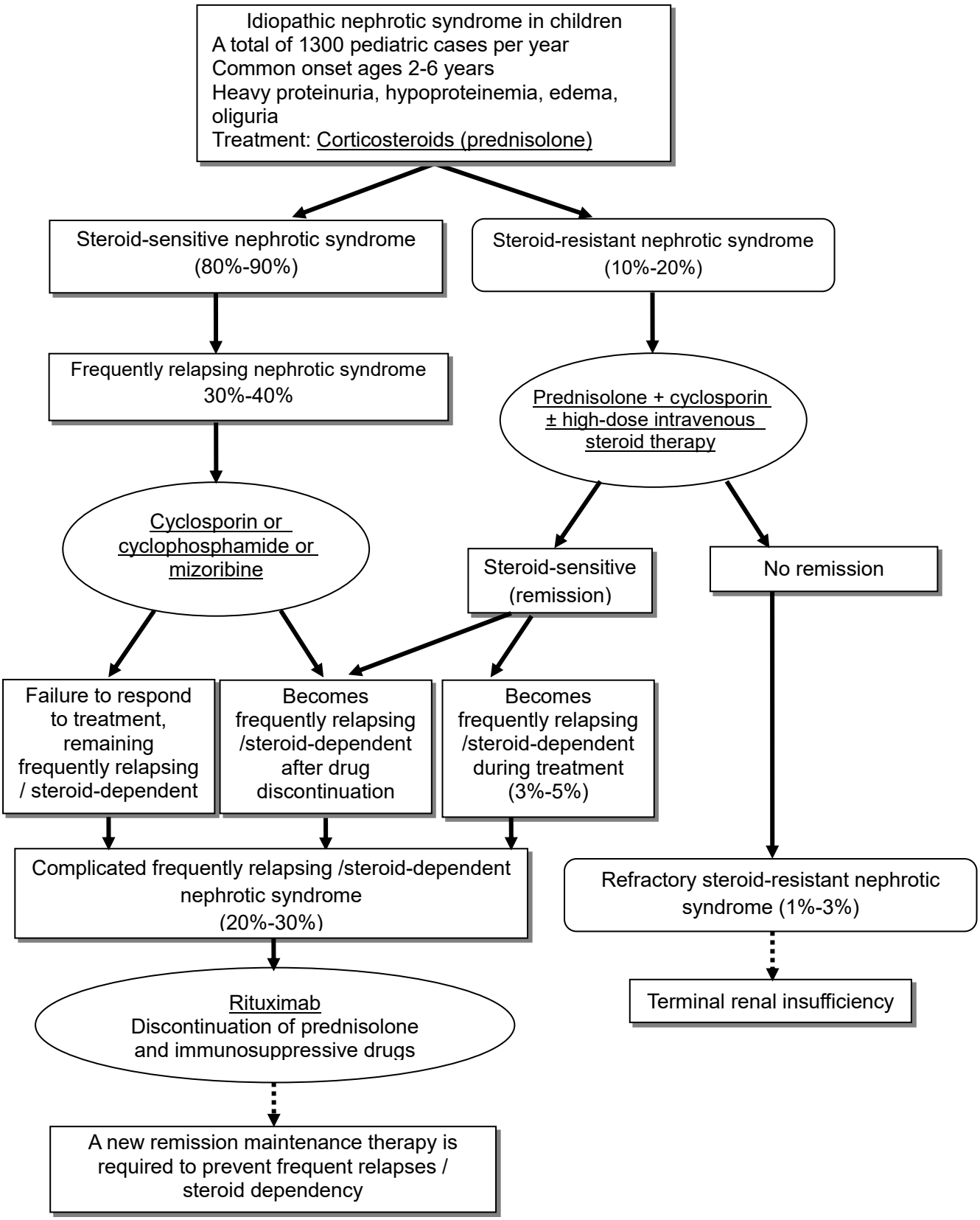

Figure 1 Clinical course of idiopathic nephrotic syndrome in children

1.2 Childhood-onset, complicated, frequently relapsing/steroid-dependent nephrotic syndrome

Childhood-onset, complicated, frequently relapsing or steroid-dependent nephrotic syndrome (hereafter referred to as this disease) is defined as any of the following conditions (1) to (4) in this study:

(1) Diagnosed as being frequently relapsing or steroid-dependent and again diagnosed as being frequently relapsing or steroid-dependent after discontinuation of treatment with immunosuppressive drugs (cyclosporin, cyclophosphamide, mizoribine*, etc.)
(2) Diagnosed as being frequently relapsing or steroid-dependent and again diagnosed as being frequently relapsing or steroid-dependent during treatment with immunosuppressive drugs (cyclosporin, cyclophosphamide, mizoribine*, etc.)
(3) Diagnosed as being steroid-resistant and achieved remission with immunosuppressive drug treatment (cyclosporin used alone or cyclosporin and methylprednisolone used in combination), but becomes frequently relapsing or steroid-dependent after discontinuation of treatment
(4) Diagnosed as being steroid-resistant and achieved remission with immunosuppressive drug treatment (cyclosporin used alone or cyclosporin and methylprednisolone used in combination), but becomes frequently relapsing or steroid-dependent during treatment

*In limited cases where mizoribine is used in combination with any other immunosuppressive drug.

Approximately 20% to 30% of children with idiopathic nephrotic syndrome are considered to develop this disease[3] (Figure 1). Many patients with this disease in their infancy and young childhood (2-6 years of age) often carry over to their puberty and adulthood, resulting in a long duration of illness throughout childhood.[9,10]

In this disease, remission cannot be maintained with existing immunosuppressive drug treatment used for the purpose of weaning from steroids (remaining frequently relapsing or steroid-dependent), and long-term administration and re-administration of existing immunosuppressive drugs are difficult because of their adverse reactions. Therefore, existing immunosuppressive drug treatment must be considered to be insufficient in both efficacy and safety. As a result, corticosteroids must be continued for a long time, and the majority of patients with this disease have significant adverse events from corticosteroids (growth disorders, osteoporosis, hypertension, cataracts, glaucoma, diabetes mellitus, central obesity, infections, gastrointestinal ulcers, psychiatric disorders, adrenal insufficiency, etc.). In children, short stature and osteoporosis are serious problems; short stature is particularly likely in patients who carry their disease from puberty to adulthood because they are treated with corticosteroids from prepuberty to puberty. Osteoporotic compression fractures and avascular necrosis of the femoral head leads to a longer hospital stay, lower the patient's quality of life, and a marked impact on daily activity. Therefore, the development of effective and safe therapy for this disease is required.

1.3 Treatment of childhood-onset, complicated, frequently relapsing/steroid-dependent nephrotic syndrome

Rituximab is a monoclonal antibody against CD20 differentiation antigens expressed on B-cell surfaces. In

Japan, it has been approved as a drug for the treatment of CD 20 positive B-cell non-Hodgkin lymphoma (B-cell lymphoma). As a drug for B-cell lymphoma, it has been approved in more than 100 countries in the world. In recent years, rituximab has been suggested to be effective against childhood-onset, complicated, frequently relapsing/steroid-dependent nephrotic syndrome (this disease) in cohort studies and randomized controlled trials in and outside Japan. In an open-label randomized controlled trial of 1 to 2 doses of rituximab 375 mg/m^2/dose (up to 500 mg/dose) versus a standard treatment (steroid plus calcineurin inhibitor), it has been demonstrated that rituximab was effective. However, relapse-free rates at 6 and 12 months were reported to be 50% and 25%, respectively, in the rituximab group.[11)] We conducted a multicenter double-blind, randomized, placebo-controlled trial and pharmacokinetic study (investigator-initiated trial) of 4 doses of rituximab in Japanese patients, and reported that rituximab was effective for preventing relapses after discontinuation of steroids and immunosuppressive drugs (50% relapse-free time: 267 days vs 101 days, $p<0.0001$) and was well tolerated.[12)] Based on the results, the use of rituximab for patients with this disease was approved by the Minister of Health, Labour and Welfare on August 29, 2014. The current standard treatments for pediatric nephrologists to perform after administration of rituximab are as follows: I) follow up without treatment while discontinuing steroids and immunosuppressive drugs such as cyclosporine until relapse, II) steroid treatment for any relapses, and III) treatment with immunosuppressive drugs such as cyclosporine considered for the first time in case of repeated relapses resulting in a frequently relapsing steroid-dependent state, or steroid resistance.

However, although rituximab therapy enables the reduction and discontinuation of corticosteroids and immunosuppressants, it has been found that rituximab therapy tends to cause relapse with the recovery of peripheral blood B cells, and prevention of relapse after rituximab therapy has become a new therapeutic target. Repeated administration of rituximab for long-term depletion of peripheral blood B cells was investigated,[13)] and no serious adverse events were reported. However, further investigations may be needed to determine whether or not to repeatedly administer rituximab, because of, for example, necessity for combination therapy with Sulfamethoxazole - Trimethoprim to prevent pneumocystis infections.

Mycophenolate mofetil (MMF), a purine metabolism antagonist similar to mizoribine in mechanisms of action, suppresses T-cell and B-cell proliferation and antibody production by selectively suppressing de novo systems in nucleic acid synthesis. While MMF is an immunosuppressive drug approved for the suppression of acute rejections following renal transplantation, its efficacy against this disease has recently been investigated in clinical studies in and outside Japan.[14-23)] The use of MMF has not been approved as the treatment for nephrotic syndrome in or outside Japan, however, MMF is currently used for nephrotic syndrome as an off-label drug. Furthermore, the efficacy of MMF as a remission maintenance therapy after rituximab treatment has been investigated in Japan. In a cohort study of 16 Japanese patients with this disease, the mean number of relapses (events/year) after rituximab administration was significantly lower in the 9 subjects receiving a single dose of rituximab followed by MMF (1000-1200 mg/m^2/day) for 1 year than in the 7 subjects receiving a single dose of rituximab alone (0.4 events/year vs 2.3 events/year, $p<0.005$). The efficacy of MMF (1000-1200 mg/m^2/day) as a remission maintenance therapy after rituximab treatment for 1 year was suggested, and mild infusion reactions (coughing, sore throat, rash, and discomfort) and transient diarrhoea due to MMF (2 subjects) occurred, but no serious adverse events were reported.[24)] In addition, 2 patients with this disease (one 11-year-old boy and

one 17-year-old boy) were treated with 4 doses of rituximab followed by oral administration of MMF at 1000-1,200 mg/m^2/day in 2 divided doses (for 19 and 8 months, respectively) at the Department of Pediatrics, Kobe University Hospital, to which the study director belongs, and no relapses were observed in either patient. Although cystitis, alopecia, and appetite loss were noted as adverse events, no serious adverse events occurred. Although MMF is expected as a remission maintenance therapy after rituximab treatment, it is necessary to conduct randomized controlled trials and studies to investigate the mechanism of action.[25)]

We therefore designed a multicenter, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of MMF as a remission maintenance therapy following rituximab treatment in patients with this disease. In view of the opinion of the Pharmaceuticals and Medical Devices Agency (PMDA) (Notification No. 0927003 from the Director of the Center for Evaluation, PMDA, dated September 27, 2013) at a face-to-face advice meeting in pharmaceutical affairs consultation on R&D strategy, this trial was to be conducted within the framework of the advanced medical care system.

1.4 Efforts by the Japanese Study Group of Kidney Disease in Children (JSKDC)

The JSKDC is headed by Kazumoto Iijima. The JSKDC has been working to build an expansive clinical trial network involving not only pediatric nephrologists, but also general pediatricians, by conducting a study titled "Multicenter Study to Formulate a Guideline for Drug Therapy for Intractable Renal Diseases in Children and to Establish a Clinical Study System" (JSKDC Studies 01-03, principal researcher Norishige Yoshikawa), which started in 2003, and a study titled "Multicenter Clinical Study for Developing an Early Treatment for Nephrotic Syndrome in Children and to Establish an Expanded Clinical Trial System" (JSKDC Study 04, principal researcher Norishige Yoshikawa), which started in 2007. Since 2010, the JSKDC has been conducting the "Multicenter Clinical Trials to Verify the Efficacy and Safety of Off-label Immunosuppressive Drugs in Nephrotic Syndrome in Children and to Establish a Standard Treatment" (JSKDC Studies 05 and 06, Research President Norishige Yoshikawa).

JSKDC01: A randomized controlled trial to compare lisinopril monotherapy with a combination therapy of lisinopril and losartan potassium in pediatric IgA nephropathy with focal mesangial proliferation

JSKDC02: A randomized controlled trial to compare cyclosporine + prednisolone combination with methylprednisolone succinate sodium + cyclosporine + prednisolone combination in patients with steroid-resistant nephrotic syndrome in children

JSKDC03: A multicenter open-label randomized controlled trial of a method of dose adjustments by blood levels at 2 hours after administration of cyclosporine in patients with frequently relapsing nephrotic syndrome in children

JSKDC04: A randomized controlled trial of the international prednisolone method (2-month treatment) and the long-term method (6-month treatment) in patients with first-onset idiopathic nephrotic syndrome in children

JSKDC05: A multicenter open-label randomized controlled trial of a combination of the standard treatment for relapses (prednisolone treatment) and high-dose mizoribine in patients with steroid-sensitive

nephrotic syndrome in children that relapse early after remission of initial onset

JSKDC06: A multicenter open-label randomized controlled trial of tacrolimus treatment and cyclosporine treatment in patients with frequently relapsing nephrotic syndrome in children

2 Objective

To evaluate the efficacy and safety of mycophenolate mofetil (MMF) as a remission maintenance therapy following rituximab treatment in patients with childhood-onset complicated frequently relapsing/steroid-dependent nephrotic syndrome. This study will demonstrate that MMF administered orally after rituximab treatment is superior to placebo in maintaining remission in a randomized controlled trial in patients with childhood-onset complicated frequently relapsing/steroid-dependent nephrotic syndrome.

3 Study design

3.1 Study period and target sample size

This study will be conducted with an enrollment period of 3.5 years and a planned treatment and follow-up period of 5 years.

Scheduled enrollment period: February 1, 2015 (date of approval for advanced medical care) to July 31, 2018

Scheduled treatment and follow-up period: February 1, 2015 to January 31, 2020

Scheduled analysis period: February 1, 2020 to January 31, 2021

Scheduled publication date for clinical study report: March 31, 2021

The target sample size will be 40 subjects each in the MMF and placebo groups, totaling 80 subjects.

In consideration of the actual situation, however, the number may be smaller by 6 cases or less than the target sample size.

3.2 Rationale for the study design

This study will evaluate the efficacy of mycophenolate mofetil (MMF) as a remission maintenance treatment following rituximab treatment in patients with childhood-onset complicated frequently relapsing/steroid-dependent nephrotic syndrome, by comparing randomly allocated groups receiving MMF and placebo, respectively.

The primary endpoint will be time to treatment failure, and a survival time analysis will be performed for the time to the event. A treatment failure will be defined as the earliest of I) frequent relapse, II) steroid dependence, and III) steroid resistance. In this disease, the key to successful treatment is to maintain remission while avoiding treatment failures: I) frequent relapses, II) steroid dependency, and III) a transition to steroid resistance. Since a follow-up period of at least 1 year is needed to fully evaluate time to treatment failure, the duration of endpoint observation will be 18 months or longer from the date of enrollment.

In this study, a patient who is steroid-sensitive but unable to maintain remission with immunosuppressive drug treatment and hence unable to withdraw from steroid drugs will be defined as a patient with childhood-onset complicated frequently relapsing/steroid-dependent nephrotic syndrome, and such patients were selected as the study population. In general, steroid dependence is considered to be a more active condition of the frequent-relapse type, and about 80% of cases of this type in children in Japan are steroid-dependent. Traditionally, clinical studies in nephrotic syndrome in children in Japan have handled the frequent-relapsing and steroid dependence together as a single patient population. Based on the above, the frequent-relapsing and steroid dependence will be regarded as the same patient population.

In many prior studies, the dosage and administration for the study treatment MMF was set at 1,000 to 1,200 mg/m^2/day based on body surface area.[14-16,18,20,24] In this study, the dosage and administration was set at 1,000 to 1,200 mg/m^2/day (up to 2 g/day) in two divided doses, according to the KDIGO Guideline[7] and The Children's Nephrotic Syndrome Consensus Conference (United States).[26]

The dosage and administration for rituximab to be used in this study, i.e., 375 mg/m^2/dose (up to 500 mg/dose) administered 4 times at 1-week intervals, is an approved regimen for B-cell lymphoma. A placebo-controlled randomized trial of rituximab in Japanese patients with this disease was conducted using this dosage and regimen, demonstrating its efficacy (50% relapse-free interval: 267 days vs. 101 days, $p<0.0001$), and reporting the absence of concerns about its safety profile.[11] Based on the results, the use of rituximab for patients with this disease was approved by the Minister of Health, Labour and Welfare on August 29, 2014.

We consider it appropriate to administer placebo to the control group for the following reasons: The treatment for the placebo group, i.e., rituximab plus placebo, is the current standard treatment. Treatment with rituximab has shown that remission can be maintained while discontinuing steroids and immunosuppressive drugs such as cyclosporine.[11] The current standard treatments for pediatric nephrologists to implement after administration of rituximab are as follows: I) follow up without treatment while discontinuing steroids and immunosuppressive drugs such as cyclosporine until relapse, II) steroid treatment for any relapses, and III) treatment with immunosuppressive drugs such as cyclosporine considered for the first time in case of repeated relapses resulting in being frequently relapsing, steroid-dependent, or steroid resistant. Since treatment with immunosuppressive drugs such as cyclosporine can cause specific adverse drug reactions, there is a consensus among experts that it is clinically reasonable to refrain from re-administering immunosuppressive drugs until the patient again experiences frequent relapses and steroid dependence or has a transition to steroid resistance, after administration of rituximab. Administration of MMF to target patients is an off-label use. While MMF is unavoidably used off-label in routine clinical practice, a past study suggested the efficacy of MMF (1000-1200 mg/m^2/day) administered for maintenance of remission after rituximab treatment in selected patients for 1 year (mean number of relapses: 2.3/years for the rituximab-single-dose group vs. 0.4/year for the rituximab-single-dose+MMF group, $p<0.005$).[24] In addition, 2 patients with this disease (11-year-old boy and 17-year-old boy) were treated with 4 doses of rituximab followed by oral administration of MMF at 1,000-1,200 mg/m^2/day in 2 divided doses (for 19 and 8 months, respectively) at the Department of Pediatrics, Kobe University Hospital, to which the study director belongs, and remission was maintained in both patients, with no major safety concerns. However, since this treatment has not been validated by well-designed clinical trials and is not yet based on

well-established evidence, an equipoise with placebos is considered valid. In consideration of benefits and safety for subjects, the study design will allow the double blinding to be promptly canceled in case of a treatment failure, and the principal investigator and attending physician to choose the treatment considered to be best. In addition, if a subject experiences a serious adverse event, the double blinding will be promptly canceled, and the independent data and safety monitoring committee will evaluate the safety. Because the primary efficacy endpoint is time to treatment failure, which is determined by urinalysis (objective measures), disclosure of the emergency-allocation code for subjects judged to suffer a treatment failure will not influence the evaluation of the primary efficacy endpoint. Because the secondary endpoints are defined by objective measures, i.e. relapse, steroid dose, and peripheral blood B-cell count, and given that data obtained by the date of judgment will be used for subjects judged to suffer a treatment failure, emergency allocation code disclosure will not influence their evaluation.

The presence or absence of concomitant use of immunosuppressive drugs, concomitant use of steroids, and disease activity at the time of the last pre-enrollment relapse are expected to influence the therapeutic effect and prognosis. Patients will be randomized with these factors as allocation adjusters, after which study treatment will be performed.

Since Immunosuppressive drugs that have been administered for the purpose of treatment of nephrotic syndrome from before their participation in the study and steroid therapy for relapses during the treatment period can influence the therapeutic effect and prognosis, the manners of their use will be specified.

Safety evaluation will be standardized by using the Common Terminology Criteria for Adverse Events version 4.0 Japanese translation by JCOG version (CTCAE v4.0-JCOG) (CTCAE v4. 03 per MedDRA v12. 0 [MedDRA/J v16. 0]-April 9, 2013).

4 Definitions used in this study

In this study, terms are defined in accordance with the Clinical Practice Guideline for Idiopathic Nephrotic Syndrome in Children 2013[8] as follows:

Term	Definition
Nephrotic syndrome	Heavy proteinuria (nocturnal urine collection ≥40 mg/h/m2) or first morning urinary protein to creatinine ratio ≥2.0 g/gCr, and hypoalbuminemia (serum albumin ≤2.5 g/dL).
Complicated frequently relapsing/steroid-dependent nephrotic syndrome	Patients who met any one of the criteria I to IV below: I. Diagnosed with frequently relapsing or steroid-dependent disease, then subsequently diagnosed with either of these conditions after discontinuation of treatment with immunosuppressive drugs (e.g., cyclosporin, cyclophosphamide, or mizoribine*). II. Diagnosed with frequently relapsing or steroid-dependent disease, then subsequently diagnosed with either of these conditions during treatment with immunosuppressive drugs (e.g., cyclosporin, cyclophosphamide, or mizoribine*). III. Diagnosed with steroid-resistant disease and achieved remission with immunosuppressive drug treatment (cyclosporin monotherapy or in combination with methylprednisolone), but became frequently relapsing or steroid-dependent after discontinuation of treatment. IV. Diagnosed with steroid-resistant disease and achieved remission with immunosuppressive drug treatment (cyclosporin monotherapy or in combination with methylprednisolone), but became frequently relapsing or steroid-dependent during treatment. *In limited cases where mizoribine was used in combination with any other immunosuppressive drug.
Remission	Tested negative for first morning urinary protein using the dipstick method for 3 consecutive days, or first morning urinary protein to creatinine ratio <0.2 g/gCr for 3 consecutive days.
Remission confirmation date	Date on which remission was confirmed at the medical institution
Steroid-sensitive	Remission achieved within 4 weeks after the start of daily administration of prednisolone (60 mg/m2/day).

Term	Definition
Relapse	Patients who met any of the following conditions and required prednisolone treatment: I. First morning urinary protein ≥3+ (≥300 mg/dL on quantitative urine protein test) using the dipstick method for 3 consecutive days. II. Urinary protein ≥2+ (≥100 mg/dL on quantitative urine protein test) using the dipstick method and serum albumin ≤3.0 g/dL.
Relapse: Just before this study	Relapse that occurred within 35 days before the date of enrollment.
Relapse date	The first of 3 consecutive days on which first morning urinary protein ≥3+ (≥300 mg/dL in urine protein quantitative test) was identified using the dipstick method or the date on which urinary protein ≥2+ (≥100 mg/dL in urine protein quantitative test) and serum albumin ≤3.0 g/dL were identified using the dipstick method (the date of diagnosis of relapse was acceptable for the last 3 relapses before enrollment).
Frequent relapse: Usual diagnosis	Two or more relapses within 6 months after first remission, or four or more relapses within any 12-month period.
Frequent relapse: Last before this study	Four or more relapses within 2 years before the last relapse date prior to this study and within any 12-month period.
Frequent relapse date	The date of last relapse that met the definition of frequent relapse.
Steroid dependence: Usual diagnosis	Two consecutive relapses during prednisolone dose reduction or within 2 weeks after its discontinuation
Steroid dependence: Just before this study	Steroid dependency diagnosed within 2 years before the last relapse date prior to this study.
Steroid dependence onset date	Date of second relapse that met the definition of steroid dependency.
Steroid-resistant	Failure to achieve complete remission even with prednisolone (60 mg/m2/day) administered for 4 consecutive weeks or longer.
Date of transition to steroid resistance	Date of confirmation that the patient was not in complete remission after 4 weeks of daily administration of prednisolone (60 mg/m2/day) at the medical institution.
Incomplete remission	First morning urinary protein ≥1+ using the dipstick method or first morning urinary protein to creatinine ratio ≥0.2 g/gCr, and serum albumin >2.5 g/dL.
Nephrotic state	Urinary protein to creatinine ratio >2.0 g/gCr and serum albumin ≤2.5 g/dL.

Cr: Creatinine

5 Subjects

Patients who meet all of the following inclusion criteria and do not fall under any of the exclusion criteria will be enrolled in this study.

5.1 Inclusion criteria

(1) Idiopathic nephrotic syndrome (diagnostic criteria for idiopathic nephrotic syndrome at the time of initial diagnosis were based on criteria of the International Study of Kidney Disease in Children [ISKDC]).

(2) Age at time of onset of idiopathic nephrotic syndrome (time of initial onset) was less than 18 years, and age at time of assignment to one of the two groups in the study was not less than 2 years.

(3) Met the criteria for complicated FRNS/SDNS (any of the requirements from 1) to 3) shown below) within 2 years before the last relapse date before the study.

1) Diagnosed with frequently-relapsing or steroid-dependent nephrotic syndrome, then subsequently diagnosed with either of these conditions following discontinuation of treatment with immunosuppressive drugs (e.g., cyclosporin, cyclophosphamide, or mizoribine*).

2) Diagnosed with frequently-relapsing or steroid-dependent nephrotic syndrome, then subsequently diagnosed with either of these conditions during treatment with immunosuppressive drugs (e.g., cyclosporin, cyclophosphamide, or mizoribine*).

3) Diagnosed with steroid-resistant nephrotic syndrome and achieved remission with immunosuppressive drug therapy (cyclosporin monotherapy or used in combination with methylprednisolone), but diagnosed with frequently-relapsing or steroid-dependent nephrotic syndrome after completion of treatment with immunosuppressive drugs.

4) Diagnosed with steroid-resistant nephrotic syndrome and achieved remission with immunosuppressive drug therapy (cyclosporin monotherapy or used in combination with methylprednisolone), but diagnosed with frequently-relapsing or steroid-dependent nephrotic syndrome during treatment with immunosuppressive drugs.

*In limited cases where mizoribine is used in combination with any other immunosuppressive drug.

(4) The last three relapse dates before assignment can be confirmed.

(5) Steroid sensitivity was noted during treatment of the last preassignment relapse.

(6) The CD20-positive cell count** in peripheral blood was not less than 5 cells/μL.
**CD19-positive cell counts were acceptable at study sites where CD20-positive cells cannot be measured.

(7) Patients who were able to be admitted to hospital for at least one night and two days from the day of administration to the day after administration on the scheduled day of the first dose of rituximab, and were able to visit the hospital throughout the study period.

(8) Patients aged 20 years or older or those whose legal guardians provided written consent to participate in the study (for any patient aged 16 years or older and younger than 20 years, written consent to participate in the study should also be obtained from the patient).

[Inclusion Criteria Justification]

(1) and (2) To limit the study population to patients with childhood-onset idiopathic nephrotic syndrome.

(3) To limit the study population to patients with complicated frequently relapsing or steroid-dependent nephrotic syndrome in accordance with the study objective.

(4) To evaluate the efficacy.

(5) Since steroid sensitivity is the most important prognostic factor.

(6) Since rituximab is a monoclonal antibody specific for CD20 antigen.

(7) To ensure safe administration of rituximab, to quickly detect adverse events occurring just after administration, and to take countermeasures.

(8) To comply with the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

5.2 Exclusion criteria

(1) Patients diagnosed with nephritic-nephrotic syndrome such as IgA nephropathy prior to assignment, or secondary nephrotic syndrome was suspected.

(2) Patients previously treated with monoclonal antibodies other than rituximab (any of mouse, rat, chimeric, or human type).

(3) Patients with any one of the infections 1) to 6) shown below.

1) Patients with serious infections (e.g., pneumonia or pyelonephritis) as complications requiring hospitalization, or past history of serious infection within 6 months before assignment.
2) Patients with opportunistic infections (e.g., cytomegalovirus infections, systemic fungal infections, pneumocystis infections, or nontuberculous mycobacterial infections) as complications, or past history of opportunistic infection within 6 months before assignment.
3) Patients with active tuberculosis as a complication.
4) Patients with history or suspicion of tuberculosis infection.
5) Patients with concomitant active hepatitis B (HB) or C as a complication or confirmed to be carriers of HB virus (HBV).
6) Patients with confirmed human immunodeficiency virus infection.

(4) Patients with angina pectoris, heart failure, myocardial infarction, or severe arrhythmia (grade-4 findings listed in the Common Terminology Criteria for Adverse Events v4.0, Japanese JCOG version (CTCAE v4.0-JCOG) [corresponding to CTCAE v4.03/MedDRA v12.0 (Japanese version: MedDRA/J v16.0), April 9, 2013]), or past history of such.

(5) Patients with autoimmune diseases (Hashimoto's disease [chronic thyroiditis], Crohn's disease, ulcerative colitis, rheumatoid arthritis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, etc.) or IgA vasculitis, or history of such.

(6) Patients with malignant tumors as complications ("suspected" cases without established diagnosis should also be excluded), or those with a history of malignant tumor.

(7) Recipients of organ transplantation (excluding corneal transplantation, hair transplantation, etc.).

(8) Patients with history of drug allergies to methylprednisolone, acetaminophen, chlorophenylamine d-maleate.

(9) Patients with poorly controlled hypertension* even with antihypertensive treatment at the time of assignment.
*Not less than 99th percentile in the table of blood pressure reference values by sex and age in children (Attachment 1)[27)]

(10) Patients with decreased renal function (estimated glomerular filtration rate** <60 mL/min/1.73 m^2) at the time of assignment.
**Estimated glomerular filtration rate: Refer to References 28-29) (Attachment 2).

(11) Patients administered a live vaccine within 4 weeks before assignment.

(12) Patients with any one of the following laboratory test parameters at the time of assignment: The measurements should be taken after obtainment of informed consent and within 2 weeks before enrollment.

1) Leukocytes: <3,000/μL
2) Neutrophils: <1,500/μL
3) Platelets: <50,000/μL
4) AST (GOT): ≥2.5 times the upper limit of reference values shown in the table of liver deviation enzyme (GOT) reference values by age in children[30)] (Attachment 3) for subjects younger than 21 years; ≥2.5 times the facility's upper limit of reference values for subjects not younger than 21 years
5) ALT (GPT): ≥2.5 times the upper limit of reference values shown in the table of liver deviation enzyme (GPT) reference values by age in children[30)] (Attachment 4) for subjects younger than 21 years; ≥2.5 times the facility's upper limit of reference values for subjects not younger than 21 years
6) HBs antigen, HBs antibody, HBc antibody, HCV antibody: Positive for any one of these parameters. Out of patients testing positive for HBs antibody only, however, those with a history of HB vaccination and an HBV-DNA content under the detection limit (-) at the time of enrollment are excluded.
7) HIV antibody: Positive

(13) Female patients of childbearing potential who did not consent to take contraceptive measures during the observation period (confirmation by serum human chorionic gonadotropin test at the time of screening was essential)

(14) Female patients who were pregnant, had the possibility of pregnancy, or were lactating.

(15) Patients considered by the principal investigator etc. to be ineligible for the study

[Exclusion Criteria Justification]

(1) To exclude secondary nephrotic syndrome.

(2) Possibly influence safety and efficacy assessments in this study.

(3) Potentially cause symptom relapses or aggravation.

(4) to (12) Undesirable to enroll in this study from the viewpoint of safety.

(13) and (14) Since rituximab is qualitatively equivalent to immunoglobulins, which are known to penetrate the placenta and migrate into fetuses, there is a concern about fetal effects of rituximab when administered to mothers.

(15) To exclude patients who are ineligible as subjects of this study.

6 Study plan

6.1 Study outline for individual subjects

The period of a subject's participation in the study will be defined as being from the date of obtaining informed consent to the date of completion of the follow-up period (scheduled date of final treatment of the last enrolled subject).

<table>
<tr><td colspan="5">Study participation period (from the date of obtaining informed consent to the date of completion of the follow-up period)</td></tr>
<tr><td colspan="3">Screening period
(up to 35 days from consent date)</td><td rowspan="2">Up to 14 days</td><td>Treatment period
(Day 1 to Day 505)</td><td>Follow-up period
(completion of the treatment period to completion of the treatment period for the last enrolled subject)</td></tr>
<tr><td>Obtainment of informed consent</td><td>Screening</td><td>Enrollment</td><td>Study treatment, assessments, and observations</td><td>Subsequent treatment and observations</td></tr>
</table>

6.2 Screening period: Informed consent to enrollment (up to 35 days)

The investigator will provide an explanation of this study to a patient who is a potential subject of this study (legal guardian if the patient is a minor) and obtain his/her written consent to participate in the study. After obtaining informed consent, screening will be performed to check the subject's eligibility as a study subject. After confirming eligibility, the subject will be enrolled immediately. Enrollment will be completed within 7 days after the remission confirmation date.

6.3 Enrollment

6.3.1 Enrollment

(1) The investigator will confirm that the patients who provided written informed consent to participate in this study meet all of the inclusion criteria (Section 5.1) and do not meet any of the exclusion criteria (Section 5.2). If the patient is eligible, the investigator will enter all required information on the Case

Registration Form (Appendix 2) and facsimile it to the contact liaison shown below.

Patient enrollment contact liaison and time

JSKDC data center (EP-CRSU Co., Ltd.)

FAX: 03-5946-8278 TEL: 03-6759-9914

Contact time: 10:00-17:00 on weekdays (not contactable on Saturdays, Sundays, national holidays, and the end and start of the year)

(2) The data center will confirm the eligibility of the patient using the received Case Registration Form (Appendix 2) and register the patient.

1) The patient should not be enrolled if the Case Registration Form (Appendix 2) is inadequately documented.
2) The enrollment of any patient once enrolled should not be canceled (should not be removed from the database).
3) In the case of double enrollment, the first enrollment information (allocation group) will be adopted.
4) If mis-enrollment/duplicate enrollment is found at a facility, it is necessary to record this fact in the database, and report it to the data center as soon as possible.

6.3.2 Randomization

At the data center, subjects will be randomized to receive either rituximab monotherapy or rituximab + MMF combination treatment in a ratio of about 1:1 by dynamic allocation with the following allocation adjusters at the time of enrollment. The allocation algorithm will be determined by the statistical analysis manager.

Allocation adjusters

1) Study Sites
   Number of sites: 27
2) Age at the time of enrollment
   I. 2-9 years
   II. 10-17 years
   III. ≥18 years
3) History of treatment
   I. Existence of immunosuppressive drug administration at the time of last relapse: Cyclosporine present, Any other drug present, None
   II. Existence of steroid drug administration at the time of last relapse: No, Yes on consecutive days, Yes every 2 days
   III. Existence of history of rituximab treatment: No, Yes
4) Interval of last 3 relapses (interval between the onset day [last] and the relapse day [earliest])
   I. Within 180 days

II. Exceeding 180 days

5) Existence of history of steroid resistance

I. Without history of steroid resistance (complicated frequent relapsing or steroid-dependent nephrotic syndrome definitions 1 and 2)

II. With history of steroid resistance (complicated frequent relapsing or steroid-dependent nephrotic syndrome definitions 3 and 4)

6.3.3 Transmission of enrollment results

(1) After enrollment, the data center will send a "Enrollment Confirmation Form" bearing the enrollment number and rituximab and investigational drug doses to the investigator.

(2) The investigator will confirm the "Enrollment Confirmation Form" sent from the data center and perform study treatment.

6.3.4 Post-enrollment exclusions

Since they are ineligible for this study, subjects who have failed to receive the first dose of rituximab within 14 days after the enrollment and those who have experienced a relapse before the first dose of rituximab will be handled as post-enrollment exclusions and reported in the Post-enrollment Exclusion Report (Appendix 3).

(1) If the patient becomes a post-enrollment exclusion, the attending physician will perform a screening test (10.2) after obtaining informed consent again to check his/her eligibility.

1) If data (obtained within 35 days before re-enrollment) for hematology and blood biochemistry testing performed after the last relapse before re-enrollment, the results may be used as screening data, and there is no need to perform the testing again.

2) If data are available for viral tests (HIV antibody, HBs antigen, HBs antibody, HBc antibody, HCV antibody) performed within 85 days before re-enrollment, there is no need to repeat them.

(2) If the screening confirms that the patient is eligible, he/she will be enrolled immediately.

6.4 Treatment period

The investigator will administer rituximab within 14 days after the enrollment and implement observations, examinations, and surveys according to the study schedule, regardless of completion or discontinuation of study treatment.

The duration of treatment will be 18 months, and the study treatment initiation date (Day 1) will be the day of first dose of rituximab.

6.5 Investigational drug treatment discontinuation criteria

If the subject meets any one of the criteria (1) to (5) below, the investigator will immediately discontinue investigational drug treatment for the subject and ensure the safety of the subject. The investigator will explore the date and reason(s) for discontinuing investigational drug treatment and record this information in the Emergency report on discontinuation of study treatment (Appendix 7). The investigational drug dosing

discontinuation date will be defined as the day of the last dose of the investigational drug.

Unless meeting the "6.7 Study Discontinuation Criteria", the study on the subject will be continued even after discontinuation of investigational drug treatment, and the investigator will continue observations, examinations, and surveys (Section 10.6) according to the study schedule (Section 10.1).

(1) Cases where a treatment failure (Section 6.5.1) is identified during the treatment period
(2) Cases where any of the prohibited concomitant medications (1) to (2) is used to treat nephrotic syndrome during the observation period
(3) Cases where the subject (20 years or older) or legal guardian wants to discontinue investigational drug treatment
(4) Cases where the attending physician considers it to be difficult to continue investigational drug treatment because of onset of adverse events etc.
(5) Cases where the subject (20 years or older) or legal guardian states that the subject has become pregnant, and pregnancy is confirmed*
(6) Others

*In case of confirmed pregnancy, the Pregnancy Case Report (Appendix 10) will be submitted.

6.5.1 Treatment failure

In this study, a treatment failure will be defined as the earliest of I) frequent relapse, II) steroid-dependence, and III) steroid resistance that have occurred during the study period.

The investigator will perform an efficacy evaluation and safety evaluation for the subject upon identifying a treatment failure. Thereafter, emergency disclosure of the allocation code will be performed according to the operating procedure for emergency disclosure of the allocation code (Section 7.3.2).

Relapse	Patients who met any of the following conditions and required prednisolone treatment: I. First morning urinary protein ≥3+ (≥300 mg/dL on quantitative urine protein test) using the dipstick method for 3 consecutive days. II. Urinary protein ≥2+ (≥100 mg/dL on quantitative urine protein test) using the dipstick method and serum albumin ≤3.0 g/dL.
Relapse date	The first of 3 consecutive days on which first morning urinary protein ≥3+ (≥300 mg/dL in urine protein quantitative test) was identified using the dipstick method or the date on which urinary protein ≥2+ (≥100 mg/dL in urine protein quantitative test) and serum albumin ≤3.0 g/dL were identified using the dipstick method (the date of diagnosis of relapse was acceptable for the last 3 relapses before enrollment).
Frequent relapse	At least 4 relapses occurring within 12 months during the observation period.
Frequent relapse date	The date of last relapse that met the definition of frequent relapse.

Steroid dependence	Two consecutive relapses during prednisolone dose reduction or within 2 weeks after its discontinuation
Steroid dependence onset date	Date of second relapse that met the definition of steroid dependency.
Steroid-resistant	Failure to achieve complete remission even with prednisolone (60 mg/m^2/day) administered for 4 consecutive weeks or longer.
Date of transition to steroid resistance	Date of confirmation that the patient was not in complete remission after 4 weeks of daily administration of prednisolone (60 mg/m^2/day) at the medical institution.

6.6 Posttreatment (treatment after completion/discontinuation of study treatment)

Subjects who are in remission at the time of completion of study treatment will be followed without treatment whenever possible until relapse. Decisions on treatment for relapses after the completion of study treatment will be made by the investigator.

Subjects who have discontinued study treatment will receive treatments considered by the investigator to be the best, including initiation of a new immunosuppressive drug.

Particulars (drug names, treatment periods) of treatments during the follow-up period will be reported in the follow-up survey report (Appendix 8).

6.7 Study discontinuation criteria

If a subject becomes unable to comply with the entire study schedule (Section 10.1), including efficacy and safety assessments, as well as discontinuation of study treatment, for any of the reasons (1) to (4) shown below, the study will be discontinued.

(1) The subject (aged 20 years or older) or legal guardian wishes to discontinue the study or withdraw consent to participate in the study
(2) The subject becomes unable to visit the hospital for their own reasons (being busy, relocation, hospital transfer, etc.)
(3) Discontinuation of this study
(4) Other cases where the principal investigator judges that continuation of the study is difficult

If any of the study discontinuation criteria is met, the investigator will promptly discontinue the study and record the date of discontinuation (date on which the decision to discontinue the study was made) and the reason for discontinuation in the Treatment Course Report (Appendix 4). The investigator should make adequate efforts to confirm the reason, while fully respecting the rights of the subject.

If the study is discontinued during the treatment period, tests to assure the safety of the subject (Section 10.6) will be performed at that time. Observations, surveys, and examinations will be performed for the survey items at the end of the treatment period (Section 10.1) if possible.

If a serious adverse event is manifested at the time of discontinuation of the study, the investigator will take appropriate measures for the serious adverse event and follow its outcome by telephone or letter as much as possible by the end date of the entire study (the last scheduled observation date for the last enrolled subject).

If this study itself is discontinued, the attending physician will provide appropriate treatment to avoid any detriment to the subject.

6.8 Follow-up period

In this study, the follow-up period will be from the end of the treatment period to the last scheduled treatment date of the last enrolled subject. During the follow-up period, the investigator will follow up all subjects according to the specified schedule (Section 10.7) using routine clinical data.

7 Blinding and key opening

7.1 Blinding

7.1.1 Type and level of blinding

This is a double-blind, placebo-controlled trial. Treatment group assignment will be performed by the person in charge of allocation.

Data center personnel will only be informed of the drug number corresponding to the assigned treatment group and will not have access to information on which treatment group has been assigned.

In addition, when delivering the investigational drugs to each facility, only the registration number is added to the individual packaging boxes of the investigational drugs, thereby ensuring blinding.

7.1.2 Procedures to ensure blinding

(1) Confirmation of investigational drugs indistinguishability

Prior to blinding for the investigational drug MMF, the investigational drug allocation manager will confirm the indistinguishability of MMF and placebo using the formulation used for the assignment.

(2) Allocation code creation and storage

The investigational drug allocation administrator will create “allocation codes” based on the Allocation Table Generation Specifications and seal and retain these allocation codes until the entire clinical trial is completed and all data and determination confirmed.

(3) Urgent allocation code creation and storage

The investigational drug allocation administrator will create “urgent allocation codes” in order to distinguish between MMF and placebo in the event of a treatment failure or medical emergency. The “urgent allocation codes” will be sealed and stored by the person in charge of allocation.

(4) Urgent allocation codes storage

After confirming the allocation results, the principal investigator will seal and retain the “urgent allocation code” in accordance with “7.3.2 Procedures for urgent disclosure of allocation codes.”

7.2 Key opening for the entire study

In order to maintain blinding, the “allocation codes” and “urgent allocation codes” will be disclosed after the entire clinical trial is completed and all data and determination secured.

7.3 Urgent disclosure of allocation codes

7.3.1 Conditions for urgent disclosure of allocation codesd

In the following cases, the investigator may request the disclosure of a subject's urgent allocation code.

(1) The subject experiences a serious adverse event that leads to death or is life-threatening.

(2) The subject experiences another serious adverse event and it is determined the information is essential in considering the relevant subject's treatment.

(3) The subject is judged to have treatment failure (Section 6.5.1).

(4) The subject become pregnant, and investigational drug administration is discontinued.

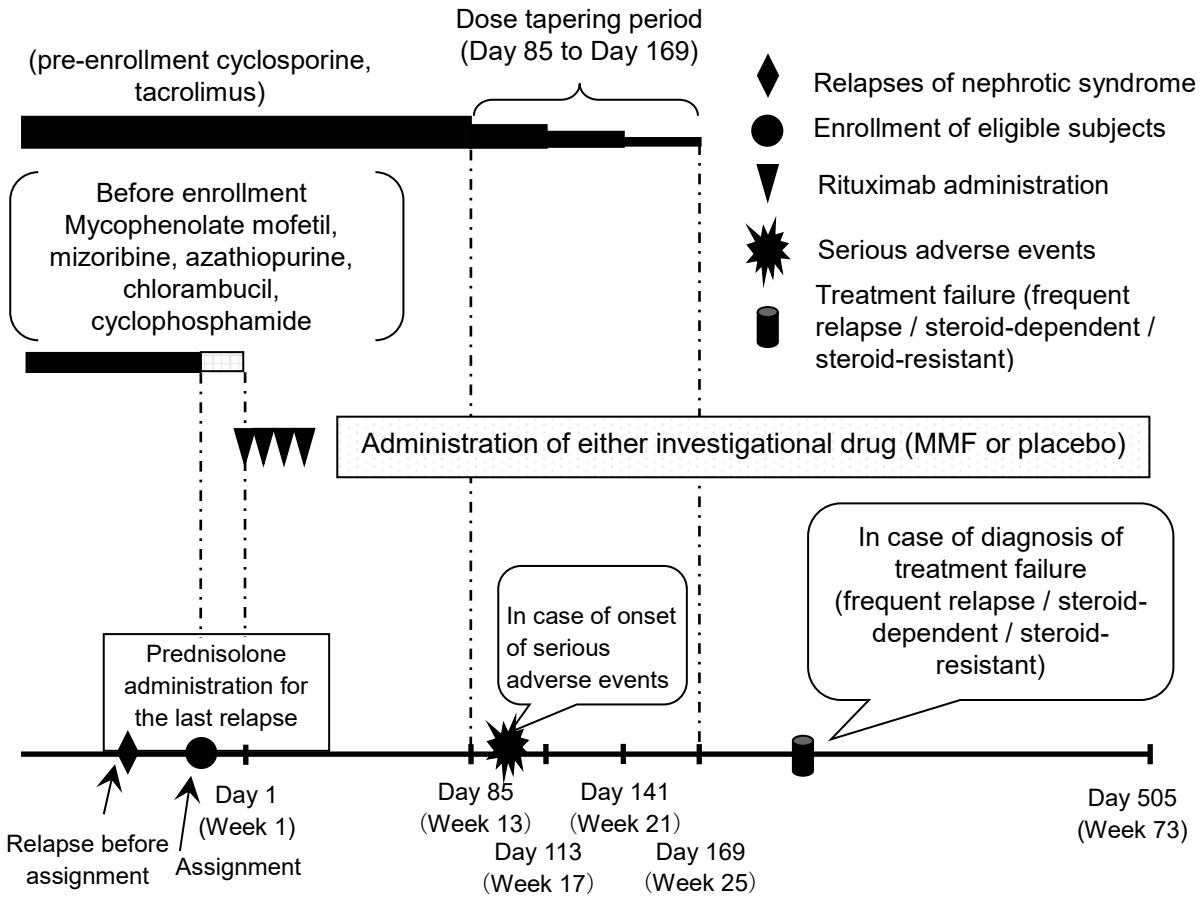

Figure 7-1. Conditions for urgent disclosure of allocation codes

7.3.2 Procedures for the disclosure of urgent allocation codes

(1) Considering that the urgent disclosure criteria are met, the investigator will enter the reason, enrollment number, and efficacy evaluation (treatment failure evaluation) and safety evaluation (existence of serious adverse events) for the subject in the Request form for disclosure of urgent allocation codes of investigational drugs (Appendix 6), and fax it to the data center.

(2) When receiving a request for the disclosure of urgent allocation code, the data center will check and fix the efficacy and safety evaluation data for the subject, and then immediately notify the JSKDC07 study director (study office).

(3) The JSKDC07 study director (study office) will consult the independent data and safety monitoring committee as required and, if considering it to be appropriate to disclose the urgent allocation code, the director will request for disclosure of the urgent allocation code for the subject to the data center.

(4) The data center, after obtaining the permission of the investigational drug allocation administrator, will send the undisclosed urgent allocation code to the investigator of the relevant study site by post.

(5) When disclosing the code, the data center will keep a record of the events that led to the disclosure as well as the destination to which the urgent allocation code was sent.

(6) The investigator will unseal the urgent allocation code after confirming safety evaluation (presence/absence of non-serious adverse events, type of event and causality) in relation to the relevant subject. The investigator will determine the following treatment at his/her clinical discretion with reference to the investigational drug allocated to the subject.

(7) The investigator will record the events that led to the disclosure of urgent allocation code for the investigational drug MMF in the medical records. Disclosed results should only be notified to the subject, his/her legal guardian, and medical professionals at the relevant study site.

(8) The investigators will seal and retain the urgent allocation code in line with the “Procedures for Disclosure of Urgent Allocation Codes.”

8 Treatment plan

8.1 Definition of study treatment

The study treatments provided in this study will be intravenous drip infusions of rituximab and oral administration of investigational drug. Of the investigational drugs, the study drug will be mycophenolate mofetil (MMF) and the control drug will be placebo.

The duration of treatment will be 18 months (Four weeks were defined as one month). If the subject completes investigational drug treatment during that period, the state will be defined as study treatment completion. The study treatment initiation date (Day 1) will be the day rituximab was started within 14 days post-enrollment. In the event of a relapse during study treatment, prednisolone will be administered for the relapse.

During the treatment period, prednisolone administration for relapse just before enrollment and administration of any immunosuppressive drugs that have been used from before enrollment will be performed in accordance with the relevant rules (Section 9.2, 9.3).

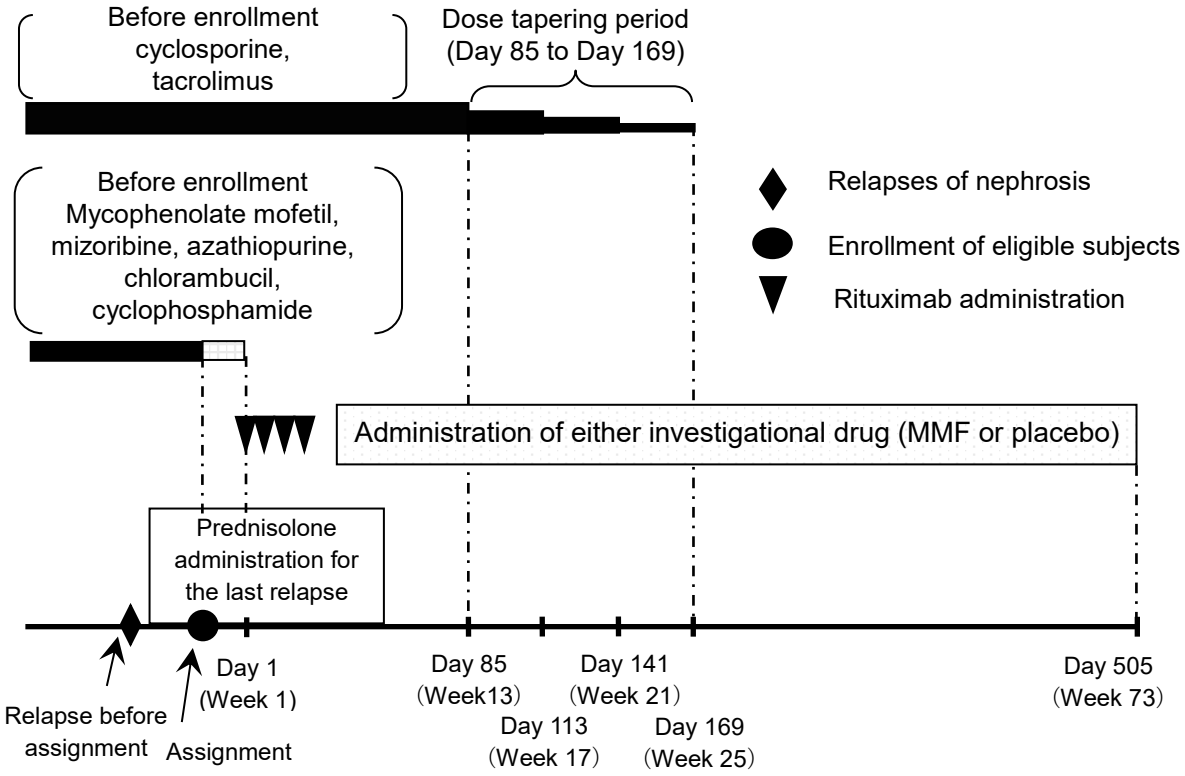

Figure 8-1 Study treatment and concomitant treatments

8.1.1 Investigational drug

Of the investigational drugs used, the study drug will be MMF (CELLCEPT® capsules 250, Chugai Pharmaceutical Co., Ltd.), and the control drug will be placebo (Shinshin Pharmaceutical Co., Ltd.).

For details of rituximab and MMF, refer to the package insert. Drug information (contraindications, important adverse reactions, concomitant medications requiring careful use, etc.) should always be the latest. The current

version of the package insert is accessible on the website (http://www.info.pmda.go.jp/).

For delivery, storage, management, and retrieval of the investigational drugs, refer to the "Standard Operating Procedures for Management of the Investigational Drugs."

8.2 Intravenous drip infusion of rituximab

The investigator will administer the first dose of rituximab within 14 days after the enrollment date (the first rituximab dosing date will be defined as Day 1 and Week 1).

8.2.1 How to prepare rituximab

(1) Rituximab will be diluted 10-fold in Japanese Pharmacopoeia isotonic sodium chloride solution immediately prior to administration and infusion will then be completed within 24 hours at a final concentration of 1 mg/mL.

(2) Dilution of the investigational drug with 5% injectable glucose solution rather than sodium chloride solution will be acceptable for subjects with salt intake restrictions. No other drugs shall be mixed into the diluent. In addition, the preparation shall not be vigorously stirred or frothed up during dilution.

8.2.2 Rituximab administration method

The first dose of rituximab will be administered while the subject is hospitalized on the dosing day and on the day that follows (a stay for 1 night and 2 days or longer); outpatient administration is unacceptable. If no infusion reaction develops or a mild (grade 1 or lower, but grade 2 or lower for pyrexia) infusion reaction develops at the time of the first dose, the second and subsequent doses may be administered at the outpatient clinic. Change of rituximab administration date will be carried out in accordance with 8.2.5.

(1) Rituximab doses

Rituximab doses will be determined from the body height at the time of enrollment according to the table of rituximab doses by body height (Attachment 6).

The specified dose per intravenous drip infusion should not be changed.

Rituximab dosage and administration Administered at 375 mg/m^2/dose (up to 500 mg/dose) at 1-week intervals in a total of 4 doses (Days 1, 8, 15, and 22)

(2) Pretreatment

To prevent infusion reactions, pretreatment with an oral antipyretic-analgesic, oral antihistamine, and intravenous methylprednisolone (Section 8.2.3) will be performed about 30 minutes before each dose of

rituximab (Figures 8-2 and 8-3).

1) Acetaminophen oral administration
2) d-chlorphenylamine maleate oral administration
3) Methylprednisolone succinate sodium intravenous administration

(3) Standard intravenous drip infusion rates for rituximab (Figures 8-2 and 8-3)

In this study, it is recommended that rituximab be administered using the new method; however, the conventional method may be used. Whichever method is used, rituximab may be administered at a low rate at the discretion of the attending physician, but administration should be completed within 24 hours after preparation of the formulation.

1) New administration method

<First dose>

Dosing will be started at an intravenous infusion rate of 50 mg/hr during the first 30 minutes, and while monitoring the subject's condition, rituximab will be administered while increasing the infusion rate by 50 mg/hr every 30 minutes (injection rate up to 300 mg/hr).

<Second and subsequent doses>

If the infusion reaction at the last dose was mild (grade 1 or lower; for pyrexia, grade 2 or lower), dosing will be started at an intravenous infusion rate of 100 mg/hr during the first 30 minutes, and while monitoring the subject's condition, rituximab will be administered while increasing the infusion rate by 100 mg/hr every 30 minutes (injection rate up to 300 mg/hr).

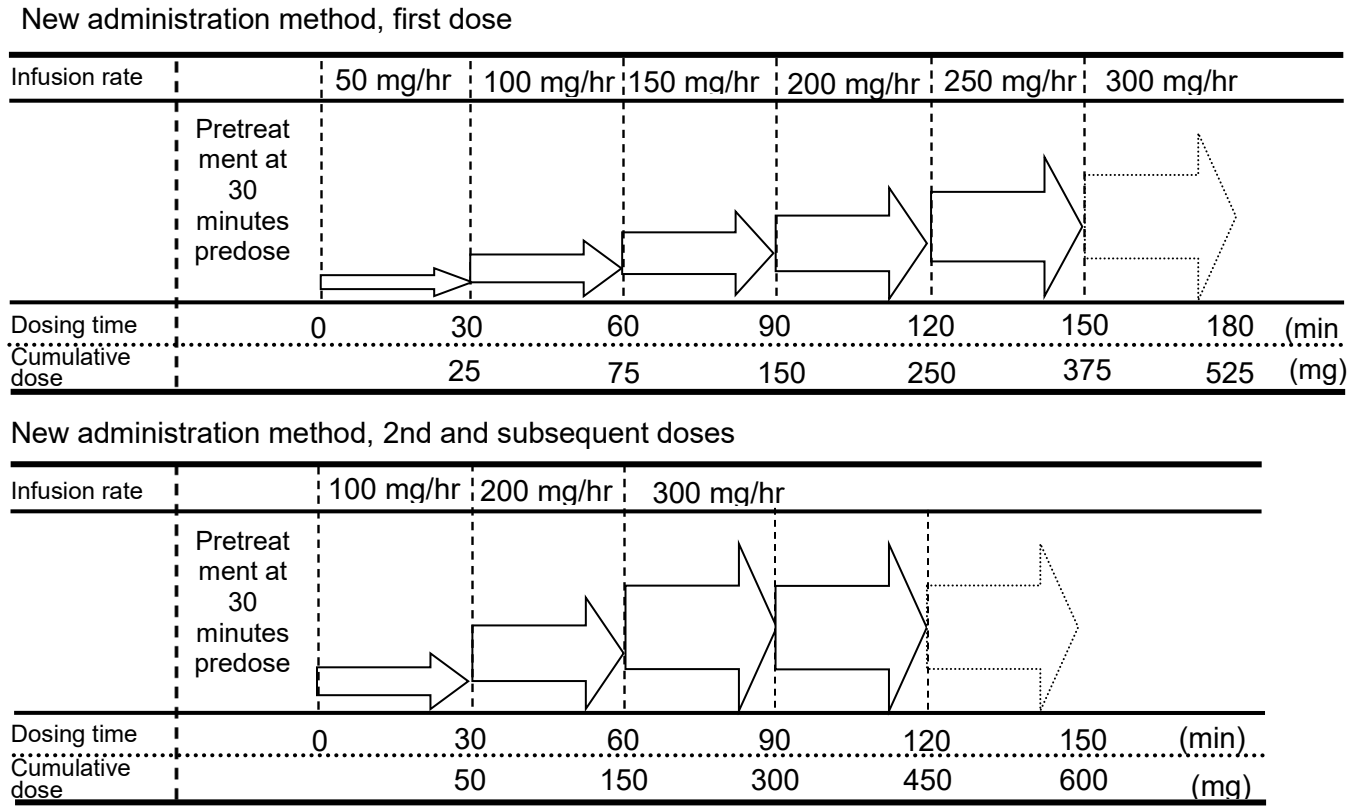

Figure 8-2. New administration method

2) Conventional administration method

<First dose>

Dosing will be started at an intravenous infusion rate of 25 mg/hr during the first 1 hour, and while monitoring the subject's condition, rituximab will be administered at 100 mg/hr during the subsequent 1 hour and then at 200 mg/hr.

<Second and subsequent doses*>

If the infusion reaction at the last dose was mild (grade 1 or lower; for pyrexia, grade 2 or lower), dosing will be started at an intravenous infusion rate of 100 mg/hr during the first 1 hour, and while monitoring the subject's condition, rituximab will thereafter be administered at 200 mg/hr.

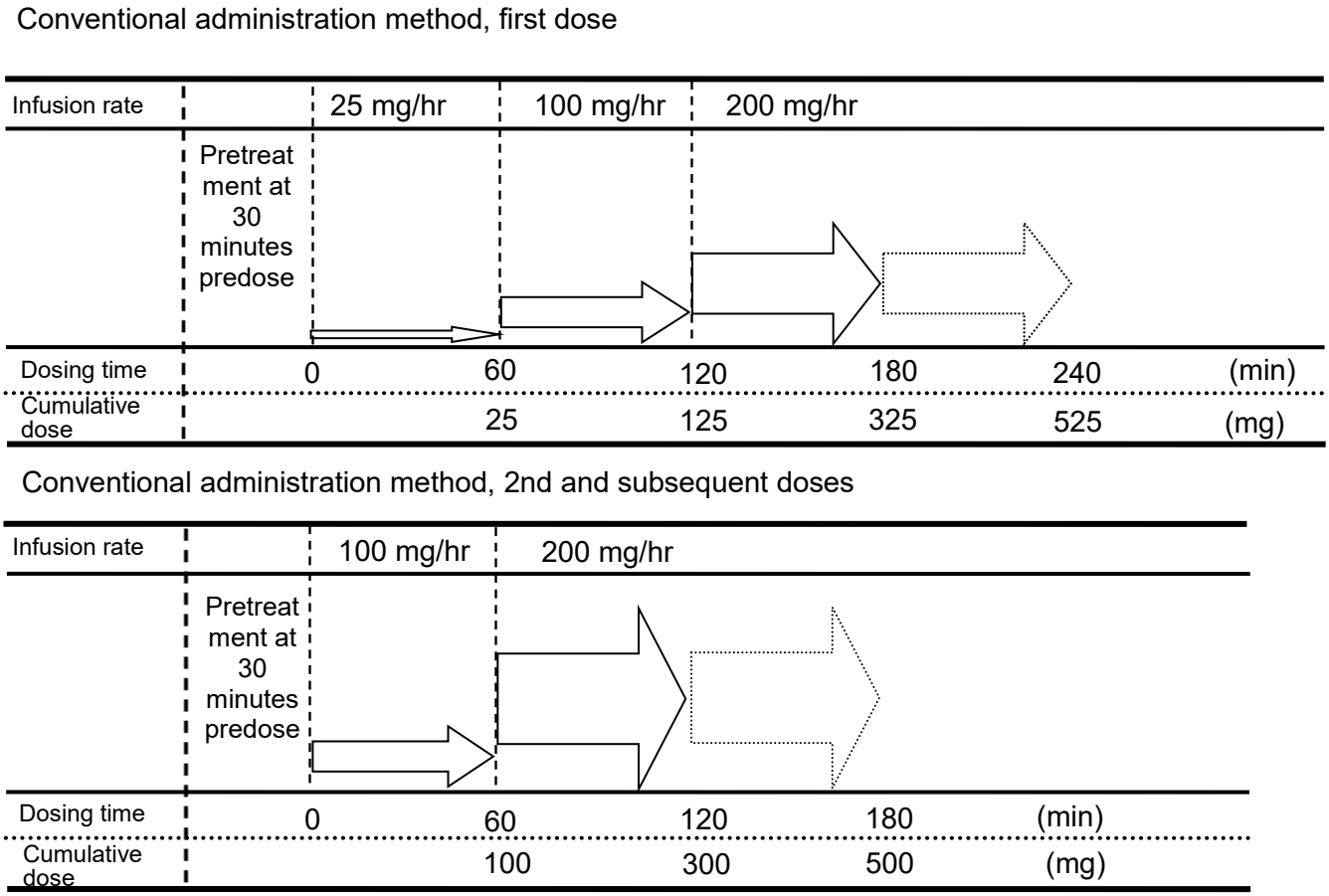

Figure 8-3. Conventional administration method

*In a study in patients with B cell lymphoma, infusion reactions with rituximab administration occurred most frequently at the time of the first dose, which rapidly destroys peripheral blood B cells, and the incidence rate at the time of the 2nd and subsequent doses was not more than 50% of the level found with the 1st dose.

(4) In a clinical study of rituximab conducted outside Japan in patients with autoimmune disease, HACA production tended to be caused in patients with insufficient reductions of B cells by rituximab. Therefore, the 2nd and subsequent doses will be administered while carefully monitoring the subject's condition.

(5) Administration of the investigational drug rituximab to patients at high risk of experiencing infusion reactions

Since subjects with complicating respiratory disease or past history of such are at high risk of experiencing dyspnea and bronchial spasms, and subjects with complicating heart disease or past history of such are at high risk of experiencing myocardial infarction and arrhythmias, rituximab should be

administered while carefully and frequently monitoring the subject's condition.
In subjects likely to experience serious infusion reactions, rituximab may be administered at a low rate (<200 mg/hr) without increasing the intravenous drip infusion rate.

8.2.3 Pretreatment for rituximab administration

To prevent infusion reactions, pretreatment with an oral antipyretic-analgesic, oral antihistamine, and intravenous methylprednisolone will be performed about 30 minutes (±15 minutes) before each dose of rituximab. Intravenous methylprednisolone will be administered to suppress HACA production as in the clinical trials of SLE.

(1) Oral antipyretic-analgesic; acetaminophen (CALONAL® etc.)

1) Patients whose height-based standard body weight is not less than 50 kg or patients aged 16 years or older
Acetaminophen 300 mg/dose (tablets)

2) Patients not meeting the criterion 1) and patients unable to take tablets
It is recommended that the single acetaminophen dose be 10 to 15 mg/kg (for syrups: 0.5 mL/kg, up to 300 mg/dose).

(2) Oral antihistamine; d-chlorphenylamine maleate (POLARAMINE® etc.)

1) Patients whose height-based standard body weight is not less than 50 kg or patients aged 16 years or older
A single dose of 2.0 mg (tablets) will be administered orally.

2) Patients not falling under 1) and patients unable to orally take tablets
Syrup (content 0.04%) will be administered at the doses shown below.

Age	Single-dose volume	Age	Single-dose volume
2 - <3 years	1.0 mL	8 - <12 years	2.5 mL
3 - <5 years	1.5 mL	12 - <15 years	3.0 mL
5 - <8 years	2.0 mL		

(3) Intravenous corticosteroid drug; methylprednisolone (Solu-Medrol® etc.)

1) Patients whose height-based standard body weight is not less than 50 kg or patients aged 16 years or older
Methylprednisolone 125 mg, intravenous administration

2) Patients not meeting criterion 1)
Dose for pediatric bronchial asthma, 1.0 to 1.5 mg/kg based on methylprednisolone

8.2.4 Countermeasures to infusion reactions due to rituximab intravenous drip infusion

If any infusion reaction develops during intravenous drip infusion, the intravenous drip infusion rate will be reduced or the infusion will be discontinued, according to its severity as described below, and supportive care will be performed as required.

(1) Grade 1 cases

The investigator will make a clinical judgement whether to continue administration at a decreased infusion rate or at the same rate, or whether to suspend intravenous drip infusion at the clinical discretion. If the infusion is suspended, it will be restarted at an infusion rate not more than 50% of the pre-suspension dose after recovery from symptoms.

(2) Grade 2 cases

The investigator will make a clinical judgement whether to continue administration at a decreased infusion rate, or whether to suspend intravenous drip infusion, at the clinical discretion. If the infusion is suspended, it will be restarted at an infusion rate not more than 50% of the pre-suspension dose after symptoms ameliorate to grade 1 or lower.

Decision on restarting drip infusion following the suspension and increasing the drip infusion rate at the time of restarting the infusion and after restarting the infusion at a rate not more than 50% of the level at the time of the suspension will be made at the clinical discretion of the investigator with reference to Figures 8-2 and 8-3.

Although no rule will be established for the time from suspension to restarting of drip infusion, administration of rituximab should be completed within 24 hours after preparation; for subjects not completing the administration, rituximab should be discontinued at that time (Section 8.2.6).

(3) Grade 3 or above non-hematological toxicity (excluding laboratory test value abnormalities):

The infusion should be discontinued, and supportive care should be provided as required. Rituximab treatment for the subject will be discontinued.

Supportive treatment will be administered in the form of I) nonsteroidal antipyretic analgesics (pyrexia, pain, etc.), II) antihistamines (allergic symptoms), III) antibiotic preparations/antiviral agents, IV) antihypertensives/hypertensives/vasodilators, V) antinauseants, VI) stomachics/antidiarrheals/laxatives, VII) oxygen inhalation, VIII) other drugs. If any serum-sickness-like symptom is noted, a symptomatic treatment with a steroid will be administered.

8.2.5 Changes in Rituximab dosage or administration date

(1) Change in dosage

The prescribed infusion dosage may not be changed. If any dose cannot be administered as prescribed due to an infusion reaction, further administration of the investigational drug to the relevant subject will be discontinued.

(2) Change in administration date

1) The second and subsequent doses of rituximab will be administered within 5 to 14 days from the last dose.
2) If any non-hematotoxic adverse event of grade 3 or higher develops before the second and subsequent doses of rituximab, treatment should be postponed.
3) If the investigator considers that the second and subsequent doses of rituximab cannot be performed as scheduled because of adverse events, the next dose will be administered within 21 days after the last dose. If the postponed date falls on a holiday, treatment may be further postponed by 2 more days (9 days in total); however, if the next dose cannot be administered within 21 days after the last dose because of any adverse event, rituximab treatment will be discontinued.

8.2.6 Rituximab treatment discontinuation criteria

In the following cases, the investigator will discontinue rituximab treatment to ensure subject's safety. Unless meeting the "6.5 Investigational drug treatment discontinuation criteria" and the "6.7 Study Discontinuation Criteria", the study on the subject will be continued even after discontinuation of rituximab treatment, and the investigator will continue study treatments, observations, examinations, and surveys according to the study schedule (Section 10.1).

(1) The subject experiences any non-hematological toxicity of grade 3 or higher (excluding abnormal laboratory values) during rituximab intravenous drip infusion

(2) Rituximab was not administered according to the specified schedule

1) Rituximab administration was not completed within 24 hours after preparation
2) Deviated from the dose change rules (Section 8.2.5)
3) Deviated of deviations from the dosing date change rules (Section 8.2.5)

8.3 Administration of investigational drugs

The investigator will start investigational drug treatment on Day 29 (-6 days to +7 days) in accordance with the allocation of the subject at the time of enrollment. However, if the last rituximab dosing day is beyond Day 22, investigational drug treatment will be started within 14 days from the day after the last rituximab dosing day. Investigational drug doses will be determined from the body height at the time of enrollment according to the table of investigational drug doses by body height (Attachment 7).

Dosage and administration of investigational drugs
1,000 to 1,200 mg/m^2/day (up to 2 g/day), 2 divided doses, postprandial, oral administration for 17 months
For a daily dose of 250 mg (1 capsule), single dose, postprandial, oral administration

The investigational drugs may be started at a half of the specified dose (up to 1 g/day). If the subject does not show any adverse events, the investigator will increased to the specified dose until 3 months after the start of study treatment. If it is difficult to increase the dose to the specified dose because of adverse events and other reasons, the dose will be determined at the discretion of the investigator (Section 8.3.1).

8.3.1 Investigational drug dose changes, suspension, and discontinuation

If a moderate (Grade 2, Section 12.3.2) or higher adverse event is noted during the treatment period, and the investigator considers it to be necessary, investigational drug dose reductions or suspension will be performed. The timing of dose reduction or suspension and the extent of reduction will be determined by the investigator. If the adverse event is ameliorated because of investigational drug dose reductions or suspension, the dose may be restored or dosing may be restarted at the discretion of the attending physician.

In case of investigational drug dose change, suspension, or discontinuation, its time (and the dose if changed) will be entered in the Treatment Course Report (Appendix 4). Adverse event evaluations (Section 12.3) will be performed before implementing investigational drug dose changes, suspension, or discontinuation.

8.3.2 Countermeasures against adverse events during treatment with investigational drugs

Reference data for actions to take against major adverse events are shown below.

(1) Pancytopenia

1) Neutrophil count reductions to ≥1000 and <1500/μL

If an investigational drug is administered at 250 mg/day, investigational drug will be suspended. When the investigational drug is administered at a dose of ≥500 mg/day, the dose will be reduced by every 250 mg; if a neutrophil count of less than 1500 persists even after 1 week, a further dose reduction or suspension of investigational drug treatment will be considered.

2) Neutrophil count reductions to <1000/μL

The investigational drug will be immediately suspended.

3) WBC count reductions to <3,000/μL
Investigational drug dose reduction or suspension by every 250 mg will be considered.

4) Severe anemia or thrombocytopenia
If serious complications are caused, erythrocytes and platelets will be transfused.

If the pancytopenia is getting better, the investigator restart the investigational drug or restore its dose.

(2) Diarrhea
The investigator need to conduct stool cultures and/or imaging to exclude infection and organic diseases. Treatment with antidiarrheals should be considered, and intravenous drip infusion should be performed for dehydration and malnutrition..

(3) Nausea/vomiting
Treatment with antinauseants should be considered, and intravenous drip infusion should be performed for dehydration and malnutrition.

(4) Cytomegalovirus (CMV) infections
If any CMV infection* is found, dose reductions and suspensions of concomitant immunosuppressive drugs and investigational drugs should be considered. In addition, treatment with ganciclovir or human immunoglobulin treatment should be considered.
*Specific findings in CMV infections: Pyrexia, leukopenia, thrombocytopenia, pneumonia, hepatitis, pancreatitis, gastrointestinal ulcers, colitis, retinitis, etc.

(5) Epstein-Barr virus (EBV) infections
If any EBV infection* is suspected, EBV DNA qualitative test (PCR), EBV DNA quantitative test (real-time PCR), EBV antibody test, and other examinations are need to be performed, and judgment will be made on the basis of the facility's reference values. If any EBV infection* is found, dose reductions and suspensions of concomitant immunosuppressive drugs and investigational drugs should be considered.
*Specific findings in EBV infections: Pyrexia, enlarged tonsil, lymph node swelling, body weight loss, diarrhea, etc.

8.4 Prednisolone administration for relapses during the treatment period

In this study, a relapse and the relapse onset date will be defined as follows:

The attending physician will evaluate relapses on the basis of urine protein testing performed at the study site at the time of medical checkup.

Relapse	Patients who met any of the following conditions and required prednisolone treatment: I. First morning urinary protein ≥3+ (≥300 mg/dL on quantitative urine protein test) using the dipstick method for 3 consecutive days. II. Urinary protein ≥2+ (≥100 mg/dL on quantitative urine protein test) using the dipstick method and serum albumin ≤3.0 g/dL.
Relapse date	The first of 3 consecutive days on which first morning urinary protein ≥3+ (≥300 mg/dL in urine protein quantitative test) was identified using the dipstick method or the date on which urinary protein ≥2+ (≥100 mg/dL in urine protein quantitative test) and serum albumin ≤3.0 g/dL were identified using the dipstick method (the date of diagnosis of relapse was acceptable for the last 3 relapses before enrollment).

Prednisolone administration for relapses during the treatment period will be performed in accordance with the ISKDC Relapse Treatment considering secondary adrenocortical dysfunction.

Prednisolone treatment will be started within 14 days after the relapse onset day. Prednisolone doses will be determined from the body height at the time of relapse diagnosis according to the table of doses by body height (Attachment 8).

If any adverse reaction due to prednisolone develops, and the investigator considers it to be necessary, the prednisolone dose can be reduced as required.

(1) 60 mg/m^2/day (up to 60 mg/day) administered in 3 divided doses for consecutive days (2 divided doses acceptable if the investigator considered it is required) until negative protein on urine dipstick test in the first morning urine is confirmed for 3 consecutive days.
(2) 60 mg/m^2/dose (up to 60 mg/day), every other morning for 14 days
(3) 30 mg/m^2/dose (up to 30 mg/day), every other morning for 14 days
(4) 15 mg/m^2/dose (up to 15 mg/day), every other morning, discontinued after the end of 14-day treatment

9 Concomitant medications and therapies

9.1 Recording concomitant medications and therapies

During the treatment period, drugs other than prohibited concomitant medications (Section 9.4) can be used. For immunosuppressive drugs (except medicine for external application), antibacterials/antibiotics/antivirals, antihyperlipidemics, antihypertensives (calcium antagonists, α-blockers, etc.), angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), and prohibited concomitant medications, out of the drugs and therapies used during the observation period, names, durations, and purposes of use will be reported in the Treatment Course Report (Appendix 4).

9.2 Prednisolone administration for the last pre-enrollment relapse

Prednisolone treatment for the last pre-enrollment relapse will be completed with dose tapering from regimen (1) to (4) in accordance with the ISKDC relapse treatment as follows: The pre-enrollment prednisolone treatment period will be included in the regimen (1) treatment period.

The regimen (1) treatment period will be chosen for each subject as described below.

1) For "28 days" if the subject is on prednisolone treatment at the last relapse before enrollment
2) "Until negative protein on urine dipstick test in the first morning urine is confirmed for 3 consecutive days" if the subject is not on prednisolone treatment at the last relapse before enrollment

Prednisolone doses will be calculated from body surface area* (calculate in 5-mg units; for doses of ≥0 and <2.5, substitute 0 in place; for doses of ≥2.5 and <7.5, substitute 5 in place; for doses of ≥7.5, round up to 10).

*Body surface areas will be calculated using the Du Bois equation from body height and body-height-based ideal body weight (Attachment 5).

Body surface area BSA (m^2) = body weight (kg) $^{0.425}$ × body height (cm) $^{0.725}$ × 0.007184 (Du Bois)

The maximum dose for the regimen (1) can be either 80 mg/day or 60 mg/day.

Prednisolone doses for the regimen (2) and beyond will be determined from the body height at the time of enrollment according to the table of prednisolone doses by body height (Attachment 8). If any adverse reaction due to prednisolone develops, and the investigator considers it to be necessary, the prednisolone dose can be reduced.

<In cases where 80 mg/day is the maximum dose for 60 mg/m^2/day>

(1) 60 mg/m^2/day (up to 80 mg/day), 3 divided doses, consecutive-day administration
(2) 60 mg/m^2/dose (up to 80 mg/day), every other morning for 14 days
(3) 30 mg/m^2/dose (up to 40 mg/day), every other morning for 14 days
(4) 15 mg/m^2/dose (up to 20 mg/day), every other morning, discontinued after the end of 14-day treatment

<In cases where 60 mg/day is the maximum dose for 60 mg/m^2/day>

(1) 60 mg/m^2/day (up to 60 mg/day), 3 divided doses, consecutive-day administration
(2) 60 mg/m^2/dose (up to 60 mg/day), every other morning for 14 days
(3) 30 mg/m^2/dose (up to 30 mg/day), every other morning for 14 days
(4) 15 mg/m^2/dose (up to 15 mg/day), every other morning, discontinued after the end of 14-day treatment

9.3 Immunosuppressive drugs that have been administered from before enrollment

Any immunosuppressive drug that has been administered from before enrollment to treat nephrotic syndrome will be administered with the regimen (target blood concentration) as of the time of enrollment and will be discontinued as described below (see Figure 8-1). Dose elevation or initiation of immunosuppressive drugs will be prohibited. However, dose changes related to immunosuppressive drug adverse reactions or those based on blood concentration monitoring will be acceptable.

(1) MMF
MMF should be discontinued between the enrollment date and the rituximab treatment starting date.

(2) Mizoribine, azathiopurine
These drugs should be discontinued between the enrollment date and the rituximab treatment starting date

(3) Cyclophosphamide, chlorambucil
These drugs should be discontinued between the enrollment date and the rituximab treatment starting date because these drugs interfere with lymphocyte proliferation.

(4) Cyclosporine, tacrolimus
These drugs should be co-administered with the same dose at the timiming of enrollment until Day 85 (±7 days) (dose changes based on blood concentration monitoring are acceptable). After Day 86, the dose should be tapered roughly every 28 days and discontinued on Day 169 (±14 days).

9.4 Prohibited concomitant medications during the treatment period

During the treatment period, concomitant use of the following drugs will be prohibited. If any prohibited concomitant medication is used during the observation period, all will be recorded in the Treatment Course Report (Appendix 4). If any prohibited concomitant medication is used to treat nephrotic syndrome, study treatment will be discontinued.

(1) Commercially available rituximab

(2) Non-prednisolone immunosuppressive drugs or alkylating agents with immunosuppressive effect except in the following cases:

I. Immunosuppressive drugs that have been administered from before enrollment

II. Cases with study treatment is discontinued

(3) Live vaccines (freeze-dried attenuated live measles vaccines, freeze-dried attenuated live rubella vaccines, oral live polio vaccines, freeze-dried BCG, etc.)

However, subjects in whom the peripheral blood B cell count has been restored to the level as of the time of screening after the start of study treatment will be excluded.

9.5 Other precautions for concomitant medications

9.5.1 Preventive administration during the peripheral blood B cell depletion period

In this study, to prevent pneumocystis infection, trimethoprim-sulfamethoxazole will be administered from the first rituximab dosing date (Day 1) to the recovery of peripheral blood B cell count (not less than 5 μL of CD19-positive cells noted). For reference, how to administer trimethoprim-sulfamethoxazole is described below.

(1) Baktar®, BACTRAMIN®

1) Patients whose height-based standard body weight is not less than 50 kg or patients aged 16 years or older

One to two tablets (1 to 2 g for granules) will be administered orally once per day, 3 days per week.

2) Patients not meeting criterion 1)

A dose of 0.05 to 0.10 g/kg/day (up to 2 g/day) will be administered orally 3 days per week.

However, if any adverse reaction due to trimethoprim-sulfamethoxazole is considered to have developed, dose changes will be acceptable at the discretion of the investigator.

9.5.2 Vaccination

In this study, patients receiving any live vaccine within 4 weeks before enrollment will be excluded, and live vaccination during the treatment period will be prohibited until a recovery of peripheral blood B cell count to the level at the time of screening because of the risk of secondary infections. When a live vaccine is administered after recovery of the peripheral blood B cell count, or when any inactivated vaccine is administered during the treatment period, they should be used with considering the possibility that there are unknown responses to vaccination and the status of use of immunosuppressive drugs, including investigational drugs, and prednisolone.

10 Observations, evaluations, surveys

10.1 List of scheduled events

The investigator will carry out observations according to the schedule shown below and record the findings in the Treatment Course Report (Appendix 4).

If rituximab is discontinued, the next observations, evaluations, and surveys will be performed at Visit 5. If rituximab treatment is completed, and blood testing and peripheral blood B cell counting are performed at Visit 4, the blood testing and peripheral blood B cell counting at Visit 5 can be skipped at the discretion of the attending physician.

After Visit 6, the rituximab dosing starting date (Day 1, Visit 1) will be the starting point. Between Visit 6 (Day 57) and Visit 10 (Day 169), change "within ±14 days" are acceptable; however, the interval between one visit and the next visit should be at least 14 days. After Visit 11 (Day 225), changes "within ±28 days" are acceptable; however, the interval between one visit and the next visit should be at least 28 days. When the survey date at the time of relapse diagnosis falls within the allowance for the next visit, observations, evaluations, and surveys at the next visit may be skipped. Even after discontinuation of investigational drug treatment, observations, examinations, and surveys will be continued as scheduled (Section 6.5).

	SC period	Treatment period (rituximab treatment period)				Treatment period (Investigational drug treatment period)												At the time of relapse	At the time of investigational drug treatment discontinuation	Follow-up period
Day (Week) after the 1st dose	-35	1 (1)	8 (2)	15 (3)	22 (4)	29 (5)	57 (9)	85 (13)	113 (17)	141 (21)	169 (25)	225 (33)	281 (41)	337 (49)	393 (57)	449 (65)	505 (73)			At Months 36 and 48, at the end of the entire study
Months after treatment initiation		0				1	2	3	4	5	6	8	10	12	14	16	18			
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
Obtainment of informed consent	○																			
Background survey	○																			
Study treatment		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	
Physical examination	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	
Concomitant medications	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	
Body height, body weight	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	Δ	○
Blood pressure	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	Δ	○
Pulse rate, body temperature	○	○	○	○	○	○					○			○			○		Δ	
Pregnancy test	○																			
Virus test	○																			
ECG	○																○		Δ	
Chest radiography	○																○		Δ	
Relapse evaluation		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Adverse events		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Subsequent therapy																				○

	SC period	Treatment period (rituximab treatment period)				Treatment period (Investigational drug treatment period)														Follow-up period
Urinalysis	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Blood test	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	Δ	
Immunoglobulins		○					○		○		○			○			○		Δ	
eGFR	○	○			○	○					○			○			○	○	○	
Peripheral blood B-cell count†	○	○	○		○	○	○		○		○	○	○	○	○	○	○	○	○	□
Amount of blood collected (mL)	8.5	9.5	7.5	4.5	7.5	7.5	9.5	4.5	9.5	4.5	9.5	7.5	7.5	9.5	7.5	7.5	9.5	7.5	9.5	

Δ: Perform if possible. □: If the peripheral blood B cell count has not normalized during the treatment period, this parameter should be measured until the normalization of B cell count.

†: During the screening period, CD20- or CD19-positive cells will be counted. During the treatment period and beyond, CD19-positive cells will be counted.

10.2 Surveys at the time of enrollment (during the screening period)

The investigator will examine the following items during the screening period.

Item	Content	Timing of survey	Survey forms	
			Case registration form	Treatment course report
Subject background	Sex, date of birth	Screening period	○	
Obtainment of informed consent	Date of informed consent		○	
History of nephrotic syndrome	Date of first diagnosis of nephrotic syndrome, dates of last three relapses before enrollment		○	
	Histological findings and date of last renal biopsy			○
History of treatment for nephrotic syndrome	History of treatment with immunosuppressive drugs Existence of prednisolone administration at the time of the last relapse, existence of immunosuppressive drug use at the time of the last relapse (If Yes, show the drug name, regimen, duration of treatment.)		○	
History of illness complications	Checking history of vaccinations and history of infections		○	
Physical findings	Body height, body weight		○	
Vital signs	Pulse rate, body temperature, blood pressure (systolic and diastolic)	Within 2 weeks before enrollment	○	
Hematology	WBC count, neutrophil count, platelet count		○	
	RBC count, hemoglobin, lymphocyte count			○

Item	Content	Timing of survey	Survey forms	
			Case registration form	Treatment course report
Blood biochemistry	AST, ALT, CRP, serum creatinine (estimated glomerular filtration rate)		○	
	BUN, uric acid, total protein, serum albumin, Na, K, Ca, P, Cl	Screening period		○
Peripheral blood B-cell count	CD20- or CD19-positive cell count	Within 2 weeks before enrollment	○	
Viral tests*	HIV antibody, HBs antigen/antibody, HBc antibody, HCV antibody		○	
Pregnancy test	Serum HCG (essential only for females following first menstruation)		○	
Urinalysis	Qualitative test for first morning urine protein, qualitative test for first morning urine occult blood, quantitative test for first morning urine protein, quantitative test for first morning urine creatinine	Remission confirmation date	○	
ECG		Screening period		○
Chest X-ray				○

*For patients who are positive for HBs antibody only and have past history of HBV vaccination, HBV-DNA should be quantified.

10.2.1 Determination of steroid sensitivity

The investigator et al. will determine steroid sensitivity within 4 weeks after the start of prednisolone treatment for the last relapse. For the results of the qualitative test for first morning urine protein at the last visit, the patient or his/her guardian (proxy consenter) will be interviewed at the time of medical examination, urinalysis will be performed and steroid sensitivity (remission) will be evaluated at the study site.

In the following cases, however, the subject will be considered negative for first morning urine protein.

(1) (±) result of urine dipstick in first morning urine protein performed at the medical institution
(2) <30 mg/dL value of quantitative test in first morning urine protein performed at the medical institution
(3) Cases with the first morning urine protein/creatinine ratio examined at the medical institution is less than 0.2 for the patient have (±) result of urine dipstick in first morning urine protein performed at home

10.3 Surveys during the treatment period: Rituximab treatment period

10.3.1 Just before rituximab administration

The investigator will examine the subject just before administration on each rituximab dosing day and make evaluations and examinations.

Item	Content
Concomitant medications and therapies	Drug name, doses, route of administration, duration of treatment, purpose of use
General symptoms	Subjective and objective findings (adverse events)
Body height, body weight	
Vital signs	Blood pressure (systolic and diastolic), pulse rate, body temperature
Relapse evaluation	
Hematology	RBC count, hemoglobin, hematocrit, WBC count, differential WBC counts (neutrophils, eosinophils, basophils, monocytes, lymphocytes), platelet count
Blood biochemistry	BUN, serum creatinine, uric acid, total protein, serum albumin, AST, ALT, Na, K, Ca, P, Cl, CRP
Immunoglobulins*	IgG, IgM, IgA
Urinalysis	Qualitative test for first morning urine protein, qualitative test for first morning urine occult blood, quantitative test for first morning urine protein, quantitative test for first morning urine creatinine
Peripheral blood B-cell count†	CD19-positive cell count

*: Performed just before the first dose of rituximab.

†: Performed just before the first, second, and fourth doses of rituximab.

10.3.2 During intravenous drip infusion of rituximab

During treatment with intravenous drip infusion of rituximab, the investigator will check the items shown below and record the findings in the treatment course report (Appendix 4). The subject will be kept at rest for at least 30 minutes after the end of each rituximab infusion.

The subject should be frequently monitored for infusion reactions. If any infusion reaction develops, appropriate measures, including intravenous drip infusion rate reductions and supportive care, should be taken (Section 8.2.4).

(1) Rituximab doses

(2) Status of rituximab treatment (existence of rate reductions or suspensions during intravenous drip infusion)

(3) Existence of onset of adverse events during intravenous drip infusion

If infusion reaction and/or any adverse event develops, the date and time, type, seriousness, causality with rituximab, and existence of supportive care (type, dose, and route of administration if performed) should be recorded in the Treatment Course Report (Appendix 4). In addition, vital signs (blood

pressure, pulse rate, body temperature) will be recorded as it needed.

(4) Reason and time of any discontinuation of rituximab treatment

10.4 Surveys during the treatment period: During the investigational drug treatment period and after discontinuation of investigational drug treatment

Unless meeting the "6.7 Study Discontinuation Criteria", the study on the subject will be continued even after discontinuation of investigational drug treatment. The investigator will survey the items shown below according to the specified schedule (Section 10.1), and record the results in the Treatment Course Report (Appendix 4). This surveys are required regardless of completion or discontinuation of investigational drug treatment.

Item	Content
Investigational drug	Doses, method of administration, treatment period, dose change reasons, adherence (drug intake status)
Concomitant medications and therapies	Drug name, doses, route of administration, duration of treatment, purpose of use
General symptoms	Subjective and objective findings
Physical findings	Body height, body weight, blood pressure (systolic and diastolic), pulse rate, body temperature
Relapse evaluation	Frequency, recurrence onset date, existence of steroid sensitivity or resistance, frequent relapse, or steroid dependence, status of implementation of treatment at the time of relapse
Evaluation of adverse events	
Hematology	RBC count, hemoglobin, hematocrit, WBC count, differential WBC counts (neutrophils, eosinophils, basophils, monocytes, lymphocytes), platelet count
Blood biochemistry	BUN, serum creatinine, uric acid, total protein, serum albumin, AST, ALT, Na, K, Ca, P, Cl, CRP
Immunoglobulins	IgG, IgM, IgA
Peripheral blood B-cell count	CD19-positive cell count
Urinalysis	Qualitative test for first morning urine protein, qualitative test for first morning urine occult blood, quantitative test for first morning urine protein, quantitative test for first morning urine creatinine
ECG, chest X-ray	

10.5 Surveys during the treatment period: At the time of relapse diagnosis

When diagnosing a relapse during study treatment, the attending physician will perform observations and surveys for the items shown below and record the findings in the Treatment Course Report (Appendix 4).

Item	Content
Physical findings	Body height, body weight, blood pressure
Relapse evaluation	Recurrence onset date, existence of frequent relapse or steroid-dependence, status of implementation of treatment at the time of relapse
Evaluation of adverse	

Item	Content
events	
Hematology	RBC count, hemoglobin, hematocrit, WBC count, differential WBC counts (neutrophils, eosinophils, basophils, monocytes, lymphocytes), platelet count
Blood biochemistry	BUN, serum creatinine, uric acid, total protein, serum albumin, AST, ALT, Na, K, Ca, P, Cl, CRP
Peripheral blood B-cell count	CD19-positive cell count
Urinalysis	Test results used for relapse diagnosis (quantitative test for first morning urine protein, quantitative test for first morning urine protein, quantitative test for first morning urine creatinine)

10.6 Survey at the time of discontinuation of the clinical trial

If the study is discontinued, the investigator will record the date of study discontinuation (date on which the decision to discontinue the study was made) and the reason for discontinuation in the Treatment Course Report (Appendix 4). The investigator should make adequate efforts to confirm the reason, while fully respecting the rights of the subject.

If the study is discontinued during the treatment period, tests to ensure the safety of the subject (peripheral blood B cell count) and adverse event evaluations will be performed at that time. In addition, observations, surveys, and examinations will be performed for the survey items at the end of the treatment period (Section 10.1) if possible.

If a serious adverse event is manifested at the time of discontinuation of the study, the investigator will take appropriate measures for the serious adverse event and follow its outcome by telephone or letter as much as possible by the end date of the follow-up period of the entire study (the last scheduled observation date for the last enrolled subject).

10.7 Surveys during the follow-up period

The follow-up period will be defined as the time from the end of the treatment period to the last scheduled treatment date of the last enrolled subject. The investigator will survey the items shown below using daily clinical practice data 36 and 48 months after study treatment initiation and at the end of the follow-up period, and record in the findings in the Follow-up Survey Report (Appendix 8). For the adverse events that develop during the treatment period, their outcomes will be followed to the maximum possible extent by telephone and mail until the follow-up period end date for the entire study.

Item	Content
Physical findings	Body height, body weight, blood pressure
Existence of progression to chronic renal insufficiency	If Yes, disease stage
Relapse evaluation	Relapse onset date, existence of transition to frequent relapse or steroid-dependence or steroid resistance
Subsequent therapy	Status of administration of prednisolone and immunosuppressive drugs (drug names, durations of treatment)
Urinalysis	Qualitative test for first morning urine protein
Status of persistence of adverse events	Status of persistence of adverse events* developing during the observation period

*Adverse events will exclude those definitely unrelated to the primary disease or study treatment (rituximab, investigational drug) (e.g., accidents).

If the follow-up survey cannot be continued until the end of the follow-up period, the follow-up survey will be discontinued, and the last follow-up survey date and follow-up survey discontinuation reason will be recorded in the Follow-up Survey Report (Appendix 8). If follow-up for a patient at the study site becomes impossible because of his/her movement or for other reasons, the patient can be referred to another study site for continued follow-up if possible, and this should be reported to the data center.

11 Endpoints

11.1 Primary endpoint

11.1.1 Time to treatment failure

Time from the enrollment date to the earliest of the dates of onset of the following events I) to III):

I) Frequent relapse, II) steroid dependence, III) steroid resistance

For subjects who have completed the treatment period without a judgment of treatment failure, evaluation will be censored on the last day of the confirmed outcome being not a treatment failure. For subjects lost to follow up without being considered a treatment failure during the study period and deceased cases, evaluation will be censored on the last day of the confirmed outcome being not a treatment failure prior to the loss to follow up. Use of any of the prohibited concomitant medications (1) and (2) during the study period (Section 9.4) will be considered an event as of the starting date.

11.2 Secondary endpoints

11.2.1 Relapse-free period

Remission period from the enrollment date to the date of first relapse after study treatment initiation. For relapse-free subjects, evaluation will be censored on the last day of confirmed absence of relapse. For subjects lost to follow up without being diagnosed with relapse and deceased cases, evaluation will be censored on the last day of confirmed absence of relapse prior to the loss to follow up. Use of any of the prohibited concomitant medications (1) and (2) during the study period (Section 9.4) will be considered an event as of the starting date.

11.2.2 Relapse rate (relapses/observed person-years)

Number of relapses per observed person-year. The relapse rate {“number of relapses ÷ observed persons-year (years)”} will be calculated for each group using the person-year method. The time window will be the treatment period. For subjects lost to follow up and deceased cases in the time window, information obtained until the last observation day will be used. For subjects considered to have a treatment failure, information obtained until the judgment date will be used. Any relapse of steroid resistance in the time window will be counted as one relapse, but evaluation will be censored on the day of transition to steroid resistance.

11.2.3 Time to frequent relapse

Period from the enrollment date to the date of onset of frequent relapses. For subjects without a transition to frequent relapses, evaluation will be censored on the last day of confirmed absence of frequent relapses. For subjects lost to follow up without being diagnosed with frequent relapses and deceased cases, evaluation will be censored on the last day of confirmed absence of frequent relapses prior to the loss to follow up. For subjects who become steroid-dependent or steroid-resistant and those using any of the prohibited concomitant medications (1) and (2) during the study period, the fact will be handled as an event.

11.2.4 Time to steroid dependence

Period from the enrollment date to the date of onset of steroid dependence. For subjects without a transition to steroid dependence, evaluation will be censored on the last day of confirmed absence of transition to steroid dependence. For subjects lost to follow up and deceased cases, evaluation will be censored on the last day of confirmed absence of transition to steroid dependence prior to the loss to follow up. For subjects becoming steroid-resistant and those using any of the prohibited concomitant medications (1) and (2) during the study period, the fact will be handled as an event.

11.2.5 Time to transition to steroid resistance

Defined as the period from the enrollment date to the date of transition to steroid resistance. For subjects without a transition to steroid resistance, evaluation will be censored on the last observation day. For subjects lost to follow up and without a transition to steroid resistance during the observation period and deceased cases, evaluation will be censored on the last observation day prior to the loss to follow up. For subjects considered to have a treatment failure, evaluation will be censored on the judgment day. For subjects using any of the prohibited concomitant medications (1) and (2) during the study period, evaluation will be censored on the starting day.

11.2.6 Total steroid dose (mg/m^2/patient-day)

Total steroid dose administered between the enrollment date and the treatment period end date.

11.2.7 Duration of peripheral blood B cell depletion

Time from the day of confirmed depletion of peripheral blood B cells to confirmation of normalization of peripheral blood B cell count (reference value ≥5 cells/μL). For subjects lost to follow up and deceased cases, evaluation will be censored on the last day of confirmed depletion of peripheral blood B cells prior to the loss to follow up or death. For subjects who have not experienced confirmed peripheral blood B cell depletion throughout the treatment period, Day 0 will be handled as the date of normalization.

11.3 Safety endpoints

11.3.1 Adverse events during the observation period

Proportion of patients with adverse events out of all enrolled patients but excluding patients not receiving study treatment at all (all treated cases). The severity (grade) of each observed adverse event will be determined using the worst grade during the treatment period.

12 Evaluation of adverse events

If any diseases occur after approval by the Kobe University Institutional Review Board, the investigator follow the “Operating Procedures for Actions to Be Taken in the Event of Disease etc.”.

12.1 Definition for adverse events

In this study, an adverse event is defined as any unwanted symptom or sign (including abnormal laboratory values) developing during the treatment period, regardless of causality with study treatment. However, symptoms and signs (including abnormal laboratory values) that have been present from before the start of study treatment will not be deemed to be adverse events; if they worsen (increased grade) after the start of study treatment, they will be handled as adverse events. Of the adverse events, those for which causality with study treatment cannot be ruled out will be handled as adverse drug reactions. Adverse events described in the package insert will be handled as foreseeable adverse events; and others, as unforeseeable adverse events.

12.2 Ensuring safety

In the event of any adverse event, the investigator will immediately perform seemingly necessary examinations and other measures to ensure subject safety. A system for first-aid measures must be available in preparation for other accidental cases.

12.3 Evaluation of adverse events

In the event of any adverse event during the treatment period, the investigator will make an evaluation as described below and report the fact as specified (Section 12.4).

12.3.1 Target adverse events for evaluation

In this study, all adverse events that have occurred during the treatment period should be evaluated. Primary disease aggravations will be excluded from the evaluation of target adverse events.

12.3.2 Diagnosis and Severity

Adverse event diagnosis and severity will be evaluated in accordance with the Common Terminology Criteria for Adverse Events version 4.0 Japanese translation by JCOG version (CTCAE v4.0-JCOG) (CTCAE v4. 03 per MedDRA v12. 0 [MedDRA/J v16. 0]-April 9, 2013). CTCAE v4.0-JCOG can be seen in the website of the Japan Clinical Oncology Group (http: //www.jcog.jp/).

(1) Severity of major adverse events

Cited from CTCAE v4.0-JCOG, major adverse events are shown by severity below.

Grade	1 Mild	2 Moderate	3 Severe	4 Life-threatening or causing disability	5 Death
Hypertension	Pre-hypertensive state (systolic blood pressure 120-139 mmHg or diastolic blood pressure 80-89 mmHg)	For stage 1 hypertension (systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-99 mmHg), medical treatment is required. For relapsing or persistent (≥24 hours) hypertension, symptomatic elevation to >20 mmHg (diastolic blood pressure) or elevation to >140/90 mmHg in previously normal cases, drug monotherapy is required. Children: For relapsing or persistent (≥24 hours) >ULN** blood pressure elevation, drug monotherapy is required.	For stage 2 hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg), medical treatment is required; drug treatment with 2 or more drugs or more-potent-than-before treatment is required. Children: The same as with adults	Life-threatening (e.g., malignant hypertension, transient or permanent neurological disorders, hypertension crisis), emergency treatment is required. Children: The same as with adults	Death
Hypotension	Blood pressure falls not requiring treatment	Treatments such as short-time (<24 hours) infusions are required; physiological function is not affected.	Continued (≥24 hours) treatment is required but a recovery is achieved without persistent physiological disorder.	Shock (e.g., acidemia, organ dysfunctions)	Death
Rigors/chills	Mild	Moderate Narcotic drugs are required.	Severe or persistent, narcotic drugs are ineffective.	-	-
Pruritus/itching	Mild or localized itching	Severe or extensive itching	Severe or extensive itching interfering with daily activity	-	-
Rash (urticaria, welt, weal)	No treatment is required	Treatment for <24 hours is required	Treatment for ≥24 hours is required	-	-
Bronchospasm, wheezing	Asymptomatic	Symptomatic but no functional disorder	Symptomatic and functional disorder	Life-threatening	Death
Cough	Symptomatic and requiring non-narcotic drugs only	Symptomatic and requiring narcotic drugs	Symptomatic and sleep and daily activity are markedly hampered	-	-
Laryngeal oedema	Asymptomatic, test findings only	Symptomatic but no dyspnea	Wheezing, dyspnea; Normal daily life is hampered	Life-threatening; Tracheotomy/intubation/laryngecto	Death

Grade	1 Mild	2 Moderate	3 Severe	4 Life-threatening or causing disability	5 Death
				my is required	
Anaemia	Hemoglobin <LLN*-10.0 g/dL; <LLN*-6.2 mmol/L; <LLN*-100 gl/L	Hemoglobin <10.0-8.0 g/dL; <6.2-4.9 mmol/L; <100-80 gl/L	Hemoglobin <8.0 g/dL; <4.9 mmol/L; <80 gl/L; blood transfusion is required.	Life-threatening; emergency treatment is required.	Death
Febrile neutropenia			ANC<1,000 /mm^3 and a fever exceeding 38.3ºC (101°F) or a fever of ≥38ºC (100.4°F) persisting for a period exceeding 1 hour.	Life-threatening; emergency treatment is required.	Death
WBC count decreased	<LLN*-3,000 /mm^3; <LLN*-3.0×10e9 /L	<3,000-2,000 /mm^3; <3.0-2.0 ×10e9 /L	<2,000-1,000 /mm^3; <2.0-1.0 ×10e9 /L	<1,000 /mm^3; <1.0 ×10e9 /L	
Neutrophil count decreased	<LLN*-1,500 /mm^3; <LLN*-1.5×10e9 /L	<1,500-1,000 /mm^3; <1.5-1.0 ×10e9 /L	<1,000-500 /mm^3; <1.0-0.5×10e9 /L	<500 /mm^3; <0.5×10e9 /L	-
Platelet count decreased	<LLN*-75,000 /mm^3; <LLN*-75.0×10e9 /L	< 75,000-50,000/mm^3; <75.0-50.0×10e9 /L	< 50,000-25,000/mm^3; <50.0-25.0×10e9 /L	<25,000 /mm^3; <25.0×10e9 /L	-
Alanine aminotransferase (SGPT) increased*	>ULN **– 3.0×ULN**	>3.0 - 5.0×ULN**	>5.0–20.0×ULN**	>20.0×ULN**	-
Aspartate aminotransferase (SGOT) increased*	>ULN** – 3.0×ULN**	>3.0 - 5.0×ULN**	>5.0–20.0×ULN**	>20.0×ULN**	-
Serum amylase increased	>ULN**–1.5×ULN**	>1.5-2.0×ULN**	>2.0–5.0×ULN**	>5.0×ULN**	-
Diarrhea	Defecation frequency increased by <4 times/day compared with baseline; excretion volume from artificial anus increased mildly compared with baseline.	Defecation frequency increased by 4-6 times/day compared with baseline; excretion volume from artificial anus increased moderately compared with baseline.	Defecation frequency increased by ≥7 times/day compared with baseline; fecal incontinence; hospitalization required excretion volume from artificial anus increased severely compared with baseline; daily self-care activity limited	Life-threatening; emergency treatment is required.	Death
Nausea	Decreased appetite that does not affect dietary lifestyle	Decreased oral food intake without marked weight loss, dehydration, or malnutrition	Insufficient oral intake of energy and water; tube feeding/TPN/hospitalization is required.	-	-
Vomiting	1-2 episodes of vomiting in 24 hours (each episode should be apart from the previous one at an interval of ≥5 minutes)	3-5 episodes of vomiting in 24 hours (each episode should be apart from the previous one at an interval of ≥5 minutes)	Not less than 6 episodes of vomiting in 24 hours (each episode should be apart from the previous one at an interval of ≥5 minutes); TPN or hospitalization is required.	Life-threatening; emergency treatment is required.	Death

*LLN: (facility's) lower limit of reference values, **ULN: (facility's) upper limit of reference values

(2) Severity of adverse events not included in the Common Terminology Criteria for Adverse Events

version 4.0 Japanese translation by JCOG version

Evaluated by the attending physician with reference to the following:

Grade 1: Mild	Not hampering normal daily activity; transient; no need for treatment or clinical discretion for the adverse event
Grade 2: Moderate	Normal daily activity is hampered; continued for a given length of time (several days); investigational drug dose reductions or suspension will be considered.
Grade 3: Severe	Normal daily activity is impossible; continued for a long time; chronic adverse event requiring clinical discretion; treatment for the adverse event is required; study treatment discontinuation will be considered.
Grade 4	Life-threatening or disability-causing adverse events, adverse events posing a risk of death
Grade 5	Fatal adverse events (death due to adverse events)

12.3.3 Seriousness

Of the adverse events observed during the observation period, an event that meets any one of the following criteria will be defined as a "serious adverse event."

(1) AEs resulting in death
(2) Life-threatening AEs
(3) AEs requiring hospitalization or prolongation of existing hospitalization for treatment
(4) AEs resulting in persistent or significant disability/incapacity
(5) Other medically critical conditions (refer to Grade 4 in CTCAE v4.0-JCOG)

12.3.4 Actions

Actions taken against the adverse event will be evaluated in the following 5 grades:

(1) No action
(2) Study treatment suspension (including reductions of rituximab infusion rate)
(3) Dosing discontinuation
(4) Drug treatment
(5) Others

12.3.5 Outcome

Adverse event outcomes will be evaluated in the following 6 grades:

(1) Recovered
(2) Relieved
(3) Unchanged
(4) Worsened
(5) Death
(6) Unknown

12.3.6 Association with the clinical trial

The association with the clinical trial (rituximab treatment and investigational drug (MMF, placebo) treatment) will be evaluated in the following 3 grades:

(1) Related
Time relevancy between adverse event and clinial trial exists, past medical history of the patient, other treatments and the environment are considered not to causes advers event and symptoms disappear or lessen after dose discontinuation or reduction.

(2) Relationship cannot be ruled out
Time relevancy between adverse event and clinial trial exists, but past medical history of the patient, other treatments and the environment are thought to likely to causes the advers event.

(3) Unrelated
Time relevancy between adverse event and clinial trial is absent, and past medical history of the patient, other treatments and the environment are thought to likely to causes the advers event.

12.4 Reporting Adverse Events

In the event of any adverse event to be evaluated during the treatment period (12.3.1), the investigator will record this in the Treatment Course Report (Appendix 4) and follow up the subject until recovered to the condition prior to onset of the adverse event or no further follow up is considered to be required.

12.4.1 Emergency Reports on Serious Adverse Events

In the event of a serious adverse event (12.3.3) during the treatment period, the investigator will make an emergency report and record the adverse event in the Treatment Course Report (Appendix 4).

(1) In the event of any serious adverse event to be reported urgently (12.3.3), the investigator will immediately notify the principal investigator. If unable to contact the principal investigator at the study site, the investigator should assume the principal investigator's responsibility.

(2) The principal investigator will immediately notify the study site administrator, also make the specified entries in the Emergency Report on Serious Adverse Events (Appendix 5) and immediately send it to the data center by facsimile (FAX No. 03-5946-8278).

(3) The data center will make an emergency report on the onset of the serious adverse event to the study director by facsimile or other means.

(4) The investigator at the study site will prepare a detailed report on the adverse event and send the report by facsimile to the data center within 10 days. However, if the adverse event is fatal or life-threatening, the fact will be transmitted by facsimile within 5 days.

(5) The data center will send the detailed report, as an urgent report, to the study director.

(6) The study director will report about the fact in writing with his/her opinions on the urgency, importance, and impact of the serious adverse event, to the study group and principal investigator at the study site. The study director will further report in writing to the independent data and safety monitoring committee and ask the committee to make a review as required.

(7) When asked to make a review by the study director, the independent data and safety monitoring committee will assess the necessity for study discontinuation, study protocol revisions, and contact with each study site, and provide written advice to the study director.

12.4.2 Reporting to the Certified Clinical Study Review Board

The "Operating Procedures for Actions to Be Taken in the Event of Disease etc." should be followed.

12.4.3 Reporting health hazard information concerning advanced medicine

The study site will endeavor to collect information on hazards that are directly relevant to people's lives and health safety related to the advanced medicine administered by the study site itself (hereinafter referred to as health hazard information), whether it is available in Japan or outside, and if obtaining health hazard information, will immediately report these facts to the Director of the Regional (Branch) Bureau of Health and Welfare and Minister of Health, Labour and Welfare in accordance with Form No. 3 "Health Hazard Information Concerning Advanced Medicine" specified in the Advanced Medicine Notification. However, reported information on serious adverse events etc. in relation to the conduct of advance medicine is excluded. The study director, after discussing with the protocol committee, may ask the independent data and safety monitoring committee to make a review as required.

13 DATA COLLECTION

13.1 Submitting reporting documents

In this study, reporting documents will be sent to the data center by mail as copies of the original for the Treatment Course Report (Appendix 4) and Follow-up Survey Report (Appendix 8), and by facsimile for other documents. The investigator will submit data for all enrolled patients to keep pace with the progress of the study. Details of the data to be submitted, means of submission, and timing of submission are shown below.

Appendices	Type	Means and timing of delivery	Means and timing of submission
2	Case registration form	Sent by e-mail to study sites in advance	Faxed at the time of registration
3	Post-enrollment exclusion report	Sent by e-mail to study sites in advance	Faxed promptly
4	Treatment course report	Leaflet sent by postal transfer for each patient	A copy sent by postal transfer every 6 months
5	Urgent report on serious adverse events	Sent by e-mail to study sites in advance	Fax transmission immediately after becoming aware of the onset of the serious adverse event
6	Request for disclosure of urgent allocation codes of investigational drugs	Sent by e-mail to study sites in advance	Fax transmission at the time of request for emergency disclosure of the allocation code
7	Urgent report on discontinuation of study treatment	Sent by e-mail to study sites in advance	Fax transmission immediately after the judgment to discontinue investigational drug treatment is made
8	Follow-up survey report	Leaflet sent by postal transfer for each patient	A copy will be sent 36 and 48 months after the start of study treatment, and at the time of the end of the entire study
9	Serious adverse event details report	Sent by e-mail to study sites in advance	Fax transmission within 10 days after becoming aware of the onset of the serious adverse event
10	Pregnancy case report form	Sent by e-mail to study sites in advance	1. Immediately after confirmation of pregnancy 2. Immediately after establishment of pregnancy outcome

14 Statistical analyses

Prior to the conduct of statistical analyses, a statistical analysis protocol including the items shown below will be prepared. After study completion, statistical analyses will be performed in accordance with the prepared statistical analysis protocol, and an analysis results report will be prepared.

If a change is made to the original statistical analysis plan, the change will be stated in the statistical analysis protocol and final report.

14.1 Description of special features of subjects

To characterize the subjects of this study, the patient selection processes from recruitment to enrollment will be described.

After the end of study treatment, finalized enrollment facilities, enrollment periods, and subject participation periods will be stated. The number of eligible patients, number of exclusions due to meeting the exclusion criteria, number of patients not providing informed consent and reasons, and other information will be tabulated where possible.

14.2 Definitions of Analysis Sets

The analysis sets used in the statistical analyses in this study will be defined as follows: As a rule, the analysis set will be the full analysis set (FAS) for the efficacy endpoints and the safety analysis set (SAS) for the safety endpoints. An analysis of the per protocol set (PPS) as the analysis set will be performed as required.

(1) Largest efficacy analysis set: Full analysis set (FAS)
A population consisting of all enrolled subjects for whom study treatment was started and efficacy endpoints were measured

(2) Analysis set meeting the study protocol: Per protocol set (PPS)
A population consisting of all patients in the FAS excluding subjects with violations of the study protocol

(3) Safety analysis set (SAS)
A population consisting of all enrolled subjects for whom study treatment was started

14.3 Rationale for setting the target sample size

Assume that time to treatment failure is an exponentially distributed probability variable, and that the effect of 4 doses of rituximab + MMF (study treatment) compared with 4 doses of rituximab + placebo treatment (control treatment) represents a proportional hazard.

Based on a previous study, assume the proportion of 1-year treatment failure for 4 doses of rituximab +

placebo is 40%. [20] If clinically more effective than 4 doses of rituximab + placebo by approximately 20%, 4 doses of rituximab + MMF can become a standard treatment for intractable frequently relapsing/steroid-dependent nephrotic syndrome in children.

If assuming a 1-year treatment failure rate of 20% for 4 doses of rituximab + MMF, and performing a log rank test with an enrollment period of 3 years, a follow-up period of 1.5 years, and a two-sided significance level of α=5%, 37 subjects in each group will be needed to ensure the test has 80% power. Taking into account possible withdrawals of consent after study participation and missing cases, target sample size will be 40 patients in each group, with 80 patients in the entire study.

If the prior assumption is correct, 74 patients will be sufficient to obtain the required test power; therefore, the actual number of patients enrolled may be smaller by 6 patients or less than the target sample size.

Study treatment group (MMF group) One-year treatment failure rate	Control treatment group (placebo group) One-year treatment failure rate	Hazard ratio	Power of test	Number of samples/group
20%	40%	0.44	0.7	29
20%	40%	0.44	0.8	37
20%	40%	0.44	0.9	50
15%	40%	0.32	0.7	17
15%	40%	0.32	0.8	22
15%	40%	0.32	0.9	29

14.4 Efficacy analysis

14.4.1 Primary endpoint

A log rank test for intergroup differences in time to event will be performed at a two-sided significance level of 5%. Intergroup hazard ratios will be estimated using a Cox proportional hazard model. An analysis will be performed using a Cox proportional hazard model including prognostic factors as required.

A cumulative event-free ratio curve will be generated for each randomization group using Kaplan-Meier estimators, and the median time to event will be calculated.

14.4.2 Secondary endpoints

Relapse-free interval, time to steroid resistance, and duration of peripheral blood B-cell depletion will be analyzed using the same methods as with the primary endpoint. Survival time analysis for first relapse will be performed with peripheral blood B-cell depletion (see Section 5.2.5 for the definition) as a time-dependent covariate. As an estimate of the effect, hazard ratios and 95% confidence intervals will be calculated using a

Cox proportional hazard model. The time to frequent relapse and the time to steroid dependence will be analyzed with the diagnosis of steroid resistance as a competitive risk.

For the number of relapses per observed person-year, the ratio of the total number of relapses within the group to the total observation time (person-years) will be calculated, and intergroup comparisons and calculations of 95% confidence interval will be performed by a rearrangement test.

The total steroid doses (mg/m^2/patient-day) will be calculated individually and compared between groups using a Wilcoxon test.

14.4.3 Sensitivity analysis

To evaluate the influence of the change in the exclusion criteria (Study Protocol as revised on December 16, 2015), the primary endpoint will be analyzed in each of the pre-change and post-change enrolled populations. In addition, a stratified analysis will be performed based on the presence or absence of a history of administration of rituximab before enrollment.

14.5 Safety analysis

14.5.1 Adverse events and adverse drug reactions

In this study, all adverse events that will have occurred during the treatment period will be analyzed. Patients who will have discontinued study treatment will also be followed for adverse events. An analysis of a partial set of interest and an analysis taking into account investigational drug discontinuations and losses to follow up will be performed as required.

The number and proportion (number of subjects with adverse events/SAS) of subjects with adverse events by adverse event and severity will be tabulated into a listing. The number and proportion (number of subjects with adverse events/SAS) of subjects with adverse events will also be tabulated by group. If the same adverse event develops more than one time in the same individual, the data will be tabulated using the higher severity grade.

Intergroup comparisons will be made using Fisher's exact test as required. Each event will be tabulated over the entire period. For terminology of adverse events, MedDRA terms will be used. Similar analyses will be performed for adverse drug reactions.

14.5.2 Laboratory test values

(1) Aggregation of measured laboratory values (hematology, blood biochemistry, and urinalysis)
Summary statistics by treatment group will be calculated for each survey time.

(2) Aggregation of abnormal laboratory values (hematology, blood biochemistry, and urinalysis)

14.5.3 Analysis of infections requiring treatment

The mean cumulative number of "infections requiring treatment" observed during the treatment period in the SAS will be calculated. The influence on infection incidences in the various treatment groups will be investigated using an AG model. Another analysis will be performed with peripheral B-cell depletion as a time-

dependent covariate.

14.6 Interim analysis

14.6.1 Interim analysis of safety data

Since there is little experience with rituximab treatment in patients with childhood-onset intractable nephrotic syndrome [4 doses at 375 mg/m^2/dose (up to 500 mg/dose) at 1-week intervals] and rituximab + MMF combination treatment, an interim analysis on safety will be performed to confirm safety when 20 subjects have received the study treatment for 3 months.

14.7 Data handling

How to handle missing data, unadopted data, and abnormal data will be specified in the Statistical Analysis Protocol.

15 Ethical considerations

All investigators involved in this study will conduct this study in compliance with the Declaration of Helsinki, the Ethical Guidelines for Medical Research in Humans, and the Clinical Trials Act, and in accordance with ICH-GCP.

15.1 Certified clinical study review board

The Kobe University Clinical Study Review Board should approve the implementation, continuation, etc. of this study at meetings held before and during this study from the viewpoint of ethical, scientific, and medical validity. The study director will submit documents that are subject to review, such as the study protocol, case report forms, and explanatory leaflet and informed consent forms to the Kobe University Clinical Study Review Board.

15.2 Explanation and informed consent

When obtaining informed consent, the investigator will provide the explanatory document for the study approved by the Kobe University Clinical Study Review Board to the subject, fully explain the contents, and obtain his/her written consent to participate in the study at his/her own free will. At the time of obtaining informed consent, the investigator will give the subject adequate time to fully examine the contents of the explanatory document and other matters related to the study, as well as an opportunity to ask questions, and will fully answer the questions.

(1) If the patient is 20 years of age or older, an explanation will be provided, and written informed consent will be obtained from himself/herself. If the patient is younger than 20 years, written informed consent will be obtained from his/her legal representative (legal guardian). If the patient is younger than 20 years but not younger than 16 years, written informed consent will also be obtained from the patient.
(2) The explanatory document (for adults) and informed consent form will be prepared assuming the understanding of a person at approximately 16 years of age. The explanatory document (for children) and assent form will be prepared in 2 types: one assuming the understanding of a child at approximately 7 to 12 years and another assuming the understanding of a child at approximately 12 to 15 years.
(3) Assent will be deemed to have been obtained from a patient aged 7 to <16 years after he/she has fully understood the content of the assent document and signed and dated it. However, if the patient is younger than 12 years but not younger than 7 years, an assent may be obtained verbally; the consent form signed by the proxy consenter (legal guardian) will state in the consent form that the assent was obtained from the patient.
(4) The informed consent form will be signed or signed and sealed, and dated, by the investigator who provided the explanation and the patient who gave the informed consent (aged 20 years or older) or his/her legal representative (legal guardian). The relationship between the subject and his/her legal representative will also be recorded.

(5) The investigator will provide a copy of the consent form to the patient (aged 20 years or older) or his/her legal representative (legal guardian), and the principal investigator will retain the original.

(6) When informed consent is obtained, the date of obtaining informed consent etc. will be recorded in the "Case Registration Form" (Appendix 2). In addition, when the investigator is informed of the subject's wish to withdraw from participation in the study by the legal representative (legal guardian) or the patient (aged 20 years or older) during the screening period or study period, the time and reason will be recorded in the "Emergency report on discontinuation of study treatment" (Appendix 7).

(7) The patient (aged 20 years or older) and the legal representative (legal guardian) may withdraw consent at any time after the consent, without suffering any detriment due to the withdrawal.

15.3 Confirmation of willingness to continue participation in the study

If obtaining any safety information that can influence the patient's decision whether to continue to participate in this study, the investigator should provide the patients already participating in the study with an explanation using the revised informed consent form, ask them whether to continue to participate in the study, and obtain written consent.

15.4 Expected benefits and detriments for study participants

With regard to rituximab treatment as performed in this study, an application for approval of a partial change in the approved drug marketing items for additional indication of for the target disease of this study was approved by Japan's Minister of Health, Labour and Welfare on August 29, 2014, in response to the results of a physician-initiated trial conducted in Japan to expand the indications, and is expected to be effective in remission maintenance (relapse-suppressing effect).

Although the investigational drug used in this study (MMF) represents an off-label prescription for the target disease of this study, it has been suggested to be effective in suppressing relapses in the patient subjects of a previous study and is expected to surpass other immunosuppressive drugs in safety. In addition, administration of the investigational drug (MMF) following rituximab treatment is expected to have a higher relapse-suppressing effect than rituximab monotherapy. In this study, the investigational drug (MMF) will be used within the dose range used in the previous study and pediatric kidney transplantation, and hence assumed not to pose a major detriment in terms of safety, judging from clinical experiences. However, no therapeutic approach has been established well in which the investigational drug (MMF) is administered after rituximab treatment, and placebo will be used as the comparator in this study; therefore, the study treatment may fail to be sufficiently effective or cause adverse events. To minimize therapeutic detriment in such cases, treatment failures were set in this study, and double blinding was urgently disclosed upon the occurrence of a treatment failure to allow the investigator to provide the optimal treatment to the patient. In addition, to prevent infections, sulfamethoxazole/trim-ethoprim will be administered for the sake of prophylaxis, and the study system will be upgraded to allow quick acquisition of safety information, including serious adverse events, and immediate actions, so as to ensure safety for the subjects.

In this study, investigational drugs will be provided at no cost; however, no reward or financial aid for study

participation will be scheduled. In addition, the examinations in this study will be basically the same as those taking place in daily practice except that the frequency of testing for peripheral blood B cell counts is slightly higher. In order to lessen the burden on the participant, the minimum volume and frequency of blood sampling for counting peripheral blood B cells will be set, and the blood sampling will be performed at the same time as the blood testing at periodic visits. Samples from this study (samples for blood testing and urinalysis) will not be stored for other studies.

15.5 Protection of personal information of subjects

As a general rule, the data for subjects obtained in this study should not be used for any purposes other than that of this study (however, analyzed data may be reused in a way that is not related to any information identifying the individual only if approved by the study director). Information that can identify subjects will not be used when publishing study results. When handling raw data and consent forms related to the conduct of the study, careful consideration should be given to protecting the privacy of subjects. In addition, names, visit ID numbers, and other information that can identify individual participants should not be shown in the Case Report Form and other documents submitted outside the study site. In the registered data, subjects will be identified only by their enrollment numbers.

Researchers participating in the study should not leak information on the privacy of registered patients obtained by access to source documents to third parties. The investigator at each study site will securely store the source documents even after completion of this study and data analysis.

15.6 Providing samples and information for other organizations

This clinical study is a multicenter study; the samples and information collected as described in “10. Observations, evaluations, and surveys” will be utilized in common within the scope specified in Appendix 1. Case report forms and other information from the individual study sites, after deleting some personal data, will be sent to the data center. The study subject identification code list will be stored at each study site and not provided outside.

15.7 Compliance with the study protocol

Researchers participating in this study will comply with this study protocol unless affecting the safety and human rights of patients.

15.8 Reporting the status of progress, adverse events, etc.

The study director will report the status of progress of this study and information on the onset of adverse events etc. to the Kobe University Clinical Study Review Board and the Minister of Health, Labour and Welfare once every year.

16 Payment of money, other compensations, and insurance

16.1 Payment of money

In this study, MMF will be administered as an approach to advanced medicine. As such, the investigational drug MMF will be provided at no cost by Chugai Pharmaceutical Co., Ltd., whereas placebo will be purchased with research funds for this study; therefore, the drug cost for the advanced medicine will not pose individual payments on the patient. The expenses for other treatments and examinations performed during participation in this study will all be paid by the patient's health insurance organization and individual payment.

16.2 Compensations for adverse health effects

In the event of an adverse event in this study, appropriate treatment will be provided, and the costs will be paid by the patient's health insurance organization and own expenses as in usual medical care.

16.3 Enrollment in clinical research insurance

With the implementation of this study, the investigator at each study site will enter a medical liability insurance before the start of the study. In addition, all persons involved in the study, such as investigators, will be covered by the clinical research insurance as insured persons in preparation for compensating for adverse health effects for which a causality with the study cannot be ruled out. This insurance will cover the liability borne by investigators etc. in the event of health damage (death or 1st- or 2nd-grade disability in the standards of the Relief System for Sufferers from Adverse Drug Reactions) attributable to this study during the study period or within 1 year after the end of the study, or the damage suffered by investigators etc. by bearing the legal liability in the event of physical disorders on the subject attributable to this study.

17 Study protocol changes or clinical trial discontinuation or suspension

17.1 Study protocol changes

When intending to make a change in the study protocol, the study director will obtain approval from the independent data and safety monitoring committee and the protocol committee, and then submit the study protocol and the change approval application (Format 3) to the Kobe University Clinical Study Review Board seeking their opinion.

When changing the study plan, the study director will inform the administrators of the study sites and submit a change notification (Form 2), the changed study plan (jRCT), and the written opinion of the Kobe University Clinical Study Review Board to the Minister of Health, Labour and Welfare.

In case of any change in the study protocol etc., the study director will provide information for other investigators. The investigators will report on the particulars of information provision to the administrators of study sites.

17.2 Clinical trial discontinuation or suspension

In the following cases, the study director will determine whether to continue the study (continuation,

discontinuation, or suspension) in consultation with the protocol committee.

(1) Significant information on the quality, safety, and efficacy of the investigational drug is obtained.
(2) The regulatory authorities advise to discontinue the study.
(3) Kobe University Clinical Study Review Board advises or directs to discontinue the study.
(4) Other situations require discontinuation or suspension of part or all of the study.

If the study is to be discontinued prematurely, the study director should obtain approval from the independent data and safety monitoring committee. In this case, the study director will immediately notify the principal investigator in writing. The study director will notify the Kobe University Clinical Study Review Board in writing and promptly notify the subjects to ensure appropriate treatment and follow-up for the subjects.

The study director will submit the clinical study report and its summary to the Kobe University Clinical Study Review Board within 1 year after the day of completion of actions on all subjects or the day of completion of the period for collecting data on all endpoints, whichever is later. The study director will record the summary of the clinical study report in the jRCT, and submit it to the Minister of Health, Labour and Welfare within 1 month after hearing the opinion of the Kobe University Clinical Study Review Board.

18 Quality control and quality assurance

The study director will implement quality control and quality assurance to ensure that the conduct of the study and data preparation, documentation, and reporting will be in accordance with the study protocol. In order to ensure the reliability and proper processing of all data related to this study, persons in charge designated by the study director will undertake the various stages of data handling (request for the study, monitoring, confirmation of the contents of the case report form, procedures for the creation and modification of the database, statistical analyses, and records and reports associated with them, etc.).

18.1 Monitoring and audits

18.1.1 Monitoring

Central monitoring will be performed in this study to ensure that the study is conducted safely and in compliance with the study protocol, and that data are accurately collected. Central monitoring will be performed on the data in the case report form collected at the data center. Details and procedures of monitoring performed by the data center for the study site and investigator will be provided separately in the operating procedures. Monitoring by visiting study sites is not planned. A monitoring report prepared on the basis of central monitoring results will be submitted to the study director (study office), protocol committee, and independent data and safety monitoring committee.

18.1.2 Audits

Site-visit audits will be implemented to evaluate the scientific and ethical reliability of the study and the study

management system. The items and procedures of audits will be established separately in dedicated standard operating procedures. Audit results will be reported to the administrator of the target study site, its investigators, and the study director (study office).

18.2 Direct access to source materials etc.

The principal investigator, investigator, and study site should provide direct access to records related to this study for the inspectors, the Kobe University Clinical Study Review Board, Ministry of Health, Labour and Welfare, Japan (MHLW), and affiliate organizations upon request during inspections to help their smooth implementation.

18.3 Non-compliance with the study protocol etc.

Non-compliance with the study protocol etc. will be classified as violations, deviations, or acceptable ranges after consideration by the study director and the protocol committee. If the principal investigator and the study site are not in compliance with the study protocol, the study director will take immediate measures to ensure the compliance. If significant or continued protocol non-compliance by the investigator or study site is found, the principal investigator will report this fact to the administrator of the study site and the study director. The study director may terminate the participation of the investigator or study site.

If important non-compliance is revealed, the study director will hear the opinion of the Kobe University Clinical Study Review Board (Format 7).

19 Archives

The study sites participating in this study and the facilities specified in Appendix 1 must appropriately store the documents specified by the study director, the ethics review committee of each study site, and the Kobe University Clinical Study Review Board to be stored, in accordance with the agreements of each study site. The duration of storage will be the longer of the time specified by each study site and 5 years from the date of completion of this clinical study. Thereafter, the documents will be disposed of in a state that does not allow personal identification.

20 Publication rules

Major study results will be submitted to academic journals after the end of the final analysis.

As a general rule, the lead author of the key article for the study results will be determined by the study director. Any coauthors will be selected by the study director in accordance with the International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

All coauthors should review the article and agree with the contents to be published prior to submission. If any researcher disagrees with the contents after discussion, the study director may exclude the researcher from the coauthors.

Major study results will be published by also recording them in the Japan Registry of Clinical Trials (jRCT).

21 Clinical trial registration

This study is registered at the UMIN-CTR database (http://www.umin.ac.jp/ctr/index-j.htm) to disclose its information.

UMIN-CTR registration No.: UMIN000014347

After approval by the Kobe University Clinical Study Review Board, the study will be registered with jRCT.

22 Research funds and conflict of interest

22.1 Research funds

This study will be conducted with the financial support of R&D grants in the Project Promoting Clinical Trials for Development of New Drugs, Japan Agency for Medical Research and Development. The investigational drug MMF in this study will be provided at no cost by Chugai Pharmaceutical Co., Ltd., and a placebo preparation manufactured by Shinshin Pharmaceutical Co., Ltd. will be purchased by research funds for this study and used in the study.

22.2 Conflict of interest

Decisions concerning the planning, implementation, analyses, and publication of this study will be made by the study director and the protocol committee. Companies etc. that manufacture and sell the investigational drugs will not be involved in the planning, implementation, analysis, or publication of this study, and there is no potential conflict of interest that can affect the scientific outcomes of this study.

With regard to the conflict of interest for this clinical trial, the Kobe University Clinical Study Review Board will review the conflict of interest management criteria and plan to ensure fair interest relationships in the study.

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Attachment 1. Table of blood pressure reference values by sex and age in children[27)]

	Boys			Girls		
	90th	95th	99th	90th	95th	99th
1 year	99/52	103/56	110/64	100/54	104/58	111/65
2 years	102/57	106/61	113/69	101/59	105/63	112/70
3 years	105/61	109/65	116/73	103/63	107/67	114/74
4 years	107/65	111/69	118/77	104/66	108/70	115/77
5 years	108/68	112/72	120/80	106/68	110/72	117/79
6 years	110/70	114/74	121/82	108/70	111/74	119/81
7 years	111/72	115/76	122/84	109/71	113/75	120/82
8 years	112/73	116/78	123/86	111/72	115/76	122/83
9 years	114/75	118/79	125/87	113/73	117/77	124/84
10 years	115/75	119/80	127/88	115/74	119/78	126/86
11 years	117/76	121/80	129/88	117/75	121/79	128/87
12 years	120/76	123/81	131/89	119/76	123/80	130/88
13 years	122/77	126/81	133/89	121/77	124/81	132/89
14 years	125/78	128/82	136/90	122/78	126/82	133/90
15 years	127/79	131/83	138/91	123/79	127/83	134/91
16 years	130/80	134/84	141/92	124/80	128/84	135/91
17 years	132/82	136/87	143/94	125/80	129/84	136/91

Systolic/diastolic blood pressure (mmHg)

For patients aged 18 years or older, the reference value range for patients aged 17 years will apply.

Attachment 2. Estimated glomerular filtration rates

<For patients aged 2 years or more and less than 19 years>

With body height represented by Ht (m), the reference value of serum Cr will be calculated, based on which the estimated glomerular filtration rate will be calculated.[28)]

Estimated glomerular filtration rate (mL/min/1.73 m^2)

= 110.2 × serum Cr reference value (mg/dL) /serum Cr actual measured value (mg/dL) + 2.93

The serum Cr reference value (mg/dL) will be calculated using the formulas shown below.[28)]

Boys: $-1.259\ Ht^5 + 7.815\ Ht^4 - 18.57\ Ht^3 + 21.39\ Ht^2 - 11.71\ Ht + 2.628$

Girls: $-4.536\ Ht^5 + 27.16\ Ht^4 - 63.47\ Ht^3 + 72.43\ Ht^2 - 40.06\ Ht + 8.778$

<For patients aged 19 years or older>

Calculated from body height and serum Cr value (enzyme method) using the calculation formulas shown below (Japanese Society of Nephrology).[29)]

The serum Cr value will be expressed to the second decimal place.

Men: Estimated glomerular filtration rate = $194 \times$ serum Cr value (enzyme method) $[mg/dL]^{-1.094} \times age\ (years)^{-0.287}$

Women: Estimated glomerular filtration rate = $194 \times$ serum Cr value (enzyme method) $[mg/dL]^{-1.094} \times age\ (years)^{-0.287} \times 0.739$

Attachment 3. Table of liver deviation enzyme (GOT) reference values by age in children[30)]

<Boys>

Age	Lower limit (U/L)	Upper limit (U/L)
0 months	19.9	62.0
1 month	21.0	64.0
2 months	22.0	65.0
3 months	22.3	66.0
4 months	23.0	67.0
5 months	24.0	68.0
6 months	24.5	68.0
7 months	25.0	67.5
8 months	24.5	66.5
9 months	24.0	65.5
10 months	23.5	63.9
11 months	23.0	61.5
1 year	23.0	56.5
2 years	24.0	49.0
3 years	24.0	43.0
4 years	24.0	40.8
5 years	24.0	38.7
6 years	24.0	37.5
7 years	24.0	36.0
8 years	22.5	34.8
9 years	19.0	33.0
10 years	17.0	32.0
11 years	16.0	31.5
12 years	15.0	31.0
13 years	14.5	31.0
14 years	14.0	30.0
15 years	14.0	30.0
16 years	14.0	30.0
17 years	14.0	30.0
18 years	14.0	30.0
19 years	14.0	31.0
20 years	14.0	32.0

<Girls>

Age	Lower limit (U/L)	Upper limit (U/L)
0 months	19.9	62.0
1 month	21.0	64.0
2 months	22.0	65.0
3 months	22.3	66.0
4 months	23.0	67.0
5 months	24.0	68.0
6 months	24.5	68.0
7 months	25.0	67.5
8 months	24.5	66.5
9 months	24.0	65.5
10 months	23.5	63.9
11 months	23.0	61.5
1 year	24.0	57.0
2 years	24.0	50.0
3 years	24.0	44.0
4 years	24.0	41.5
5 years	24.0	39.0
6 years	24.0	37.5
7 years	24.0	35.5
8 years	22.5	33.5
9 years	18.5	32.0
10 years	17.0	31.0
11 years	16.0	30.0
12 years	15.0	29.5
13 years	14.0	29.0
14 years	13.5	28.0
15 years	13.0	28.0
16 years	12.5	28.0
17 years	12.0	28.0
18 years	12.0	28.0
19 years	12.0	27.5
20 years	12.0	27.0

For patients of either sex aged 21 years or older, the reference value range will be 10 to 40 U/L.

Attachment 4. Table of liver deviation enzyme (GPT) reference values by age in children[30)]

<Boys>

Age	Lower limit (U/L)	Upper limit (U/L)
0 months	11.0	45.0
1 month	11.7	50.0
2 months	12.5	54.5
3 months	13.0	56.0
4 months	13.0	56.0
5 months	12.9	55.5
6 months	12.5	54.5
7 months	12.3	53.0
8 months	12.0	50.5
9 months	11.5	48.0
10 months	10.5	45.0
11 months	9.5	42.0
1 year	9.4	38.4
2 years	9.0	34.0
3 years	9.0	30.0
4 years	9.0	28.0
5 years	9.0	28.0
6 years	9.0	28.0
7 years	9.0	28.0
8 years	9.0	28.5
9 years	9.0	29.0
10 years	9.0	30.0
11 years	9.0	31.0
12 years	9.0	32.0
13 years	9.0	33.0
14 years	9.0	34.0
15 years	9.0	35.0
16 years	9.0	36.0
17 years	9.0	37.0
18 years	9.0	38.0
19 years	9.0	39.0
20 years	9.0	41.0

<Girls>

Age	Lower limit (U/L)	Upper limit (U/L)
0 months	11.0	45.0
1 month	11.7	50.0
2 months	12.5	54.5
3 months	13.0	56.0
4 months	13.0	56.0
5 months	12.9	55.5
6 months	12.5	54.5
7 months	12.3	53.0
8 months	12.0	50.5
9 months	11.5	48.0
10 months	10.5	45.0
11 months	9.5	42.0
1 year	9.4	38.4
2 years	9.0	34.0
3 years	9.0	30.0
4 years	9.0	28.0
5 years	9.0	27.0
6 years	9.0	27.0
7 years	9.0	27.0
8 years	9.0	27.0
9 years	9.0	27.0
10 years	9.0	27.0
11 years	9.0	27.5
12 years	9.0	28.0
13 years	9.0	28.0
14 years	9.0	28.5
15 years	9.0	29.0
16 years	9.0	29.5
17 years	9.0	30.0
18 years	9.0	30.5
19 years	9.0	31.0
20 years	9.0	32.0

For patients of either sex aged 21 years or older, the reference value range will be 10 to 40 U/L.

Attachment 5. Year 2000 Table of Ideal Body Heights and Body Weights

<Boys>

Age (years	Ideal body height (cm)	Ideal body weight (kg)
0•0	49.0 (2.1)	3.0 (0.4)
0•1	53.9 (2.5)	4.3 (0.6)
0•2	58.0 (2.7)	5.5 (0.7)
0•3	61.1 (2.9)	6.4 (0.8)
0•4	64.0 (2.8)	7.1 (0.9)
0•5	66.4 (2.6)	7.7 (0.8)
0•6	67.9 (2.5)	8.0 (0.9)
0•7	68.9 (2.4)	8.2 (0.9)
0•8	70.1 (2.5)	8.6 (1.0)
0•9	71.8 (2.5)	8.9 (1.0)
0•10	72.9 (2.6)	9.1 (0.9)
0•11	73.8 (2.6)	9.2 (0.9)
1•0	74.9 (2.6)	9.3 (0.9)
1•1	75.9 (2.5)	9.5 (1.0)
1•2	77.0 (2.6)	9.8 (1.0)
1•3	78.0 (2.6)	9.9 (1.0)
1•4	78.9 (2.8)	10.1 (1.0)
1•5	79.8 (3.4)	10.3 (1.1)
1•6	80.5 (3.4)	10.5 (1.2)
1•7	81.3 (3.0)	10.6 (1.1)
1•8	82.3 (3.0)	10.9 (1.1)
1•9	83.5 (3.6)	11.2 (1.2)
1•10	84.4 (3.3)	11.3 (1.2)
1•11	85.0 (2.8)	11.4 (1.1)
2•0	85.5 (3.0)	11.6 (1.2)
2•1	86.0 (3.1)	11.8 (1.2)
2•2	86.5 (3.2)	12.0 (1.2)
2•3	87.0 (3.3)	12.1 (1.3)
2•4	87.7 (3.3)	12.3 (1.3)
2•5	88.4 (3.3)	12.5 (1.3)
2•6	89.2 (3.3)	12.7 (1.3)
2•7	89.9 (3.3)	12.8 (1.3)
2•8	90.6 (3.3)	13.0 (1.4)
2•9	91.3 (3.3)	13.2 (1.4)
2•10	91.9 (3.4)	13.3 (1.4)
2•11	92.5 (3.5)	13.5 (1.5)

Age (years	Ideal body height (cm)	Ideal body weight (kg)
3•0	93.2 (3.6)	13.7 (1.5)
3•1	93.8 (3.6)	13.9 (1.6)
3•2	94.4 (3.7)	14.0 (1.7)
3•3	95.0 (3.8)	14.2 (1.7)
3•4	95.6 (3.8)	14.4 (1.7)
3•5	96.2 (3.8)	14.5 (1.8)
3•6	96.8 (3.8)	14.7 (1.8)
3•7	97.3 (3.8)	14.8 (1.8)
3•8	97.9 (3.8)	15.0 (1.8)
3•9	98.5 (3.8)	15.1 (1.8)
3•10	99.1 (3.9)	15.3 (1.9)
3•11	99.7 (4.0)	15.4 (1.9)
4•0	100.4 (4.1)	15.6 (2.0)
4•1	101.0 (4.1)	15.8 (2.0)
4•2	101.6 (4.2)	15.9 (2.1)
4•3	102.2 (4.3)	16.1 (2.1)
4•4	102.7 (4.3)	16.3 (2.1)
4•5	103.1 (4.2)	16.4 (2.1)
4•6	103.6 (4.2)	16.6 (2.2)
4•7	104.0 (4.2)	16.7 (2.2)
4•8	104.5 (4.1)	16.9 (2.2)
4•9	104.9 (4.1)	17.0 (2.2)
4•10	105.5 (4.2)	17.3 (2.3)
4•11	106.0 (4.3)	17.5 (2.4)
5•0	106.6 (4.4)	17.7 (2.5)
5•1	107.2 (4.4)	17.9 (2.6)
5•2	107.7 (4.5)	18.1 (2.8)
5•3	108.3 (4.6)	18.3 (2.9)
5•4	108.9 (4.6)	18.5 (2.9)
5•5	109.4 (4.6)	18.7 (2.9)
5•6	110.0 (4.7)	18.9 (3.0)
5•7	110.5 (4.7)	19.1 (3.0)
5•8	111.1 (4.7)	19.3 (3.0)
5•9	111.6 (4.7)	19.6 (3.0)
5•10	112.2 (4.7)	19.8 (3.1)
5•11	112.7 (4.8)	20.1 (3.2)

Age (years	Ideal body height (cm)	Ideal body weight (kg)
6•0	113.3 (4.8)	20.3 (3.3)
6•1	113.9 (4.8)	20.6 (3.4)
6•2	114.4 (4.8)	20.8 (3.5)
6•3	115.0 (4.9)	21.1 (3.5)
6•4	115.6 (4.9)	21.3 (3.6)
6•5	116.1 (4.9)	21.6 (3.7)
6•6	116.7 (5.0)	21.8 (3.8)
6•7	117.2 (5.0)	22.0 (3.8)
6•8	117.7 (5.0)	22.2 (3.9)
6•9	118.2 (5.0)	22.5 (3.9)
6•10	118.6 (5.0)	22.7 (4.0)
6•11	119.1 (5.0)	22.9 (4.1)
7•0	119.6 (5.1)	23.1 (4.1)
7•1	120.1 (5.1)	23.3 (4.2)
7•2	120.6 (5.1)	23.5 (4.2)
7•3	121.1 (5.1)	23.8 (4.3)
7•4	121.5 (5.1)	24.0 (4.3)
7•5	122.0 (5.1)	24.2 (4.4)
7•6	122.5 (5.1)	24.4 (4.4)
7•7	123.0 (5.2)	24.7 (4.5)
7•8	123.4 (5.2)	25.0 (4.6)
7•9	123.9 (5.2)	25.2 (4.7)
7•10	124.4 (5.2)	25.5 (4.8)
7•11	124.8 (5.3)	25.8 (4.9)
8•0	125.3 (5.3)	26.1 (5.0)
8•1	125.8 (5.3)	26.3 (5.1)
8•2	126.2 (5.3)	26.6 (5.2)
8•3	126.7 (5.4)	26.9 (5.3)
8•4	127.2 (5.4)	27.2 (5.4)
8•5	127.6 (5.4)	27.4 (5.5)
8•6	128.1 (5.5)	27.7 (5.6)
8•7	128.6 (5.5)	28.0 (5.7)
8•8	129.0 (5.5)	28.3 (5.8)
8•9	129.5 (5.5)	28.6 (5.9)
8•10	129.9 (5.5)	28.9 (6.0)
8•11	130.4 (5.6)	29.2 (6.1)

<Boys (continued)>

Age (years	Ideal body height (cm)	Ideal body weight (kg)
9•0	130.9 (5.6)	29.5 (6.2)
9•1	131.3 (5.6)	29.7 (6.3)
9•2	131.8 (5.6)	30.0 (6.4)
9•3	132.2 (5.7)	30.3 (6.5)
9•4	132.7 (5.7)	30.6 (6.6)
9•5	133.1 (5.7)	30.9 (6.7)
9•6	133.6 (5.7)	31.2 (6.8)
9•7	134.1 (5.8)	31.5 (6.9)
9•8	134.5 (5.8)	31.9 (7.0)
9•9	135.0 (5.8)	32.2 (7.1)
9•10	135.4 (5.9)	32.5 (7.2)
9•11	135.9 (5.9)	32.8 (7.3)
10•0	136.4 (5.9)	33.2 (7.4)
10•1	136.8 (6.0)	33.5 (7.5)
10•2	137.3 (6.0)	33.8 (7.6)
10•3	137.7 (6.0)	34.1 (7.7)
10•4	138.2 (6.1)	34.5 (7.8)
10•5	138.6 (6.1)	34.8 (7.9)
10•6	139.1 (6.1)	35.1 (7.9)
10•7	139.6 (6.2)	35.5 (8.0)
10•8	140.1 (6.3)	35.8 (8.1)
10•9	140.7 (6.4)	36.2 (8.2)
10•10	141.2 (6.5)	36.5 (8.3)
10•11	141.7 (6.6)	36.9 (8.4)
11•0	142.2 (6.6)	37.3 (8.6)
11•1	142.7 (6.7)	37.6 (8.7)
11•2	143.2 (6.8)	38.0 (8.8)
11•3	143.8 (6.9)	38.3 (8.9)
11•4	144.3 (7.0)	38.7 (9.0)
11•5	144.8 (7.1)	39.0 (9.1)
11•6	145.3 (7.1)	39.4 (9.2)
11•7	145.9 (7.2)	39.9 (9.3)
11•8	146.6 (7.3)	40.4 (9.4)
11•9	147.2 (7.4)	40.9 (9.5)
11•10	147.8 (7.4)	41.4 (9.6)
11•11	148.5 (7.5)	41.9 (9.7)

Age (years	Ideal body height (cm)	Ideal body weight (kg)
12•0	149.1 (7.6)	42.4 (9.8)
12•1	149.7 (7.7)	42.9 (9.9)
12•2	150.4 (7.8)	43.4 (10.0)
12•3	151.0 (7.8)	43.9 (10.1)
12•4	151.6 (7.9)	44.4 (10.2)
12•5	152.3 (8.0)	44.9 (10.3)
12•6	152.9 (8.1)	45.4 (10.4)
12•7	153.5 (8.0)	45.8 (10.4)
12•8	154.1 (8.0)	46.2 (10.4)
12•9	154.7 (8.0)	46.7 (10.4)
12•10	155.3 (7.9)	47.1 (10.4)
12•11	155.9 (7.9)	47.5 (10.4)
13•0	156.5 (7.9)	47.9 (10.4)
13•1	157.0 (7.8)	48.3 (10.4)
13•2	157.6 (7.8)	48.7 (10.5)
13•3	158.2 (7.8)	49.2 (10.5)
13•4	158.8 (7.8)	49.6 (10.5)
13•5	159.4 (7.7)	50.0 (10.5)
13•6	160.0 (7.7)	50.4 (10.5)
13•7	160.5 (7.6)	50.8 (10.5)
13•8	160.9 (7.5)	51.2 (10.5)
13•9	161.4 (7.4)	51.7 (10.5)
13•10	161.8 (7.3)	52.1 (10.4)
13•11	162.3 (7.2)	52.5 (10.4)
14•0	162.8 (7.1)	52.9 (10.4)
14•1	163.2 (7.0)	53.3 (10.4)
14•2	163.7 (6.9)	53.7 (10.4)
14•3	164.1 (6.8)	54.2 (10.4)
14•4	164.6 (6.7)	54.6 (10.4)
14•5	165.0 (6.6)	55.0 (10.4)
14•6	165.5 (6.5)	55.4 (10.3)
14•7	165.8 (6.4)	55.8 (10.4)
14•8	166.0 (6.4)	56.1 (10.4)
14•9	166.3 (6.3)	56.5 (10.5)
14•10	166.5 (6.3)	56.8 (10.5)
14•11	166.8 (6.2)	57.2 (10.5)

Age (years	Ideal body height (cm)	Ideal body weight (kg)
15•0	167.1 (6.2)	57.6 (10.6)
15•1	167.3 (6.1)	57.9 (10.6)
15•2	167.6 (6.1)	58.3 (10.7)
15•3	167.8 (6.0)	58.6 (10.7)
15•4	168.1 (6.0)	59.0 (10.8)
15•5	168.3 (5.9)	59.3 (10.8)
15•6	168.6 (5.9)	59.7 (10.8)
15•7	168.7 (5.9)	59.8 (10.8)
15•8	168.9 (5.9)	60.0 (10.7)
15•9	169.0 (5.9)	60.1 (10.7)
15•10	169.1 (5.9)	60.2 (10.6)
15•11	169.2 (5.8)	60.3 (10.5)
16•0	169.4 (5.8)	60.5 (10.5)
16•1	169.5 (5.8)	60.6 (10.4)
16•2	169.6 (5.8)	60.7 (10.4)
16•3	169.7 (5.8)	60.8 (10.3)
16•4	169.9 (5.8)	61.0 (10.3)
16•5	170.0 (5.8)	61.1 (10.2)
16•6	170.1 (5.8)	61.2 (10.1)
16•7	170.2 (5.8)	61.3 (10.2)
16•8	170.2 (5.8)	61.4 (10.2)
16•9	170.3 (5.8)	61.6 (10.2)
16•10	170.3 (5.8)	61.7 (10.2)
16•11	170.4 (5.8)	61.8 (10.2)
17•0	170.5 (5.8)	61.9 (10.2)
17•1	170.5 (5.8)	62.0 (10.2)
17•2	170.6 (5.8)	62.1 (10.3)
17•3	170.6 (5.8)	62.3 (10.3)
17•4	170.7 (5.8)	62.4 (10.3)
17•5	170.7 (5.8)	62.5 (10.3)
17•6	170.8 (5.8)	62.6 (10.3)

For patients aged 17 years and 7 months or older, the reference value range for patients aged 17 years and 6 months will apply.

<Girls>

Age (years	Ideal body height (cm)	Ideal body weight (kg)
0•0	48.4 (2.1)	3.0 (0.4)
0•1	53.2 (2.2)	4.1 (0.5)
0•2	57.1 (2.4)	5.2 (0.6)
0•3	60.2 (2.3)	6.0 (0.7)
0•4	62.6 (3.0)	6.6 (0.8)
0•5	64.4 (3.3)	7.0 (0.8)
0•6	66.2 (2.7)	7.5 (0.8)
0•7	67.4 (2.5)	7.8 (0.8)
0•8	68.8 (2.5)	8.0 (0.9)
0•9	70.2 (2.5)	8.2 (0.9)
0•10	71.2 (2.5)	8.5 (0.9)
0•11	72.0 (2.5)	8.6 (0.9)
1•0	73.1 (2.7)	8.7 (1.0)
1•1	74.4 (2.8)	9.0 (0.9)
1•2	75.4 (2.8)	9.2 (0.9)
1•3	76.5 (3.0)	9.3 (1.0)
1•4	77.7 (2.9)	9.5 (0.9)
1•5	78.4 (2.7)	9.7 (1.0)
1•6	79.4 (2.8)	9.9 (1.0)
1•7	80.6 (2.7)	10.2 (1.1)
1•8	81.4 (2.6)	10.4 (1.1)
1•9	82.1 (2.8)	10.4 (1.0)
1•10	83.1 (3.2)	10.7 (1.2)
1•11	83.9 (3.0)	11.0 (1.2)
2•0	84.5 (2.8)	11.0 (1.1)
2•1	85.0 (2.9)	11.2 (1.2)
2•2	85.4 (3.0)	11.4 (1.3)
2•3	85.9 (3.1)	11.6 (1.3)
2•4	86.6 (3.2)	11.8 (1.3)
2•5	87.3 (3.3)	12.0 (1.4)
2•6	88.0 (3.4)	12.2 (1.4)
2•7	88.6 (3.4)	12.3 (1.4)
2•8	89.3 (3.5)	12.5 (1.4)
2•9	90.0 (3.6)	12.7 (1.5)
2•10	90.7 (3.7)	12.8 (1.5)
2•11	91.4 (3.8)	13.0 (1.5)

Age (years	Ideal body height (cm)	Ideal body weight (kg)
3•0	92.1 (3.9)	13.1 (1.6)
3•1	92.7 (3.9)	13.3 (1.6)
3•2	93.4 (4.0)	13.4 (1.6)
3•3	94.1 (4.1)	13.6 (1.7)
3•4	94.6 (4.0)	13.8 (1.7)
3•5	95.2 (4.0)	13.9 (1.7)
3•6	95.7 (3.9)	14.1 (1.7)
3•7	96.2 (3.8)	14.3 (1.7)
3•8	96.8 (3.8)	14.4 (1.7)
3•9	97.3 (3.7)	14.6 (1.7)
3•10	98.0 (3.9)	14.8 (1.8)
3•11	98.7 (4.0)	15.0 (1.9)
4•0	99.4 (4.2)	15.2 (2.0)
4•1	100.0 (4.3)	15.4 (2.1)
4•2	100.7 (4.5)	15.6 (2.2)
4•3	101.4 (4.6)	15.8 (2.4)
4•4	102.0 (4.5)	15.9 (2.3)
4•5	102.5 (4.4)	16.1 (2.2)
4•6	103.1 (4.3)	16.3 (2.2)
4•7	103.7 (4.1)	16.4 (2.1)
4•8	104.2 (4.0)	16.6 (2.1)
4•9	104.8 (3.9)	16.8 (2.0)
4•10	105.3 (4.0)	17.0 (2.1)
4•11	105.7 (4.1)	17.2 (2.2)
5•0	106.2 (4.2)	17.4 (2.3)
5•1	106.7 (4.2)	17.6 (2.4)
5•2	107.1 (4.3)	17.2 (2.5)
5•3	107.6 (4.4)	18.0 (2.6)
5•4	108.1 (4.4)	18.1 (2.6)
5•5	108.6 (4.3)	18.2 (2.6)
5•6	109.1 (4.3)	18.4 (2.7)
5•7	109.6 (4.3)	18.5 (2.7)
5•8	110.1 (4.2)	18.6 (2.7)
5•9	110.6 (4.2)	18.7 (2.8)
5•10	111.2 (4.3)	19.0 (2.8)
5•11	111.8 (4.3)	19.3 (2.9)

Age (years	Ideal body height (cm)	Ideal body weight (kg)
6•0	112.3 (4.4)	19.6 (3.0)
6•1	112.9 (4.5)	19.9 (3.1)
6•2	113.5 (4.6)	20.2 (3.2)
6•3	114.1 (4.6)	20.4 (3.3)
6•4	114.6 (4.7)	20.7 (3.4)
6•5	115.2 (4.8)	21.0 (3.5)
6•6	115.8 (4.9)	21.3 (3.6)
6•7	116.3 (4.9)	21.5 (3.6)
6•8	116.8 (4.9)	21.7 (3.7)
6•9	117.3 (4.9)	21.9 (3.7)
6•10	117.8 (5.0)	22.1 (3.8)
6•11	118.3 (5.0)	22.3 (3.8)
7•0	118.8 (5.0)	22.6 (3.9)
7•1	119.2 (5.0)	22.8 (3.9)
7•2	119.7 (5.0)	23.0 (4.0)
7•3	120.2 (5.1)	23.2 (4.1)
7•4	120.7 (5.1)	23.4 (4.1)
7•5	121.2 (5.1)	23.6 (4.2)
7•6	121.7 (5.1)	23.8 (4.2)
7•7	122.2 (5.2)	24.1 (4.3)
7•8	122.7 (5.2)	24.3 (4.4)
7•9	123.2 (5.2)	24.6 (4.5)
7•10	123.6 (5.3)	24.9 (4.6)
7•11	124.1 (5.3)	25.1 (4.7)
8•0	124.6 (5.4)	25.4 (4.7)
8•1	125.1 (5.4)	25.7 (4.8)
8•2	125.6 (5.4)	25.9 (4.9)
8•3	126.1 (5.5)	26.2 (5.0)
8•4	126.5 (5.5)	26.5 (5.1)
8•5	127.0 (5.5)	26.7 (5.2)
8•6	127.5 (5.6)	27.0 (5.3)
8•7	128.0 (5.6)	27.3 (5.4)
8•8	128.5 (5.7)	27.6 (5.5)
8•9	129.0 (5.7)	27.9 (5.6)
8•10	129.5 (5.8)	28.2 (5.6)
8•11	130.0 (5.8)	28.5 (5.7)

<Girls (continued)>

Age (years	Ideal body height (cm)	Ideal body weight (kg)
9•0	130.5 (5.9)	28.9 (5.8)
9•1	131.0 (5.9)	29.2 (5.9)
9•2	131.5 (6.0)	29.5 (6.0)
9•3	132.0 (6.0)	29.8 (6.1)
9•4	132.5 (6.1)	30.1 (6.2)
9•5	133.0 (6.1)	30.4 (6.3)
9•6	133.5 (6.2)	30.7 (6.4)
9•7	134.1 (6.2)	31.1 (6.5)
9•8	134.6 (6.3)	31.4 (6.6)
9•9	135.2 (6.3)	31.8 (6.7)
9•10	135.8 (6.4)	32.1 (6.8)
9•11	136.3 (6.4)	32.5 (6.9)
10•0	136.9 (6.5)	32.8 (7.0)
10•1	137.5 (6.5)	33.2 (7.1)
10•2	138.0 (6.6)	33.5 (7.1)
10•3	138.6 (6.6)	33.9 (7.2)
10•4	139.2 (6.7)	34.2 (7.3)
10•5	139.7 (6.7)	34.6 (7.4)
10•6	140.3 (6.8)	34.9 (7.5)
10•7	140.9 (6.8)	35.3 (7.6)
10•8	141.4 (6.8)	35.8 (7.7)
10•9	142.0 (6.8)	36.2 (7.7)
10•10	142.6 (6.8)	36.6 (7.8)
10•11	143.1 (6.7)	37.1 (7.9)
11•0	143.7 (6.7)	37.5 (7.9)
11•1	144.3 (6.7)	37.9 (8.0)
11•2	144.8 (6.7)	38.4 (8.1)
11•3	145.4 (6.7)	38.8 (8.1)
11•4	146.0 (6.7)	39.2 (8.2)
11•5	146.5 (6.7)	39.7 (8.3)
11•6	147.1 (6.7)	40.1 (8.4)
11•7	147.5 (6.6)	40.5 (8.4)
11•8	147.9 (6.5)	40.9 (8.4)
11•9	148.4 (6.5)	41.3 (8.4)
11•10	148.8 (6.4)	41.7 (8.4)
11•11	149.2 (6.4)	42.1 (8.5)

Age (years	Ideal body height (cm)	Ideal body weight (kg)
12•0	149.6 (6.3)	42.6 (8.5)
12•1	150.0 (6.2)	43.0 (8.5)
12•2	150.4 (6.2)	43.4 (8.5)
12•3	150.9 (6.1)	43.8 (8.5)
12•4	151.3 (6.1)	44.2 (8.6)
12•5	151.7 (6.0)	44.6 (8.6)
12•6	152.1 (5.9)	45.0 (8.6)
12•7	152.4 (5.9)	45.3 (8.6)
12•8	152.6 (5.8)	45.6 (8.5)
12•9	152.9 (5.8)	45.8 (8.5)
12•10	153.1 (5.8)	46.1 (8.5)
12•11	153.4 (5.7)	46.4 (8.4)
13•0	153.6 (5.7)	46.7 (8.4)
13•1	153.9 (5.6)	46.9 (8.4)
13•2	154.1 (5.6)	47.2 (8.4)
13•3	154.4 (5.5)	47.5 (8.3)
13•4	154.6 (5.5)	47.8 (8.3)
13•5	154.9 (5.4)	48.0 (8.3)
13•6	155.1 (5.4)	48.3 (8.2)
13•7	155.2 (5.4)	48.5 (8.2)
13•8	155.4 (5.4)	48.7 (8.2)
13•9	155.5 (5.4)	48.9 (8.2)
13•10	155.7 (5.4)	49.1 (8.1)
13•11	155.8 (5.4)	49.3 (8.1)
14•0	156.0 (5.4)	49.5 (8.1)
14•1	156.1 (5.3)	49.7 (8.1)
14•2	156.2 (5.3)	49.9 (8.1)
14•3	156.4 (5.3)	50.1 (8.0)
14•4	156.5 (5.3)	50.3 (8.0)
14•5	156.7 (5.3)	50.5 (8.0)
14•6	156.8 (5.3)	50.7 (8.0)
14•7	156.8 (5.3)	50.8 (8.0)
14•8	156.9 (5.3)	50.9 (8.0)
14•9	156.9 (5.3)	51.1 (8.0)
14•10	157.0 (5.3)	51.2 (8.1)
14•11	157.0 (5.3)	51.3 (8.1)

Age (years	Ideal body height (cm)	Ideal body weight (kg)
15•0	157.1 (5.3)	51.4 (8.1)
15•1	157.1 (5.3)	51.5 (8.1)
15•2	157.1 (5.2)	51.6 (8.2)
15•3	157.2 (5.2)	51.8 (8.2)
15•4	157.2 (5.2)	51.9 (8.2)
15•5	157.3 (5.2)	52.0 (8.2)
15•6	157.3 (5.2)	52.1 (8.3)
15•7	157.3 (5.2)	52.2 (8.2)
15•8	157.4 (5.2)	52.3 (8.2)
15•9	157.4 (5.2)	52.3 (8.2)
15•10	157.4 (5.2)	52.4 (8.1)
15•11	157.5 (5.2)	52.5 (8.1)
16•0	157.5 (5.2)	52.6 (8.0)
16•1	157.5 (5.2)	52.6 (8.0)
16•2	157.6 (5.2)	52.7 (8.0)
16•3	157.6 (5.2)	52.8 (7.9)
16•4	157.6 (5.2)	52.9 (7.9)
16•5	157.7 (5.2)	52.9 (7.9)
16•6	157.7 (5.2)	53.0 (7.8)
16•7	157.7 (5.2)	53.0 (7.8)
16•8	157.8 (5.2)	53.0 (7.8)
16•9	157.8 (5.2)	53.0 (7.8)
16•10	157.8 (5.2)	53.0 (7.8)
16•11	157.9 (5.2)	53.0 (7.8)
17•0	157.9 (5.2)	53.1 (7.9)
17•1	157.9 (5.2)	53.1 (7.9)
17•2	158.0 (5.2)	53.1 (7.9)
17•3	158.0 (5.2)	53.1 (7.9)
17•4	158.0 (5.2)	53.1 (7.9)
17•5	158.1 (5.2)	53.1 (7.9)
17•6	158.1 (5.3)	53.1 (7.9)

For patients aged 17 years and 7 months or older, the reference value range for patients aged 17 years and 6 months will apply.

Attachment 6. Table of rituximab doses by body height

<Boys>

Body height (cm)			Amount administered (mg/dose)
59.6	-		120
62.6	-		130
67.2	-		140
69.5	-		150
73.4	-		160
76.5	-		170
80.2	-		180
82.9	-		190
86.3	-		200
88.8	-		210
91.6	-		220
94.7	-		230
97.6	-		240
100.1	-		250
102.9	-		260
105.2	-		270
108.0	-		280
110.3	-		290
112.5	-		300
114.7	-		310
116.4	-		320
118.9	-		330
120.9	-		340
122.8	-		350
124.6	-		360
126.5	-		370
128.4	-		380
130.0	-		390
132.0	-		400
133.9	-		410
135.2	-		420
137.1	-		430
138.4	-		440
140.4	-		450
142.0	-		460
143.5	-		470
145.6	-		480
146.9	-		490
148.2	-		500

<Girls>

Body height (cm)			Amount administered (mg/dose)
61.4	-		120
63.5	-		130
66.8	-		140
70.7	-		150
73.8	-		160
77.1	-		170
81.0	-		180
83.5	-		190
86.3	-		200
89.0	-		210
92.4	-		220
95.5	-		230
97.7	-		240
100.4	-		250
103.4	-		260
105.5	-		270
107.9	-		280
110.9	-		290
112.6	-		300
114.9	-		310
117.1	-		320
119.0	-		330
121.0	-		340
123.0	-		350
124.9	-		360
126.8	-		370
128.8	-		380
130.3	-		390
132.3	-		400
133.8	-		410
136.1	-		420
137.8	-		430
139.5	-		440
141.2	-		450
142.9	-		460
144.6	-		470
145.7	-		480
147.3	-		490
149.0	-		500

Attachment 7. Table of investigational drug doses by body height

Investigational drug doses will be calculated from the body surface area at the time of enrollment, and the closest dosage unit amount will be adopted.

■Body surface areas were calculated using the Du Bois equation from body heights and body-height-based ideal body weights.

Body surface area BSA (m^2) = body weight (kg) $^{0.425}$ × body height (cm) $^{0.725}$ × 0.007184 (Du Bois)

■Height-based ideal body weights were calculated using the 2000 Table of Ideal Body Heights and Body Weights.

<Boys>

Ideal body height (cm)	Investigational drug dose		
	500mg/m^2	1000mg/m^2	1200mg/m^2
-62.5	250	250	250
62.6-	250	250	500
68.4-	250	500	500
86.3-	250	500	750
97.6-	250	750	750
107.5-	250	750	1000
109.2-	500	750	1000
119.4-	500	1000	1000
124.2-	500	1000	1250
136.6-	500	1250	1250
138-	500	1250	1500
144.1-	750	1250	1500
150.7-	750	1250	1750
152-	750	1500	1750
163-	750	1500	2000
166.2-	750	1750	2000

<Girls>

Ideal body height (cm)	Investigational drug dose		
	500mg/m^2	1000mg/m^2	1200mg/m^2
-61.3	250	250	250
61.4-	250	250	500
69.5-	250	500	500
86.3-	250	500	750
97.7-	250	750	750
107.4-	250	750	1000
109.9-	500	750	1000
120-	500	1000	1000
124.4-	500	1000	1250
137.2-	500	1250	1250
138.3-	500	1250	1500
145.1-	750	1250	1500
150.7-	750	1250	1750
151.5-	750	1500	1750

Attachment 8. Table of prednisolone doses by body height

Calculated from body surface area based on body height, prednisolone doses will be determined in 5-mg units (for doses of ≥0 and <2.5, substitute 0 in place; for doses of ≥2.5 and <7.5, substitute 5 in place; for doses of ≥7.5, round up to 10).

Body surface areas were calculated using the Du Bois equation from body heights and body-height-based ideal body weights.

Body surface area BSA (m^2) = body weight (kg) $^{0.425}$ × body height (cm) $^{0.725}$ × 0.007184 (Du Bois)

Height-based ideal body weights were calculated using the 2000 Table of Ideal Body Heights and Body Weights. If there was no applicable body height, “a close body height” was used; “if two close body heights were present, the larger body height was adopted.”

■In cases where 60 mg/day is the maximum dose for 60 mg/m^2/day

<Boys>

Body height (cm)	Prednisolone dose (daily dose or single dose per unit body surface area)			
	(1)	(2)	(3)	(4)
	60mg/m^2 (mg/day)	60mg/m^2 (mg/dose)	30mg/m^2 (mg/dose)	15mg/m^2 (mg/dose)
	3 divided doses Daily dosing	Every 2 mornings Single dose	Every 2 mornings Single dose	Every 2 mornings Single dose
59.6-	20	20	10	5
68.4-	25	25	10	5
73.4-	25	25	15	5
79.4-	30	30	15	5
84.0-	30	30	15	10
88.1-	35	35	15	10
92.9-	35	35	20	10
97.6-	40	40	20	10
105.8-	45	45	20	10
109.2-	45	45	25	10
113.0-	50	50	25	10
115.9-	50	50	25	15
119.4-	55	55	25	15
122.8-	55	55	30	15
125.6-	60	60	30	15

<Girls>

Body height (cm)	Prednisolone dose (daily dose or single dose per unit body surface area)			
	(1)	(2)	(3)	(4)
	60mg/m^2 (mg/day)	60mg/m^2 (mg/dose)	30mg/m^2 (mg/dose)	15mg/m^2 (mg/dose)
	3 divided doses Daily dosing	Every 2 mornings Single dose	Every 2 mornings Single dose	Every 2 mornings Single dose
58.7-	20	20	10	5
69.5-	25	25	10	5
73.8-	25	25	15	5
80.0-	30	30	15	5
84.8-	30	30	15	10
89.0-	35	35	15	10
93.8-	35	35	20	10
97.7-	40	40	20	10
106.0-	45	45	20	10
109.9-	45	45	25	10
113.2-	50	50	25	10
116.1-	50	50	25	15
119.5-	55	55	25	15
123.0-	55	55	30	15
125.9-	60	60	30	15

■In cases where 80 mg/day is the maximum dose for 60 mg/m^2/day

<Boys>

Body height (cm)	Prednisolone dose (daily dose or single dose per unit body surface area)			
	(1)	(2)	(3)	(4)
	60mg/m^2 (mg/day)	60mg/m^2 (mg/dose)	30mg/m^2 (mg/dose)	15mg/m^2 (mg/dose)
	3 divided doses Daily dosing	Every 2 mornings Single dose	Every 2 mornings Single dose	Every 2 mornings Single dose
59.6-	20	20	10	5
68.4-	25	25	10	5
73.4-	25	25	15	5
79.4-	30	30	15	5
84.0-	30	30	15	10
88.1-	35	35	15	10
92.9-	35	35	20	10
97.6-	40	40	20	10
105.8-	45	45	20	10
109.2-	45	45	25	10
113.0-	50	50	25	10
115.9-	50	50	25	15
119.4-	55	55	25	15
122.8-	55	55	30	15
125.6-	60	60	30	15
131.1-	65	65	30	15
133.9-	65	65	35	15
136.6-	70	70	35	15
138.9-	70	70	35	20
141.5-	75	75	35	20
144.1-	75	75	40	20
146.9-	80	80	40	20

<Girls>

Body height (cm)	Prednisolone dose (daily dose or single dose per unit body surface area)			
	(1)	(2)	(3)	(4)
	60mg/m^2 (mg/day)	60mg/m^2 (mg/dose)	30mg/m^2 (mg/dose)	15mg/m^2 (mg/dose)
	3 divided doses Daily dosing	Every 2 mornings Single dose	Every 2 mornings Single dose	Every 2 mornings Single dose
58.7-	20	20	10	5
69.5-	25	25	10	5
73.8-	25	25	15	5
80.0-	30	30	15	5
84.8-	30	30	15	10
89.0-	35	35	15	10
93.8-	35	35	20	10
97.7-	40	40	20	10
106.0-	45	45	20	10
109.9-	45	45	25	10
113.2-	50	50	25	10
116.1-	50	50	25	15
119.5-	55	55	25	15
123.0-	55	55	30	15
125.9-	60	60	30	15
131.8-	65	65	30	15
134.4-	65	65	35	15
137.2-	70	70	35	15
139.5-	70	70	35	20
142.3-	75	75	35	20
145.1-	75	75	40	20
147.3-	80	80	40	20

Japanese Study Group of Kidney Disease in Children
JSKDC07 study team

Study director
Kazumoto Iijima (Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan)

Clinical trial steering committee
Kazumoto Iijima (Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan), Mayumi Sako (National Center for Child Health and Development, Tokyo, Japan), Kandai Nozu (Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan)

Protocol committee
Kenji Ishikura (Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan), Shuichi Ito (Graduate School of Medicine, Yokohama City University, Yokohama, Kanagawa, Japan), Koichi Nakanishi (Graduate School of Medicine, University of the Ryukyus, Nishihara, Okinawa, Japan), Hidefumi Nakamura (National Center for Child Health and Development, Tokyo, Japan), Mayumi Sako (National Center for Child Health and Development, Tokyo, Japan)

Independent data and safety monitoring committee
Masataka Honda (Tokyo Metropolitan Children's Medical Center, Fuchu, Tokyo, Japan), Kenichi Yoshimura (Kanazawa University Hospital, Kanazawa, Ishikawa, Japan), Motoshi Hattori (Tokyo Women's Medical University, Tokyo, Japan)

Biostatistician
Mari Oba (Faculty of Medicine, Toho University, Tokyo, Japan)

Investigators
Takayuki Okamoto, Yasuyuki Sato, Asako Hayashi, Toshiyuki Takahashi (Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan), Yoshinori Araki, Yoshinobu Nagaoka, Azusa Kawaguchi, Masayoshi Nagao (National Hospital Organization Hokkaido Medical Center, Sapporo, Hokkaido, Japan), Naonori Kumagai, Noriko Sugawara (Tohoku University School of

Medicine, Sendai, Miyagi, Japan), Takeshi Yamada (Niigata University Medical and Dental Hospital, Niigata City, Niigata, Japan), Yoko Ohwada (Dokkyo Medical University School of Medicine, Mibu, Tochigi, Japan), Shori Takahashi, Tamaki Morohashi, Hiroshi Saito (Nihon University School of Medicine, Tokyo, Japan), Koichi Kamei (National Center for Child Health and Development, Tokyo, Japan), Riku Hamada, Hiroshi Hataya, Ryoko Harada, Naoaki Mikami, Tomohiro Inoguchi (Tokyo Metropolitan Children's Medical Center, Fuchu, Tokyo, Japan), Eriko Tanaka (Tokyo Medical and Dental University, Tokyo, Japan), Shuichi Ito, Hiroyuki Machida, Aya Inaba (Graduate School of Medicine, Yokohama City University, Yokohama, Kanagawa, Japan), Naoya Fujita, Satoshi Hibino, Kazuki Tanaka (Aichi Children's Health and Medical Center, Obu, Aichi, Japan), Yoshimitsu Gotoh, Katsuaki Kasahara, Hisakazu Majima (Japanese Red Cross Nagoya Daini Hospital, Nagoya, Aichi, Japan), Yohei Ikezumi (Fujita Health University School of Medicine, Toyoake, Aichi, Japan), Masaki Shimizu, Tadafumi Yokoyama (School of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Ishikawa, Japan), Tomoyuki Sakai, Toshihiro Sawai, Yusuke Okuda, Toshiki Masuda (Shiga University of Medical Science, Otsu, Shiga, Japan), Takuo Kubota, Taichi Kitaoka, Hirofumi Nakayama (Graduate School of Medicine, Osaka University, Suita, Osaka, Japan), Rika Fujimaru (Osaka City General Hospital, Osaka, Japan), Katsusuke Yamamoto (Osaka Women's and Children's Hospital, Osaka, Japan), Takahisa Kimata (Kansai Medical University, Osaka, Japan), Kazumoto Iijima, Kandai Nozu, Takeshi Ninchoji, Tomohiko Yamamura, Tomoko Horinochi, China Nagano, Nana Sakakibara (Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan), Ryojiro Tanaka, Hiroshi Kaito, Yosuke Inaguma (Hyogo Prefectural Kobe Children's Hospital, Kobe, Hyogo, Japan), Yuko Shima (Wakayama Medical University, Wakayama City, Wakayama, Japan), Kunihiko Aya (Kurashiki Central Hospital, Kurashiki, Okayama, Japan), Toshiyuki Ohta (Hiroshima Prefectural Hospital, Hiroshima, Japan), Yoshitsugu Kaku (Fukuoka Children's Hospital, Fukuoka, Japan), Seiji Tanaka, Takuya Esaki, Satoko Kurata (Kurume University School of Medicine, Kurume, Fukuoka, Japan), Yasufumi Ohtsuka (Faculty of Medicine, Saga University, Saga City, Saga, Japan)