Report on the Deliberation Results

June 8, 2022

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Rituxan Intravenous Infusion 100 mg
	Rituxan Intravenous Infusion 500 mg
Non-proprietary Name	Rituximab (Genetical Recombination) (JAN*)
Applicant	Zenyaku Kogyo Co., Ltd.
Date of Application	October 29, 2021

Results of Deliberation

In its meeting held on June 2, 2022, 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 is 10 years.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

May 16, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Rituxan Intravenous Infusion 100 mg Rituxan Intravenous Infusion 500 mg
Non-proprietary Name	Rituximab (Genetical Recombination)
Applicant	Zenyaku Kogyo Co., Ltd.
Date of Application	October 29, 2021
Dosage Form/Strength	Injection: Each vial contains 100 mg or 500 mg of Rituximab (Genetical Recombination).
Application Classification	Prescription drug: (4) Drug with a new indication and (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 466 of 2020 [*R2 yaku*]; PSEHB/PED Notification No. 0605-1 dated June 5, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in prevention of the relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica), and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indications

1. CD20-positive B-cell non-Hodgkin’s lymphoma

2. CD20-positive chronic lymphocytic leukemia
3. CD20-positive B-cell lymphoproliferative disorder associated with immunosuppression
4. Granulomatosis with polyangiitis, microscopic polyangiitis
5. Refractory nephrotic syndrome (frequently relapsing or steroid-dependent)
6. Chronic idiopathic thrombocytopenic purpura
7. Acquired thrombotic thrombocytopenic purpura
8. Systemic scleroderma
9. Refractory pemphigus vulgaris and pemphigus foliaceous
10. Prevention of the relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)
11. Prevention of antibody-mediated rejection in ABO-incompatible renal or liver transplant
12. Premedication for indium (^{111}In) ibritumomab tiuxetan (genetical recombination) injection and yttrium (^{90}Y) ibritumomab tiuxetan (genetical recombination) injection

(Underline denotes additions.[1)])

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 in combination with other antineoplastic drugs, Rituximab (Genetical Recombination) is administered once in each cycle based on the dosing interval of concomitant antineoplastic drugs.
   For maintenance therapy, the usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 approximately once every 8 weeks administered as an intravenous infusion for up to 12 doses.

   When used to treat CD20-positive chronic lymphocytic leukemia:
   In combination with other antineoplastic drugs, the usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 for the first dose, followed by 500 mg/m^2 for the second and subsequent doses, administered as an intravenous infusion. Administer 1 dose per cycle based on the dosing interval of the concomitant antineoplastic drugs for up to 6 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 granulomatosis with polyangiitis, microscopic polyangiitis, chronic idiopathic thrombocytopenic purpura, acquired thrombotic thrombocytopenic purpura, and systemic scleroderma:
   The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for 4 doses.

1) Dotted underline denotes additions made at the partial change approval dated December 24, 2021.

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 dose is 500 mg.

When used to treat refractory pemphigus vulgaris and pemphigus foliaceous:
The usual dosage of Rituximab (Genetical Recombination) is two 1000 mg/body doses, separated by 2 weeks, administered as an intravenous infusion.

When used to prevent the relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica):
The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly for 4 doses, followed by two 1000 mg/body fixed doses (separated by 2 weeks) at 6 months after the first dose and every 6 months thereafter, all administered as an intravenous infusion.

When used to prevent antibody-mediated rejection in ABO-incompatible renal or liver transplant:
The usual dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 administered as a single intravenous infusion. The dose may be adjusted according to the patient's condition.

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 dilution to 1 to 4 mg/mL with either saline or 5% glucose injection before use.

(Underline denotes additions.[1)])

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

March 30, 2022

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Rituxan Intravenous Infusion 100 mg Rituxan Intravenous Infusion 500 mg
Non-proprietary Name	Rituximab (Genetical Recombination)
Applicant	Zenyaku Kogyo Co., Ltd.
Date of Application	October 29, 2021
Dosage Form/Strength	Injection: Each vial contains 100 mg or 500 mg of Rituximab (Genetical Recombination).

Proposed Indications

1. CD20-positive B-cell non-Hodgkin's lymphoma
2. CD20-positive chronic lymphocytic leukemia
3. CD20-positive B-cell lymphoproliferative disorder associated with immunosuppression
4. Granulomatosis with polyangiitis, microscopic polyangiitis
5. Refractory nephrotic syndrome (frequently relapsing or steroid-dependent)
6. Chronic idiopathic thrombocytopenic purpura
7. Acquired thrombotic thrombocytopenic purpura
8. Systemic scleroderma
9. Prevention of the relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)
10. Prevention of antibody-mediated rejection in ABO-incompatible renal or liver transplant
11. Premedication for indium (^{111}In) ibritumomab tiuxetan (genetical recombination) injection and yttrium (^{90}Y) ibritumomab tiuxetan (genetical recombination) injection

(Underline denotes additions.)

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 in combination with other antineoplastic drugs, Rituximab (Genetical Recombination) is administered once in each cycle based on the dosing interval of concomitant antineoplastic drugs.
   For maintenance therapy, the usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 approximately once every 8 weeks administered as an intravenous infusion for up to 12 doses.

When used to treat CD20-positive chronic lymphocytic leukemia:
In combination with other antineoplastic drugs, the usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 for the first dose, followed by 500 mg/m^2 for the second and subsequent doses, administered as an intravenous infusion. Administer 1 dose per cycle based on the dosing interval of the concomitant antineoplastic drugs for up to 6 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 granulomatosis with polyangiitis, microscopic polyangiitis, chronic idiopathic thrombocytopenic purpura, acquired thrombotic thrombocytopenic purpura, and systemic scleroderma:
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 dose is 500 mg.

When used to prevent the relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica):
The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly for 4 doses (induction treatment), followed by two 1000 mg/body doses (separated by 2 weeks) approximately every 6 months (maintenance treatment), all administered as an intravenous infusion.

When used to prevent antibody-mediated rejection in ABO-incompatible renal or liver transplant:
The usual dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 administered as a single intravenous infusion. The dose may be adjusted according to the patient's condition.

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 dilution to 1 to 4 mg/mL with either saline or 5% glucose injection before use.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disease in the central nervous system, which is characterized by severe optic neuritis and transverse myelitis. In Japan, NMOSD is designated as the intractable disease, "neuromyelitis optica." The potential major pathogenesis of NMOSD is the complement-dependent cytotoxic activity of anti-aquaporin-4 (AQP4) antibodies against astrocytes in the central nervous system (*Acta Neuropathol*. 2013;126:699-709). Meanwhile, some patients with NMOSD are negative for anti-AQP4 antibodies or positive for anti-myelin oligodendrocyte glycoprotein (MOG) antibodies (*Neurology*. 2014;82:474-481), suggesting that autoantibodies other than anti-AQP4 antibodies may also contribute to the pathogenesis of the disease (*2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica* [in Japanese]. *Igaku Shoin*; 2017). Untreated patients with NMOSD experience 1 to 1.5 relapses on average within 1 year (*Brain*. 2012;135:1834-49), with their disability increasing with each relapse. Most relapses are severe, and even a single attack, if severe, can potentially lead to blindness or wheelchair-dependence. Rituximab (genetical recombination) (hereinafter, referred to as "rituximab") has been designated as an orphan drug with the intended indication of "neuromyelitis optica and neuromyelitis optica-related diseases" (Orphan Drug Designation No. 466 of 2020 [*R2 yaku*]).

Rituximab, which was discovered by IDEC Pharmaceuticals (in the US), is a chimeric anti-CD20 monoclonal antibody consisting of a mouse variable region and a human constant region. In Japan, rituximab was approved for the treatment of CD20-positive low-grade or follicular B cell non-Hodgkin's lymphoma and Mantle cell lymphoma in June 2001, after which its indications have expanded.

Outside Japan, as of October 2021, rituximab has been approved in roughly 140 countries and regions, including the US and EU, but is not indicated for NMOSD in any country or region.

As part of the development of rituximab in Japan, a Japanese phase II/III study was conducted from June 2014 as an investigator-initiated clinical trial funded by a Health and Labour Sciences Research Grant in Fiscal Years 2013 to 2014 (Research Program for Overcoming Intractable Diseases), and a Practical Research Project for Rare/Intractable Diseases in Fiscal Years 2015 to 2017 of the Japan Agency for Medical Research and Development. The applicant has recently filed the present application for partial change approval, based on their conclusion that the results from the Japanese phase II/II study had demonstrated the efficacy and safety of rituximab in patients with NMOSD.

Currently, the following 3 drugs are available for the treatment of NMOSD in Japan: eculizumab (genetical recombination) (approved in November 2019), satralizumab (genetical recombination) (approved in June 2020), and inebilizumab (genetical recombination) (approved in March 2021), all of which are indicated for "prevention of the relapse of NMOSD (including neuromyelitis optica)."

2. Quality and Outline of the Review Conducted by PMDA

Since the present partial change application is intended for a new indication and a new dosage, no additional data relating to the quality of rituximab have been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication and a new dosage, no new data on non-clinical pharmacology have been submitted. The non-clinical pharmacology of rituximab was evaluated during the review for the initial approval.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication and a new dosage, no new data on non-clinical pharmacokinetics have been submitted. The non-clinical pharmacokinetics of rituximab were evaluated during the review for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication and a new dosage, no new toxicity data have been submitted. The toxicity of rituximab was evaluated during the review for the initial approval.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

No data on biopharmaceutic studies have been submitted. Serum rituximab concentrations were measured by an enzyme-linked immunosorbent assay (ELISA) with a lower quantification limit of 5.0 ng/mL. Concentrations of anti-drug antibodies (ADAs) against rituximab were measured by an ELISA with a lower detection limit of 1.42 ng/mL or 1.0 relative units (RU)/mL. The clinical studies of rituximab used the commercial formulation.

6.2 Clinical pharmacology

The applicant submitted (a) the results of a Japanese phase II/III study in patients with NMOSD (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1) as evaluation data and (b) the results of a Japanese phase I/II study in patients with systemic lupus erythematosus (SLE) (Reference CTD 5.3.5.4-1, Study IDEC-C2B8-A1) as reference data.

6.2.1 Japanese phase I/II study (Reference CTD 5.3.5.4-1, Study IDEC-C2B8-A1)

Japanese patients with SLE received (a) rituximab 500 mg once weekly for 4 intravenous infusions or (b) 2 intravenous infusions of rituximab 1000 mg separated by 2 weeks (15 patients evaluable for the pharmacokinetic analysis). Tables 1 shows the pharmacokinetic parameters and Table 2 shows changes in serum B cell (CD19+ B cell) counts[2)] in these patients [for the study design and safety data, see Section 7.1.1]. ADAs against rituximab were detected in 1 patient in the 500 mg group and 3 patients in the 1000 mg group.

2) B cell counts were determined by counting CD19+ B cells, because rituximab may hinder the CD20-based detection of B cells.

Table 1. Pharmacokinetic parameters of rituximab (500 mg once weekly for 4 infusions or two 1000 mg infusions separated by 2 weeks) in Japanese patients with SLE

Dosage regimen	N	C_{max} (μg/mL)	$AUC_{0\text{-}196day}$ (μg·h/mL)	$t_{1/2}$ (h)	V (L)
500 mg Q1W[a)]	5	379	237000	151	4.45
1000 mg Q2W[b)]	10	451	205000	127	3.90

Mean
a) once weekly, b) separated by 2 weeks

Table 2. Changes in B cell counts in Japanese patients with SLE who received rituximab (500 mg once weekly for 4 infusions or two 1000 mg infusions separated by 2 weeks)

Time point	Percentage of CD19+ B cells in all lymphocytes (%)	
	500 mg (N = 5)	1000 mg (N = 10)
Day 0 (baseline)	7.48 ± 5.04	9.46 ± 7.74
Day 2	3.24 ± 3.28	4.43 ± 4.69
Day 14	0.40 ± 0.37	0.66 ± 0.64
Day 28	0.28 ± 0.13	0.27 ± 0.22
Day 56	0.16 ± 0.09	0.39 ± 0.64
Day 112	0.18 ± 0.08	0.61 ± 1.31
Day 168	4.70 ± 9.28	1.20 ± 1.90
Day 196	1.42 ± 1.93	1.16 ± 1.73

Mean ± SD
The final dose was administered on Day 21 in the 500 mg group and Day 14 in the 1000 mg group.

6.2.2 Pharmacodynamics (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1)

Patients with anti-AQP4 antibody-positive NMOSD (N = 38) received rituximab 375 mg/m^2 once weekly for 4 infusions, then 2 infusions of 1000 mg (separated by 2 weeks) at Week 24 (Day 168) and Week 48 (Day 336). Table 3 shows changes in the serum B cell (CD19+ B cell) counts.[2)] ADAs against rituximab were detected in 2 patients.

Table 3. Changes in CD19+ B cell counts in Japanese patients with anti-AQP4 antibody-positive NMOSD who received rituximab (375 mg/m^2 once weekly for 4 infusions, followed by two 1000 mg infusions separated by 2 weeks at Weeks 24 and 48)

Time point	Percentage of CD19+ B cells in all lymphocytes (%)	
	Placebo	Rituximab
Day 0 (baseline)	5.73 ± 2.98 (19)	8.61 ± 6.94 (19)
Day 28	5.08 ± 2.92 (19)	0.16 ± 0.07 (19)
Day 56	5.04 ± 2.40 (19)	0.26 ± 0.22 (18)
Day 84	4.92 ± 2.69 (19)	0.17 ± 0.08 (18)
Day 168	4.82 ± 2.87 (17)	0.16 ± 0.11 (18)
Day 252	3.86 ± 2.61 (16)	0.20 ± 0.20 (17)
Day 336	3.99 ± 2.45 (14)	0.18 ± 0.09 (16)
Day 420	3.62 ± 1.98 (13)	0.17 ± 0.13 (16)
Day 504	4.54 ± 2.67 (12)	0.21 ± 0.12 (16)
At relapse/ treatment discontinuation	3.83 ± 2.87 (7)	0.30 ± 0.28 (2)

Mean ± SD (number of patients evaluated)
The final dose was administered on Day 350

6.R Outline of the review conducted by PMDA

6.R.1 Appropriateness of the dosage regimen from a clinical pharmacological perspective

The applicant provided the following rationale for the dosage regimen used in the Japanese phase II/III study in patients with NMOSD (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1), from a clinical pharmacological perspective:

- The development of rituximab for NMOSD is intended to prevent relapses. For this aim, maintaining B cell depletion was considered important.

- Taking account of the risk of infusion reaction, the dosage regimen of rituximab for induction treatment to deplete systemic B cells was set at 375 mg/m^2 once weekly for 4 doses, which was the same as the approved dosage and administration for the treatment of B-cell non-Hodgkin's lymphoma,.
- Rituximab has not been approved for the treatment of NMOSD either in or outside Japan. Nevertheless, some NMOSD treatment guidelines, including the Japanese guidelines for multiple sclerosis and neuromyelitis optica and the European Federation of Neurological Societies (EFMS) guidelines on the diagnosis and management of neuromyelitis optica (*Eur J Neurol.* 2010;17:1019-32), recommended 2 dosage regimens of rituximab for maintenance treatment: (i) 375 mg/m^2 once weekly for 4 doses and (ii) two 1000 mg doses separated by 2 weeks. A meta-analysis using 46 clinical studies involving 438 patients with NMOSD revealed that the post-treatment annualized relapse rate and Expanded Disability Status Scale (EDSS) score did not differ between these 2 dosage regimens (*JAMA Neurol.* 2016:73;1342-8). Furthermore, clinical studies in non-Japanese patients with NMOSD demonstrated the efficacy of 2 infusions of rituximab 1000 mg separated by 2 weeks (*Neurology.* 2005;64:1270-2, *Arch Neurol.* 2008;65:1443-8). In view of these findings and taking account of patient convenience, Study RIN-1 used "two 1000 mg intravenous infusions separated by 2 weeks" as the dosage of maintenance treatment. Since B cell depletion by rituximab lasts for at least roughly 6 months (*Neurology*. 2005;64:1270-2), the maintenance treatment was administered every 6 months.

The applicant explained the appropriateness of the proposed dosage and administration from a clinical pharmacological perspective, based on the results from Study RIN-1 and the Japanese phase I/II study in patients with SLE (Reference CTD 5.3.5.4-1: Study IDEC-C2B8-A1) in which, as in Study RIN-1, patients received 2 infusions of rituximab 1000 mg separated by 2 weeks.

The applicant's explanation:

- In Study IDEC-C2B8-A1 involving patients with SLE, 2 infusions of rituximab 1000 mg separated by 2 weeks successfully depleted blood B cells (CD19+ B cells) by Day 14, and the B cell depletion lasted for roughly 6 months (Table 2). In Study RIN-1 involving patients with NMOSD, blood B cells (CD19+ B cells) were depleted by Day 28, which was the first assessment point after the first dose of rituximab, and the B cell depletion was maintained by rituximab infusion every 6 months (Table 3).
- Thus, blood B cell depletion was achieved by rituximab 375 mg/m^2 once weekly for 4 infusions, and was maintained by subsequent two 1000 mg infusions (separated by 2 weeks) at 6 months after the first dose and every 6 months thereafter. Therefore, the proposed dosage and administration is appropriate from a clinical pharmacological perspective.

PMDA's view:

- There are no problems with the following dosage regimen used in Study RIN-1, which was determined according to the approved dosage and administration for rituximab, the Japanese guidelines for multiple sclerosis and neuromyelitis optica, etc.:

  375 mg/m^2 once weekly for 4 infusions, followed by two 1000 mg infusions separated by 2 weeks (at Weeks 24 and 48)

- However, patients with NMOSD are expected to repeatedly receive rituximab for a long time, and therefore potentially have a risk of prolonged B cell depletion. Since the reduction in B cells lasted even after the completion of treatment with rituximab in Studies RIN-1 and IDEC-C2B8-A1 (Tables 2 and 3), the package insert should include a precautionary statement to raise awareness about this issue.
- The appropriateness of the above PMDA's view will be finalized taking into account the comments from the Expert Discussion. The appropriateness of the proposed dosage and administration is discussed further in Section 7.R.5.1.

6.R.2 Effects of ADAs

PMDA asked the applicant to explain the impact of ADAs on the pharmacokinetics, pharmacodynamics, efficacy, and safety of rituximab.

The applicant's explanation:

- In the rituximab group of the Japanese phase II/III study in patients with NMOSD (CTD 5.3.5.1-1 and 5.3.5.1-2: Study RIN-1), 2 patients tested positive for ADAs. However, their positivity was transient, and the patients became ADA-negative during the treatment period. One of the 2 patients was positive for ADAs at screening, then became ADA-negative at Week 12. Meanwhile, since the CD19+ B cells were depleted by Week 4, the ADAs had no effects on the pharmacodynamics of rituximab. The patient experienced no adverse events from the start of treatment through Day 106, when treatment was discontinued. The other patient tested negative for ADAs at screening but became positive at Week 24 and then negative again at Week 36. Meanwhile, CD19+ B cells were depleted by Week 4, and the depletion was maintained thereafter; therefore, the emergence of ADAs had no effects on the pharmacodynamics of rituximab. The patient experienced no adverse events between Weeks 12 and 36, during which ADAs may have existed.
- A clinical research study investigated the impact of ADAs in 19 patients receiving long-term treatment with rituximab for NMOSD (*J Neuroimmunol*. 2018;316:107-11). In the research study, rituximab 100 mg was infused once weekly for 3 doses. Then, CD19+ B cells were counted every ≤12 weeks, and if CD19+ B cells accounted for >1% of all peripheral blood mononuclear cells, rituximab 100 mg was re-infused. Seven of the 19 patients tested positive for ADAs; their ADA-positivity was found before administration of the second or third dose of rituximab. The number of rituximab re-infusions during the first year of treatment was higher in the ADA-positive patients than in the ADA-negative patients. However, both the ADA-positive and -negative populations had a lower annual relapse rate after the start of treatment with rituximab than before, with no difference in the percent reduction in annual relapse rate between the populations; rituximab was thus shown to have efficacy in ADA-positive patients as well. In a research report that evaluated serum samples from 339 patients with multiple sclerosis who were on treatment with rituximab[3)] (*Mult Scler*. 2018;24:1224-33), ADAs were detected in roughly half of patients who had previously received 1 dose of rituximab; however, the percentage of ADA-positive patients decreased

3) At least 95% of the patients were receiving rituximab 500 or 1000 mg/body every 6 months.

proportionately with the increase in the number of doses. Only approximately 15% of patients receiving 5 doses of rituximab tested positive for ADA.

- Although the emergence of ADAs may accelerate the elimination of rituximab from the body, the results of Study RIN-1 showed that treatment with rituximab accomplished B cell depletion in ADA-positive patients as well, without causing ADA-related adverse events. Further, the clinical research study of rituximab in patients with NMOSD showed no difference in the percent reduction in the annual relapse rate between ADA-positive and -negative patients. In view of these and other findings, ADAs are unlikely to affect the efficacy or safety of rituximab.

PMDA's view:

Although only a small number of ADA-positive patients have been evaluated, no evident impact of the development of ADAs on the efficacy or safety of rituximab have been found, and no new concerns have been identified regarding the use of rituximab in patients with NMOSD or long-term treatment with rituximab.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted results from the clinical studies listed in Table 4 for efficacy and safety evaluation.

Table 4. Clinical studies submitted for efficacy and safety evaluation

Data category	Region	Study identifier CTD	Phase	Study population	No. of patients treated	Dosage regimen	Main endpoints
Evaluation	Japan	RIN-1 5.3.5.1-1 5.3.5.1-2	II/III	Patients with NMOSD	38	Placebo or rituximab 375 mg/m^2 once weekly for 4 infusions, followed by 2 infusions of placebo or rituximab 1000 mg separated by 2 weeks, at Weeks 24 and 48	Efficacy Safety
Reference	Japan	IDEC-C2B8-A1 5.3.5.4	I/II	Patients with SLE	15	Rituximab 500 mg once weekly for 4 infusions, or 2 infusions of rituximab 1000 mg separated by 2 weeks	Safety Pharmacokinetics

7.1 Phase I/II study

7.1.1 Japanese phase I/II study (Reference CTD 5.3.5.4, Study IDEC-C2B8-A1 [November 2004 to March 2006])

An open-label, uncontrolled study was conducted to evaluate the safety and pharmacokinetics of rituximab in patients with SLE[4)] (target sample size, 3 or 4 patients in the rituximab 500 mg group and 6 patients in the 1000 mg group) [for pharmacokinetics, see Section 6.2.1].

Patients received (a) rituximab 500 mg once weekly for 4 infusions or (b) 2 infusions of rituximab 1000 mg separated by 2 weeks.

All 15 treated patients (5 patients in the 500 mg group and 10 patients in the 1000 mg group) were included in the safety analysis set. No treatment discontinuations occurred.

4) Patients aged ≥20 to <70 years who were diagnosed with SLE according to the 1997 update of the 1982 American College of Rheumatology Revised Criteria for classification of systemic lupus erythematosus

Adverse events (including laboratory abnormalities) were reported in all patients, in both the 500 mg group (5 of 5 patients) and the 1000 mg group (10 of 10 patients). One patient in the 500 mg group died (subdural haematoma/brain herniation). The death was unrelated to the study drug. Serious adverse events other than death were reported in 2 patients in the 500 mg group (pneumonia bacterial and osteomyelitis [sacral pressure sore secondary infection] in 1 patient each) and 3 patients in the 1000 mg group (enteritis infectious/depressed state, pleural effusion/pneumonia bacterial, and low back pain/pain in left hip in 1 patient each). A causal relationship to the study drug could not be ruled out for the pneumonia bacterial in the 500 mg group, and the enteritis infectious and pneumonia bacterial in the 1000 mg group.

Adverse events (including laboratory abnormalities) for which a causal relationship to the study drug could not be ruled out were reported in all patients, in both the 500 mg group (5 of 5 patients) and the 1000 mg group (10 of 10 patients). The common events were upper respiratory tract infection (2 patients in the 500 mg group, 2 patients in the 1000 mg group), nasopharyngitis (1 patient, 3 patients), headache (1 patient, 2 patients), and blood pressure increased (1 patient, 2 patients).

There were no clinically relevant changes in vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) or in electrocardiogram parameters.

7.2 Phase II/III study

7.2.1 Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1 [June 2014 to January 2019])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of rituximab in Japanese patients with anti-AQP4 antibody-positive NMOSD who had a history of either myelitis or optic neuritis[5)] (target sample size, 40 patients [20 in the placebo group and 20 in the rituximab group]).[6)]

Patients received placebo or rituximab 375 mg/m^{2}once weekly for 4 infusions (induction treatment) and then 2 infusions of placebo or rituximab 1000 mg separated by 2 weeks at Weeks 24 and 48 (maintenance treatment). Concurrently, all patients started to receive oral prednisolone during the screening period; its dose was tapered by 10% per month to a minimum of 2 mg from Week 8 through Week 72.[7)] The follow-up period was 72 weeks.

5) Eligible patients were required to test (or to have previously tested) positive for anti-AQP4 antibodies, be under treatment with oral corticosteroids (at a prednisolone equivalent dose of ≥5 mg for ≥3 consecutive months prior to provisional registration, with a ≤10% dose fluctuation during the 3 months prior to the provisional registration), have an EDSS score of ≤7, and have a neurologically stable disease with no relapses within 1 month before the start of study treatment.

6) According to the mean relapse rates before and after treatment with rituximab (pre-treatment, 2.65 events/patient/year; post-treatment, 0.29 events/patient/year) from the published literature (e.g., *Neurology.* 2005;64:1270-2, *Arch Neurol*. 2008;65:1443-8), the relapse rate in the placebo group was conservatively assumed to be 0.79 events/patient/year (with a cumulative relapse-free rate of 40% at Week 60), and that in the rituximab group to be 0.0869 events/patient/year (with a cumulative relapse-free rate of 90% at Week 60). To detect a hazard ratio of 0.115 of rituximab over placebo, with a power of 80% at a 2-sided significance level of 0.05, 38 patients (19 per group) would be required, and the expected number of events would be 13.

7) The oral corticosteroids that had been taken before provisional registration were changed to equivalent doses of oral prednisolone, from the day after screening.

All 38 randomized patients[8] (19 in the placebo group and 19 in the rituximab group) were included in the intention to treat (ITT) population, which was used as the full analysis set (FAS) for efficacy and safety analyses. Treatment discontinuation occurred in 3 patients (0 patients in the placebo group, 3 patients in the rituximab group). The reasons for discontinuation were use of prohibited concomitant therapies, consent withdrawal, and investigator's decision in 1 patient each.

Table 5 and Figure 1 show the time from allocation to the first relapse, the primary endpoint.[9] There was a statistically significant difference between the rituximab group and the placebo group.

Table 5. Time from allocation to the first relapse (FAS)

	Placebo	Rituximab
N	19	19
No. of patients experiencing a relapse (%)	7 (36.8)	0
Weeks to the first relapse[a]	38.4 ± 19.6	- [b]
P-value[b]	*P* = 0.0058	

a) Mean ± SD
b) Not determinable
c) Log-rank test with a 2-sided significance level of 0.05

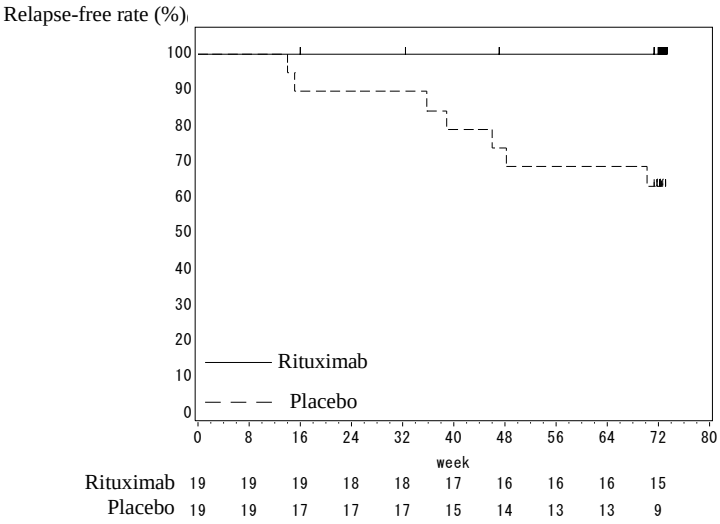

Figure 1. Kaplan-Meier curves for the time from allocation to the first relapse (FAS)

Adverse events (including laboratory abnormalities) were reported in 89.5% (17 of 19) of patients in the placebo group and 89.5% (17 of 19) of patients in the rituximab group. No patients died. Serious adverse events other than death were reported in 2 patients in the placebo group (glaucoma/eye haemorrhage and visual acuity reduced/white matter lesion in 1 patient each) and 3 patients in the rituximab group (spinal compression

8) Due to noncompliance with treatment assignment, a drug number that was supposed to be assigned to placebo was assigned to rituximab, and 1 patient in the placebo group thus received rituximab in the first cycle of maintenance treatment.
9) The date of relapse was defined as: (a) the date when the patient reported the relapse, or (b) the date when the relapse was confirmed by objective examinations such as MRI, whichever came first. A relapse was defined as any symptom reported by the patient or any new symptom that was consistent with a lesion in the central nervous system such as the optic nerves or spinal cord, and that was accompanied by objective abnormalities (new lesions in T2 or Gd-enhanced images) on MRI. However, a relapse of optic neuritis was required to meet all of the following (i) to (iii):
(i) New abnormalities in ophthalmologic examinations (e.g., visual acuity, visual field testing, central flicker levels);
(ii) Objective abnormalities in either MRI (new lesions in T2 or Gd-enhanced images) or electrophysiologic testing (visual evoked potential); and,
(iii) Optic neuritis is considered to be the cause the symptom.

fracture/nail infection, diplopia, and uterine cancer in 1 patient each). A causal relationship to the study drug could not be ruled out for the nail infection and uterine cancer in the rituximab group.

Adverse events (including laboratory abnormalities) for which a causal relationship to the study drug could not be ruled out were reported in 63.2% (12 of 19) of patients in the placebo group and 89.5% (17 of 19) of patients in the rituximab group. The common events were infusion related reaction (0 patients in the placebo group, 7 patients in the rituximab group), nasopharyngitis (4 patients, 5 patients), cystitis (1 patient, 2 patients), headache (1 patient, 2 patients), lymphocyte count decreased (1 patient, 2 patients), pyrexia (0 patients, 2 patients), pharyngitis (0 patients, 2 patients), conjunctivitis (0 patients, 2 patients), cellulitis (0 patients, 2 patients), upper respiratory tract inflammation (0 patients, 2 patients), diarrhoea (4 patients, 1 patient), stomatitis (2 patients, 0 patients), and bronchitis (2 patients, 0 patients).

There were no clinically relevant changes in vital signs (blood pressure, pulse rate, and body temperature) or in electrocardiogram parameters.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation about the appropriateness of the primary endpoint (the time to the first relapse) in the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1):

- NMOSD is an inflammatory disease of the central nervous system characterized by severe optic neuritis and transverse myelitis. Optic neuritis causes severely reduced visual acuity and severe visual field defect, potentially leading to blindness. Myelitis often results in paraplegia, and bladder and rectal disorders. Since relapses of NMOSD often result in severe disability, and such disability increases with each relapse, the prevention of relapse is important for a good long-term prognosis. Therefore, relapse was selected as an endpoint for evaluating the efficacy of rituximab in patients with NMOSD.
- In Study RIN-1, a relapse[9)] was defined according to the definition of a relapse[10)] by the Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria (*Ann Neurol.* 2011;69:292-302). The diagnosis of a relapse as the primary endpoint for Study RIN-1 was required to be confirmed by either abnormal findings on MRI or electrophysiological examination, and only objectively proven relapses were classified as "relapses," for the following reasons: (1) if a relapse is diagnosed solely by a physician, the diagnosis will depend on the physicians' abilities and experience; and (2) clinical symptoms may not always be consistent with MRI findings. The Japanese guidelines for multiple sclerosis and neuromyelitis optica states that a relapse means neurologic symptoms lasting for ≥24 hours in the absence of fever or infection, but the guidelines do not provide specific criteria for the determination of a relapse.
- In Study RIN-1, no independent relapse adjudication committee was established. However, the appropriateness of relapse adjudication was reviewed at case conferences[11)] by a coordinating committee composed of 3 NMOSD experts, to minimize the variability of relapse adjudication.

10) A subjective or objective finding characteristic of an acute inflammatory demyelinating lesion in the central nervous system that lasts for ≥24 hours with no fever or infection.
11) Reviewed before the blind was broken.

- Based on the above, the primary endpoint "the time from allocation to the first relapse" in Study RIN-1 was appropriate for evaluating the efficacy of rituximab in patients with NMOSD, and there were no problems with the definition or adjudication of relapses in the study.

PMDA asked the applicant to explain why the number of relapse events in Study RIN-1 was smaller than the expected number of events at the planning of the study.

The applicant's explanation:

- In sample size determination for Study RIN-1,[6] the annual relapse rate in the placebo group was conservatively assumed to be 0.79 events/patient/year, and the annual relapse rate in the rituximab group was assumed to be 0.087 events/patient/year, based on the mean relapse rates before and after treatment with rituximab (pre-treatment, 2.65 events/patient/year; post-treatment, 0.29 events/patient/year) from the published literature (e.g., *Neurology.* 2005;64:1270-2, *Arch Neurol.* 2008;65:1443-8). Accordingly, the required number of study subjects was set at 19 patients for each treatment group (38 patients in total), with an expected number of relapse events of 13.
- Seven relapse events occurred in the placebo group of Study RIN-1. No relapses occurred in the rituximab group. The relapse rate in the placebo group was 0.32 events/patient/year. As a result, the annual relapse rate was roughly 40% of the expected relapse rate. Study RIN-1 enrolled patients who were under treatment with an oral corticosteroid, and they were required to gradually reduce the dose of the concomitant corticosteroid.[7] The slow dose reduction of concomitant corticosteroids may have contributed to the low relapse rate.
- To investigate the effects of the concomitant corticosteroid dose (at enrollment in Study RIN-1) on the efficacy of rituximab, the applicant conducted a subgroup analysis of the number of relapsing patients by the concomitant corticosteroid dose at baseline (low dose, prednisolone equivalent dose of 5 to 10 mg/day; intermediate dose, 11 to 20 mg/day; high dose, 21 to 30 mg/day). The results of the analysis (Table 6) revealed that relapses occurred in the placebo group but not in the rituximab group, across all the subgroups; this means that the concomitant corticosteroid dose did not affect the efficacy of rituximab.

Table 6. Subgroup analysis of the number of relapsing patients by concomitant corticosteroid dose at baseline (Study RIN-1, FAS)

	Treatment	Dose level	N	No. of relapsing patients (%)
Concomitant corticosteroid dose[a] at baseline	Placebo	Low 5-10 mg/day	6	2 (33.3)
	Rituximab		5	0
	Placebo	Intermediate 11-20 mg/day	9	2 (22.2)
	Rituximab		10	0
	Placebo	High 21-30 mg/day	4	3 (75.0)
	Rituximab		4	0

a) Prednisolone-equivalent dose

PMDA requested that the applicant (a) present the frequency of relapse by patient characteristics other than the concomitant corticosteroid dose and (b) explain whether any characteristics might affect the efficacy of rituximab.

The applicant's explanation:

- Table 7 shows the results of subgroup analyses for the number of relapsing patients by patient characteristics in Study RIN-1. Although the absence of relapsing patients in the rituximab group precluded a precise evaluation of efficacy, the frequency of relapse in the placebo group did not differ substantially among all the subgroups by patient characteristics. Thus, no patient characteristics were identified as affecting the efficacy of rituximab.

Table 7. Subgroup analyses for the number of relapsing patients by patient characteristics (Study RIN-1, FAS)

	Treatment	Category	N	No. of relapsing patients (%)
Body weight[a)]	Placebo	<58 kg	9	3 (33.3)
	Rituximab		9	0
	Placebo	≥58 kg	10	4 (40.0)
	Rituximab		10	0
Duration of NMOSD[a)]	Placebo	<8.1 years	11	4 (36.4)
	Rituximab		8	0
	Placebo	≥8.1 years	8	3 (37.5)
	Rituximab		11	0
Any relapse within 2 years before allocation	Placebo	Yes	8	3 (37.5)
	Rituximab		7	0
	Placebo	No	11	4 (36.4)
	Rituximab		12	0
EDSS score at baseline[a)]	Placebo	<3.5	9	2 (22.2)
	Rituximab		8	0
	Placebo	≥3.5	10	5 (50.0)
	Rituximab		11	0

a) Categorized by median

PMDA's view regarding the efficacy of rituximab:

- There are no problems with evaluating the efficacy of rituximab based on the time to the first relapse, which served as the primary endpoint, for the following reasons:
  (a) NMOSD is considered to exacerbate with each relapse.
  (b) The time to the first relapse was also used as the primary endpoint in confirmatory studies of other drugs recently approved for prevention of the relapse of NMOSD.
- There were no major problems with (i) defining "a relapse" according to the definition of a relapse stated in the Japanese guidelines for multiple sclerosis and neuromyelitis optica, (ii) requiring the confirmation of a relapse by either abnormal findings on MRI or an electrophysiological examination, and (iii) classifying only objectively proven events as relapses.
- In Study RIN-1, the rituximab group had no relapses, and the placebo group had fewer relapse events than expected at the planning of the study. The fewer number of relapse events may have been due to the slow dose reduction of concomitant oral corticosteroids. However, the subgroup analysis by the oral corticosteroid dose at baseline revealed that relapses occurred independently from the oral corticosteroid dose in the placebo group. The percent reduction in the oral corticosteroid dose at the final assessment point was greater in the rituximab group (75.1%) than in the placebo group (65.3%); this suggests that the reduction in the oral corticosteroid dose did not lead to an overestimation of the efficacy of rituximab.
- Further, the assessment of patient characteristics identified no factors that evidently affected the efficacy of rituximab.

- Based on the above, the results of the primary endpoint in Study RIN-1 demonstrated the efficacy of rituximab in patients with NMOSD.

7.R.2 Safety

7.R.2.1 Differences in the safety profile between patients with NMOSD and patients treated for the approved indications

PMDA asked the applicant to explain the differences in the safety profile of rituximab between patients with NMOSD in the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1) and adult patients who participated in the clinical studies that evaluated rituximab for the treatment of pemphigus or systemic scleroderma (approved indications), which are diseases associated with immune abnormalities as with NMOSD.

The applicant's explanation:

Table 8 shows the incidences of common adverse events in Study RIN-1 involving patients with NMOSD and clinical studies for the approved indications.[12)] There were no events that were reported only in patients with NMOSD, or more frequently in patients with NMOSD than in patients with pemphigus or systemic scleroderma. Thus, there are no substantial differences in the safety profile of rituximab between patients with NMOSD and patients with pemphigus or systemic scleroderma, approved indications.

Table 8. Incidences of common adverse events in clinical studies in patients with NMOSD, pemphigus, and systemic scleroderma

	NMOSD		Pemphigus		Systemic scleroderma	
	Study RIN-1		PEMPHIX study		Study IDEC-C2B8	
	Placebo	Rituximab	MMF	Rituximab	Placebo	Rituximab
N	19	19	68	67	26	28
Any adverse event	17 (89.5)	17 (89.5)	59 (86.8)	57 (85.1)	23 (88.5)	28 (100.0)
Death	0	0	1 (1.5)	0	0	0
Serious adverse events other than death	2 (10.5)	3 (15.8)	10 (14.7)	15 (22.4)	1 (3.8)	1 (3.6)
Common adverse events						
Infusion related reaction	0 (0.0)	7 (36.8)	6 (8.8)	15 (22.4)	0 (0.0)	0 (0.0)
Nasopharyngitis	9 (47.4)	7 (36.8)	7 (10.3)	6 (9.0)	10 (38.5)	11 (39.3)
Headache	3 (15.8)	4 (21.1)	6 (8.8)	10 (14.9)	0 (0.0)	1 (3.6)
Pharyngitis	1 (5.3)	4 (21.1)	3 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract inflammation	1 (5.3)	4 (21.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	1 (5.3)	2 (10.5)	0 (0.0)	0 (0.0)	1 (3.8)	2 (7.1)
Pyrexia	0 (0.0)	2 (10.5)	1 (1.5)	1 (1.5)	0 (0.0)	0 (0.0)
Conjunctivitis	0 (0.0)	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	4 (21.1)	1 (5.3)	10 (14.7)	3 (4.5)	1 (3.8)	3 (10.7)
Neutrophil count decreased	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.7)
White blood cell count decreased	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.7)
Pulmonary valve incompetence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	5 (17.9)
C-reactive protein increased	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	3 (10.7)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	5 (7.4)	7 (10.4)	0 (0.0)	1 (3.6)
Stomatitis	3 (15.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.7)

n (%)

PMDA asked the applicant to explain whether the latest post-marketing information for rituximab (as of November 2021) contained any events, etc. that will require new safety measures.

12) The outlines of the clinical studies for pemphigus and systemic sclerosis are as follows:
Foreign phase III study (PEMPHIX study): A randomized, double-blind, active-controlled, double-dummy, parallel-group study in which patients with moderate to severe pemphigus vulgaris received an oral corticosteroid in combination with either (a) rituximab 1000 mg infused intravenously on Days 1, 15, 168, and 182, or (b) oral mycophenolate mofetil (MMF) 500 mg twice daily for 2 weeks, followed by oral MMF 1 g twice daily for 50 weeks.
Japanese phase II study (Study IDEC-C2B8): A placebo-controlled, randomized, double-blind, parallel-group study in which patients with systemic sclerosis received either placebo or rituximab 375 mg/m^2, infused intravenously once weekly for 4 doses.

The applicant's explanation:

- The current package insert for rituximab states that the following events require attention: infusion reaction, tumor lysis syndrome, hepatitis B virus-induced hepatitis fulminant/hepatitis aggravated, hepatic function disorder/jaundice, mucocutaneous symptoms such as oculomucocutaneous syndrome/toxic epidermal necrolysis, cytopenia (pancytopenia, leukopenia, neutropenia, agranulocytosis, and thrombocytopenia), infection, progressive multifocal leukoencephalopathy (PML), interstitial pneumonia, cardiopathy, renal disorder, gastrointestinal perforation/obstruction, decreased blood pressure, and reversible posterior leukoencephalopathy syndrome. A risk assessment regarding these events was conducted based on the adverse reaction data collected in Japan during the period for the latest Periodic Safety Update Report.[13)] The events reported as serious adverse events during the period were tumor lysis syndrome (1 event in 1 patient), hepatitis B virus reactivation-induced hepatitis fulminant/hepatitis aggravated (8 events in 8 patients), hepatic function disorder/jaundice (6 events in 6 patients), cytopenia (56 events in 43 patients), infection (109 events in 92 patients), PML (4 events in 4 patients), interstitial pneumonia (2 events in 2 patients), cardiopathy (8 events in 6 patients), renal disorder (1 event in 1 patient), gastrointestinal perforation/obstruction (3 events in 3 patients), and reversible posterior leukoencephalopathy syndrome (1 event in 1 patient). However, the incidences of these adverse reactions did not differ substantially from the previously reported incidence trends, with no events that were identified as requiring new safety measures or additional pharmacovigilance activities.
- In addition, with regard to reduced immunoreactivity and malignant tumors, which were specified as important potential risks in the risk management plan, no adverse reactions requiring new safety measures or additional safety pharmacovigilance activities were reported in Japan during the period for the latest Periodic Safety Update Report. Further, none of the events reported as unknown serious adverse reactions[14)] were considered to require new safety measures or additional safety pharmacovigilance activities, due to the presence of causative factors other than rituximab therapy or for other reasons.

PMDA accepted the applicant's explanation.

In the subsequent subsections [Sections 7.R.2.2 to 7.R.2.7], infusion reaction, infection-related adverse events, adverse events relating to leukopenia, neutropenia, and lymphopenia, and decreased immunoglobulin concentrations, PML, hepatitis B virus reactivation, and malignant tumor-related adverse events are further discussed, based on the mechanism of action and precautionary statements included in the package insert for rituximab, as well as the safety profile of inebilizumab (genetical recombination), an approved NMOSD drug with a mechanism of action similar to that of rituximab.

7.R.2.2 Infusion reaction

Infusion reaction is mentioned as requiring attention in the "1. Warnings," "8. Important Precautions," and "11. Adverse Reactions" sections of the package insert for rituximab. PMDA asked the applicant to explain

13) The reporting period was between November 18, 2020 and November 17, 2021.

14) At least 5 events each were accrued for disseminated intravascular coagulation syndrome, thrombotic microangiopathy, haemophagocytic syndrome, respiratory failure, bone marrow depression, gastrointestinal haemorrhage/ulcer, cardiac arrest, cardio-respiratory arrest, Crohn's disease, nephritis, vein embolism and thrombosis, cerebral infarction, pericarditis, low birth weight infant, transplant rejection, and bile duct stenosis.

the incidence of infusion reaction-related adverse events[15] in the rituximab group of the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1).

The applicant's explanation:

- In Study RIN-1, patients were premedicated with an antihistamine and an antipyretic 30 minutes prior to each dose of the study drug to prevent the onset of infusion reaction, according to the precautionary statement[16] in the package insert.
- In Study RIN-1, no infusion-reaction-related adverse events were reported in the placebo group, while infusion-related reaction was reported in 7 patients (36.8%) in the rituximab group. All of the events were non-serious and Grade 1 or 2 in severity.
- Table 9 shows the timing of the onset of infusion reaction in Study RIN-1. Infusion reaction occurred frequently during the induction treatment with rituximab, and the incidence of infusion reaction did not tend to increase with an increase in the number of doses.

Table 9. Timing of the onset of infusion reaction in the rituximab group

	Induction treatment (375 mg/m^2)				Maintenance treatment (1000 mg)			
					Cycle 1[a)]		Cycle 2[a)]	
	First dose	Second dose	Third dose	Fourth dose	First dose	Second dose	First dose	Second dose
N	19	19	19	19	18	18	16	16
Rituximab	7 (36.8)	4 (21.1)	0	1 (5.3)	1 (5.6)	1 (5.6)	1 (6.3)	3 (18.8)

n (%)
a) The incidence was calculated after excluding untreated patients

- The package insert for rituximab already includes precautionary statements regarding the occurrence of infusion reaction in the "1. Warnings," "8. Important Precautions," and "11. Adverse Reactions" sections. In addition, no new concerns regarding the occurrence of infusion reaction have arisen from patients with NMOSD. Thus, no additional precautionary advice will be necessary in the package insert.

PMDA accepted the above applicant's explanation.

7.R.2.3 Infection-related adverse events

Since there are concerns regarding the occurrence of infections attributable to B cell reduction associated with rituximab, PMDA asked the applicant to explain the incidence of infection-related adverse events.

The applicant's explanation:

- Table 10 shows the incidences of infection-related adverse events[17] in the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1). The incidence of infection-related adverse events was similar

15) Events coded to any of the following MedDRA preferred terms (PTs), which occurred on the day of, or the day following the administration of rituximab: "infusion related reaction," "hypersensitivity," and "anaphylactic reaction"
16) Precautions Concerning Dosage and Administration "7.1 Administer an antihistamine, antipyretics, etc. 30 minutes before the administration of rituximab to reduce infusion reactions, which occur frequently in association with rituximab therapy. Consider pretreatment with corticosteroids in cases where rituximab is administered without concomitant corticosteroids."
17) Events coded to the MedDRA SOC "infections and infestations"

in the placebo group and the rituximab group. One patient in the rituximab group had a serious adverse event (nail infection) for which a causal relationship to rituximab could not be ruled out.

Table 10. Incidences of infection-related adverse events (Study RIN-1)

	Placebo	Rituximab
N	19	19
Any adverse event	12 (63.2)	14 (73.7)
Serious adverse events	0	1 (5.3)
Common adverse events		
Nasopharyngitis	9 (47.4)	7 (36.8)
Pharyngitis	1 (5.3)	4 (21.1)
Cystitis	1 (5.3)	2 (10.5)
Cellulitis	0	2 (10.5)
Urinary tract infection	0	2 (10.5)
Conjunctivitis	0	2 (10.5)
Bronchitis	2 (10.5)	0

n (%)

- The package insert for rituximab already includes precautionary statements regarding the occurrence of infections in the "8. Important Precautions," "9. Precautions Concerning Patients with Specific Characteristics," and "11. Adverse Reactions" sections. In addition, no new concerns regarding the occurrence of infection-related adverse events have arisen from patients with NMOSD. Thus, no additional precautionary advice will be necessary in the package insert.

PMDA accepted the above applicant's explanation. However, the risk of infections associated with rituximab is likely to increase in patients with NMOSD because they are expected to use rituximab repeatedly for a long time, unlike patients treated for the approved indications (pemphigus and systemic sclerosis and other indications). Therefore, relevant information should continue to be collected in the post-marketing setting.

7.R.2.4 Adverse events relating to leukopenia, neutropenia, and lymphopenia, and decreased immunoglobulin concentrations

PMDA asked the applicant to explain the incidences of adverse events relating to leukopenia, neutropenia, and lymphopenia in patients receiving rituximab.

The applicant's explanation:

- In the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1), the incidence of cytopenia-related adverse events[18)] was 5.3% (1 of 19 patients [lymphocyte count decreased]) in the placebo group and 10.5% (2 of 19 patients [lymphocyte count decreased in one patient and neutrophil count decreased/white blood cell count decreased in the other]) in the rituximab group. A causal relationship to the study drug could not be ruled out for all of these events. The white blood cell count decreased/neutrophil count decreased in 1 patient in the rituximab group were Grade 3 in severity, which resolved 5 days after the onset without treatments. All of the other events were Grade 1.

18) Events coded to the MedDRA high level term (HLT) "neutropenias," "leukopenias," or "thrombocytopenias," or those coded to the MedDRA PT "neutrophil count decreased," "white blood cell count decreased," "lymphocyte count decreased," "granulocyte count decreased," "neutrophil count abnormal," "band neutrophil count decreased," "white blood cell count abnormal," "pancytopenia," or "platelet count decreased"

- The package insert for rituximab already includes precautionary statements regarding the occurrence of events relating to leukopenia, neutropenia, and lymphopenia in the "8. Important Precautions" and "11. Adverse Reactions" sections. In addition, no new concerns regarding the occurrence of leukopenia, neutropenia, and lymphopenia have arisen from patients with NMOSD. Thus, no additional precautionary advice will be necessary in the package insert.

Patients with NMOSD may receive treatment with rituximab for a long time, as compared with those treated for the approved indications (pemphigus and systemic sclerosis and other indications). PMDA therefore asked the applicant to explain the incidences of adverse events relating to decreased immunoglobulin concentrations in patients receiving rituximab.

The applicant's explanation:

- In Study RIN-1, only patients receiving rituximab were expected to experience decreased immunoglobulins. Thus, no immunoglobulin examination was conducted to maintain the blind of the study.
- In the Japanese phase I/II study in patients with SLE (Reference CTD 5.3.5.4-1, Study IDEC-C2B8-A1), 2 patients in the 1000 mg group presented with IgG decreased for which a causal relationship to rituximab could not be ruled out, while no patients had abnormal IgM or IgA levels for which a causal relationship to rituximab could not be ruled out.
- Treatment with rituximab reduces B cells, thereby impairing antibody production, which may result in decreased immunoglobulins. However, immunoglobulin levels were stable in a Japanese phase II study in patients with recurrent or refractory indolent B-cell non-Hodgkin's lymphoma (Study IDEC-C2B8-2).[19)] In a Japanese phase II study, rituximab was administered for a long time to patients with untreated CD20-positive indolent B-cell non-Hodgkin's lymphoma (Study IDEC-C2B8-6).[20)] In the participants of this study, immunoglobulins decreased in the remission induction period and remained low throughout the maintenance treatment period, but showed a recovery trend during the follow-up period.
- Patients with NMOSD on rituximab therapy are expected to receive the drug repeatedly for a long time for maintenance treatment. They therefore experience B cell depletion for a long time, which may lead to an increased risk of decreased immunoglobulins. However, the package insert for rituximab already includes precautionary statements informing physicians that decreased immunoglobulins associated with decreased peripheral lymphocytes have been reported, and that bacterial or viral infections may occur or worsen through immunosuppression by rituximab in the "8. Important Precautions" section. Therefore, no additional precautionary advice will be necessary in the package insert.

19) An open-label, uncontrolled study in which patients with recurrent or refractory indolent B-cell non-Hodgkin's lymphoma received rituximab 375 mg/m^2 once weekly for 4 doses

20) An open-label, uncontrolled study in which patients with untreated CD20-positive indolent B-cell non-Hodgkin's lymphoma received the following treatments:
Remission induction treatment: The RCHOP regimen (rituximab 375 mg/m^2 plus CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisolone/prednisone/methylprednisolone]) every 3 weeks for 6 doses (6 cycles), followed by rituximab 375 mg/m^2 at 21 days later (Cycle 7) and 42 days later (Cycle 8) (Cycles 1 to 8, 29 weeks); and
Maintenance treatment: Rituximab 375 mg/m^2 at 8 weeks after Cycle 8 and every 8 weeks thereafter, for up to 12 doses (12 cycles, 96 weeks)

PMDA accepted the applicant's explanation. However, leukopenia, neutropenia, and lymphopenia, and decreased immunoglobulin concentrations are expected to occur in view of the mechanism of action of rituximab, and only a limited number of patients with NMOSD received rituximab for a limited duration in Study RIN-1. Therefore, in the post-marketing setting, the applicant should continue to collect information on the relationship of leukopenia, neutropenia, and lymphopenia, and decreased immunoglobulin concentrations with infections in patients who repeatedly received rituximab for a long time.

7.R.2.5 Progressive multifocal leukoencephalopathy

PMDA asked the applicant to explain the incidence of PML in patients receiving rituximab.

The applicant's explanation:

- In the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1), no events suggestive of PML were reported in the rituximab group.
- During the period for the latest Periodic Safety Update Report for rituximab,[13)] adverse reactions of PML were newly reported (4 events in 4 patients). As a result, 47 events of PML have been reported from 47 patients since the first approval of rituximab in Japan. According to the latest post-marketing information in and outside Japan (as of November 2021), PML has been reported from 1072 patients receiving rituximab. Outside Japan, 4 events of PML have occurred in patients treated with rituximab for NMOSD, but no information suggesting that NMOSD would be a risk factor for PML has been reported.
- The 2020 guidelines for the management of progressive multifocal leukoencephalopathy (Research Group on Prion Disease and Slow Virus Infection) classifies the risks associated with drugs that possibly contribute to the development of PML, such as corticosteroids, anticancer drugs (e.g., alkylating agents), immunosuppressants, and biological products, based on the frequency of PML. In the guidelines, the estimated frequency of PML in patients receiving rituximab is 1 out of 30,000.
- The package insert for rituximab already includes a precautionary statement regarding PML in the "11. Adverse Reactions" section. In addition, no new concerns regarding the occurrence of PML have arisen from patients with NMOSD. Thus, no additional precautionary advice will be necessary in the package insert.

PMDA accepted the applicant's explanation. However, PML may lead to serious adverse reactions because it often results in death or functional disabilities. Therefore, emphasizing the risk of PML associated with the use of rituximab in the "Clinically Significant Adverse Reactions" section will be necessary. Further, since only a limited number of patients with NMOSD received rituximab for a limited duration in Study RIN-1, the applicant should continue to collect relevant information in the post-marketing setting.

7.R.2.6 Hepatitis B virus reactivation

PMDA asked the applicant to explain the incidence of hepatitis B virus reactivation in patients receiving rituximab.

The applicant's explanation:

- The Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1) excluded hepatitis B virus-positive patients to ensure patient safety. Therefore, no patients experienced the reactivation of hepatitis B virus in Study RIN-1.
- During the period for the latest Periodic Safety Update Report for rituximab,[13)] 8 events of hepatitis fulminant/hepatitis aggravated due to hepatitis B virus reactivation were reported from 8 patients. As a result, 289 events have been reported from 289 patients since the first approval of rituximab in Japan. The latest incidence did not differ substantially from the previous incidence trends of the adverse reactions, with no events that were identified as requiring new safety measures or additional pharmacovigilance activities.
- The guidelines for the management of hepatitis B (Guidelines for the Management of Hepatitis B Virus Infection, the Japan Society of Hepatology, 2021) includes the following advice:
    (a) Potent immunosuppressive therapy or chemotherapy, including anti-CD20 monoclonal antibodies such as rituximab requires due attention to the possible reactivation of hepatitis B virus in HBs antigen-positive patients or patients with a history of hepatitis B virus infection including patients with inactive carriers.
    (b) Hepatitis B virus reactivation occurring during combination treatment with rituximab and corticosteroids for hematologic malignancies frequently causes hepatitis fulminant that may be highly fatal
    (c) Patients, regardless of liver function abnormalities, should be screened for hepatitis B virus infection prior to the start of immunosuppressive therapy or chemotherapy.
- For hepatitis B virus carriers, the "1. Warnings," "8. Important Precautions," "9. Precautions Concerning Patients with Specific Backgrounds," and "11. Adverse Reactions" sections of the package insert for rituximab already include precautionary advice to the following effect:

  Hepatitis B virus reactivation, which may result in hepatitis fulminant or hepatitis, may occur. Therefore, the development of symptoms or signs of hepatis B virus reactivation should be detected by continuously monitoring liver function test values and hepatitis virus markers, during and after treatment with rituximab, and by other means.

  The precautionary advice on hepatitis B virus reactivation is already included in the "Warnings," "Important Precautions," "Clinically Significant Adverse Reactions," and other sections of the package insert. This precautionary advice should be emphasized for patients with NMOSD as well.

PMDA accepted the applicant's explanation.

7.R.2.7 Malignant tumor-related adverse events

Since B cell reduction caused by rituximab may incur the risk of malignant tumors, PMDA asked the applicant to explain the incidence of malignant tumor-related adverse events.[21)]

The applicant's explanation:

21) Events coded to the MedDRA SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)"

- In the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2: Study RIN-1), a malignant tumor-related adverse event (uterine cancer) was reported in 1 patient in the rituximab group. It was a serious adverse event and its causal relationship to rituximab could not be ruled out. This patient was found to have uterine cancer on Day 519 (167 days after the last dose of rituximab) and underwent a total hysterectomy, with an outcome of "resolved." However, the timing of the onset of the tumor was unknown, and the malignant tumor may have already existed prior to the start of treatment with rituximab, or may have developed accidentally. Accordingly, no concerns regarding the occurrence of malignant tumor-related adverse events in patients with NMOSD receiving rituximab have been identified. Therefore, any advice through the package insert will be unnecessary.

PMDA accepted the applicant's explanation. However, the possibility that B cell reduction associated with rituximab therapy increases the incidence of malignant tumors cannot be ruled out. Further, only a limited number of patients with NMOSD received rituximab for a limited duration in Study RIN-1. Therefore, information regarding malignant tumor-related adverse events should continue to be collected in the post-marketing setting.

7.R.3 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of rituximab.

The applicant's explanation:

- NMOSD is an inflammatory disease of the central nervous system, which is characterized by severe optic neuritis and transverse myelitis. The definition of the disease has undergone changes over the years. After Wingerchuk, et al. proposed diagnostic criteria in 2006 (*Neurology*. 2006;66:1485-9), patients with both optic neuritis and acute myelitis have been diagnosed with neuromyelitis optica. Subsequently, serum anti-AQP4 antibodies were found to involve in the pathology of neuromyelitis optica, and it has become evident that, in anti-AQP4 antibody-positive patients, brain syndrome is not rare and can even develop as the first main manifestation of neuromyelitis optica. On the other hand, in anti-AQP4 antibody-negative patients the pathology remains undetermined, but the involvement of multiple disease groups with different etiologies (e.g., anti-MOG antibodies) has been implicated. In 2015, new international diagnostic criteria for NMOSD were established, which proposed the use of the unifying term "NMOSD" (*Neurology.* 2015;85:177-89).
- In the Japanese guidelines for multiple sclerosis and neuromyelitis optica, NMOSD treatments are recommended separately for the acute exacerbation phase and for the prevention of relapse (suppression of progression). For the acute exacerbation phase, steroid-pulse therapy to accelerate recovery from neurologic symptoms is recommended as the first-line treatment, and if the response is inadequate, plasmapheresis may be selected. For the prevention of relapse (suppression of progression), the use of corticosteroids and immunosuppressants (azathioprine or mycophenolate mofetil [MMF]) is recommended, although azathioprine and MMF have not been approved for NMOSD.
- Recently, the following 3 drugs were approved in Japan for the indication of "prevention of the relapse of NMOSD (including neuromyelitis optica)": eculizumab (genetical recombination) in November 2019,

satralizumab (genetical recombination) in June 2020, and inebilizumab (genetical recombination) in March 2021.

- No clinical studies have directly compared the efficacy and safety of rituximab with those of eculizumab (genetical recombination), satralizumab (genetical recombination), or inebilizumab (genetical recombination), which precludes a determination of when to choose rituximab rather than the currently approved drugs. However, since all of these drugs have been demonstrated to prevent the relapse of NMOSD, an appropriate drug can be selected according to the patient's condition, in consideration of the safety, convenience, and characteristics of the patient, based on the following:
  - Differences in the mechanism of action between rituximab and the approved drugs:
    Eculizumab (genetical recombinant), an anti-complement C5 antibody, binds specifically to C5 and inhibits the cleavage of C5 in complement activation. Satralizumab (genetical recombination), an anti-interleukin-6 (IL-6) receptor antibody, binds specifically to IL-6 receptors and inhibits IL-6 signaling. Inebilizumab (genetical recombination), an anti-CD19 antibody, binds specifically to CD19, a B cell-specific surface antigen, and reduces CD19+ B cells. Rituximab, an anti-CD20 antibody, has a different mechanism of action from that of eculizumab (genetical recombination) or satralizumab (genetical recombination). Rituximab and inebilizumab (genetical recombination) share a mechanism of action by which they reduce B cells, but have different target molecules.
  - Differences in safety between rituximab and the approved drugs:
    There are concerns regarding the risk of (a) meningococcal infection in patients receiving eculizumab (genetical recombination), (b) serious infections due to suppressed defenses (e.g., induced inflammatory reaction, neutrophil migration, and increased antibody production in B cells) attributable to the inhibition of IL-6 signaling in patients receiving satralizumab (genetical recombination), and (c) infections due to B cell reduction in patients receiving inebilizumab (genetical recombination) or rituximab.
  - Differences in dosage and administration between rituximab and the approved drugs:
    During maintenance treatment, eculizumab (genetical recombination) is infused intravenously every 2 weeks, satralizumab (genetical recombination) is subcutaneously administered every 4 weeks, and inebilizumab (genetical recombination) is infused intravenously every 6 months, while the dosage of rituximab is 2 doses (separated by 2 weeks) infused intravenously every 6 months. The dosing interval of rituximab is longer than that of eculizumab (genetical recombination) or satralizumab (genetical recombination), and similar to that of inebilizumab (genetical recombination).
- The efficacy and safety of rituximab in patients with anti-AQP4 antibody-positive NMOSD have been demonstrated in the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1).
- Accordingly, rituximab can become a therapeutic option for the prevention of the relapse of NMOSD.

Based on the submitted clinical study results and other data, PMDA accepted the applicant's explanation that rituximab can become a therapeutic option for the prevention of the relapse of NMOSD.

7.R.4 Indication

PMDA asked the applicant to explain the rationale for the proposed indication and its appropriateness.

The applicant's explanation:

- The Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1) enrolled anti-AQP4 antibody-positive patients with a history of myelitis or optic neuritis, who were under treatment with oral corticosteroids and had a neurologically stable disease with no relapses within 1 month prior to the start of study treatment.
- Study RIN-1, which started in 2014, enrolled patients with the limited form of neuromyelitis optica meeting the 2006 diagnostic criteria for neuromyelitis optica (*Neurology*. 2006;66:1485-9), or the 2007 criteria for neuromyelitis optica spectrum (*Lancet Neurol.* 2007;6:805-15). In 2015, the definition of NMOSD was refined by the international diagnostic criteria for NMOSD (*Neurology*. 2015;85:177-89), and as a result, the limited form of neuromyelitis optica, the target disease of Study RIN-1, was encompassed by NMOSD. Study RIN-1 enrolled patients with anti-AQP4 antibody-positive NMOSD who met the 2015 international diagnostic criteria for NMOSD, except that the study did not include patients with anti-AQP4 antibody-positive NMOSD presenting with a core clinical characteristic of area postrema syndrome or brain involvement.[22)]
- In the 2015 international diagnostic criteria for NMOSD, anti-AQP4 antibody-positive NMOSD and -negative NMOSD are defined separately. Study RIN-1 enrolled only patients with anti-AQP4 antibody-positive NMOSD. However, because anti-AQP4 antibodies can disappear depending on treatments or disease stages, patients who had previously tested positive for anti-AQP4 antibodies were deemed as anti-AQP4 antibody-positive patients. Given the population of Study RIN-1, the "5. Precautions Concerning Indications" section of the package insert will include a precautionary statement that rituximab should be administered to anti-AQP4 antibody-positive patients in the post-marketing setting.
- Based on the above, there are no problems with the proposed indication of rituximab: "prevention of the relapse of NMOSD (including neuromyelitis optica)."

PMDA's view:

- The definition and diagnostic criteria for NMOSD were revised from the 2006 diagnostic criteria for neuromyelitis optica or the 2007 diagnostic criteria for neuromyelitis optica spectrum, to the 2015 international diagnostic criteria for NMOSD. The current Japanese guidelines for multiple sclerosis and neuromyelitis optica recommend the 2015 international diagnostic criteria for NMOSD as the NMOSD diagnostic criteria in Japan. According to the criteria, the core clinical characteristics of NMOSD include area postrema syndrome, acute brainstem syndrome, etc., as well as optic neuritis and acute myelitis. Study RIN-1 did not enroll patients with core clinical characteristics of area postrema syndrome, acute brainstem syndrome, etc., but there are no problems with including these patients in the eligible population for rituximab therapy, for the following reasons:
  (a) These patients have a pathology similar to that observed in the patients enrolled in Study RIN-1 and are diagnosed with NMOSD according to the current diagnostic criteria.
  (b) These patients may have risks of blindness and paraplegia due to a relapse of optic neuritis or

22) At least 1 of the following was met: "acute brainstem syndrome," "symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions," or "symptomatic cerebral syndrome with NMOSD-typical MRI lesions."

acute myelitis.

- Since Study RIN-1 enrolled only anti-AQP4 antibody-positive patients, the indication in the present application should be limited to AQP4 antibody-positive NMOSD.
- Based on the above, the indication should be NMOSD. The "5. Precautions Concerning Indications" section of the package insert should include the following precautionary statement: "Rituximab should be administered to anti-AQP4 antibody-positive patients." PMDA will draw a conclusion based on comments from the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Appropriateness of the proposed dosage and administration

PMDA asked the applicant to explain the appropriateness of the proposed dosage and administration.

The applicant's explanation:

- In the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1), the dosage regimen for induction treatment was rituximab 375 mg/m^2 once weekly for 4 intravenous infusions, which was the same as the approved dosage and administration for B-cell non-Hodgkin's lymphoma and other indications. The dosage regimen for maintenance treatment was 2 intravenous infusions of rituximab 1000 mg separated by 2 weeks, performed at Months 6 and 12; this dosage was determined according to the dosage regimen of rituximab for patients with NMOSD recommended by the Japanese guidelines for multiple sclerosis and neuromyelitis optica and the EFMS guidelines (*Eur J Neurol.* 2010;17:1019-32), and in view of the reported duration of B cell depletion by rituximab therapy (*Neurology.* 2005;64:1270-2) [see Section 6.R.1].
- Rituximab is intended for the prevention of the relapse of NMOSD. In Study RIN-1, blood B cell (CD19+ B cell) depletion was accomplished by Week 4 in all patients in the rituximab group, and the depletion was maintained throughout the 72-week follow-up period (Table 3). Relapses occurred in the placebo group, but not in the rituximab group. The safety profile of rituximab shown in Study RIN-1 was similar to that observed in patients treated for the approved indications, with no new safety concerns identified in patients with NMOSD [see Section 7.2.1]. Further, in the Japanese phase I/II study in Japanese patients with SLE (Reference CTD 5.3.5.4-1, Study IDEC-C2B8-A1), 2 infusions of rituximab 1000 mg separated by 2 weeks caused no safety problems [see Section 7.1.1].
- The maintenance of B cell depletion and the reduction in relapses are important for patients with NMOSD because their disability increases with each relapse. Therefore, no maximum number of doses was determined for patients with NMOSD, although the total number of doses was limited for some of the approved indications. A total of 33 patients who completed Study RIN-1 continued treatment with rituximab in a clinical research study.[23)] In the research, serious adverse events were reported in 6 patients (femur fracture/cholangitis acute/urinary tract infection/pneumonia aspiration/lower gastrointestinal

23) The safety and efficacy of continued treatment with rituximab were evaluated in 33 Japanese patients with anti-AQP4 antibody-positive NMOSD who completed Study RIN-1 ≥16 weeks to <6 months before. The dosage for initial treatment was "375 mg/m^2 once weekly for 4 intravenous infusions," but "two 1000 mg intravenous infusions separated by 2 weeks" was also allowed only if adequate safety management could be ensured. After the initial treatment, re-administration of rituximab (two 1000 mg intravenous infusions separated by 2 weeks) was performed when the percentage of either CD19+ or CD20+ B cells in lymphocytes increased to ≥1%. Re-administration was performed in 26 of 33 patients. The median number of infusions in each patient was 3, with a maximum of 5.

haemorrhage/cholangitis, eyelid ptosis/upper respiratory tract inflammation, myelopathy/drug eruption/pyelonephritis acute, osteoarthritis, urinary retention, and campylobacter gastroenteritis in 1 patient each). A causal relationship to rituximab could not be ruled out for the urinary tract infection, eyelid ptosis, upper respiratory tract inflammation, pyelonephritis acute, and campylobacter gastroenteritis, all of which improved or resolved.

- Based on the above, the dosage and administration was initially proposed as follows:

  "The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly for 4 doses (induction treatment), followed by two 1000 mg/body doses (separated by 2 weeks) approximately every 6 months (maintenance treatment), all administered as an intravenous infusion."

Subsequently, the initially proposed dosage and administration was modified as shown below, to explicitly point out that maintenance treatment starts 6 months after the first dose, as with the dosage regimen used in Study RIN-1.

Modified proposed dosage and administration:

The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly for 4 doses (induction treatment), followed by two 1000 mg/body doses (separated by 2 weeks) ~~approximately~~ at 6 months after the first dose and every 6 months thereafter (maintenance treatment), all administered as an intravenous infusion.

(The underlined words were added to the initially proposed text. The strikethrough word was deleted from the initially proposed text.)

PMDA's view:

- There are no particular problems with the following proposed dosage and administration.

  Induction treatment: 375 mg/m^2 once weekly administered as an intravenous infusion for 4 doses. This dosage was used in Study RIN-1 and has been approved for previously approved indications.

  Maintenance treatment: Two doses of 1000 mg (separated by 2 weeks) administered as an intravenous infusion at 6 months after the first dose and every 6 months thereafter. This dosage was determined according to the Japanese guidelines for multiple sclerosis and neuromyelitis optic, etc.

- PMDA will draw a conclusion on the appropriateness of the dosage and administration based on comments from the Expert Discussion

7.R.5.2 Discontinuation of rituximab

PMDA asked the applicant to explain when to consider the discontinuation of rituximab.

The applicant's explanation:

- NMOSD, once relapsed, may cause severe symptoms such as blindness, transverse spinal cord disorder and the associated complete paraplegia, complete sensory loss, and bladder and rectal disorders, possibly

leading to severe sequelae. Therefore, if the frequency of relapse decreases during treatment with rituximab, the treatment need not be discontinued.

- Meanwhile, rituximab, which induces blood B cell depletion, results in the reduction in B cells and a consequent decrease in immunoglobulins, which may increase the risk of infections, etc. Discontinuation of treatment with rituximab and switching to other treatments should be considered if the reduction in B cells cannot be maintained and the frequency of relapse does not evidently decrease during maintenance treatment with rituximab, as compared with before the treatment, or if the patient experiences any event posing a safety concern.
- Based on the above, the package insert will include a precautionary statement advising physicians to assess the frequency of relapse after a certain period of treatment with rituximab, and then to consider discontinuation of the treatment if the frequency of relapse was not reduced.

PMDA asked the applicant to explain the duration of B cell reduction after discontinuation of rituximab therapy.

The applicant's explanation:

- In the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1), the reduction in B cells was still observed at 6 months after the last dose of rituximab (Table 3). In a Japanese phase II study in patients with untreated CD20-positive indolent B-cell non-Hodgkin's lymphoma (Study IDEC-C2B8-4),[24)] the mean time from the last dose of rituximab to the last confirmation of B cell depletion was 155.5 days, and the mean time from the last dose of rituximab to the first confirmation of the recovery of the B cell count to the pretreatment count was 353.8 days. This suggests that the reduction in B cell count is retained after treatment with rituximab is discontinued.
- Accordingly, patients who have discontinued rituximab should be closely monitored for infections and other conditions because of the prolonged reduction in B cells. Therefore, the package insert will include a precautionary statement advising physicians to continue to closely monitor the patient's condition for symptoms of infections through periodic blood tests and other means, after the discontinuation of rituximab.

PMDA's view:

- The objective of administering rituximab to patients with NMOSD is the prevention of relapses. Since the disability associated with NMOSD increases with each relapse, there are no problems with the applicant's explanation that rituximab need not be discontinued as long as the frequency of relapse is reduced during the treatment.
- Meanwhile, the applicant explained that if relapses occur during the treatment, the discontinuation of rituximab should be decided after considering the risks versus benefits of the continuation of treatment. The applicant's explanation is also acceptable, in view of the fact that other drugs with different mechanisms are available to prevent relapses of NMOSD. This precautionary advice should be

24) A Japanese phase II study in patients with CD20-positive indolent B-cell non-Hodgkin's lymphoma. The patients received either of the following regimen: (a) rituximab 375 mg/m^2 every 3 weeks for 6 doses (the first dose at 2 days before the start of CHOP therapy) or (b) 375 mg/m^2 once weekly for 6 doses (the first dose at 1 month after the completion of 6 cycles of CHOP therapy at 3-week intervals).

included in the package insert.

- Since the reduction in B cells is expected to be retained after the discontinuation of rituximab, the applicant's explanation (i.e., the patient's condition should be monitored for infections, etc., also after the discontinuation of rituximab) is acceptable and a precautionary statement to this effect should be included in the package insert. Further, the incidence of adverse events, etc. after the discontinuation of rituximab should continue to be collected in the post-marketing setting.

7.R.6 Post-marketing investigations

PMDA's view:

Based on the clinical study results submitted, the safety of rituximab should be further evaluated in the post-marketing setting, because only a very small number of patients were enrolled in the clinical study. Therefore, information on infections (including leukopenia/neutropenia/lymphopenia and decreased immunoglobulins), PML, and malignant tumors should be collected through post-marketing surveillance.

The applicant plans to conduct a specified drug use-results survey to evaluate the safety of rituximab in patients with NMOSD treated with rituximab in clinical practice. The observation period of the survey will be 4 to 8 years and the planned sample size will be 200 patients.

PMDA will draw a conclusion on the appropriateness of the post-marketing investigations based on comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing. The results and the conclusion of the PMDA will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. The results and the conclusion of the PMDA will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that rituximab has efficacy in the prevention of the relapse of NMOSD, and that rituximab has acceptable safety in view of its benefits. Rituximab is clinically meaningful because it offers a new treatment option for patients with NMOSD. The appropriateness of the indication, dosage and administration, post-marketing investigations, etc. should be further evaluated.

PMDA has concluded that rituximab may be approved if rituximab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 12, 2022

Product Submitted for Approval

Brand Name	Rituxan Intravenous Infusion 100 mg
	Rituxan Intravenous Infusion 500 mg
Non-proprietary Name	Rituximab (Genetical Recombination)
Applicant	Zenyaku Kogyo Co., Ltd.
Date of Application	October 29, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, 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).

1.1 Efficacy and indication

PMDA's conclusion on the efficacy and indication of rituximab for patients with NMOSD:

- In the Japanese phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study RIN-1), the placebo group had fewer relapse events than expected at the planning of the study. The fewer relapse events than expected may have been due to the slow dose reduction of concomitant oral corticosteroids. However, a subgroup analysis by oral corticosteroid dose at baseline revealed that relapses in the placebo group occurred independently of oral corticosteroid dose. Further, the assessment of patient characteristics identified no factors that evidently affected the efficacy of rituximab. Thus, rituximab was shown to have efficacy in preventing the relapse of NMOSD, based on the results for the primary endpoint in Study RIN-1 [see Section 7.R.1 of the Review Report (1)].
- The 2015 international diagnostic criteria for NMOSD (*Neurology*. 2015;85:177-89) are shown in the current Japanese guidelines for multiple sclerosis and neuromyelitis optica. According to the criteria, the core clinical characteristics of NMOSD include area postrema syndrome, acute brainstem syndrome, etc., as well as optic neuritis and acute myelitis. Study RIN-1 did not enroll patients with core clinical characteristics of area postrema syndrome, acute brainstem syndrome, etc., but there are no problems with including these patients in the eligible population for rituximab therapy, for the following reasons:
  (a) These patients have a pathology similar to that observed in the patients enrolled in Study RIN-1 and are diagnosed with NMOSD according to the current diagnostic criteria.

(b) These patients may have risks of blindness and paraplegia due to a relapse of optic neuritis or acute myelitis.

- Further, since Study RIN-1 enrolled only anti-AQP4 antibody-positive patients, the indication in the present application should be limited to AQP4 antibody-positive NMOSD [see Section 7.R.4 of the Review Report (1)].

The above PMDA's conclusion was supported by the expert advisors.

1.2 Dosage and administration

PMDA's conclusion on the dosage and administration of rituximab for patients with NMOSD [see Sections 6.R.1 and 7.R.5.1 of the Review Report (1)]:

- There are no particular problems with the following proposed dosage and administration.

  Induction treatment: 375 mg/m^2 once weekly administered as an intravenous infusion for 4 doses. (This dosage was used in Study RIN-1 and has been approved for previously approved indications.)

  Maintenance treatment: Two doses of 1000 mg (separated by 2 weeks) administered as an intravenous infusion at 6 months after the first dose and every 6 months thereafter. (This dosage was determined according to the Japanese guidelines for multiple sclerosis and neuromyelitis optic, etc.)

- Since the reduction in B cells is expected to be retained after the discontinuation of rituximab, the patient's condition should be monitored for infections, etc., also after the discontinuation of rituximab. Therefore, a precautionary statement to this effect should be included in the package insert.

At the Expert Discussion, the expert advisors generally supported the above PMDA's conclusion. Some of the experts advisors made the following comments:

- There is a report that relapses of NMOSD may occur shortly after the start of rituximab therapy even in patients with depleted B cells (*Mult Scler Relat Disord.* 2021;54:103143). Therefore, physicians should be informed that Study RIN-1 was designed to administer rituximab in combination with oral corticosteroids.
- The dose of induction treatment is expressed as mg/m^2 of body surface, but the dose of maintenance treatment is a fixed dose. The "Dosage and Administration" of the package insert should clearly states that the 1000 mg fixed dose should be used for maintenance treatment, regardless of body surface area.

Based on the above, PMDA instructed the applicant to inform healthcare professionals that relapses of NMOSD may occur shortly after the start of treatment with rituximab, and about how concomitant oral corticosteroids were used at the start of rituximab therapy in Study RIN-1, through written materials for healthcare professionals. The applicant took appropriate actions accordingly. PMDA also instructed the applicant to modify the dosage and administration of rituximab, as presented below. The applicant took appropriate actions accordingly.

Dosage and administration

The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly for 4 doses, followed by two 1000 mg/body fixed doses (separated by 2 weeks) at 6 months after the first dose and every 6 months thereafter, all administered as an intravenous infusion.

1.3 Risk management plan (draft)

In view of the discussion presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for rituximab should include the safety specifications presented in Table 11, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 12.

Table 11. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infusion reaction • Hepatitis B virus-induced hepatitis fulminant/hepatitis aggravated • Hepatic function disorder and jaundice • Mucocutaneous symptoms such as oculomucocutaneous syndrome (Stevens-Johnson syndrome [SJS]) and toxic epidermal necrolysis (TEN) • Pancytopenia, leukopenia, neutropenia, agranulocytosis, and thrombocytopenia • Infections • Progressive multifocal leukoencephalopathy (PML) • Interstitial pneumonia • Cardiopathy • Renal disorder • Gastrointestinal perforation/obstruction • Decreased blood pressure • Reversible posterior leukoencephalopathy syndrome (RPLS) • Tumor lysis syndrome (TLS)	• Reduced immunoreactivity • Malignant tumors	• Long-term safety in patients with NMOSD[a)]
Efficacy specification[b)]		
Not applicable		

a) Safety specifications added for the present application
b) Only efficacy specifications relating to the present application are listed.

Table 12. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities[a)]	Additional risk minimization activities[a)]
• Early post-marketing phase vigilance in patients with NMOSD • Specified drug use-results survey in patients with NMOSD	• Organize and disseminate information materials regarding NMOSD for healthcare professionals (a proper use guide) • Early post-marketing phase vigilance in patients with NMOSD

a) Only additional pharmacovigilance activities and additional risk minimization activities relating to the present application are listed.

Based on the above, PMDA instructed the applicant to conduct post-marketing surveillance to investigate the items shown above. The applicant explained that a specified drug use-results survey shown in Table 13 will be conducted, involving patients with NMOSD.

Table 13. Outline of the specified drug use-results survey (draft)

Objective	To collect information on the long-term safety of rituximab in clinical practice
Survey method	Central registration system
Population	Patients treated with rituximab for NMOSD
Observation period	4 to 8 years
Planned sample size	200
Main survey items	Patient characteristics (sex, age, body weight, core clinical characteristics, complications, prior therapies, etc.) Exposure to rituximab (date of administration, dose, premedication, cause of discontinuation, etc.) Concomitant treatments Laboratory data (white blood cell count, neutrophil count, lymphocyte count, percentage of B cells, immunoglobulin levels [IgM, IgG], etc.) Adverse events Relapse status (relapses, steroid-pulse therapy [yes/no], plasmapheresis [yes/no], etc.)

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1 and 5.3.5.1-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indication and the dosage and administration shown below (the dosage and administration was modified from the proposed one). Since the product has been designated as an orphan drug with the proposed indication, the re-examination period for the indication is 10 years.

Indications

1. CD20-positive B-cell non-Hodgkin's lymphoma
2. CD20-positive chronic lymphocytic leukemia

3. CD20-positive B-cell lymphoproliferative disorder associated with immunosuppression
4. Granulomatosis with polyangiitis, microscopic polyangiitis
5. Refractory nephrotic syndrome (frequently relapsing or steroid-dependent)
6. Chronic idiopathic thrombocytopenic purpura
7. Acquired thrombotic thrombocytopenic purpura
8. Systemic scleroderma
9. Refractory pemphigus vulgaris and pemphigus foliaceous
10. Prevention of the relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)
11. Prevention of antibody-mediated rejection in ABO-incompatible renal or liver transplant
12. Premedication for indium (^{111}In) ibritumomab tiuxetan (genetical recombination) injection and yttrium (^{90}Y) ibritumomab tiuxetan (genetical recombination) injection

(Underline denotes additions.[25])

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 in combination with other antineoplastic drugs, Rituximab (Genetical Recombination) is administered once in each cycle based on the dosing interval of concomitant antineoplastic drugs.
   For maintenance therapy, the usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 approximately once every 8 weeks administered as an intravenous infusion for up to 12 doses.

   When used to treat CD20-positive chronic lymphocytic leukemia:
   In combination with other antineoplastic drugs, the usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 for the first dose, followed by 500 mg/m^2 for the second and subsequent doses, administered as an intravenous infusion. Administer 1 dose per cycle based on the dosing interval of the concomitant antineoplastic drugs for up to 6 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 granulomatosis with polyangiitis, microscopic polyangiitis, chronic idiopathic thrombocytopenic purpura, acquired thrombotic thrombocytopenic purpura, and systemic scleroderma:
   The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly administered as an intravenous infusion for 4 doses.

25) Dotted underline denotes additions made at the partial change approval dated December 24, 2021.

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 dose is 500 mg.

When used to treat refractory pemphigus vulgaris and pemphigus foliaceous:
The usual dosage of Rituximab (Genetical Recombination) is two 1000 mg/body doses, separated by 2 weeks, administered as an intravenous infusion.

When used to prevent the relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica):
The usual adult dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 once weekly for 4 doses, followed by two 1000 mg/body fixed doses (separated by 2 weeks) at 6 months after the first dose and every 6 months thereafter, all administered as an intravenous infusion.

When used to prevent antibody-mediated rejection in ABO-incompatible renal or liver transplant:
The usual dosage of Rituximab (Genetical Recombination) is 375 mg/m^2 administered as a single intravenous infusion. The dose may be adjusted according to the patient's condition.

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 dilution to 1 to 4 mg/mL with either saline or 5% glucose injection before use.

(Underline denotes additions.[25])

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ADA	Anti-drug antibody
AQP4	Aquaporin-4
AUC	Area under the serum concentration versus time curve
CD19	Cluster of Differentiation 19
CD20	Cluster of Differentiation 20
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone/Prednisone/Methylprednisolone
C_{max}	maximum drug concentration
CTD	Common Technical Document
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Full Analysis Set
Gd	Gadolinium
HLT	High-Level Terms
HBs	Hepatitis B surface
HBV	Hepatitis B Virus
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-6	Interleukin 6
ITT	Intention to Treat
Japanese guidelines for multiple sclerosis and neuromyelitis optica	2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica [in Japanese]. *Igaku Shoin*; 2017
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
MOG	Myelin Oligodendrocyte Glycoprotein
MRI	Magnetic Resonance Imaging
NMOSD	Neuromyelitis Optica Spectrum Disorders
PMDA	Pharmaceuticals and Medical Devices Agency
PML	Progressive Multifocal Leukoencephalopathy
PT	Preferred Term
RMP	Risk Management Plan
SLE	Systemic Lupus Erythematosus
SOC	System Organ Class
$t_{1/2}$	Elimination Half-life
V	Volume of Distribution