Report on the Deliberation Results

August 22, 2014

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Rituxan Injection 10 mg/mL
[Non-proprietary name]	Rituximab (Genetical Recombination) (JAN*)
[Name of applicant]	Zenyaku Kogyo Co., Ltd.
[Date of application]	December 26, 2013

[Results of deliberation]
In the meeting held on August 1, 2014, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period for the product is 10 years.

[Conditions for approval]
Refractory nephrotic syndrome (frequently relapsing or steroid-dependent)
Because of the very limited number of subjects included in Japanese clinical studies, the applicant is required to conduct a use-results survey covering all patients treated with Rituxan until data from a specific number of patients are accumulated after market introduction, and then to understand the characteristics of patients treated with Rituxan and compile safety and efficacy data of Rituxan in the earlier post-marketing phase, thereby taking necessary actions to ensure the proper use of Rituxan.

**Japanese Accepted Name (modified INN)*

Review Report

July 22, 2014

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Rituxan Injection 10 mg/mL
[Non-proprietary name]	Rituximab (Genetical Recombination)
[Name of applicant]	Zenyaku Kogyo Co., Ltd.
[Date of application]	December 26, 2013
[Dosage form/Strength]	Injection: A single-use vial contains either 100 mg (in 10 mL) or 500 mg (in 50 mL) of Rituximab (Genetical Recombination).
[Application classification]	Prescription drug, (4) Drug with a new active ingredient and (6) Drug with a new dosage
[Items warranting special mention]	Orphan drug (Designation No. [24 yaku] No. 282, Notification No. 0913-5 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 13, 2012
[Review Office]	Office of New Drug I

Review Results

July 22, 2014

[Brand name] Rituxan Injection 10 mg/mL
[Non-proprietary name] Rituximab (Genetical Recombination)
[Name of applicant] Zenyaku Kogyo Co., Ltd.
[Date of application] December 26, 2013

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of Rituximab (Genetical Recombination) in treatment of refractory nephrotic syndrome (frequently relapsing or steroid-dependent) has been demonstrated and its safety is acceptable in view of its observed benefits. However, PMDA has concluded that it will be necessary to further investigate the safety and efficacy of Rituximab (Genetical Recombination) by conducting post-marketing surveillance covering all patients treated with Rituximab (Genetical Recombination).

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indications]

1. CD20-positive B-cell non-Hodgkin's lymphoma
2. CD20-positive B-cell lymphoproliferative disorder associated with immunosuppression
3. Wegener's granulomatosis and microscopic polyangiitis
4. Refractory nephrotic syndrome (frequently relapsing or steroid-dependent)
5. Premedication for indium (^{111}In) ibritumomab tiuxetan (genetical recombination) injection and yttrium (^{90}Y) ibritumomab tiuxetan (genetical recombination) injection

(Underline denotes new addition.)

[Dosage and administration]

1. When used to treat CD20-positive B-cell non-Hodgkin's lymphoma:
The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for up to 8 doses.

When used to treat CD20-positive B-cell lymphoproliferative disorder associated with immunosuppression:
The usual dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for up to 8 doses.

When used to treat Wegener's granulomatosis and microscopic polyangiitis:
The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for 4 doses.

When used to treat refractory nephrotic syndrome (frequently relapsing or steroid-dependent):
The usual dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for 4 doses. The maximum single dosage is 500 mg.

When used as premedication for indium (^{111}In) ibritumomab tiuxetan (genetical recombination) injection and yttrium (^{90}Y) ibritumomab tiuxetan (genetical recombination) injection:
The usual adult dosage of Rituximab (Genetical Recombination) is 250 mg/m^2 administered as a single intravenous infusion.

2. The Rituxan solution for infusion is prepared by diluting 10-fold with either saline or 5% glucose solution before use.

(Underline denotes new addition.)

[Conditions for approval] Refractory nephrotic syndrome (frequently relapsing or steroid-dependent)
Because of the very limited number of subjects included in Japanese clinical studies, the applicant is required to conduct a use-results survey covering all patients treated with Rituxan until data from a specific number of patients are accumulated after market introduction, and then to understand the characteristics of patients treated with Rituxan and compile safety and efficacy data of Rituxan in the earlier post-marketing phase, thereby taking necessary actions to ensure the proper use of Rituxan.

Review Report (1)

June 17, 2014

I. Product Submitted for Registration

[Brand name] Rituxan Injection 10 mg/mL
[Non-proprietary name] Rituximab (Genetical Recombination)
[Name of applicant] Zenyaku Kogyo Co., Ltd.
[Date of application] December 26, 2013
[Dosage form/Strength] Injection: A single-use vial contains either 100 mg (in 10 mL) or 500 mg (in 50 mL) of Rituximab (Genetical Recombination).
[Proposed indications]
1. CD20-positive B-cell non-Hodgkin's lymphoma
2. CD20-positive B-cell lymphoproliferative disorder associated with immunosuppression
3. Wegener's granulomatosis and microscopic polyangiitis
4. Refractory nephrotic syndrome (frequently relapsing or steroid-dependent)
5. Premedication for indium (^{111}In) ibritumomab tiuxetan (genetical recombination) injection and yttrium (^{90}Y) ibritumomab tiuxetan (genetical recombination) injection

(Underline denotes new addition.)

[Proposed dosage and administration]

1. When used to treat CD20-positive B-cell non-Hodgkin's lymphoma:
   The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for up to 8 doses.

   When used to treat CD20-positive B-cell lymphoproliferative disorder associated with immunosuppression:
   The usual dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for up to 8 doses.

   When used to treat Wegener's granulomatosis and microscopic polyangiitis:
   The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for 4 doses.

   When used to treat refractory nephrotic syndrome (frequently relapsing or steroid-dependent):
   The usual dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for 4 doses. The maximum single dosage is 500 mg.

   When used as premedication for indium (^{111}In) ibritumomab tiuxetan (genetical recombination) injection and yttrium (^{90}Y) ibritumomab tiuxetan (genetical recombination) injection:
   The usual adult dosage of Rituximab (Genetical Recombination) is 250 mg/m^2 administered as a single intravenous infusion.

2. The Rituxan solution for infusion is prepared by diluting 10-fold with either saline or 5% glucose solution before use.

(Underline denotes new addition.)

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Nephrotic syndrome is a disease characterized by hypoproteinemia, edema, and dyslipidemia (high LDL) due to severe proteinuria. The disease is classified into either idiopathic nephrotic syndrome originating in the kidney or secondary nephrotic syndrome associated with systemic diseases. Idiopathic nephrotic syndrome is subdivided into some histological subtypes: including minimal change nephrotic syndrome (MCNS), membranous nephropathy, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis. Response to therapy and kidney prognoses vary depending on the histological subtype. Therefore, it is important to diagnose histological subtypes at an earlier stage and to determine appropriate treatments and prognoses accordingly. However, in the case of childhood-onset nephrotic syndrome, histological diagnosis is not essential because a great majority of patients with idiopathic nephrotic syndrome have a diagnosis of MCNS. MCNS is often steroid-sensitive and remission is achieved by steroid monotherapy,[1] but the disease subsequently develops into frequently relapsing nephrotic syndrome,[2] in which symptoms recur continually[3] with relatively brief remissions, or steroid-dependent nephrotic syndrome, in which symptoms recur when steroid therapy is reduced or discontinued.[4] Immunosuppressants are used in such cases, but refractory nephrotic syndrome unresponsive to any immunosuppressants will lead to renal failure. Most of patients with childhood-onset idiopathic nephrotic syndrome need to receive steroids for prolonged periods and adverse reactions to steroids are often problematic. In particular, growth disorders are an issue with growing children. The discontinuation of immunosuppressants is frequently necessary due to adverse reactions (Guideline for Drug Therapy of Pediatric Idiopathic Nephrotic Syndrome [version 1.0], *The Journal of the Japan Pediatric Society*. 2005;109:1066-1075, *Japanese Journal of Nephrology.* 2005;47:790-803, *Japanese Journal of Pediatric Nephrology*. 2005;18:170-181, The Japanese Society for Pediatric Nephrology ed. Guideline for Treatment of Pediatric Idiopathic Nephrotic Syndrome 2013. 2013;Shindan To Chiryo Sha). Based on the above, new options are needed for treatment of patients with refractory nephrotic syndrome who cannot achieve or maintain remission or who cannot withdraw from steroids.

T cell abnormalities have been suggested as a causal factor for nephrotic syndrome, while it has been reported that B cells may be involved in the development of MCNS directly or in association with T cells (*J Am Soc Nephrol*. 2009;20:260-266, etc.). Studies have reported a relationship between B cells counts and MCNS disease activity (*Clin Exp Immunol*. 1982;48:201-204, *Clin Exp Immunol*. 1985;61:601-607).

Rituximab (Genetical Recombination) (hereinafter referred to as "rituximab") is a chimeric anti-CD20 monoclonal antibody consisting of a mouse variable region and a human constant region, which exhibits cytotoxic action by binding to CD20 antigens expressing on mature human B cells. Rituximab is expected to be effective against idiopathic nephrotic syndrome by acting on B cells, and results from clinical usage in and outside Japan have been reported (*Pediatr Nephrol*. 2004;19:794-797, *Pediatr Nephrol*. 2005;20:1660-1663, *Pediatr Nephrol*. 2006;21:1698-1700, *Pediatr Nephrol*. 2007;22:893-898, *Pediatr Nephrol*. 2008;23:481-485, *N Engl J Med.* 2007;356:2751-2752, etc.). The applicant has filed a partial change approval application, claiming that the efficacy and safety of rituximab for the treatment of childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) has been demonstrated in investigator-initiated studies. Rituximab was designated as an orphan drug on September 13, 2012 with the expected indication of refractory nephrotic syndrome (Designation No. [24 yaku] No. 282).

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[1] Achieved remission within 4 weeks of daily prednisolone administration (as indicated in the Guideline for Pediatric Idiopathic Nephrotic Syndrome 2013; also applicable for Footnotes 2-4.)

[2] At least 2 relapses within 6 months of initial remission or at least 4 relapses over any 12-month period

[3] Morning urinary protein of ≥3+ as assessed by the test paper method lasting 3 consecutive days

[4] Two successive relapses within 14 days of reducing or discontinuing prednisolone therapy

In Japan, rituximab was first approved for the treatment of "CD20-positive low-grade or follicular B-cell non-Hodgkin's lymphoma or Mantle cell lymphoma" in June 2001, and then for "CD20-positive B-cell non-Hodgkin's lymphoma" in September 2003; "Premedication for indium (^{111}In) ibritumomab tiuxetan (genetical recombination) injection and yttrium (^{90}Y) ibritumomab tiuxetan (genetical recombination) injection" in January 2008; "CD20-positive B-cell lymphoproliferative disorder associated with immunosuppression" and "Wegener's granulomatosis and microscopic polyangiitis" in June 2013. As of November 2013, rituximab has been approved in 126 countries and regions but is not indicated for nephrotic syndrome in any country or region.

2. Data relating to quality

No data relating to quality was submitted.

3. Non-clinical data

No data relating to pharmacokinetic and toxicity studies was submitted. Since no animal model studies have been established to appropriately evaluate the efficacy of rituximab, no new pharmacological data were submitted. The pharmacological actions of rituximab (specific cytotoxic actions on CD20-positive B cells) have been confirmed in studies supporting its efficacy submitted at the initial regulatory application (see the Review Report for "Rituxan Injection 10 mg/mL," dated April 24, 2001 [no English translation available]).

4. Clinical data

4.(i) Summary of biopharmaceutical studies and related analytical procedures

4.(i).A Summary of the submitted data

No data relating to biopharmaceutical studies was submitted.

In the clinical studies (Studies RCRNS-01 and RCRNS-02) of which data were submitted as the evaluation data in this application, an enzyme-linked immunosorbent assay (ELISA) was used to measure serum rituximab concentrations and human anti-chimeric antibody (HACA) titers. The lower limits of quantitation were 5 ng/mL and 5.0 RU/mL,[5] respectively. Furthermore, a flow cytometry was used to measure peripheral blood B cell counts.[6]

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

4.(ii).A.(1) Phase III confirmatory study (5.3.5.1-1, Study Number RCRNS-01 (Study 01), from November 2008 to November 2011)

For the study summary, see "4.(iii).A.(1) Phase III confirmatory study (RCRNS-01)."

To patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent), 375 mg/m^2/infusion of rituximab (maximum of 500 mg/infusion)[7] was administered as an intravenous infusion once weekly for a total of 4 doses. Table 1 shows the pharmacokinetic (PK) parameters of rituximab (reference values[8]). On Day 365 of rituximab administration, the serum concentration of rituximab was below the lower limit of quantitation in all subjects. Of 31 patients receiving rituximab,[9] 26 subjects underwent the administration of rituximab and blood sample collection as specified in the protocol.

[5] RU: Relative Unit. [redacted]

[6] B cell counts were determined by counting CD20-positive and CD19-positive cells.

[7] Body surface area was calculated based on standard body weight relative to height.

[8] Blood samples were collected immediately before administration on Days 1 and 22, and on Days 85, 169 and 365, or at discontinuation. Time points of blood sampling were limited and sampling immediately after administration was not specified. Therefore, PK parameters were calculated for reference purposes only.

[9] A total of 24 subjects to whom rituximab was administered before the randomization and 7 subjects to whom rituximab was administered after the randomization

Table 1. PK parameters of serum rituximab

Serum rituximab concentrations on Day 22 (μg/mL)[a)]	AUC_{all} (μg × h/mL)	$t_{1/2}$ (h)	CL (L/h)	MRT (h)	Vds (L)
170 ± 33.3	241,000 ± 58,300	609 ± 254	0.00733 ± 0.00266	894 ± 191	7.63 ± 3.10

Mean ± standard deviation, n = 26

a) Serum rituximab concentrations immediately before the fourth dose

Figure 1 shows the time-course of peripheral B cell counts. The median value (95% confidence interval [CI]) of the peripheral blood B cell depletion period[10] was 148.0 days [131.0, 170.0 days] for the rituximab group. HACA was confirmed in 9.7% of the rituximab group (3 of 31 subjects9).

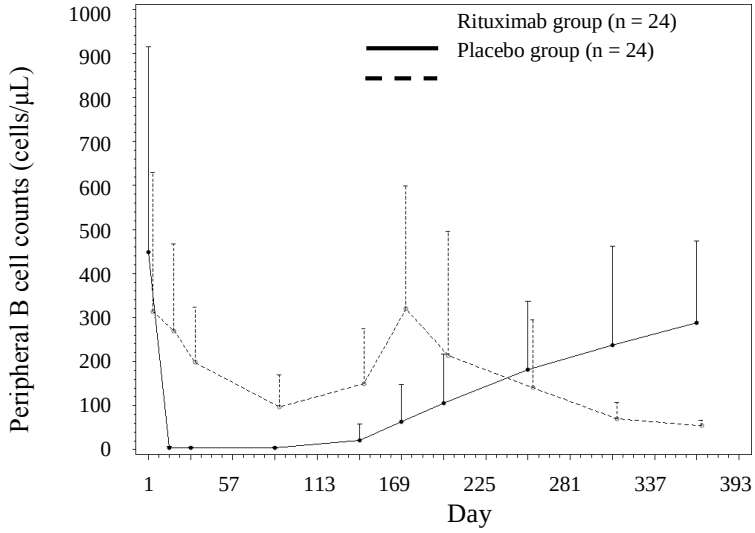


Figure 1. Peripheral B cell counts over time

4.(ii).A.(2) Pharmacokinetic study (5.3.5.2-1, Study Number RCRNS-02 (Study 02), from November 2008 to December 2011)

For the study summary, see "4.(iii).A.(2) Pharmacokinetic Study (RCRNS-02)."

To patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent), 375 mg/m^2/infusion of rituximab (maximum of 500 mg/infusion)[7] was administered as an intravenous infusion once weekly for a total of 4 doses. Figure 2 and Table 2 show changes in serum rituximab concentrations and PK parameters of rituximab, respectively. On Day 365 after the start of rituximab administration, serum rituximab concentrations decreased to 52 ± 173 ng/mL (mean ± SD). Of the 23 subjects in the PK analysis set, 22 subjects underwent the administration of rituximab and blood sample collection as specified in the protocol.[11]

[10] Time elapsed from day on which peripheral B cell depletion (<5/μL) was first confirmed and day on which recovery (≥5/μL) was confirmed.

[11] Blood samples were collected immediately before and immediately after administration and 24 hours after administration on Day 1 (first dose); immediately before and after administration on Day 8 (second dose), Day 15 (third dose), and Day 22 (fourth dose); and on Days 29, 57, 85, 113, 169, and 365 or at discontinuation.

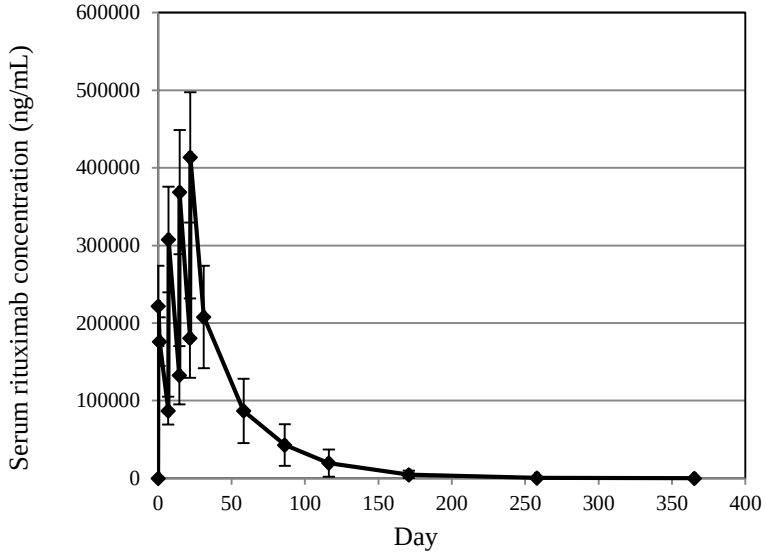


Figure 2. Changes in serum rituximab concentrations (n = 22)

Table 2. PK parameters of serum rituximab

C_{max} (μg/mL)[a)]	AUC_{all} (μg × h/mL)	$t_{1/2}$ (h)	CL (L/h)	MRT (h)	Vds (L)
421 ± 84.7	366,000 ± 110,000	234 ± 86.7	0.00750 ± 0.00236	337 ± 125	2.42 ± 0.877

Mean ± standard deviation, n = 22
a) The highest serum concentrations of the 4 values measured immediately after each administration

Figure 3 shows the time course of peripheral B cell counts. The median value [95% CI] of the peripheral B cell depletion period was 166.0 days [124.0, 184.0 days]. HACA was confirmed in 17.4% (4 of 23 subjects).

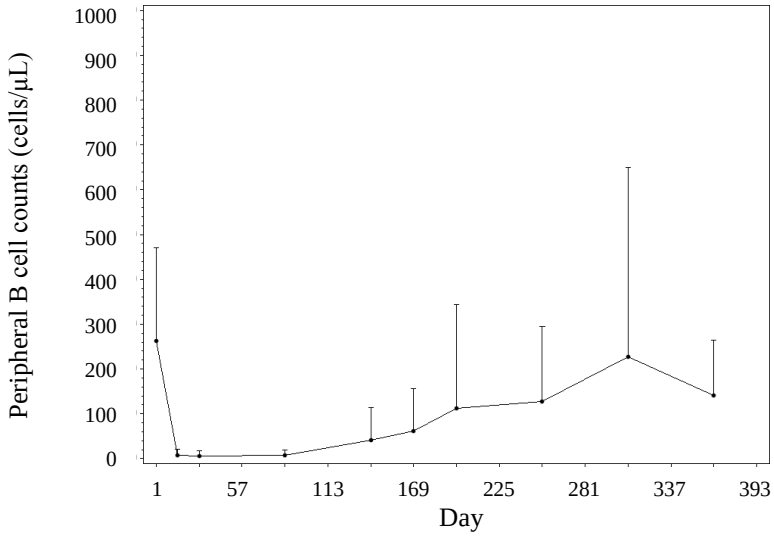


Figure 3. Peripheral B cell counts (n = 23) over time

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) HACA

Of the subjects who received rituximab in Studies 01 and 02, HACA was confirmed in 9.7% (3 of 31 subjects[9]) and in 17.4% (4 of 23 subjects), respectively. The applicant explained the impact of HACA on the efficacy and safety of rituximab as follows:

Efficacy was evaluated in 54 subjects to whom rituximab was administered in Studies 01 and 02. The relapse-free periods (median [95% CI]) for HACA-negative subjects was 274.0 days [234.0, 367.0 days] (relapse in 31 of 47 subjects). The relapse-free period for HACA-positive subjects was 374.0 days [163.0 days, not reached (NR)] (relapse in 4 of 7 subjects). No clear difference was seen in time to the first relapse between HACA-negative and HACA-positive subjects.

Among the 54 subjects who received rituximab in Studies 01 and 02, safety was evaluated in HACA-positive patients. No clear correlation was confirmed between HACA and adverse events or laboratory abnormalities.

Although it should be noted that the limited numbers of subjects were included in Studies 01 and 02, PMDA considers that no new measures are needed because no clear effects of HACA production on the efficacy and safety of rituximab have been confirmed.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The results of 2 Japanese clinical studies were submitted as the evaluation data for efficacy and safety. Table 3 gives the definitions of the terms and endpoints for the submitted clinical studies.

Table 3. Definitions of terms and endpoints

Nephrotic syndrome	Urinary protein/creatinine ratio ≥1.8 and serum albumin ≤2.5 g/dL
Remission	Negative morning urinary protein, as tested by the paper method, for 3 consecutive days
Relapse	Morning urinary protein ≥2+, as tested by the paper method, for at least 3 consecutive days and requiring prednisolone therapy
Frequently relapsing	At least 2 relapses within 6 months of initial remission or at least 4 relapses within any 12-month period
Steroid dependency	Two successive relapses during the treatment with the reduced dose of prednisolone or within 2 weeks after the discontinuation of prednisolone
Steroid resistance	No remission within 4 weeks of daily doses of 60 mg/m^2/day prednisolone.
Refractory nephrotic syndrome	Nephrotic syndrome patients meeting any one of the following 3 criteria: (a) Diagnosed as frequently relapsing or steroid-dependent nephrotic syndrome and diagnosed again as frequently relapsing or steroid-dependent nephrotic syndrome after immunosuppressant therapy (cyclosporine, cyclophosphamide, mizoribin, etc.) (b) Diagnosed as frequently relapsing or steroid-dependent nephrotic syndrome and diagnosed again as frequently relapsing or steroid-dependent nephrotic syndrome during immunosuppressant therapy (cyclosporine, cyclophosphamide, mizoribin, etc.) (c) Diagnosed as steroid resistant nephrotic syndrome and diagnosed as frequently relapsing or steroid-dependent nephrotic syndrome during or after immunosuppressant therapy (cyclosporine monotherapy or cyclosporine and methylprednisolone combination)

4.(iii).A.(1) Phase III confirmatory study (5.3.5.1-1, Study Number RCRNS-01, from November 2008 to November 2011)

A multicenter, randomized, placebo-controlled, double-blind study was conducted at 9 centers in Japan to investigate the efficacy, safety, and pharmacokinetics of rituximab in patients with childhood-onset refractory nephrotic syndrome of ≥2 years of age [see Table 4] (target sample size, 60 subjects).

Table 4. Key inclusion criteria

Patients meeting all of the following criteria:
- Patients with idiopathic nephrotic syndrome in whom the age of onset (initial onset) was ≥1 year and <18 years
- Patients satisfying 1) or 2) below:
  1) Diagnosed as frequently relapsing or steroid-dependent nephrotic syndrome and once again diagnosed as frequently relapsing[a)] or steroid-dependent[b)] nephrotic syndrome during or after immunosuppressant therapy (cyclosporine, cyclophosphamide, mizoribin)
  2) Diagnosed as steroid-resistant nephrotic syndrome and diagnosed as frequently relapsing[a)] or steroid-dependent[b)] nephrotic syndrome during or after immunosuppressant therapy (cyclosporine monotherapy or cyclosporine and methylprednisolone combination therapy)
- Patients who exhibit steroid sensitivity for treatment for relapses within 35 days prior to enrollment
- Patients with peripheral blood CD20-positive cells ≥5/μL

a) At least 4 relapses over any 12-month period within 2 years of the relapse immediately before the study
b) Diagnosed within 2 years of a relapse immediately before the study

Subjects received either the placebo or 375 mg/m^2/infusion of rituximab (maximum of 500 mg/infusion)[7] was administered as an intravenous infusion once weekly for a total of 4 doses. The subjects followed for 1 year after the initial administration. The rate of intravenous infusion was set to 25 mg/hour for the first hour of infusion, 100 mg/hour for the next hour, and 200 mg/hour thereafter. When rituximab was administered at a slower rate (<200 mg/hour) at the investigator's discretion, the infusion was completed within 24 hours after preparation of the rituximab solution. The infusion was allowed to be started at 100 mg/hour for the second and subsequent doses if infusion reactions were mild during the previous infusion.

When the number of subjects with an initial relapse reached 30, an interim analysis was to be performed to evaluate the superiority of rituximab over placebo by the Efficacy and Safety Assessment Committee to decide whether to continue the study from the standpoint of efficacy and safety.[12]

The interim analysis was conducted once 30 subjects with an initial relapse were confirmed (data cutoff date: May 7, 2010). The superiority of rituximab over placebo[13] was verified based on the relapse-free period[14] (the primary endpoint) as well as the incidence of relapse[15] and time to second relapse[16] (endpoints subjected to interim analysis). No statistically significant difference was found in the incidence of serious adverse events between the 2 groups. Based on the above results, randomization was stopped when 48 subjects (24 subjects per group) were enrolled; that enrollment in the rituximab group alone was continued for up to 30 subjects enrolled; and the study was continued until the 1-year follow-up period for the last subject was completed. Only the decision of study continuation based on the result of the interim analysis was planned to be passed on to investigators and participating medical institutions, but some information suggestive of the superiority of rituximab over placebo was also communicated. However, its impact on the efficacy and safety of rituximab was judged to be minimal [see "4.(iii).B.(1) Efficacy"]. In the subsequent part of this section, efficacy is discussed based on the results of the interim analysis and safety discussed based on the results of interim and final analyses [see "4.(iii).B.(1) Efficacy" for the results of final efficacy analysis].

In the interim analysis, all 42 subjects who were randomized and given the investigational drug at least once (21 subjects per group) were included in the full analysis set (FAS), which was the efficacy analysis (interim period) and safety analysis (interim period) populations. Of the 42 subjects, 19 subjects discontinued the study. Details are as follows: 15 subjects in the placebo group, "consent withdrawal/subject's own request" (1 subjects) and "investigator's/subinvestigator's discretion" (14 subjects); and 4 subjects in the rituximab group, "investigator's/subinvestigator's discretion".

For the final analysis, all 48 subjects who were randomized and given the investigational drug at least once (24 subjects per group) were included in the safety analysis. Of the 48 subject, 24 subjects discontinued the study. Details are as follows: 20 subjects in the placebo group, investigator's discretion (due to exacerbated primary disease associated with relapse) (18 subjects), investigator's discretion (due to difficult remission maintenance) (1 subject), consent withdrawal (1 subject); and 4 subjects in the rituximab group, investigator's discretion (due to exacerbated primary disease associated with relapse).

With respect to efficacy, Table 5 and Figure 4 show the relapse-free period (primary endpoint) as calculated by the Kaplan-Meier method. Compared to the placebo group, statistically significant prolongation of the relapse-free period was noted in the rituximab group (P = 0.00015, log-rank test, one-sided significance level 0.25%[17]).

[12] The study was designed as follows: once the superiority of rituximab was verified, randomization including the placebo group was to be stopped; that enrollment was to be continued for up to 30 subjects for the rituximab group; and that the study was to be continued until the 1-year follow-up period was completed for the last subject.

[13] The study was designed as follows: the superiority of rituximab over placebo was to be verified when the P value for relapse-free period, incidence of relapse, and time to second relapse were to be below pre-defined one-sided significance levels of 0.25%, 2.5%, and 2.5%, respectively.

[14] Length of time from the day of randomization to the first relapse after the start of investigational drug administration

[15] Number of relapses per year per person per group

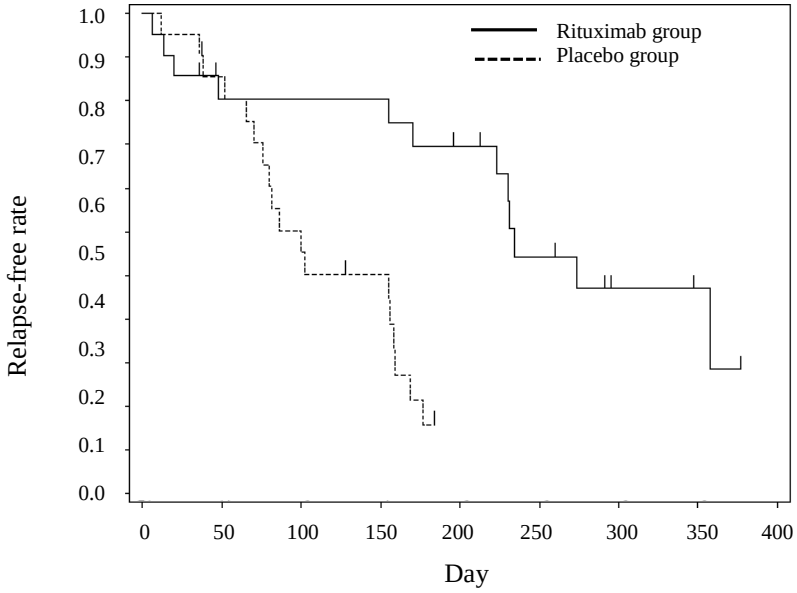
[16] Length of time from the day of randomization to the second relapse after the start of investigational drug administration

[17] The O'Brien-Fleming method was used for adjustment of multiplicity. For the final analysis, the significance level was set to one-sided 2.25% so that the type I error probability for the entire study would be one-sided 2.5%.

Table 5. Relapse-free period (FAS) (interim analysis)

	Placebo group (n = 21)	Rituximab group (n = 21)
Number of relapse	18 subjects	12 subjects
Relapse-free period[a] (days) (Median [95% CI])	100.0 [76.0, 156.0]	234.0 [170.0, 358.0]
Hazard ratio [95% CI][b]	0.1917 [0.0728, 0.5043]	
P value[c]	*P* = 0.00015	

a) Estimated by the Kaplan-Meier method
b) Estimated by the Cox proportional hazard model
c) Log-rank test, the one-sided significance level for the interim and final analyses was set to 0.25 and 2.25%, respectively, for adjustment of multiplicity.



Number of at-risk subjects								
Rituximab group	21	15	15	15	12	7	3	2
Placebo group	21	17	9	7	0	0	0	0

Figure 4. Relapse-free period by the Kaplan-Meier method (FAS) (interim analysis)

Table 6 summarizes the time to first and second relapses (endpoints subjected to interim analysis). For both figures, statistically significant differences were noted between the placebo and rituximab groups (*P* = 0.0000, sorting test, one-sided significance level 2.5%, *P* < 0.0001, log-rank test, one-sided significance level 2.5%).

Table 6. Incidence of relapse and time to second relapse (FAS) (interim analysis)

	Placebo group (n = 21)	Rituximab group (n = 21)
Total number of relapses (times)	34	22
Total follow-up period (patient-year)	7.19	16.61
Incidence of relapse (times/patint-year)[95% CI]	4.73 [3.22, 7.64]	1.32 [0.90, 2.14]
P value[a]	*P* = 0.0000	
Number of subjects with second relapse	9 subjects	6 subjects
Time to second relapse[b] (days) (Median [95% CI])	183.0 [160.0, 235.0]	NR [261.0, NR]
P value[c]	*P* < 0.0001	

a) Sorting test, one-sided significance level 2.5%, b) Estimated by the Kaplan-Meier method, and
c) Log-rank test, one-sided significance level 2.5%

With respect to safety, adverse events up to the interim analysis occurred in 95.2% of the placebo group (20 of 21 subjects) and in 100.0% of the rituximab group (21 of 21 subjects). Adverse events for which a causality to the administration could not be ruled out (adverse drug reactions) were noted in 95.2% of the placebo group (20 of 21 subjects) and in 100.0% of the rituximab group (21 of 21 subjects). Tables 7 and 8 summarize adverse events and adverse drug reactions, respectively, occurring with incidences of ≥10% in any group.

Table 7. Adverse events occurring with incidence of ≥10% in any group (interim analysis)

	Placebo group (n = 21)		Rituximabgroup (n = 21)			Placebo group (n = 21)		Rituximab group (n = 21)	
	Incidence	n	Incidence	n		Incidence	n	Incidence	n
Total adverse events	95.2%	20	100.0%	21	Flushing	9.5%	2	14.3%	3
Upper respiratory tract infection	33.3%	7	38.1%	8	Gastroenteritis	9.5%	2	14.3%	3
Nasopharyngitis	23.8%	5	28.6%	6	White blood cell count increased	0.0%	0	14.3%	3
Hypertension	14.3%	3	28.6%	6	Oropharyngeal discomfort	0.0%	0	14.3%	3
Acne	14.3%	3	23.8%	5	Dyspnea	0.0%	0	14.3%	3
Pruritus	0.0%	0	23.8%	5	Cough	0.0%	0	14.3%	3
CRP increased	19.0%	4	19.0%	4	Hordeolum	14.3%	3	9.5%	2
Lymphocyte count decreased	14.3%	3	19.0%	4	Blood uric acid increased	23.8%	5	4.8%	1
Fever	4.8%	1	19.0%	4	Tremor	14.3%	3	0.0%	0
ALT increased	14.3%	3	14.3%	3	AST increased	14.3%	3	0.0%	0

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Table 8. Adverse drug reactions occurring with incidence of ≥10% in any group (interim analysis)

	Placebo group (n = 21)		Rituximab group (n = 21)			Placebo group (n = 21)		Rituximab group (n = 21)	
	Incidence	n	Incidence	n		Incidence	n	Incidence	n
Total adverse reactions	95.2%	20	100.0%	21	Gastroenteritis	9.5%	2	14.3%	3
Upper respiratory tract infection	28.6%	6	33.3%	7	Flushing	9.5%	2	14.3%	3
Hypertension	14.3%	3	23.8%	5	Cough	0.0%	0	14.3%	3
Pruritus	0.0%	0	23.8%	5	Dyspnea	0.0%	0	14.3%	3
Lymphocyte count decreased	14.3%	3	19.0%	4	Oropharyngeal discomfort	0.0%	0	14.3%	3
Nasopharyngitis	14.3%	3	19.0%	4	White blood cell count increased	0.0%	0	14.3%	3
Fever	4.8%	1	19.0%	4	Hordeolum	14.3%	3	9.5%	2
CRP increased	19.0%	4	14.3%	3	Blood uric acid increased	23.8%	5	4.8%	1
ALT increased	9.5%	2	14.3%	3	Tremor	14.3%	3	0.0%	0

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No deaths occurred. Serious adverse events occurred in 23.8% (5 of 21 subjects) of the placebo group (hypoproteinemia in 4 subjects, and seizure in 1 subject) and in 38.1% (8 of 21 subjects) of the rituximab group (hypoproteinemia, gastritis/hypoproteinemia, cellulitis, neutrophil count decreased, respiratory disorder/hypoproteinemia/hemorrhagic cystitis, adrenal gland dysfunction/acute renal failure, hypoproteinemia/gingival infection, and gastroenteritis in 1 subject each). A causal relationship to investigational drug could not be ruled out for gastritis, cellulitis, neutrophil count decreased, respiratory disorder, hemorrhagic cystitis, adrenal gland dysfunction, gingival infection, and gastroenteritis in the rituximab group.

In the final analysis, adverse events were noted in 95.8% (23 of 24 subjects) of the placebo group and in 100.0% (24 of 24 subjects) of the rituximab group. Adverse drug reactions were observed in 95.8% (23 of 24 subjects) of the placebo group and in 100.0% (24 of 24 subjects) of the rituximab group. Tables 9 and 10 show the adverse events and adverse drug reactions, respectively, occurring with incidences ≥10% in any group.

Table 9. Adverse events occurring with incidence of ≥10% in any group (final analysis)

	Placebo group (n = 24)		Rituximab group (n = 24)			Placebo group (n = 24)		Rituximab group (n = 24)	
	Incidence	n	Incidence	n		Incidence	n	Incidence	n
Total adverse events	95.8%	23	100.0%	24	Dyspnea	0.0%	0	16.7%	4
Upper respiratory tract infection	58.3%	14	66.7%	16	Atopic dermatitis	0.0%	0	16.7%	4
CRP increased	29.2%	7	45.8%	11	Hordeolum	16.7%	4	12.5%	3
Lymphocyte count decreased	41.7%	10	37.5%	9	Weight increased	16.7%	4	12.5%	3
Nasopharyngitis	25.0%	6	33.3%	8	Blood uric acid increased	16.7%	4	12.5%	3
Hypertension	16.7%	4	33.3%	8	Flushing	8.3%	2	12.5%	3
Eosinophil count increased	4.2%	1	29.2%	7	Arthropod sting	8.3%	2	12.5%	3
ALT increased	33.3%	8	25.0%	6	Eczema	4.2%	1	12.5%	3
Hypoproteinemia	20.8%	5	25.0%	6	Vomiting	0.0%	0	12.5%	3
Gastroenteritis	12.5%	3	25.0%	6	Influenza	0.0%	0	12.5%	3
Pruritus	0.0%	0	25.0%	6	Impetigo	0.0%	0	12.5%	3
Acne	12.5%	3	20.8%	5	Oropharyngeal discomfort	0.0%	0	12.5%	3
Fever	4.2%	1	20.8%	5	Arthralgia	16.7%	4	8.3%	2
White blood cell count decreased	4.2%	1	20.8%	5	Feeling hot	12.5%	3	8.3%	2
Neutrophil count decreased	0.0%	0	20.8%	5	AST increased	12.5%	3	8.3%	2
Abdominal pain	12.5%	3	16.7%	4	Allergic conjunctivitis	12.5%	3	4.2%	1
Pharyngitis	4.2%	1	16.7%	4	Hypotension	12.5%	3	0.0%	0
Conjunctivitis	0.0%	0	16.7%	4	Sinus bradycardia	12.5%	3	0.0%	0
Cough	0.0%	0	16.7%	4	Tremor	12.5%	3	0.0%	0

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Table 10. Adverse drug reactions occurring with incidence of ≥10% in any group (final analysis)

	Placebo group (n = 24)		Rituximab group (n = 24)			Placebo group (n = 24)		Rituximab group (n = 24)	
	Incidence	n	Incidence	n		Incidence	n	Incidence	n
Total adverse reactions	95.8%	23	100.0%	24	Dyspnea	0.0%	0	16.7%	4
Upper respiratory tract infection	50.0%	12	62.5%	15	Atopic dermatitis	0.0%	0	16.7%	4
CRP increased	29.2%	7	45.8%	11	Hordeolum	16.7%	4	12.5%	3
Lymphocyte count decreased	41.7%	10	37.5%	9	Blood uric acid increased	16.7%	4	12.5%	3
Hypertension	16.7%	4	29.2%	7	Weight increased	12.5%	3	12.5%	3
ALT increased	25.0%	6	25.0%	6	Flushing	8.3%	2	12.5%	3
Gastroenteritis	12.5%	3	25.0%	6	Arthropod sting	0.0%	0	12.5%	3
Nasopharyngitis	12.5%	3	25.0%	6	Eczema	4.2%	1	12.5%	3
Eosinophil count increased	4.2%	1	25.0%	6	Vomiting	0.0%	0	12.5%	3
Pruritus	0.0%	0	25.0%	6	Influenza	0.0%	0	12.5%	3
Fever	4.2%	1	20.8%	5	Impetigo	0.0%	0	12.5%	3
White blood cell count decreased	4.2%	1	20.8%	5	Oropharyngeal discomfort	0.0%	0	12.5%	3
Neutrophil count decreased	0.0%	0	20.8%	5	Arthralgia	16.7%	4	8.3%	2
Abdominal pain	8.3%	2	16.7%	4	Feeling hot	12.5%	3	8.3%	2
Pharyngitis	4.2%	1	16.7%	4	Allergic conjunctivitis	12.5%	3	4.2%	1
Conjunctivitis	0.0%	0	16.7%	4	Hypotension	12.5%	3	0.0%	0
Cough	0.0%	0	16.7%	4	Sinus bradycardia	12.5%	3	0.0%	0
Conjunctivitis	0.0%	0	16.7%	4	Tremor	12.5%	3	0.0%	0

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No deaths occurred. Serious adverse events occurred in 25.0% (6 of 24 subjects) of the placebo group (hypoproteinemia in 5 subjects and seizure in 1 subject) and in 41.7% (10 of 24 subjects) of the rituximab group (hypoproteinemia in 3 subjects, gastritis/hypoproteinemia, cellulitis, neutrophil count decreased, respiratory disorder/hypoproteinemia/hemorrhagic cystitis, adrenal gland dysfunction/acute renal failure, hypoproteinemia/gingival infection, and gastroenteritis in 1 subject each). A causal relationship to investigational drug could not be denied for gastritis, cellulitis, neutrophil count decreased, respiratory disorder, hemorrhagic cystitis, adrenal gland dysfunction, gingival infection, and gastroenteritis in the

rituximab group. All serious adverse events in the rituximab group, for which a causal relationship could not be ruled out, resolved.

With respect to PK, see "4.(ii).A.(1) Phase III confirmatory study (RCRNS-01)."

4.(iii).A.(2) Pharmacokinetics study (5.3.5.2-1, Study Number RCRNS-02, from November 2008 to December 2011)

A multicenter, open-label, uncontrolled study was conducted at 9 centers in Japan to investigate the pharmacokinetics, efficacy, and safety of rituximab in patients with childhood-onset refractory nephrotic syndrome of ≥2 years of age[18] (target number sample size, n = 20).

Subjects received 375 mg/m^2/infusion of rituximab (the maximum dose of 500 mg/infusion)[7] once weekly as an intravenous infusion for a total of 4 doses. The duration of the follow-up was set to 1 year after the first administration. The rate of intravenous infusion was set to 25 mg/hour for the first hour of administration, 100 mg/hour for the next hour, and 200 mg/hour thereafter. When rituximab was administered at a slower rate (<200 mg/hour) at the investigator's discretion, the infusion was completed within 24 hours of preparation of the rituximab solution. With subsequent administrations, the infusion was allowed to start at 100 mg/hour if infusion reactions were mild during the previous infusion.

All 23 patients receiving rituximab[19] were included in the FAS and safety analysis population. FAS was use for the primary efficacy analysis. Of the 23 patients, 8 discontinued the study (exacerbated primary disease associated with relapse [5 subjects] and consent withdrawal [3 subjects]).

With respect to efficacy, the median relapse-free period [95% CI] was 287.0 days [211.0, 344.0 days].

With respect to safety, adverse events and adverse drug reactions were observed in all subjects (23 of 23 subjects). Tables 11 and 12 show adverse events and adverse drug reactions, respectively, occurring with incidences ≥10%.

Table 11. Adverse events occurring at ≥10% incidence

	Incidence	n		Incidence	n
Total adverse events	100.0%	23	Hypoproteinemia	17.4%	4
Upper respiratory tract infection	56.5%	13	Acne	17.4%	4
Lymphocyte count decreased	52.2%	12	Diarrhea	13.0%	3
CRP increased	39.1%	9	Fever	13.0%	3
ALT increased	30.4%	7	Perionychia	13.0%	3
Gastroenteritis	26.1%	6	Oropharyngeal discomfort	13.0%	3
Nasopharyngitis	26.1%	6	Arthropod sting	13.0%	3
Eczema	26.1%	6	AST increased	13.0%	3
Influenza	21.7%	5	Eosinophil count increased	13.0%	3
Pharyngitis	21.7%	5	White blood cell count decreased	13.0%	3
Conjunctivitis	21.7%	5	Headache	13.0%	3
Hypertension	17.4%	4	Xeroderma	13.0%	3
Hordeolum	17.4%	4			

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[18] Patients with childhood-onset refractory nephrotic syndrome [see Table 4] meeting one of the 3 criteria below:
1) In Study 01, subjects who received placebo and experienced a relapse before Week 13 (Day 85) of the start of investigational drug administration
2) In Study 01, subjects who received placebo and were diagnosed with either frequently relapsing or steroid-dependent nephrotic syndrome between Weeks 13 and 53 (Days 86 and 365)
3) Subjects who received rituximab prior to December 31, 2007.

[19] Twenty subjects received the placebo in Study 01 and 3 subjects received rituximab ≥1 year ago.

Table 12. Adverse reactions occurring with an incidence of ≥10%

	Incidence	n		Incidence	n
Total adverse reactions	100.0%	23	Hordeolum	17.4%	4
Upper respiratory tract infection	56.5%	13	Diarrhea	13.0%	3
Lymphocyte count decreased	52.2%	12	Fever	13.0%	3
CRP increased	34.8%	8	Perionychia	13.0%	3
ALT increased	30.4%	7	Oropharyngeal discomfort	13.0%	3
Gastroenteritis	26.1%	6	Headache	13.0%	3
Nasopharyngitis	26.1%	6	Acne	13.0%	3
Eczema	26.1%	6	Xeroderma	13.0%	3
Influenza	21.7%	5	AST increased	13.0%	3
Pharyngitis	21.7%	5	Eosinophil count increased	13.0%	3
Conjunctivitis	21.7%	5	White blood cell count decreased	13.0%	3
Hypertension	17.4%	4			

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No deaths occurred. Serious adverse events occurred in 4 subjects (hypoproteinemia in 3 subjects and hypoproteinemia/gastroenteritis in 1 subject). A causal relationship to investigational drug could not be ruled out for gastroenteritis. These serious adverse events resolved or were resolving.

With respect to PK, see "4.(ii).A.(2) Pharmacokinetic study (RCRNS-02)."

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Efficacy

Based on the following investigations 1) to 3), PMDA concluded that the submitted data demonstrated the efficacy of rituximab in patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent). However, given the limited number of subjects included in Study 01, and information should be collected through post-marketing surveillance to confirm the efficacy of rituximab in patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent).

The efficacy of rituximab will be finalized by taking account of comments from the Expert Discussion.

4.(iii).B.(1).1) Blind in Study 01

4.(iii).B.(1).1).(a) Unblinding of subjects assessed as treatment failures

In Study 01, the protocol specified that information on treatment assignments would be disclosed to the investigator when the treatment was assessed as a failure in which the patient met any one of the criteria listed below.

(i) Had relapsed nephrotic syndrome by Week 13 (Day 85)
(ii) Diagnosed as frequently relapsing or steroid-dependent nephrotic syndrome between Day 86 (the day after Week 13) and Day 365 (Week 53).
(iii) Diagnosed as steroid resistant during the follow-up period (Days 1-365)

The applicant gave the rationale for unblinding of the study and the impact of the unblinding on the blinding of the study and the evaluation of efficacy and safety.

a) Rationale for unblinding procedures

For the following reasons, the details and duration of prior treatments and adverse drug reactions should be taken into account when investigators choose the next therapy for patients whose treatment was judged as a failure:

- In the rituximab group, subjects assessed as treatment failures involving the above (i) or (ii) were considered to have experienced rituximab-induced B cell depletion. The risk of excessive immunosuppression would have been a concern for starting a new steroid or immunosuppressant therapy. B and T cells counts were not measured at participating medical institutions.

- In the placebo group, subjects assessed as treatment failures involving the above (i) or (ii) were allowed to be enrolled in Study 02.
- Subjects assessed as treatment failures involving the above (iii) were to receive therapy for steroid-resistant nephrotic syndrome.

b) Impact on blinding of study and evaluation of efficacy and safety

With respect to the impact of unblinding of subjects assessed as treatment failures on the blinding of the study, it cannot be ruled out that the disclosure of a part of the assignment information to the investigators may have resulted in an increase in the predictability of treatment assignments for other subjects at the same site. However, the treatment assignment for other subjects remained blinded, which prevents exact prediction, ensuring the validity of the placebo-controlled double-blind study.

To assess the relapse-free period (primary endpoint), the first relapse was evaluated prior to the assessment of a treatment failure. As a result, assignment information did not impact efficacy assessments. Additionally, assignment information was unlikely to impact safety assessment because (1) a treatment failure in the placebo group resulted in study discontinuation in most subjects (20 of 24 subjects), (2) the duration of the follow-up after the assessment of treatment failure (unblinding) was short, and (3) safety was assessed based mainly on data prior to treatment failure. On the other hand, a treatment failure resulted in withdrawal in 10 of the 24 subjects in the rituximab group, and the duration of the follow-up after the assessment of treatment failure (unblinding) was long for a relatively large number of subjects. However, among the unblinded subjects assessed as treatment failures, the causal relationship of rituximab was often taken into consideration. Unblinding may have impacted safety assessments; however, blinding information of the rituximab group is thought to have encouraged the investigators to pay closer attention to safety issues. Therefore, the applicant considered that evaluating safety based on the results of Study 01 posed no concerns.

PMDA considers as follows:

With respect to efficacy evaluation, unblinding of subjects assessed as treatment failures would pose no major issues since relapse-free periods (primary endpoints of Study 01) were assessed by urinary protein assessed by the paper method, an objective parameter.

With respect to safety evaluation, it cannot be ruled out that the disclosure of assignment information of some subjects to the investigators may have resulted in an increase in the predictability of assignment information for the other subjects at the same site. As a result, assessments of the causal relationship of adverse events with the treatment may have been affected not just in subjects with treatment failures, but for other subjects.

As mentioned above, the unblinding procedures specified in Study 01 may have impacted safety evaluations. However, given the extremely limited range of therapeutic options for refractory nephrotic syndrome (patient population of the study), unblinding was necessary for investigators to choose the best therapeutic option for subjects assessed as treatment failures.

4.(iii).B.(1).1).(b) Some interim analysis results from Study 01 were communicated to investigators and participating medical institutions

In Study 01, only the decision of study continuation based on the results of the interim analysis was planned to be passed on to investigators and participating medical institutions, but some information suggestive of the superiority of rituximab over placebo was also communicated.

The applicant explained the impact of disclosed results of efficacy and safety assessments included in the interim analysis as follows:

The impact of communicating interim analysis results on efficacy and safety assessments was considered to be minimal for the following reasons: (1) The assignment codes were properly sealed by the person in charge of assignment until the final analysis after completion of Study 01 and the results of randomization were not disclosed until the data lock after the study completion; (2) When interim analysis results were reported to the investigators and participating medical institutions, the administration of rituximab had been completed for the subjects for main efficacy and safety analyses; and (3) Relapse-free periods (primary endpoint) were assessed by an objective indicator.

PMDA considers as follows:
In Study 01, randomization was to be stopped once the interim analysis verified the superiority of rituximab over placebo, and while maintaining the blind status, enrollment was to be continued for up to 30 subjects for the rituximab group. Therefore, the results of the interim analysis enable the investigators to deduce that all the subjects enrolled subsequently enrolled would receive rituximab. It cannot be ruled out that this may have affected the judgments of investigator and the assessments of causal relationships resulting in bias in the study results after the interim analysis.

Based on the above, PMDA considers that the efficacy for Study 01 should be evaluated based mainly on interim analysis results, with consideration for final analysis results.

4.(iii).B.(1).2) Efficacy in Study 01

For the interim analysis in Study 01, statistically significant results were obtained for relapse-free period (primary endpoint) and for the incidence of relapse and time to second relapse (endpoints subjected to the interim analysis). These results verified the superiority of rituximab over placebo [see "4.(iii).A.(1) Phase III confirmatory study (RCRNS-01)"].

The results of the final analysis were as follows:
Table 13 summarizes relapse-free periods (primary endpoint). The relapse-free period for the rituximab group was significantly longer than that for the placebo group ($P < 0.001$, log-rank test, one-sided significance level 2.25%[20]). Table 14 shows the secondary endpoints.

Table 13. Relapse-free period (FAS) (Study 01 final analysis)

	Placebo group (n = 24)	Rituximab group (n = 24)
Number of subjects who relapsed	23 subjects	17 subjects
Relapse-free period[a)] (days) (Median [95% CI])	101.0 [70.0, 155.0]	267.0 [223.0, 374.0]
Hazard ratio[b)] [95% CI]	0.267 [0.135, 0.528]	
P value[c)]	*P* < 0.001	

a) Estimated by the Kaplan-Meier method
b) Estimated by the Cox proportional hazard model
c) Log-rank test, the one-sided significance level for the interim and final analyses was set to 0.25 and 2.25%, respectively, for adjustment of multiplicity.

Table 14. Secondary endpoints (FAS) (Study 01 final analysis)

Endpoints	Placebo group (n = 24)	Rituximab group (n = 24)	Hazard ratio[a)] [95% CI]	*P* value
Time to treatment failure[b)] (Number of cases)	163.0 days [70.0 days, 251.0 days] (20 subjects)	Not reached [287.0 days, NR] (10 subjects)	0.268 [0.122, 0.589]	*P* < 0.001[c)]
Incidence of relapse	4.171 times/subject/year	1.542 times/subject/year	-	*P* < 0.001[d)]

a) Estimated by the Cox proportional hazard model, b) Median [95% CI], c) Log-rank test and d) Sorting test

Based on the above results, PMDA considers that the efficacy of rituximab for childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) has been demonstrated.

4.(iii).B.(1).3) Efficacy in different age groups

Table 15 shows the relapse-free period for 54 subjects classified by age group. These subjects received rituximab in Studies 01[9] and 02.

[20] The O'Brien-Fleming method was used for adjustment of multiplicity. For the final analysis, the significance level was set to one-sided 2.25% so that the type I error probability for the entire study would be one-sided 2.5%.

Table 15. Relapse-free period in different age groups
(subjects in the rituximab group in Studies 01 and all subjects in Study 02)

	Number of subjects who relapsed	Relapse-free period[a)] (days) (Median [95% CI])
≤6 years (n = 7)	7 subjects	179.0 [10.0 , 223.0]
≥7 years and <15 years (n = 27)	17 subjects	291.5 [207.0 , -]
≥15 years and <18 years (n = 10)	5 subjects	367.0 [13.0 , -]
≥18 years (n = 10)	6 subjects	287.0 [231.0 , -]

a) Estimated by the Kaplan-Meier method

Based on the results of the Studies 01 and 02, PMDA considers that there is no need for age adjustments of the dosage and administration at present, although the median relapse-free period for the group of subjects aged ≤6 years was slightly shorter than for other age groups. However, since the number of studied subjects is limited, efficacy should be confirmed in different age groups by collecting information through post-marketing surveillance.

4.(iii).B.(2) Safety

Based on the results described in Sections 4.(iii).B.(2).1) to 4.(iii).B.(2).4), and given the fact that no new adverse events other than those reported for the approved indications were noted in Studies 01 and 02, PMDA considers that the safety of rituximab in patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) is acceptable as far as the drug is administered under the supervision of physicians with adequate knowledge and experience at a medical institution capable of appropriately handling emergencies, although due attention should be paid to infections and infusion reactions associated with administration of rituximab. Nevertheless, given the limited numbers of subjects in Studies 01 and 02, the safety of rituximab should be investigated in patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) by collecting information through post-marketing surveillance.

The safety of rituximab will be finalized by taking into account comments from the Expert Discussion.

4.(iii).B.(2).1) Safety in Japanese clinical studies

(a) Incidence of adverse events and reactions

Tables 16 and 17 summarize the adverse events and advserse drug reactions, respectively, occurring in≥10% of the 54 subjects receiving rituximab in Studies 01[9] and 02.

Table 16. Adverse events occurring in ≥10% of subjects
(subjects in the rituximab group in Study 01 and all subjects in Study 02)

	Rituximab administration (n = 54)			Rituximab administration (n = 54)	
	Incidence	n		Incidence	n
Total adverse events	100.0%	54	Acne	16.7%	9
Upper respiratory tract infection	61.1%	33	Neutrophil count decreased	16.7%	9
Lymphocyte count decreased	46.3%	25	White blood cell count decreased	16.7%	9
CRP increased	42.6%	23	Influenza	14.8%	8
Nasopharyngitis	31.5%	17	Dyspnea	14.8%	8
Gastroenteritis	25.9%	14	Hordeolum	13.0%	7
ALT increased	25.9%	14	Arthropod sting	13.0%	7
Hypertension	22.2%	12	Impetigo	11.1%	6
Hypoproteinemia	22.2%	12	Oropharyngeal discomfort	11.1%	6
Eosinophil count increased	22.2%	12	Headache	11.1%	6
Conjunctivitis	18.5%	10	Atopic dermatitis	11.1%	6
Eczema	18.5%	10	Pruritus	11.1%	6
Fever	16.7%	9	Asteatotic Eczema	11.1%	6
Pharyngitis	16.7%	9			

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Table 17. Adverse reactions occurring in ≥10% of subjects (subjects in the rituximab group in Study 01 and all subjects in Study 02)

	Rituximab administration (n = 54)			Rituximab administration (n = 54)	
	Incidence	n		Incidence	n
Total adverse reactions	100.0%	54	Pharyngitis	16.7%	9
Upper respiratory tract infection	59.3%	32	Neutrophil count decreased	16.7%	9
Lymphocyte count decreased	46.3%	25	White blood cell count decreased	16.7%	9
CRP increased	40.7%	22	Influenza	14.8%	8
Nasopharyngitis	27.8%	15	Dyspnea	14.8%	8
Gastroenteritis	25.9%	14	Hordeolum	13.0%	7
ALT increased	25.9%	14	Impetigo	11.1%	6
Hypertension	20.4%	11	Oropharyngeal discomfort	11.1%	6
Eosinophil count increased	20.4%	11	Headache	11.1%	6
Conjunctivitis	18.5%	10	Pruritus	11.1%	6
Eczema	18.5%	10	Asteatotic eczema	11.1%	6
Fever	16.7%	9			

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PMDA considers that these events warrant separate investigations [see "4.(iii).B.(2).2) Infections" and "4.(iii).B.(2).3) Infusion reactions"] since relatively large numbers of events involving infections and infusion reactions (hypertension, dyspnea, oropharyngeal discomfort, etc.) were confirmed.

(b) Adverse event onset to different time points

Table 18 shows adverse events occurring in ≥10% of the 31 subjects[9] receiving rituximab in Study 01.

Table 18. Summary of adverse events occurring at different time points for the rituximab group in Study 01

Onset	-Day 90	Day 91-180	Day 181-270	Day 271-360	Day 361-	Entire study
n	31 subjects	30 subjects	29 subjects	27 subjects	25 subjects	31 subjects
Total adverse events	100.0% (31 subjects)	86.7% (26 subjects)	93.1% (27 subjects)	66.7% (18 subjects)	44.0% (11 subjects)	100.0% (31 subjects)
Serious adverse events	22.6% (7 subjects)	13.3% (4 subjects)	13.8% (4 subjects)	7.4% (2 subjects)	8.0% (2 subjects)	41.9% (13 subjects)
Upper respiratory tract infection	38.7% (12 subjects)	33.3% (10 subjects)	37.9% (11 subjects)	14.8% (4 subjects)	4.0% (1 subject)	64.5% (20 subjects)
CRP increased	32.3% (10 subjects)	13.3% (4 subjects)	17.2% (5 subjects)	7.4% (2 subjects)	0.0% (0 subjects)	45.2% (14 subjects)
Lymphocyte count decreased	35.5% (11 subjects)	6.7% (2 subjects)	3.4% (1 subject)	0.0% (0 subjects)	0.0% (0 subjects)	41.9% (13 subjects)
Nasopharyngitis	19.4% (6 subjects)	16.7% (5 subjects)	17.2% (5 subjects)	18.5% (5 subjects)	0.0% (0 subjects)	35.5% (11 subjects)
Eosinophil count increased	9.7% (3 subjects)	13.3% (4 subjects)	3.4% (1 subject)	0.0% (0 subjects)	4.0% (1 subject)	29.0% (9 subjects)
Hypertension	22.6% (7 subjects)	0.0% (0 subjects)	6.9% (2 subjects)	3.7% (1 subject)	0.0% (0 subjects)	25.8% (8 subjects)
Gastroenteritis	9.7% (3 subjects)	6.7% (2 subjects)	17.2% (5 subjects)	3.7% (1 subject)	0.0% (0 subjects)	25.8% (8 subjects)
Neutrophil count decreased	12.9% (4 subjects)	10.0% (3 subjects)	3.4% (1 subject)	3.7% (1 subject)	4.0% (1 subject)	25.8% (8 subjects)
Hypoproteinemia	6.5% (2 subjects)	3.3% (1 subject)	10.3% (3 subjects)	3.7% (1 subject)	8.0% (2 subjects)	25.8% (8 subjects)
ALT increased	22.6% (7 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	22.6% (7 subjects)
Pruritus	9.7% (3 subjects)	6.7% (2 subjects)	0.0% (0 subjects)	3.7% (1 subject)	0.0% (0 subjects)	19.4% (6 subjects)
Fever	12.9% (4 subjects)	6.7% (2 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	19.4% (6 subjects)
Dyspnea	19.4% (6 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	19.4% (6 subjects)
White blood cell count decreased	9.7% (3 subjects)	13.3% (4 subjects)	3.4% (1 subject)	0.0% (0 subjects)	0.0% (0 subjects)	19.4% (6 subjects)
Acne	12.9% (4 subjects)	3.3% (1 subject)	0.0% (0 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	16.1% (5 subjects)
Conjunctivitis	9.7% (3 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	7.4% (2 subjects)	0.0% (0 subjects)	16.1% (5 subjects)
Cough	16.1% (5 subjects)	3.3% (1 subject)	0.0% (0 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	16.1% (5 subjects)
Weight increased	16.1% (5 subjects)	0.0% (0 subjects)	3.4% (1 subject)	0.0% (0 subjects)	0.0% (0 subjects)	16.1% (5 subjects)
Asteatotic eczema	6.5% (2 subjects)	6.7% (2 subjects)	6.9% (2 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	16.1% (5 subjects)
Abdominal pain	6.5% (2 subjects)	0.0% (0 subjects)	6.9% (2 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	12.9% (4 subjects)
Pharyngitis	3.2% (1 subject)	3.3% (1 subject)	6.9% (2 subjects)	3.7% (1 subject)	4.0% (1 subject)	12.9% (4 subjects)
Atopic dermatitis	6.5% (2 subjects)	6.7% (2 subjects)	0.0% (0 subjects)	3.7% (1 subject)	0.0% (0 subjects)	12.9% (4 subjects)
Flushing	12.9% (4 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	12.9% (4 subjects)
Arthropod sting	3.2% (1 subject)	6.7% (2 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	4.0% (1 subject)	12.9% (4 subjects)
Eczema	6.5% (2 subjects)	6.7% (2 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	12.9% (4 subjects)
Vomiting	9.7% (3 subjects)	0.0% (0 subjects)	3.4% (1 subject)	0.0% (0 subjects)	0.0% (0 subjects)	12.9% (4 subjects)
Impetigo	9.7% (3 subjects)	6.7% (2 subjects)	6.9% (2 subjects)	0.0% (0 subjects)	0.0% (0 subjects)	12.9% (4 subjects)

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Adverse events occurring at different time points in Study 01 were analyzed and PMDA confirmed that the incidence of the total adverse events decreased on and after Day 271 and that the onset of any events did not increase over time.

4.(iii).B.(2).2) Infections

In Study 01, the incidence of adverse events involving infections was 87.5% (21 of 24 subjects) for the placebo group and 95.8% (23 of 24 subjects) for the rituximab group. Three events (gastroenteritis, gingival infection, and cellulitis for the rituximab group) were Grade 3, and the other events were ≤ Grade 2. The incidence of infection requiring therapy was 75.0% (18 of 24 subjects) for the placebo group and 95.8% (23 of 24 subjects) for the rituximab group. The 3 events mentioned above were Grade 3 and the other events were ≤ Grade 2.

The incidence of adverse events involving infections among the 54 subjects administered rituximab in Studies 01[9] and 02 was 92.6% (50 of 54 subjects). There were five Grade-3 events (the above-mentioned 3 events and gastroenteritis and cellulitis) and the other events were ≤ Grade 2. The incidence of infections requiring therapy was 90.7% (49 of 54 subjects). Of the events, 5 events were Grade 3 (the above-mentioned 5 events) and the other events were ≤ Grade 2.

The applicant explained as follows:

The incidence of adverse events involving infections in Studies 01 and 02 was higher than that in a Japanese clinical study[21] in patients with CD20-positive B-cell non-Hodgkin's lymphoma, an approved indication. One of the reasons for the higher incidence of adverse events involving infections in Studies 01 and 02 was the use of steroids and immunosuppressants as premedication in the study subjects. Infection is listed in the "Clinically Significant Adverse Reaction" section in the current package insert, and the incidence of adverse events involving infections in Studies 01 and 02 will be included in the package insert.

PMDA considers as follows:

The incidence of adverse events involving infections was high for the rituximab group in Study 01 and for Study 02. However, most infections noted in these studies were ≤ Grade 2, upper respiratory tract infection and nasopharyngitis account for the majority of the cases of these infections, and all Grade-3 infections and serious infections resolved. Thus, as with the approved indications, the safety of rituximab is acceptable if the precautions against infection mentioned in the package insert are followed. However, given the limited numbers of subjects in Studies 01 and 02, it will be necessary to further investigate infections associated with rituximab by collecting information through post-marketing surveillance.

4.(iii).B.(2).3) Infusion reactions

The incidence of adverse events involving infusion reactions in Study 01[22] was 54.2% (13 of 24 subjects) for the placebo group and 79.2% (19 of 24 subjects) for the rituximab group. All events were ≤ Grade 2. The incidence of adverse events involving infusion reactions among the 54 subjects receiving rituximab in Studies 01[9] and 02 was 63.0% (34 of 54 subjects). All events were ≤ Grade 2.

The applicant explained as follows:

The incidence of adverse events involving infusion reactions in Studies 01 and 02 was lower than in Japanese clinical studies in patients with CD20-positive B-cell non-Hodgkin's lymphoma (approved indication)[23]. The results is considered attributable to the use of steroids and immunosuppressants in premedication or combination therapy in Studies 01 and 02.

[21] Japanese clinical studies on patients with CD20-positive B-cell non-Hodgkin's lymphoma (IDEC-C2B8-2 and IDEC-C2B8-3 Studies), 7.6% (12 of 157 subjects) (Recoded using MedDRA/J version 14.0).

[22] Adverse events which occurred within 24 hours of the start of infusion and for which a causal relationship with the investigational drug could not be ruled out.

[23] Japanese clinical studies of patients with CD20-positive B-cell non-Hodgkin's lymphoma (Studies IDEC-C2B8-2 and IDEC-C2B8-3), 92.4% (145 of 157 subjects) (Recoded using MedDRA/J version 14.0. Adverse events which occurred between the start of infusion and the following day of the infusion and for which a causal relationship with the investigational drug could not be ruled out were counted as infusion reaction).

PMDA considers as follows:
The infusion reactions noted for the rituximab group in Study 01 and Study 02 were all ≤ Grade 2. Most reactions were Grade 1. Thus, as was the case with the approved indication, the safety of rituximab is acceptable if the precautions against infection mentioned in the package insert are followed. However, given the limited numbers of subjects in Studies 01 and 02, it will be necessary to further investigate infection reactions associated with rituximab by collecting information through post-marketing surveillance.

4.(iii).B.(2).4) Safety in different age groups

Table 19 summarizes adverse events, infections requiring therapy, and infusion reactions in different age groups among the 54 subjects receiving rituximab in Studies 01[9] and 02.

Table 19. Adverse events in different age groups (subject in the rituximab group in Study 01 and all subjects in Study 02)

	Total (n = 54)		≤6 years (n = 7)		≥7 years and <15 years (n = 27)		≥15 years and <18 years (n = 10)		≥18 years (n = 10)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Total adverse events	100.0%	54	100.0%	7	100.0%	27	100.0%	10	100.0%	10
Infection requiring therapy	90.7%	49	85.7%	6	96.3%	26	100.0%	10	70.0%	7
Infusion reaction	63.0%	34	42.9%	3	63.0%	17	70.0%	7	70.0%	7

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PMDA confirmed that there were no significant age differences in the incidence of infusion reactions or infections requiring therapy in Studies 01 and 02. However, given the limited numbers of enrolled subjects, the safety of rituximab in different age groups should be further investigated through post-marketing surveillance.

4.(iii).B.(3) Clinical positioning and intended patient population

The proposed indication by the applicant was refractory nephrotic syndrome (frequently relapsing or steroid-dependent). The applicant explained its rationale, including the clinical positioning of rituximab in the treatment of nephrotic syndrome, as follows:
Pathology, diagnostic methods, treatment regimens, and therapeutic efficacy assessment criteria for idiopathic nephrotic syndrome vary depending on the timing of onset (childhood-onset vs. adult-onset), and treatment guidelines have been prepared for individual types of diseases.[24]

In the case of childhood-onset idiopathic nephrotic syndrome, while most patients are required to receive steroids for prolonged periods, adverse drug reactions are often problematic. In particular, growth disorders are an issue with growing children, and the use of immunosuppressants is frequently discontinued due to adverse drug reactions (Guideline for Drug Therapy of Pediatric Idiopathic Nephrotic Syndrome [version 1.0]). Therefore, new therapies are needed for patients with childhood-onset idiopathic nephrotic syndrome who have relapses frequently after transient remission achieved by administration of steroids but the condition (frequently relapsing type), or reducing or in whom discontinuing steroid administration results in relapse and weaning from steroid administration is difficult (steroid-dependent type).

The efficacy and safety of rituximab were confirmed in Study 01 in patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent). Thus, rituximab may become a new therapeutic option. Furthermore, alleviating the adverse reactions to steroids and immunosuppressants using rituximab has clinical significance.

Based on the above, the applicant selected refractory nephrotic syndrome (frequently relapsing or steroid-dependent) as the indication. In addition, the package insert must clearly indicate that the intended population of the clinical study is subjects with childhood-onset nephrotic syndrome and that no clinical studies have been conducted in those with adult-onset nephrotic syndrome.

[24] "Guideline for Drug Therapy of Pediatric Idiopathic Nephrotic Syndrome (version 1.0)," its revised version "Clinical Practice Guideline for Pediatric Idiopathic Nephrotic Syndrome 2013," and "Guidelines for the Treatment of Nephrotic Syndrome" (*Japanese Journal of Nephrology.* 2011;53:78-122).

PMDA considers as follows:
Study 01 in subjects with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) confirmed the efficacy of rituximab [see "4.(iii).B.(1) Efficacy"] and its safety is acceptable [see "4.(iii).B.(2) Safety"]. Based on the results of Study 01, it is acceptable to include childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) in the indication of rituximab.

The indication of rituximab will be finalized after taking into account comments from the Expert Discussion.

4.(iii).B.(4) Dosage and administration and infusion rate
PMDA reviewed the dosage and administration of rituximab as stated below in 4.(iii).B.(4).1) and 4.(iii).B.(4).2). The dosage and administration will be finalized after taking into account comments from the Expert Discussion.

4.(iii).B.(4).1) Dosage and administration
The applicant provided the following justification for proposed dosage and administration of rituximab in Studies 01 and 02:

- Administering 375 mg/m^2/infusion of rituximab once weekly for 4 doses is within the range of the dosage and administration for the approved indication (CD20-positive B-cell non-Hodgkin's lymphoma). Safety information was obtained.
- In clinical studies in pediatric patients with autoimmune diseases (*Br J Haematol*. 2002;116:465-467, *J Pediatr*. 2006;148:623-627, etc.), rituximab was administered within the range of 375 mg/m^2/infusion once weekly for 4 doses. The data from the studies demonstrated the efficacy and safety.
- According to overseas reports, when rituximab was administered in accordance with the proposed dosage and administration to 6 patients with childhood-onset refractory nephrotic syndrome (12-23 years of age), peripheral blood B cells were depleted in 5 of the 6 patients for 5 to 12 months. In all 6 patients, remission was maintained for 7 to 13 months, and the use of steroids and immunosuppressants was either reduced or stopped. Furthermore, no serious adverse events were noted (*Pediatr Nephrol*. 2004;19:794-797, *Pediatr Nephrol*. 2006;21:1698-1700, etc.).
- In Japan, the maximum dose of 500 mg/infusion was administered to patients with childhood-onset refractory nephrotic syndrome (*Pediatr Nephrol*. 2009;24:1321-1328, etc.).

Tables 20 and 21 show the efficacy (relapse-free period) and safety of rituximab for 375 mg/m^2/infusion (n = 35) and 500 mg/infusion (n = 19) in Studies 01 and 02.[25] The median period of peripheral blood B cell depletion [95% CI] was 141.0 days [120.0, 160.0 days] for 375 mg/m^2/infusion[26] and 184.0 days (135, 252.0 days) for 500 mg/infusion. With respect to PK, the C_{max} and AUC_{all} (mean ± SD) in Study 02 were 458.0 ± 73.4 μg/mL and 395,000 ± 114,000 μg × h/mL, respectively, for 375 mg/m^2/infusion (n = 14) and 355.0 ± 61.8 μg/mL and 317,000 ± 87,000 μg × h/mL, respectively, for 500 mg/infusion (n = 8) were.[27]

Table 20. Relapse-free periods for 375 mg/m^2/infusion and 500 mg/infusion (subjects in the rituximab group in Study 01 and all the subjects in Study 02)

	Number of subjects who relapsed	Relapse-free period[a)] (days) (Median [95% CI])
375 mg/m^2/infusion (n = 35)	26 subjects	234.0 [193.0, 294.0]
500 mg/infusion (n = 19)	9 subjects	Not reached [260.0, NR]

a) Estimated by the Kaplan-Meier method

[25] The body surface area for 19 patients was 1.57 ± 0.18 m^2 (mean ± SD).
[26] n = 34
[27] The body surface area of the 8 subjects was 1.61 ± 0.18 m^2 (mean ± SD).

Table 21. Adverse events for 375 mg/m^2/infusion and 500 mg/infusion (subjects in the rituximab group in Study 01 and all the subjects in Study 02)

	375 mg/m^2/infusion (n = 35)		500 mg/infusion (n = 19)	
	Incidence	n	Incidence	n
Total adverse events	100.0%	35	100.0%	19
Infection requiring therapy	94.3%	33	84.2%	16
Infusion reaction	57.1%	20	73.7%	14

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PMDA asked the applicant to explain the readministration of rituximab to patients experiencing relapse of the disease.

The applicant responded as follows:
In patients experiencing relapse of the disease after the administration of rituximab, the readministration of rituximab may not be effective, but there is no clear evidence to deny the readministration. The risks and benefits of readministering rituximab should be carefully balanced before the readministration.

Study 02 enrolled 3 subjects who had received rituximab prior to enrollment and rituximab was readministered to the subjects during the study. Efficacy was evaluated in these subjects. Of the 3 subjects, 1 subject did not experience relapse during the follow-up period (for 385 days). The relapse-free period for the other 2 subjects was 294 and 344 days. There was no significant difference in the relapse-free period between the 2 subjects and the entire population for Study 02 (median [95% CI], 287.0 days [211.0, 344.0 days]). With respect to safety, 1 subject experienced Grade-3 adverse events (hypertension, gastroenteritis, and hypoproteinemia), but all events eventually resolved. The "hypertension" which had been noted prior to treatment with rituximab was asymptomatic, and there was no causal relationship between the hypoproteinemia and rituximab. A causal relationship of the gastroenteritis with rituximab could not be ruled out, but the gastroenteritis occurred 10 months after the start of treatment with rituximab and was therefore considered unlikely related to the treatment. Thus, the adverse events experienced by the 3 subjects were similar to those noted in the entire population of Study 02, showing no major differences in safety [see "4.(iii).A.(2) Pharmacokinetic study (RCRNS-02)"].

PMDA considers as follows:
In Study 01, the efficacy of rituximab was demonstrated with the proposed dosage and administration [see "4.(iii).B.(1) Efficacy"], and the safety of rituximab was deemed acceptable [see "4.(iii).B.(2) Safety"]. Additionally, no data indicate that the efficacy of rituximab 500 mg/infusion is inferior to that of rituximab 375 mg/m^2/infusion. Nor is there any clear difference in safety between 375 mg/m^2/infusion and 500 mg/infusion. Consequently, it is appropriate to select 375 mg/m^2/infusion of rituximab (maximum of 500 mg/infusion) once weekly for a total of 4 doses as the dosage and administration of rituximab for the treatment of childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent), as in the case with the dosage regimen used in Study 01. However, given the limited number of subjects, information on the dosage and administration should be collected through post-marketing surveillance to confirm the efficacy and safety of rituximab.

Rituximab was readministered to very few subjects experiencing relapse after the treatment with. The safety and efficacy of rituximab readministered is unclear, but currently, there are no specific concerns that require the limitation of readministration of rituximab. Thus, the package insert should include a precaution statement that the risks and benefits of readministering rituximab should be carefully assessed before the readministration, and information should be collected through post-marketing surveillance to investigate the safety and efficacy of readministration of rituximab.

4.(iii).B.(4).2) Infusion rate

The infusion rate of rituximab for the approved indication was changed to a new infusion rate in June 2013.[28] In Studies 01 and 02, however, rituximab was administered at the old infusion rate.[29] Most patients with childhood-onset refractory nephrotic syndrome are young children, and clinical data have not been obtained for the new infusion rate, even for the approved indication in pediatric patients. For this reason, the applicant has selected the old infusion rate used in Studies 01 and 02 as the infusion rate for the proposed indication.

PMDA considers as follows:

The use of the old infusion rate that was employed in in Study 01 is appropriate for administration of rituximab because most patients with childhood-onset refractory nephrotic syndrome would be young children, and because no pediatric patients have received rituximab at the new infusion rate and the increased infusion rate may therefore result in an increase in the incidence of infusion reactions. However, the package insert for rituximab should state that infusion rates is different from the approved indication. In addition, if post-marketing surveillance reveals that rituximab was administered to pediatric patients with refractory nephrotic syndrome at the new infusion rate, information on such subjects should be collected to further investigate the safety of rituximab.

4.(iii).B.(5) Post-marketing investigations

The applicant explained that the use-results survey listed in Table 22 would be carried out:

Table 22. Use-results survey protocol outline (draft)

Objective	Confirm the safety and efficacy of rituximab in patients with refractory nephrotic syndrome in routine clinical practice
Survey method	Central registry system
Intended population	Patients with refractory nephrotic syndrome (frequently relapsing or steroid-dependent)
Target sample size	520 patients (300 pediatric patients)
Medical institutions that will participate in the surevy	About 100 medical institutions
Survey period	Survey period of 5 years and 6 months, and enrollment period of 4 years
Follow-up period	1 year
Main investigation items	• Patient characteristics (disease type, primary disease onset, prior treatments, number of relapses within past year, prior rituximab treatments, hepatitis B virus marker, medical history, complications, etc.) • Rituximab administration (date, dosage, discontinuation [and its reason] and pretreatment) • Concomitant medication • Clinical laboratory tests (hematology, urinary protein, etc.) • Efficacy (date of relapse) • Adverse events (onset date, seriousness, rituximab discontinuation, outcome, causality, etc.)

PMDA considers that because of the limited number of subjects enrolled in Studies 01 and 02, post-marketing surveillance covering all patients treated with rituximab should be conducted to collect data from a specific number of patients (conditions for approval). PMDA considers that information should be collected not only for the main investigation items presented by the applicant but also for the following items; the details will be finalized by taking into account comments from the Expert Discussion.

- Safety and efficacy of rituximab in different age groups (in particular ≤6 years of age)
- Safety and efficacy of rituximab at different dose levels (375 mg/m^2/infusion and 500 mg/infusion)
- Safety and efficacy of rituximab administered at the new infusion rate
- Safety and efficacy of rituximab readministered in patients who relapsed after treatment with rituximab

[28] At the first intravenous infusion, set the infusion rate at 50 mg/hour for the first 30 minutes. While the patient's condition is closely monitored, the infusion rate can be increased by 50 mg/hour every 30 minutes up to a maximum of 400 mg/hour. For the second and subsequent doses, as long as adverse reactions occurring during and after the first infusion were mild, the starting infusion rate can be set as high as 100 mg/hour and the infusion rate will be increased by 100 mg/hour every 30 minutes up to a maximum of 400 mg/hour. With all infusions, the starting rate should be adjusted based on the patient's condition.

[29] At the first intravenous infusion, set the infusion rate at 25 mg/hour for the first hour. While the patient's condition is closely monitored, the infusion rate can be increased to 100 mg/hour for the next hour, and to a maximum of 200 mg/hour thereafter. For the second and subsequent doses, as long as adverse reactions associated with the first infusion were mild, the starting infusion rate can be set as high as 100 mg/hour.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Compliance assessment is ongoing and the results and PMDA's conclusion are reported in Review Report (2).

2. PMDA's conclusion on the results of GCP on-site inspection

Compliance assessment is ongoing and the results and PMDA's conclusion are reported in Review Report (2).

IV. Overall evaluations

PMDA concluded that the submitted data suggest the efficacy of rituximab for refractory nephrotic syndrome (frequently relapsing or steroid-dependent) and that its safety is acceptable based on its observed benefits. PMDA also concluded that further evaluation is needed for the efficacy, safety, indications, dosage and administration, and post-marketing investigations of rituximab.

This application for Rituxan (rituximab) may be approved if it can be concluded based on comments from the Expert Discussion that that there are no particular problems.

Review Report (2)

July 17, 2014

I. Product Submitted for Registration

[Brand name]	Rituxan Injection 10 mg/mL
[Non-proprietary name]	Rituximab (genetical recombination)
[Name of applicant]	Zenyaku Kogyo Co., Ltd.
[Date of application]	December 26, 2013

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

Based on the results of the interim analysis of the Phase III confirmatory study on patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) (Study RCRNS-01; hereinafter referred to as "Study 01"), statistically significant results were obtained for relapse-free period (primary endpoint) and for incidence of relapse and time to second relapse (endpoints for the interim analysis). These results verify the superiority of rituximab over placebo. Furthermore, the final analysis confirmed that the relapse-free period (primary endpoint) for rituximab demonstrated statistically significant prolongation compared to that of placebo.

Based on the above, PMDA has concluded that the efficacy of rituximab for the treatment of childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) was demonstrated. However, given the limited number of subjects included in Study 01, information should be collected through post-marketing surveillance to further investigate the efficacy of rituximab.

The expert advisors supported PMDA's conclusion given above.

(2) Safety

Based on the results of Study 01 and the pharmacokinetics study (Study RCRNS-02; hereinafter referred to as "Study 02"), PMDA has concluded that the safety of rituximab in patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) is acceptable when the drug is used under the supervision of a physician with sufficient knowledge and experience at a medical institution capable of appropriately handling emergencies, although attention should be paid to infections and infusion reactions associated with rituximab administration. However, given the limited numbers of subjects in Studies 01 and 02, information should be collected through post-marketing surveillance to further investigate the safety of rituximab in patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) .

The expert advisors supported PMDA's conclusion given above.

(3) Indications

Based on the discussions in "(1) Efficacy" and "(2) Safety", PMDA has concluded that, as in Study 01, patients with childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent) may be the intended population of rituximab.

The expert advisors supported PMDA's conclusion given above. Thus, PMDA instructed the applicant to specify the "Indications" and "Precautions for Indications" for rituximab as described below. The applicant responded appropriately and PMDA accepted it.

[Indications]
Refractory nephrotic syndrome (frequently relapsing or steroid-dependent)

[Precautions for indications]
The use of rituximab (genetical recombination) in the treatment of refractory nephrotic syndrome should be limited to patients with steroid-sensitive childhood-onset idiopathic nephrotic syndrome in whom remission cannot be maintained using existing therapies (steroids and immunosuppressants). Rituxan (rituximab) should be used only in patients eligible for treatment with rituximab in accordance with the latest information such as clinical practice guidelines. Efficacy and safety have not been established in adult-onset nephrotic syndrome patients.

(Denoted additional sentences only.)

(4) Dosage and administration, and infusion rate

1) Dosage and administration

Based on the discussions in "(1) Efficacy" and "(2) Safety", and given that no data indicate that 500 mg/infusion would be less effective than 375 mg/m^2/infusion, and that there have not been any clear differences in safety between 375 mg/m^2/infusion and 500 mg/infusion at present, PMDA has concluded that it is appropriate to select 375 mg/m^2/infusion (maximum of 500 mg/infusion) once weekly for a total of 4 doses as the dosage and administration of rituximab for the treatment of childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent). The dosage regimen is the same as that used in Study 01. However, given the limited number of subjects, information on the dosage and administration should be collected through post-marketing surveillance to investigate the safety and efficacy.

Rituximab was readministered to a limited number of patients who relapsed after treatment with rituximab, and the safety and efficacy of rituximab readministered have not been clarified. At this point of time, however, there is no particular concerns that require limitation of the readministration of rituximab. Thus, the package insert should include a separate precaution statement that rituximab should be readministered by carefully weighing risks and benefits. In addition, the safety and efficacy of rituximab readministered should be confirmed through post-marketing surveillance.

2) Infusion rate

Most patients with childhood-onset refractory nephrotic syndrome would be young children. Because no pediatric patients have received rituximab at the new infusion rate,[30] the increased infusion rate may result in an increase in the incidence of infusion reactions. Thus, PMDA has concluded that in principle, the use of the old infusion rate[31] that was employed in in Study 01 is appropriate for administration of rituximab in pediatric patients. However, the infusion rate for the proposed indications is different from that for the other indications, for which precautions should be appropriately provided in the package insert separately from those for other indications. If post-marketing surveillance reveals that rituximab was administered to pediatric patients with refractory nephrotic syndrome at the new infusion rate, information on such subjects should be collected to further investigate the safety of rituximab.

The above conclusions 1) and 2) of PMDA were generally supported by the expert advisors, but following comment was also raised:

- In recent years, the usefulness of a single infusion of rituximab for the treatment of nephrotic syndrome has been reported (*Pediatr Nephrol*. 2013;28:257-264, *Eur J Pediatr*. 2013;172:513-518). Compared to single-dose infusion, the relapse-free period is likely to be prolonged by 4 infusions which results in long-term peripheral B-cell depletion. In order to reduce the burden on patients, single-dose infusion may also be a useful option in the future.

[30] At the first intravenous infusion, set the infusion rate at 50 mg/hour for the first 30 minutes. While the patient's condition is closely monitored, the infusion rate can be increased by 50 mg/hour every 30 minutes up to a maximum of 400 mg/hour. For the second and subsequent doses, as long as adverse reactions associated with the first infusion were mild, the starting rate can be set as high as 100 mg/hour and increased by 100 mg/hour every 30 minutes up to a maximum of 400 mg/hour. With all infusions, the starting rate should be adjusted based on the patient's condition.

[31] At the first intravenous infusion, set the infusion rate at 25 mg/hour for the first hour. While the patient's condition is closely monitored, the infusion rate can be increased to 100 mg/hour for the next hour, and to a maximum of 200 mg/hour thereafter. For the second and subsequent doses, as long as adverse reactions associated with the first infusion were mild, the starting infusion rate can be set as high as 100 mg/hour.

In Study 01 that confirmed the efficacy and safety of rituximab for the treatment of childhood-onset refractory nephrotic syndrome (frequently relapsing or steroid-dependent), rituximab was administered as intravenous infusion for 4 doses, and the efficacy of single-dose infusion was not investigated. At this point of time, the proposed dosage and administration should be set to 4 infusions as in the case with Study 01.

Based on the above discussion, PMDA instructed the applicant to specify the "Dosage and Administration" and "Precautions for Dosage and Administration" for the proposed indication of refractory nephrotic syndrome (frequently relapsing or steroid-dependent) as described below. The applicant responded appropriately and PMDA accepted it.

[DOSAGE AND ADMINISTRATION]
The usual dose of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly as an intravenous infusion for 4 doses. The maximum dose per infusion is 500 mg.

[Precautions for Dosage and Administration]
When treating pediatric patients with nephrotic syndrome, set the rate of the first intravenous infusion at 25 mg/hour for the first hour of administration. While the patient's condition is closely monitored, set the rate at 100 mg/hour for the next hour, and a maximum of 200 mg/hour thereafter is recommended. For the second and subsequent infusions, the infusion rate can be started at a maximum of 100 mg/hour as long as adverse reactions associated with the first infusion are mild, but it should be adjusted based on the patient's condition [see "Clinical data"].

(Denoted additional sentences only.)

(5) Risk management plan (draft)

PMDA has concluded that because of the limited number of subjects enrolled in Studies 01 and 02, post-marketing surveillance covering all patients treated with rituximab should be conducted to collect data from a specific number of patients (conditions for approval). PMDA has also concluded that information should be collected not only for the main investigation items presented by the applicant in the outline of post-marketing surveillance plan (draft) (Table 22), but also for the following items:

- Safety and efficacy of rituximab in different age groups (≤6 years in particular)
- Safety and efficacy of rituximab at different dose levels (375 mg/m^2/infusion and 500 mg/infusion)
- Safety and efficacy of rituximab administered at the new infusion rate
- Safety and efficacy of rituximab readministered in patients who relapsed after treatment with rituximab

The expert advisors supported PMDA's conclusion given above.

Based on the above discussion, PMDA instructed the applicant to review the current risk management plan (draft) for rituximab. The applicant submitted the risk management plan (draft) and the outline of use-results survey protocol (draft) shown in the Tables 23-25, which PMDA accepted.

Table 23. Safety specifications and efficacy follow-up items in risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Infusion reaction • Infection • Progressive multifocal leucoencephalopathy • Pancytopenia, leukopenia, neutropenia, agranulocytosis and thrombocytopenia • Hepatitis B virus-induced fulminant hepatitis and exacerbated hepatitis • Mucocutaneous symptoms such as oculomucocutaneous syndrome and toxic epidermal necrolysis • Gastrointestinal perforation/obstruction • Reversible posterior leukoencephalopathy syndrome • Hepatic function disorder and jaundice • Interstitial pneumonia • Cardiopathy • Renal disorder • Decreased blood pressure • Tumor lysis syndrome a)	• Reduced immunoreactivity • Malignant tumor	None
Efficacy follow-up items		
• Efficacy of rituximab for treatment of refractory nephrotic syndrome (frequently relapsing or steroid-dependent) in routine clinical practice		

a) Only for CD20-positive B-cell non-Hodgkin's lymphoma and CD20-positive B-cell lymphoproliferative disorder associated with immunosuppresion

Table 24. Summary of additional pharmacovigilance and risk minimization activities in the risk management plan (draft) (for the additional indication)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results surveys [see Table 25 for survey outlines]	• Preparation and provision of information materials for healthcare professionals (materials to promote proper usage) • Provision of information obtained through early post-marketing phase vigilance

Table 25. Use-results survey protocol outline (draft)

Objective	Confirm the safety and efficacy of rituximab in patients with refractory nephrotic syndrome (frequently relapsing or steroid-dependent) in routine clinical practice.
Survey method	All patients by central registry system
Intended patinet population	Patients with refractory nephrotic syndrome (frequently relapsing or steroid-dependent)
Target sample size	300 pediatric patients[a)]
Survey period	2 years
Main investigation items	• Patient characteristics (age, disease type, primary disease onset, prior treatments, number of relapses within the past year, history of treatment with rituximab, hepatitis B virus marker, medical history, complications, etc.) • Rituximab treatment (date, dosage, infusion rate, number of infusions (rationale if <4 infusions), and pretreatment) • Concomitant medication • Clinical laboratory tests (hematology, urinary protein, etc.) • Efficacy (time to relapse [date of relapse], and study period [rationale for discontinuation of follow-up if it discontinued within <2 years]) • Adverse events (onset date, seriousness, rituximab discontinuation, outcome, causality, etc.)

a) Enroll all patients (includint other than pediatric patients) until the number of pediatric patients is reached to the target number.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.2-1). As a result, the studies were generally performed in accordance with GCP, and PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents. However, the following findings were noted at some medical institutions where trials were conducted. Although it had no significant impact on the overall results of the study, the issue was communicated to the heads of the medical institutions concerned.

Areas of improvement:
Medical institutions

- In sponsor-investigator studies, the head of the medical institutions failed to seek the opinion of the Institutional Review Board (IRB) after receiving a monitoring report or an audit report with respect to whether the clinical trial had been conducted properly at the medical institutions.

IV. Overall evaluation

As a result of the above review, PMDA has concluded that Rituxan (rituximab) may be approved after modifying the indication, and dosage and administration as shown below. Since rituximab has an orphan designation for the proposed additional indication, the 10-year re-examination period is appropriate.

[Indications]

1. CD20-positive B-cell non-Hodgkin's lymphoma
2. CD20-positive B-cell lymphoproliferative disorder associated with immunosuppression
3. Wegener's granulomatosis and microscopic polyangiitis
4. Refractory nephrotic syndrome (frequently relapsing or steroid-dependent)
5. Premedication for indium (^{111}In) ibritumomab tiuxetan (genetical recombination) injection and yttrium (^{90}Y) ibritumomab tiuxetan (genetical recombination) injection

(Underline denotes new addition.)

[Dosage and administration]

1. When used to treat CD20-positive B-cell non-Hodgkin's lymphoma:
   The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for up to 8 doses.

   When used to treat CD20-positive B-cell lymphoproliferative disorder associated with immunosuppression:
   The usual dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for up to 8 doses.

   When used to treat Wegener's granulomatosis and microscopic polyangiitis:
   The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for 4 doses.

When used to treat refractory nephrotic syndrome (frequently relapsing or steroid-dependent):
The usual dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for 4 doses. The maximum single dosage is 500 mg.

When used as premedication for indium (^{111}In) ibritumomab tiuxetan (genetical recombination) injection and yttrium (^{90}Y) ibritumomab tiuxetan (genetical recombination) injection:
The usual adult dosage of Rituximab (Genetical Recombination) is 250 mg/m^2 administered as a single intravenous infusion.

2. The Rituxan solution for infusion is prepared by diluting 10-fold with either saline or 5% glucose solution before use.

(Underline denotes new addition.)

[Conditions for approval] Refractory nephrotic syndrome (frequently relapsing or steroid-dependent):
Because of the very limited number of subjects included in Japanese clinical studies, the applicant is required to conduct a use-results survey covering all patients treated with Rituxan until data from a specific number of patients are accumulated after market introduction, and then to understand the characteristics of patients treated with Rituxan and compile safety and efficacy data of Rituxan in the earlier post-marketing phase, thereby taking necessary actions to ensure the proper use of Rituxan.