Study Protocol

(English translated version of the original Japanese protocol version 2.4 that was approved by the Institutional Review Boards at sites)

Phase II/III Clinical trial

A multi-center, randomized, double-blind, placebo-controlled trial to determine the efficacy of rituximab against a relapse of neuromyelitis optica spectrum disorders with anti-aquaporin 4 antibody

Clinical trial Protocol Number: RIN-1
Clinical trial Protocol Version 2.4
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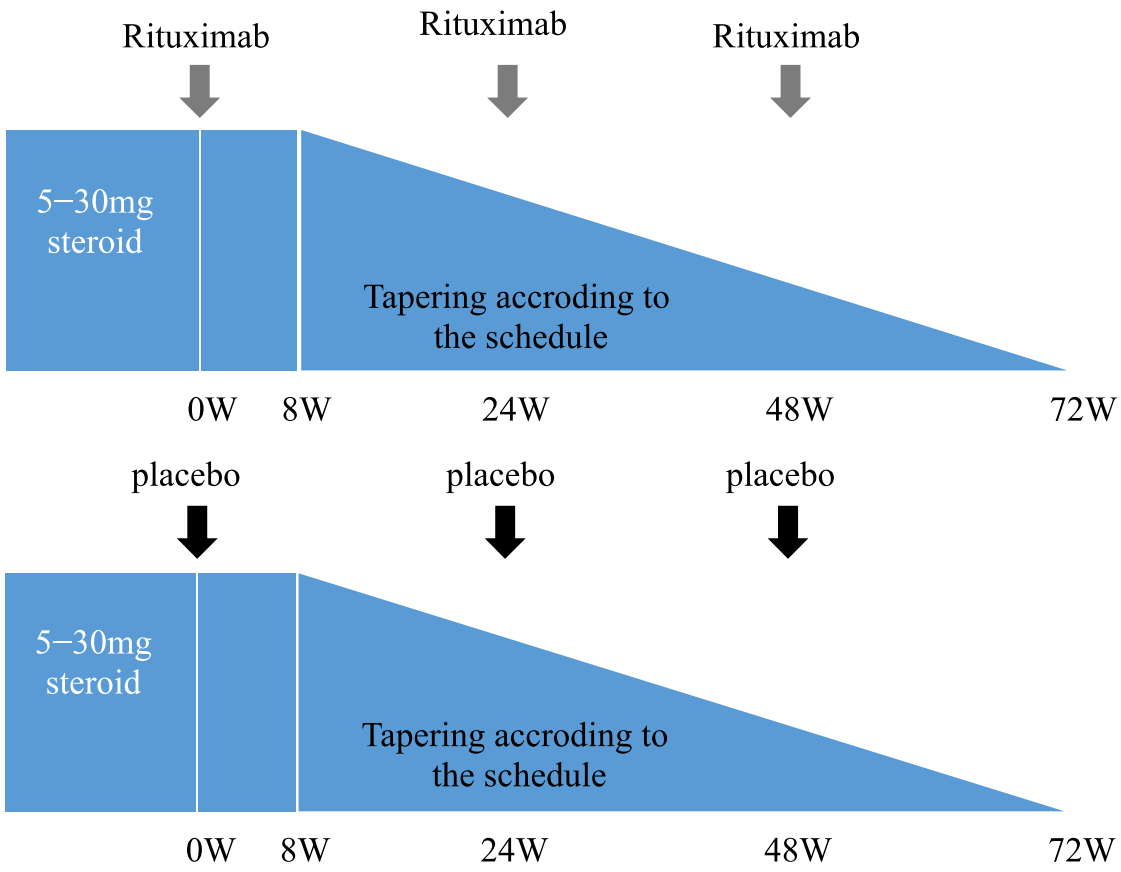
Clinical trial Summary Chart

Primary outcome: Time to the first relapse from randomization

Secondary outcomes: Change in EDSS and QOSI from baseline, and steroid reduction rate



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Summary of the Clinical Trial Protocol

Title: A multi-center, randomized, double-blind, placebo-controlled trial to determine the efficacy of rituximab against a relapse of neuromyelitis optica spectrum disorders with anti-aquaporin 4 antibody

Purpose: To evaluate the efficacy of rituximab (recombinant, anti-CD20 monoclonal antibody) in preventing relapses in patients with neuromyelitis optica

Phase of Development: Phase II/III

Design: Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial

Treatment period: 72 weeks

Patient Eligibility: Patients with neuromyelitis optica who meet all of the following inclusion criteria and does not meet any of the following exclusion criteria.

【Inclusion criteria】

1) Patients who are seropositive for anti-aquaporin 4 antibody (Patients who have previously been seropositive are also included.).

2) Patients who have at least one episode of either optic neuritis or myelitis.

3) Patients who are treated with oral corticosteroids of a dosage of 5 mg /day or more, in prednisolone-conversion dose for 3 months before registration, and the dosage is fixed or change within 10% of the dosage at the registration for 3 months.

4) EDSS between 0 and 7.0.

5) Patients who have no recurrence of NMO within a month before registration and are neurologically stable.

6) Patients between the ages of 16 and 80

7) Either male or female. Either inpatients or outpatients.

8) Women of childbearing ages can be involved if a pregnancy test on Visit 1 is negative and she agree with contraception during the trial.

9) Patients who give written informed consent. Patients under 20 years of age are required parental consent study collaborators study collaborators.

10) Patients who are able to follow the study protocol and schedule, and who can report their symptoms.

【Exclusion Criteria】

1) Patients who have a history of hypersensitivity to mouse protein derivatives or anaphylactic reaction to components of rituximab.

2) Patients infected with hepatitis B virus, hepatitis C virus, or human immunodeficiency virus, and those having active infectious diseases.

3) Patients who have a history of severe recurrent or chronic infections.

4) Patients who have used a live vaccine within 6 months before randomization.
5) Patients under treatment with oral corticosteroid drugs of dosage of 30 mg/day or more in prednisolone-conversion dose.
6) Patients with previous use of cladribine or a monoclonal antibody, such as natalizumab or rituximab.
7) Patients with a history of radiation treatment (whole body irradiation or lymphoid irradiation) or a stem cell transplant.
8) Patients who are treated with mitoxantrone or cyclophosphamide within 12 months before randomization.
9) Patients who are treated with immunomodulatory drugs (interferon beta, glatiramer acetate) or immunoglobulin therapy within 6 months before randomization.
10) Patients who are treated with oral immunosuppressive agents other than steroids (e.g., azathioprine, tacrolimus, cyclosporine, cyclophosphamide, methotrexate, or fingolimod) within 3 months before randomization.
11) Patients who have received plasma exchange or intravenous steroid pulse therapy within 3 months before tentative enrollment.
12) Patients with autoimmune diseases, such as Sjögren's syndrome or systemic lupus erythematosus, requiring treatment with immunosuppressants.
13) Patients who are pregnant or feeding a baby.
14) Patients who participate in other clinical trials.
15) Patients diagnosed as having a cancer.
16) Patients who are judged inappropriate for enrollment in the trial by the principal investigator / co-investigator.

Investigational drug: Rituximab
Control drugs: placebo undistinguished from the investigational drug

Expected clinical benefits: Prophylactic effect against relapses of neuromyelitis optica

Protocol Treatment
[Induction therapy]
Investigational drug (rituximab 375mg /m^2 or placebo) is administrated intravenously (the drug is diluted 10-fold with saline), following pre-medication of an oral non-steroidal anti-inflammatory drug and an anti-histamine drug (30 minutes before administration of the investigational drug).
In Visit 2, the intravenous administration described above is repeated weekly 4 times.

[Maintenance therapy]
In Visit 8 and Visit 14, study drug (1g rituximab or placebo) was intravenous biweekly (the drug is

diluted 10-fold with saline), following premedication (a non-steroidal anti-inflammatory drug and an anti-histamine drug). Confirm no active infections before the drug administration. Prohibited concomitant drugs and therapy: During the trial period, the combination of the following drugs and therapies are prohibited. 1) Steroid pulse therapy (methylprednisolone 500 to 1000mg per day, 3 to 5 days) 2) Plasma exchange therapy (including simple plasma exchange and immunoadsorption therapy) 3) Monoclonal antibodies (natalizumab, alemtuzumab, tocilizumab, etc.) 4) Intravenous immunoglobulin therapy 5) immunosuppressive agents / anticancer agents (cladribine, mitoxantrone, cyclophosphamide, azathioprine, tacrolimus, cyclosporine, methotrexate, fingolimod, etc.) 6) Immunomodulatory (interferon beta, glatiramer acetate, etc.) 7) Live vaccine or live-attenuated vaccine 8) Study drugs except for the investigational drug of the current trial
Discontinued criteria: In case of any of the following conditions, the subjects will discontinue the trial. (1) When a prohibited concomitant drug is administered (2) When a prohibited concomitant therapy is performed (3) When the consent is withdrawn by participants (4) Adverse events that should be discontinued the trial occur (5) When the entire trial is discontinued due to the conditions of the investigational drug provider or the trial (6) If the pregnancy of participants is confirmed (7) When it is judged appropriate to discontinue the trial by the principal investigator / co-investigator for other reasons.
Efficacy evaluations: Primary outcome measure: time to the first NMO relapse in the trial Secondary outcome measures: Score changes in EDSS and QOSI from the baseline, steroid reduction rate from the baseline Safety evaluations: Frequency of adverse events Frequency of severe adverse events

List of abbreviations

AQP-4: aquaporin-4

EDC: electronic data capture

EDSS: Krutzke's expanded disability status scale

GCP: good clinical practice

Gd: gadolinium

HIV: human immunodeficiency virus

IDMC: Independent Data Monitoring Committee

IRB: Institutional review board

MRI: magnetic resonance imaging

MS: multiple sclerosis

NMO: neuromyelitis optica

NMOSD: neuromyelitis optica spectrum disorder

QOSI: quantification of optic nerve and spinal cord impairment

RCT: randomized control trial

1. Objectives

The objective of this study is to determine the efficacy of rituximab (a recombinant, anti-CD20 monoclonal antibody) in preventing relapses in patients with neuromyelitis optica (NMO) in a multicenter, placebo-controlled, double-blind study. Study subjects are the patients with NMO who fulfill the 2006 revised NMO diagnostic criteria (1) and those with anti-aquaporin 4 antibody-positive neuromyelitis or optic neuritis (referred to as NMO spectrum disorders, hereafter, NMOsp) that are under treatment with corticosteroids. During the observation period, steroids are tapered according to the protocol. The primary outcome is the time to the first relapse from randomization, and the secondary outcomes are changes in EDSS and QOSI from baselines, and steroid reduction rate.

2. Background and rationale

2.1 Medical background

Background of NMO

The first report of NMO was a serious case of acute myelitis and optic neuritis in 1894 in a patient who died after a month from diagnosis. At that time, NMO was thought to be a subtype of multiple sclerosis (MS). The poor prognoses of NMO continued for a long time, according to a report of 1999, half of the patients used wheelchairs within 5 years after the onset of symptoms, and 60% of patients lost their eyesight (2). In 2004, autoantibodies were discovered in the sera of patients with NMO (3) and revealed to be antibodies to aquaporin 4 (AQP-4) that are water channels expressing in astrocytic foot processes which form blood-brain barrier) (4). In addition, the loss of AQP-4 at NMO lesions was pathologically proven (5); hence, NMO has been regarded as an immunological neurological disorder, and anti-AQP-4 antibodies may play an important role for the disease.

Based on findings described above, the diagnostic criteria for NMO were revised (1). Most patients with optico-spinal MS, which had been considered to account for about 30% of MS in Japan, were positive for anti-AQP-4 antibodies, and NMO is not considered to be a rare disease in Japan. Patients with NMO does not respond to clinical treatment for MS; interferon-β, treatment for MS, has been shown to be ineffective or may even exacerbate disease in patients with NMO (6, 7).

The assessment of the efficacy of corticosteroids has been retrospectively conducted in a small number of patients as a treatment for NMO (8); however, adequate evidence on the steroid efficacy has not been shown, and there is no guidance on dose reductions, raising concern about side effects due to long-term steroid treatment. The incidence of NMO is higher in Japan than foreign countries and NMO relapses can be fatal or may leave serious sequelae such as blindness or wheelchair-bound, and therefore, it is urgent to develop effective therapies for the disease.

2.2 Rationale

Rituximab, originally a therapeutic agent for B-cell non-Hodgkin's lymphoma, is a pharmaceutical product that specifically depletes only anti-CD20 positive B cells. Therefore, rituximab is expected to

be effective against autoimmune diseases in which B cells are considered to be involved in the pathogenesis. In clinical practice, the therapeutic effects on various autoimmune diseases including rheumatoid arthritis and MS are confirmed.

In terms of the therapeutic effects in NMO, the annual relapse rate for NMO reportedly decreased from 2.6 to 0 by rituximab in 8 patients with recurrent NMO (9). A subsequent retrospective review of the efficacy of rituximab in 25 patients with NMO (comparison of pre- and post-treatment) showed that the annual relapse rate decreased from 1.7 (median, range 0.5-5) to 0 (range 0-3.2) (10). In addition, in a similar retrospective study (11) and a prospective report of long-term efficacy, 10 patients with NMO were observed during the period of 10 to 45 months, for whom the mean annual relapse rate was reduced from 2.4 (pre) to 0.93 (post) (12). We also reported that the annual relapse rate decreased from 4.8 to 1.1 and EDSS improved from 8.7 to 8.0 in three patients with NMO (13).

Based on these results, rituximab, along with corticosteroids, is defined to be first-line therapy in the 2010 guideline of the European Federation of Neurological Societies (EFNS) (14); however, none of these are approved in Japan.

Since then, no randomized controlled trials (RCTs) have been conducted, and only an open-label study was conducted. In the study, 30 patients with NMO or NMOsp, who had experienced at least one relapse in the 12 months prior to rituximab treatment, were enrolled and observed for 2 years. Annual relapse rate, the primary outcome, was significantly reduced from 2.4 (0.4-8) to 0.3 (0-4) by rituximab and there was statistical significance between the pre-treatment and the post-treatment periods ($p<0.001$), demonstrating a 70% complete response rate without relapse. As the Secondary outcome, EDSS decreased significantly from 4.4 (1.0-8.5) to 3.0 (1.0-7.5) ($p<0.001$) and was stable or improved in 97% of patients. No serious adverse reactions were reported in the report (15).

Preliminary we analyzed the data of 5 NMO patients treated with rituximab (a total of 20 courses were conducted) at Utano National Hospital and found that the relapse was not observed in 17 of the 20 courses, demonstrating a very high response rate. The response rate to rituximab was 95% in the period excluding the induction period until rituximab works and the period when the efficacy of rituximab had expired.

year	design	n (AQP4-Ab+)	duration (month)	ARR pre	post	EDSS pre	post
2005 (ref. 9)	pilot	8 (NA)	12 (6-18)	2.6	0	7.5	5.5
2008 (ref. 10)	retrospective	25 (14)	19 (6-40)	1.7 (0.5-5)	0 (0-3.2)	7 (3-9.5)	5 (3-10)
2011(ref. 11)	retrospective	23 (15)	32.5 (7-63)	1.87 (0.31-5.14)	0 (0-1.33)	7.0 (3.0-9.0)	5.5 (0-8.0)
2011(ref. 12)	prospective	10 (10)	27 (10-45)	2.4 (per 12M) 1.72 (per 24M)	0.93	5.3 (1.5-9)	5.5 (1.5-10)
2011(ref. 15)	open	32 (21)	24	2.4 (0.4-8)	0.3 (0-4)	4.4 (1.0-8.5)	3.0 (1.0-7.5)

3. Investigational product

3.1 Overview of investigational product

The test drug used in this study is a clear and colorless injection drug containing anti-human CD20 monoclonal antibodies. The control drug is an injection drug that is indistinguishable from the aforementioned test drug in appearance and has no pharmacological effects.

3.2 Identity of investigational product

Test and control drugs will be provided in a dedicated box.

3.3 Chemical name, structural formula, and other information on test drug

Generic name: JAN (Japanese name) rituximab (recombinant product)

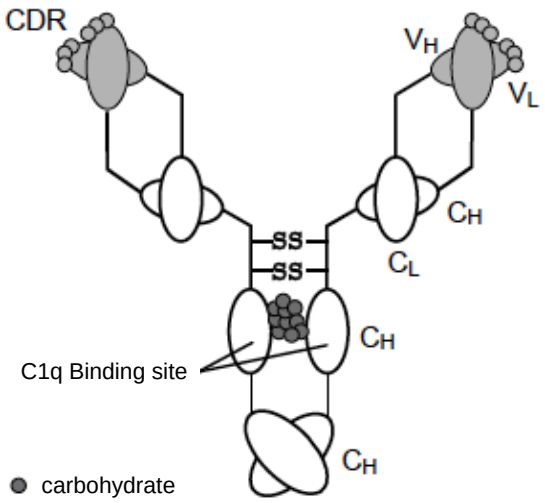
(English name) rituximab (genetic recombinant)

INN rituximab

Chemical formula: $C_{6426}H_{9900}N_{1700}O_{2008}S_{44}$

Molecular weight: 144,510 Daltons (1,328 amino acid residues)

Structural formula:



3.4 Contents of investigational product label

The following information shall be displayed on the investigational product label.

Notice that the product is for the clinical trial

Name, title, and address of the head of the study coordinating committee

Medication number

Manufacturing number or manufacturing code

Storage conditions and shelf-life

3.5 Storage conditions for the investigational product

The investigational product is to be stored in a refrigerator and appropriately managed according to the Procedure of the Investigational Product Management.

3.6 Rationale for the dosage and administration of the investigational product

Induction therapy: 375 mg/m^2 four times weekly administration was adopted because a repeated administration could deplete B cells throughout the body (according to the protocol for the treatment of B-cell non-Hodgkin's lymphoma). We consider the protocol of lymphoma can be partially adopted in patients with NMO.

Maintenance therapy: rituximab-induced B-cell depletion lasts at least 6 months but does not last 12 months in many patients; therefore, rituximab is to be re-administered at 6 months (Visit 8) and 12 months (Visit 14). Dosing is to be repeated twice, 1 g every other week.

4. Eligibility criteria

4.1 Inclusion criteria

(1) Patients who are seropositive for anti-aquaporin 4 antibody (Patients who have previously been seropositive are also included.).
(2) Patients who have at least one episode of either optic neuritis or myelitis.
(3) Patients who are treated with oral corticosteroids of a dosage of 5 mg /day or more, in prednisolone-conversion dose for 3 months before registration, and the dosage is fixed or change within 10% of the dosage at the registration for 3 months.
(4) EDSS between 0 and 7.0.
(5) Patients who have no recurrence of NMO within a month before registration and are neurologically stable.
(6) Patients between the ages of 16 and 80
(7) Either male or female. Either inpatients or outpatients.
(8) Women of childbearing ages can be involved if a pregnancy test on Visit 1 is negative and she agree with contraception during the trial.
(9) Patients who give written informed consent. Patients under 20 years of age are required parental consent study collaborators study collaborators.
(10) Patients who are able to follow the study protocol and schedule, and who can report their symptoms.

[Rationale]

(1) Anti-AQP-4 antibodies are extremely helpful in diagnosing NMO (specificity is reportedly close to 100% and sensitivity >90% (1)). However, it is well-known that the antibodies frequently convert to seronegative according to treatment or disease activity. Therefore patients who previously showed antibody-positive are allowed to participate in the study. (2) Patients with positive AQP-4 antibodies and either optic neuritis or myelitis are referred to as NMOsp and are considered as having localized forms of NMO. In a study by Kittley et al., 86% of patients with positive anti-AQP-4 antibodies experienced relapse, and the median for the time from onset of symptoms to relapse was reported to

be 14 months (16). From these points, assuming that the pathophysiology was common to NMO participation was allowed. (3) This was considered so that patients might participate without discontinuing oral corticosteroid treatment, which is the current standard treatment for NMO. The rationale for setting a lower limit of 5 mg for the steroid dose is due to the limited necessity to include patients who are stable with very low doses of corticosteroids without causing a major issue in terms of adverse reactions. In addition, the range of fluctuation in dose was set for the reason that large dose fluctuations of steroid may affect the efficacy assessment, although a fluctuation within 10% of the steroid dose at the time of tentative enrollment was allowed for clinical purposes. (4) This was set since severe neurological sequelae make appropriate assessment difficult. (5) This was set to accurately evaluate the primary outcome of relapse. (6) The lower limit of age was set in accordance with the patients' ability to give voluntary consent and the upper limit was set in terms of safety. (7) This was set for the reason that efficacy can be assessed in both hospitalized patients and outpatients. In addition, since the tolerability and safety of the study drug and the expected benefits are not limited to males or females, this criterion was set. (8) Since the safety of the test drug in pregnant women has not been established, a decision was made to require women of childbearing potential to consent to the use of contraception. (9) This was set to ensure that the patients' interests are not compromised from an ethical point of view. (10) This was set to allow for appropriate assessments.

4.2 **Exclusion criteria**

(1) Patients who have a history of hypersensitivity to mouse protein derivatives or anaphylactic reaction to components of rituximab.
(2) Patients infected with hepatitis B virus, hepatitis C virus, or human immunodeficiency virus, and those having active infectious diseases.
(3) Patients who have a history of severe recurrent or chronic infections.
(4) Patients who have used a live vaccine within 6 months before randomization.
(5) Patients under treatment with oral corticosteroid drugs of dosage of 30 mg/day or more in prednisolone-conversion dose.
(6) Patients with previous use of cladribine or a monoclonal antibody, such as natalizumab or rituximab.
(7) Patients with a history of radiation treatment (whole body irradiation or lymphoid irradiation) or a stem cell transplant.
(8) Patients who are treated with mitoxantrone or cyclophosphamide within 12 months before randomization.
(9) Patients who are treated with immunomodulatory drugs (interferon beta, glatiramer acetate) or immunoglobulin therapy within 6 months before randomization.
(10) Patients who are treated with oral immunosuppressive agents other than steroids (e.g., azathioprine, tacrolimus, cyclosporine, cyclophosphamide, methotrexate, or fingolimod) within

3 months before randomization.

(11) Patients who have received plasma exchange or intravenous steroid pulse therapy within 3 months before tentative enrollment.

(12) Patients with autoimmune diseases, such as Sjögren's syndrome or systemic lupus erythematosus, requiring treatment with immunosuppressants.

(13) Patients who are pregnant or feeding a baby.

(14) Patients who participate in other clinical trials.

(15) Patients diagnosed as having a cancer.

(16) Patients who are judged inappropriate for enrollment in the trial by the principal investigator / co-investigator.

[Rationale]

For the purpose of the safe conduct of the clinical trial, patients who meet criterion (1) should not be included from the perspective of test drug administration.

In particular, since some patients died of fulminant hepatitis, patients with hepatitis virus infections or those at high risk of infection according to (2), (3), and (4) should not be included in the study. (5) To keep detection power of efficacy of rituximab, patients concomitantly using corticosteroids exceeding the equivalent of 30 mg of prednisolone per day are excluded. Based on the necessity to exclude the effects of immunosuppressive agents other than the investigational product on the clinical trial and in consideration of an excessive immunosuppressive state, those meeting criteria (6), (7), (8), (9), and (10) are excluded. In addition, based on the potential impact of steroid pulse therapy on efficacy assessments and to allow for an accurate assessment of disease status, criterion (11) and, to exclude the impact of other diseases, criterion (12) were set. Considering the effects on pregnancy and breast-feeding, the criterion (13) should not be included. (Patients who are of childbearing potential should not be excluded from the study if adequate contraception is being used). In addition, patients who meet criteria (14), (15), and (16) are not included in the study to ensure the appropriate conduct of the study.

5. Explanation provided to patients and obtaining informed consent

5.1 Preparation of explanatory documents and informed consent forms

The written explanatory documents and informed consent form will be prepared by the principal investigator and approved by the IRB of each study site and will be used to obtain informed consent from patients to participate in the clinical trial.

5.2 Revision of explanatory documents and informed consent forms

The principal investigator shall promptly revise the explanatory documents and informed consent form and obtain IRB approval as soon as the principal investigator becomes aware of the need to revise the informed consent form or other relevant information that may be relevant to the patients' consent.

5.3 Topics to be explained to patients

The explanatory documents and informed consent forms should include the following:

- ☐ That the clinical trial involves research
- ☐ Study objectives
- ☐ The name, title and contact information of the principal investigator
- ☐ Study methods
- ☐ Expected benefits on patients' physical and mental health with the use of investigational product (or that such benefits cannot be expected if benefits are not expected) and potential disadvantages to the patient (in particular, an explanation for the risk of progressive multifocal leukoencephalopathy, one of the serious adverse reactions associated with the investigational product, should be included)
- ☐ Information regarding other treatments for NMO relapse
- ☐ Duration of participation in the clinical trial
- ☐ That the patient may withdraw from the clinical trial at any time
- ☐ That the patient will not receive unfavorable treatment due to not participating in the clinical trial or by withdrawing the participation in the clinical trial
- ☐ That source documents may be accessed by the monitor, auditor, and IRB, provided that the confidentiality of patients is maintained
- ☐ That the patient's identity will be kept confidential
- ☐ The contact information of the study site in the event of study-related injuries
- ☐ That necessary treatment will be provided to the patient in the event of study-related injuries
- ☐ Information on compensation in the event of any study-related injury
- ☐ Type of IRB reviewing and deliberating the appropriateness and other aspects of the clinical trial, topics to be reviewed and deliberated by the IRB, and other matters related to the IRB reviewing the clinical trial
- ☐ The number of patients that will participate in the clinical trial
- ☐ That, in the event that information that may affect the decision of the patient to continue participation in the clinical trial is obtained, such information will be promptly communicated to the patient
- ☐ Requirements or reasons for discontinuing participation in the clinical trial
- ☐ In the event that the patient is paid, the details regarding such payment
- ☐ Instructions the patient must comply with
- ☐ Other necessary matters concerning the clinical trial

5.4 Timing and method of obtaining informed consent

Written informed consent should be obtained from prospective participants prior to participating in the study (on the day of Visit 1 or by the day prior) according to the following procedures.

(1) The principal/co-investigator will fully explain the information specified in "5.3 Topics to be

explained to patients" using explanatory documents and the informed consent form to patients who are considered eligible to participate in the clinical trial. In addition, as necessary, clinical research coordinators will provide additional explanation.

(2) Prior to obtaining consent, the principal/co-investigator will provide the patient with the opportunity to ask questions and sufficient time to decide whether or not to participate in the study.

(3) Principal/co-investigators or clinical research coordinators providing supplementary explanations should respond to all questions from prospective participants and ensure prospective participants are satisfied with responses.

(4) If a prospective participant agrees to participate in the clinical trial, the principal/co-investigator who provided the explanation and clinical research coordinators (when providing supplementary explanations), and the prospective participant will sign and affix their seal or sign and date the consent form.

(5) Prior to participation in the study, the principal investigator or co-investigator shall hand over a copy of the informed consent form and explanatory documents to the prospective participant and retain the original informed consent form and explanatory documents at the participating study site

5.5 In the event that information which may affect patient consent to participate or continue participation in the study becomes available

In the event that information which may affect the patient's willingness to participate or continue participation in the study (safety information, etc.) becomes available, the principal/co-investigator will inform the patient of such information, confirm the patient's willingness to continue participation in the study, and document the decision and date of confirmation.

5.6 Obtaining informed consent again after revision of explanatory documents and informed consent forms

If explanatory documents and informed consent forms are revised, the principal/co-investigator must obtain informed consent from the patient according to the following procedures.

(1) The principal investigator or co-investigator shall inform patients who are already participating in the study of the revision, confirm their willingness to continue participation in the study, provide an explanation using the revised explanatory documents and informed consent and obtain written informed consent to continue participation in the study.

(2) Prior to obtaining consent, the principal/co-investigator will provide the patient with the opportunity to ask questions and sufficient time to decide whether or not to participate in the study.

(3) Principal/co-investigators or clinical research coordinators providing supplementary explanations should respond to all questions from patients and ensure participants are satisfied with responses.

(4) If a patient agrees to continue participation in the clinical trial, the principal/co-investigator who provided the explanation and clinical research coordinators (when providing supplementary explanations), and the participant will sign and date the consent form.

(5) The principal/co-investigator shall hand over a copy of the informed consent form and explanatory documents to the patient, and the principal/co-investigator will retain the original information consent form at the participating study site.

5.7 Obtaining consent from minors

If the patient is younger than 20 years of age, consent from the patient's legally acceptable representative should be obtained.

6. Enrollment/randomization

6.1 Procedures for patient enrollment (tentative enrollment, definitive enrollment, and randomization)

6.1.1 Tentative enrollment

The principal investigator or co-investigator will provide an explanation to patients eligible for the clinical trial using specified documents and, if consent is obtained, shall enter the information required for tentative enrollment into the electronic data capture (EDC) system, and perform tentative enrollment.

The required information is as follows.

1) Date of birth
2) Sex
3) Race
4) Date informed consent was obtained
5) Form of consent obtained
6) Age at the time informed consent was obtained
7) Date of onset of NMO
8) Corticosteroid dose

6.1.2 Definitive enrollment and randomization

The principal investigator or a co-investigator will evaluate whether the patient meets the inclusion criteria described in Section 4.1 and does not meet the exclusion criteria described in Section 4.2 after the tentative enrollment and, at the time eligibility is confirmed, will enter the required information for definitive enrollment in EDC and perform definitive enrollment.

6.2 Randomization method and randomization adjustment factors

Assuming that the allocation in Section 6.1.2 is performed using as stratification factors, the dose of concomitant corticosteroids entered in EDC (three strata: A (5-10 mg/day), B (11-20 mg/day), and C (21-30 mg/day) according to the steroid dose at the time of tentative enrollment) and the relapses in

the 2 years prior to allocation (groups with or without relapse), patients formally enrolled will be randomized by the registration center to either the active treatment group or the placebo group. The results of randomization (medication number) will be sent by the registration center to the principal/co-investigator by FAX during the day of definitive enrollment, and the investigational product with the assigned medication number will subsequently be supplied by the investigational product provider.

6.3 Key code

The information linking each investigational product as an active drug or placebo is called a key code. The key code will be retained by the allocation manager and will not be disclosed until the emergency unblinding specified in Section 20 after the completion of the clinical trial, except for emergency unblinding specified in Section 10.

7. Treatment plan

7.1 Protocol treatment

☐ Visit 2

For patients who have completed definitive enrollment, observations for "relapse" (relapse of NMO as defined in Section 13) will be started and the investigational product will be administered. As a general rule, the investigational product should be administered in the hospital.

☐ Investigational product administration

The investigational product should be administered within one week after definitive enrollment. Rituximab 375 mg/m^2 is administered as an intravenous drip infusion after 10-fold dilution with physiological saline or placebo is administered as an intravenous drip infusion. Four repeated doses are administered once a week. However, the 4th dose should be administered no later than the day before Visit 3. Oral premedication (anti-inflammatory drugs, antihistamines) should be administered 30 minutes prior to administration. Administration method details are provided in Appendix 1.

☐ Visit 4 and thereafter

The dose of corticosteroids should be reduced according to Section 7.3. At visits every 4 weeks, checks for "relapses" based on neurologic findings and safety concerns are to be performed.

☐ For visits every 12 weeks (Visit 5, 8-1, 11, 14-1, 17, 20), plain and Gd-enhanced cerebral MRI are to be performed. At Visits 8-1, 14-1, and 20, plain and Gd-enhanced spinal cord MRI should also be attempted.

7.2 Rituximab maintenance therapy (additional doses)

☐ Visit 8, 14

Additional doses will be administered to maintain the efficacy of rituximab. Rituximab 1 g, diluted 10-fold with physiological saline, is administered as an intravenous drip infusion or placebo is administered as an intravenous drip infusion. Two doses are given every other week. As with induction therapy, planned premedication should be given 30 minutes prior to dosing.

Prior to administration, patients should be confirmed as not having active infection by checking for pyrexia, examining physical findings, complete blood count, biochemistry tests, urinalysis, and chest X-rays. If the attending physician decides that administration is inappropriate, a delay of up to 2 weeks may be permitted; however, the second dose should be administered the day prior to Visit 9 or 15.

7.3 Corticosteroid tapering protocol

The dose of corticosteroids is converted to prednisolone equivalents as follows. The day after Visit 1, the patient will be switched to prednisolone. However, if steroids are being administered as an every-other-day regimen, a dose close to the mean (rounded off) should be administered daily.

Prednisolone 5 mg = 25 mg of cortisone = 10 mg of cortisol = 5 mg of prednisone = 4 mg of methylprednisolone = 4 mg of triamcinolone = 2 mg of paramethasone = 0.5 mg of dexamethasone = 0.5 mg of betamethasone

For example: 12 mg of methylprednisolone is 15 mg (prednisolone equivalent).

Thereafter, prednisolone is tapered from Visit 4 (8 weeks after rituximab administration) until Visit 20 in both groups by 10% per month, to a minimum of 2 mg, if no relapse is observed. (In the instance of dose reduction from a dose of 10 mg or less, dose reduction shall be by 1 mg steps). Reductions for each visit are to be performed in the following order.

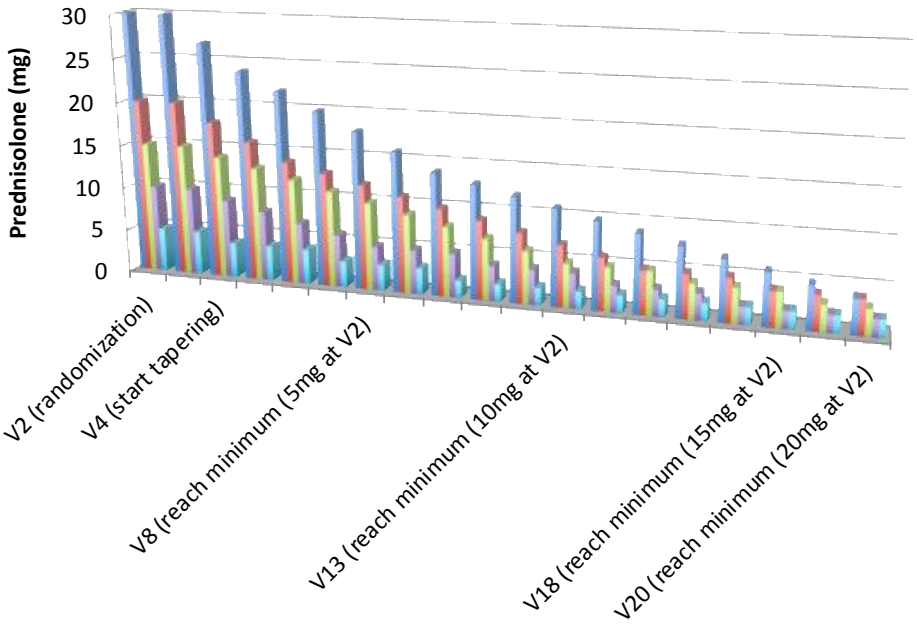
However, if the starting dose does not correspond to any of the following entries, the nearest dose should be used as a starting point for reductions.

(In order of dose reduction, in terms of prednisolone [mg] equivalents)

30→27→24→22→20→18→16→14→13→12→11→10→9→8→7→6→5→4→3→2

Reductions in corticosteroid doses during the study are to be initiated at Visit 4.

The dose reduction steps based on the steroid dose at the time of tentative enrollment (when starting from 30 mg, 20 mg, 15 mg, 10 mg, and 5 mg in the figure, as shown in the bar graph on the left) are as shown in the following figure.



7.4 Rationale for reducing corticosteroid dose

There are no clear guidelines for the dosage and duration of use of corticosteroids for the prevention of relapse of NMO, as objective measures of NMO disease activity have not been established (14, 17). In this clinical trial, the dose is to be gradually reduced to minimize the effect on NMO disease activity, taking safety into consideration. The dose is to be reduced by 10% per month. At this dose reduction rate, steroid rebound is considered to be less likely to occur and steroid withdrawal syndrome from dose reductions can also be avoided. Analyses of our data showed that, assuming that the corticosteroid dose (prednisolone equivalent) and risk of relapse was set to 1 when the dose was ≥21 mg/day, the risk of relapse increased with dose reduction to 3.58-fold when the dose was ≤20 mg/day and 5.22-fold when the dose was ≤10 mg/day (refer to the subsequent table).

Based on this finding, assuming that the dose is reduced to 5 mg from 30 mg, there is an estimated 5-fold increase in the frequency of relapse; however, this increase in the frequency of relapse is offset to 0.11- to 0.15-fold with the administration of rituximab.

Based on these findings, the risk of relapse becomes negligible in the active treatment group even if the dose is tapered from 30 mg and, even in the placebo group, the dose is gradually reduced in a manner comparable to typical clinical use, thus avoiding excessive burden on patients.

Medications	Doses	OR (95% CI)	P
Steroid	5-10mg/day	5.22 (1.08 - 25.25)	0.04
	11-20mg/day	3.58 (0.52 - 24.56)	0.20
	21mg/day or more (Ref)	1	

7.5 Treatment options at the time of "relapse" (relapse of NMO as defined in Section 13)

After completing the observation period in this study, treatment with (1) below will be started immediately, and concomitant use of (2) will be considered as necessary. If the treatment with (1) and (2) is considered difficult or does not improve outcome measures, other appropriate treatment should be given.

(1) Steroid pulse therapy (methylprednisolone at a dose of 500 to 1000 mg for 3 to 5 days)
(2) Plasmapheresis (irrespective of the type of plasmapheresis, immunoadsorption therapy, etc.)

7.6 Study discontinuation

Discontinue investigational product administration and remove the patient from the clinical trial if any of the following occur.

(1) If prohibited concomitant drugs were administered
(2) If prohibited concomitant therapy was administered/performed
(3) If consent is withdrawn
(4) In the event of an adverse event that requires discontinuation of treatment
(5) If the study is discontinued at the discretion of the principal investigator or sponsor providing the investigational product
(6) If the pregnancy of the patient is confirmed
(7) If the principal or co-investigator determines it necessary to withdraw patients from the study for other reasons

If the patient discontinues the study, the principal/co-investigator will identify the reason for withdrawal and enter this in EDC. The assessments described in Section 11.1 (at the time of withdrawal) should be performed as much as possible. Also, the outcome of any previous adverse events will be followed for the required period of time. The required period will be determined at the discretion of the principal/co-investigator.

7.7 Restricted concomitant drugs and therapies

For corticosteroids, Section 7.3 should be followed during the study period.

Steroid pulse therapy and plasmapheresis should not be used until the relapse of NMO as defined in Section 13 is observed. If relapse of NMO as defined in Section 13 has not occurred and steroid pulse therapy or plasmapheresis has been administered, withdraw the patient from the study (Section 7.6 (1))

7.8 Prohibited concomitant drugs and therapies

The concomitant use of the following drugs and therapies is prohibited during the course of the clinical trial.

1) Steroid pulse therapy
2) Plasmapheresis
3) Monoclonal antibodies
4) High-dose immunoglobulin therapy

5) Immunosuppressive agents/Anti-cancer drugs
6) Immunomodulators
7) Live or live-attenuated vaccines
8) Investigational products other than the study drug

A list of drugs/therapies corresponding to 1-8) are shown in Appendix 2.

8. Adverse event assessment and reporting

8.1 Definition of adverse events

Any disease and signs and symptoms that occur in a patient, for whom definitive enrollment has been completed, are regarded as adverse events. Specifically, any untoward medical adverse event and its signs (including abnormal laboratory changes), symptoms, or onset or worsening of disease in a patient, for whom confirmed enrollment has been completed, whether or not considered related to the investigational product.

8.2 Assessment and reporting of adverse events

The principal/co-investigator will determine the presence or absence of an adverse event as defined in Section "8.1 Definition of adverse events" based on the results of interviews, examinations, and laboratory tests. If an adverse event occurs, this will be entered in EDC and severity will be evaluated in accordance with the "Classification Criteria for Severity of Adverse Drug Reactions (Appendix 3)." Serious adverse events occurring within 28 days of completion of protocol treatment should be reported and followed up.

8.3 Definition of serious adverse events

A serious adverse event is defined as follows.

(1) Death
(2) Adverse events that may result in death
(3) Adverse events requiring hospitalization in a hospital or clinic for treatment or requiring prolongation of hospitalization (except for the relapse of NMO as defined in Section 13)
(4) Permanent or severe* impairment or dysfunction (*refers to the degree of impairment in daily life)
(5) Adverse events that are considered serious based on the above events
(6) Any congenital disease or abnormalities in the offspring of a treated patient

8.4 Expected adverse events

The main known serious adverse reactions of rituximab and the corresponding frequencies are as follows.

8.4.1 Details of serious adverse reactions, frequency, and recommended measures

Refer to the description in the Investigator's Brochure.

8.4.2 Other adverse reactions and corresponding frequencies

Adverse reactions in Japanese clinical studies in non-Hodgkin's lymphoma patients were observed in 147 out of 157 patients (93.6%). The most common adverse reactions (≥10%) were fever in 101 patients (64.3%), white blood cell count decreased in 75 patients (47.8%), neutrophil count decreased in 72 patients (45.9%), chills in 54 patients (34.4%), pruritus in 34 patients (21.7%), headache in 33 patients (21.0%), hot flush in 32 patients (20.4%), increased blood pressure in 28 patients (17.8%), tachycardia in 27 patients (17.2%), hyperhidrosis in 25 patients (15.9%), rash in 22 patients (14.0%), and decreased blood pressure in 18 patients (11.5%), hemoglobin decreased in 18 patients (11.5%), nausea and vomiting in 17 patients (10.8%), malaise in 17 patients (10.8%), pain in 17 patients (10.8%), AST (GOT) increased in 17 patients (10.8%), and platelet count decreased in 16 patients (10.2%).

9. Expedited reporting of and response to serious adverse events

9.1 Expedited reporting of serious adverse events and response to these events

1) In the event of a serious adverse event, the principal/co-investigator will consider medical treatment/procedures as necessary to ensure the safety of patients.
2) If medical treatment becomes necessary, the principal/co-investigator will inform the patient of the necessity of treatment.
3) The principal investigator will promptly report the occurrence of the events to the head of the study site and the study coordinating office regardless of relationship to the investigational products.
4) The clinical trial coordinating office will report the information to the coordinating committee, other principal investigators, and the investigational product provider. The coordinating committee will consult with other principal investigators to determine whether the adverse event meets Article 273 of the Enforcement Regulations of the Pharmaceutical Affairs Law. In the event that criteria are met, the principal investigator shall report the event to the Ministry of Health, Labor and Welfare (MHLW) in accordance with the "Procedures for Handling of Safety Information."
5) The principal/co-investigator will confirm that the serious adverse event that occurred resolves or stabilizes. In addition, the expectedness of the occurrence of this event in this patient will be assessed based on information on trends such as the onset or number of events, frequency, and conditions of onset based on the Investigator's Brochure, and events that cannot be predicted shall be classified as unknown, and those that can be predicted classified as known.

9.2 Establishment of an Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) will be called if any of the following events, (1) to (5), occurs to determine whether or not the study can be continued.

(1) First observation of relapse of NMO as defined in Section 13
(2) If a relapse that leads to death or may lead to death is observed

(3) If an unknown adverse event that leads to death or may lead to death occurs
(4) If there is a concern that the scientific validity of the investigational product development may have been lost
(5) Other than the above, if the coordinating committee or the principal investigators determine there is a necessity

The members are shown in Appendix 4.

10. Emergency unblinding

In the event of an emergency and there is a need to know what treatment the patient is receiving, the principal/co-investigator will discontinue administration of the investigational product to the patient and report this to the coordinating committee. The coordinating committee will discuss this with the principal investigator to determine whether key code unlocking is necessary. If deemed necessary, the key code will be unlocked only for the investigational product in question. In other words, the allocation manager will be instructed to unlock the code in writing and to notify the clinical trial coordinating committee and the principal investigator of the results of unblinding in writing.

11. Observation, testing, and reporting items and schedule of assessments

11.1 Observation/test items and treatment information to be reported

Visit 1 (Screening tests)

Perform EDSS (Appendix 5) and QOSI (Appendix 6). Measure body temperature, blood pressure, pulse, and assess physical findings. Perform laboratory tests specified in Section 11.5 (complete blood count, biochemistry, urinalysis, human anti-chimeric antibodies (HACA) to rituximab, etc.), standard 12-lead electrocardiography (ECG), and chest X-ray.

Perform urine hCG pregnancy test for women who are premenopausal and <1 year after menopause.

Perform an ophthalmologic examination (including at least visual acuity, visual field test, and central flicker value), visual evoked potential, and plain and Gd-enhanced brain (including optic neurography (plain)) and spinal cord MRI (imaging conditions are specified in Appendix 7)

Whenever feasible, assess somatosensory evoked potential and perform cerebrospinal fluid (CSF) testing, which may be performed between Visit 1 and Visit 2.

Record the prescriptions for the day and collect the types and doses of medications other than corticosteroids.

Measure and record weight and height. Collect information on relapses before and after starting oral steroid administration, particularly the presence or absence and frequency of relapses during the two years prior to randomization, by Visit 2.

Visit 2 (definitive study enrollment)

Measure height and body weight, body temperature, blood pressure, pulse rate, assess physical

findings, perform EDSS and QOSI, clinical laboratory tests specified in Section 11.5 (blood tests, urinalysis, anti-AQP-4 antibodies, lymphocyte subsets), record details on prescriptions for the day, medical history, and complications as medical background information.

Observation starts on this day. Start study administration within one week.

Visit 3 and thereafter

Measure body temperature, blood pressure, pulse rate, assess physical findings, perform EDSS and QOSI, and laboratory tests specified in Section 11.5 (such as blood tests and urinalysis) according to the schedule shown in Appended Table 1. At Visits 5, 8-1, 11, 14-1, 17, and 20, perform ophthalmologic examination (including visual evoked potential, if feasible), plain and Gd-enhanced brain and spinal cord MRIs (preferably Gd-enhanced) to determine whether "relapse" (relapse of NMO, as defined in Section 13) has occurred. If Visit 2-4 and Visit 3 are on the same day, perform assessments specified in Visit 3 the day after administration of the investigational product in Visit 2-4.

At discontinuation of treatment

In principle, height and body weight, body temperature, blood pressure, and pulse are measured, physical findings assessed, complete blood count, biochemistry test, urinalysis, EDSS, QOSI, ECG, and chest X-ray are performed. If not performed, the brain (including optic neurography) and spinal cord MRI, ophthalmologic examination, and visual evoked potential should also be evaluated. In addition, record the details of prescriptions for the day.

If the patient is a woman of childbearing potential, a pregnancy test (urine hCG) should be performed, and somatosensory evoked potential and CSF tests should be performed whenever possible. These should be performed within 7 days after discontinuation.

11.2 Evaluation method

EDSS and QOSI are assessed by interview and neurologic examination. These are applicable to all visits.

11.3 Rationale for performing observations, tests, and collecting treatment information to be reported

This information is collected to appropriately determine the relapse of NMO as defined in Section 13 and to collect information on the safety of the investigational product.

11.4 Observation, testing and reporting schedule, and acceptable windows

The schedule of observations, tests, and acceptable windows for each visit are shown in Appendix 1. (e.g., +4D refers to up to 4 days after the specified visit and -4D refers to up to 4 days prior to the specified visit)

These schedules were designed to ensure patient convenience and to adequately assess the primary outcome of relapse. On Visits 8 and 14 of administration of the investigational product, an allowance (+14D) was set to ensure safe administration of the investigational product in instances where deferred

administration of the investigational product due to infectious diseases, etc. is deemed necessary.

11.5Laboratory tests

11.5.1 Test items

Laboratory test items are as follows.

(1) Lymphocyte subsets (CD19, 20) (*)
(2) Anti-AQP-4 antibodies (*)
(3) Complete blood count: white blood cell count, differential white blood count (neutrophils, lymphocytes), red blood cell count, hemoglobin, hematocrit, and platelet count
(4) Biochemistry (in serum): C-reactive protein (CRP), total protein, albumin, total bilirubin, AST (GOT), ALT (GPT), alkaline phosphatase, γ-GTP, creatine kinase (CK) (CPK), glucose, electrolytes (Na, K, Cl), total cholesterol, triglycerides, BUN, creatinine
(5) Infectious disease tests (HBs antigen, HBs antibody, HBc antibody, HCV antibody, TPHA, RPR, HIV, anti-JC virus antibody (*)) (*only at Visit 1)
(6) Urinalysis (qualitative): urinary glucose, urinary protein, urinary occult blood
(7) Urine hCG pregnancy test for women of childbearing potential (Visits 1, 8-1, 14-1, 20)
(8) HACA in serum (Visits 1, 5, 8-1, 11, 14-1, 17, 20) (*)
(9) CSF: cell counts, glucose, protein, chloride, oligoclonal bands, IgG index

11.5.2 Test methods

Laboratory tests will be performed at the study site except for those marked with * in Section 11.5.1. Lymphocyte subsets, anti-AQP-4 antibodies, anti-JC virus antibodies, and HACA should be assayed on an outsourced basis. The results will not be disclosed to the participating study site until key unblocking. In addition, sample collection and handling instructions for anti-AQP-4 antibody, anti-JC virus antibody, and HACA samples are provided in Appendix 8.

11.6Collection of information on concomitant medication use

For concomitant medications after obtaining informed consent, details of prescriptions will be recorded at each visit.

11.7End of observation (the completion of observation will mark the end of the study)

The observation of patients in this study will be deemed complete in the following situations.

1) Once specified assessments are completed at Visit 20. However, if the number of NMO relapses during the entire study reaches the expected number of NMO relapses (13 relapses) as stipulated in Section 16.1, the patient will be deemed as having reached the end of the study after completing Visit 17.
2) On the date of discontinuation. However, if adverse events have not resolved, the date of completion of follow-up should be used.
3) If relapse as defined in Section 13.1 is confirmed and the patient is enrolled in a separate rituximab re-challenge study (clinical trial)

12. Target sample size and study duration

12.1Target sample size

The target sample size is a total of 40 patients, including 20 in the active treatment group and 20 in the placebo group.

12.2Study duration

Informed consent will be obtained starting from May 10, 2014, and the enrollment period (planned) will continue until August 15, 2017, with study completion by February 1, 2019.

13. Relapse of neuromyelitis optica

13.1Definition of relapse

Relapse is defined as any symptom reported by the patient or any new symptom that is consistent with a central nervous system lesion, such as the optic nerve or spinal cord, and that is associated with objective abnormalities (new lesion in T2 or Gd-enhanced images) on MRI. However, the relapse of optic neuritis will need to meet all of the following conditions, (1), (2), and (3).

(1) New abnormalities in ophthalmologic examinations (e.g., visual acuity, visual field testing, central flicker levels, etc.)
(2) Objective abnormalities on either MRI (new lesions on T2 or Gd-enhanced images) or electrophysiologic testing (visual evoked potential)
(3) The cause is presumably due to optic neuritis

This definition was established in accordance with the definition of relapse in the 2010 revised McDonald diagnostic criteria for multiple sclerosis (18). In this clinical trial, only objectively proven relapse is considered, and confirmation by either abnormal findings on MRI or electrophysiological examination is required.

13.2Evaluation and testing at the time of relapse

The presence or absence of new neurologic findings is assessed by EDSS and QOSI. Plain and contrast-enhanced MRI, ophthalmologic examination, and visual evoked potential are performed as needed to objectively evaluate relapse. Body temperature, blood pressure, pulse rate, height, body weight, ECG, chest X-ray, pregnancy tests, anti-AQP-4 antibody, HACA, blood tests, urinalysis, and lymphocyte subset measurements (blinded) also need to be obtained. In addition, somatosensory evoked potential and CSF testing are to be performed as much as possible. These procedures should be performed within 7 days of relapse.

13.3Retreatment with rituximab at the time of relapse

Patients experiencing relapses identified during the course of the study, regardless of whether on active treatment or placebo, may be enrolled in a separately-defined rituximab re-administration study, provided consent is obtained from the patient (in this case, observation of the patient in this study

protocol will be discontinued). The re-administration study will be conducted as an open study associated with this clinical trial.

14. Endpoints

14.1Efficacy endpoints

14.1.1 Primary outcome

Time to the first relapse from randomization

The date of relapse will be as follows, whichever comes first.

(1) Date reported by the patient

(2) Date of confirmed relapse based on objective tests such as MRI

14.1.2 Secondary outcome

Changes from baseline in EDSS and QOSI, and steroid reduction rate

14.2 Safety endpoint

The following items are subject to evaluation as safety endpoints.

☐ Adverse events and adverse reactions, comparison of adverse events between the two groups

15. Pregnancy

If a patient has a positive urine hCG pregnancy test during the course of the study, the principal investigator will report this to the coordinating office using a specified form and will follow-up on the status of pregnancy.

Patients who become pregnant during the study period will be withdrawn from the study. Pregnancies are to be reported to the study coordinating office within 2 weeks of the day the principal investigator becomes aware of the pregnancy. Follow-up must be performed to determine outcomes and the status of the mother and child. Pregnancy itself is not considered an adverse event or a serious adverse event; however, pregnancy complications and termination for medical reasons should be reported as adverse events or serious adverse events.

16. Statistical Analysis

16.1Rationale for setting the target number of patients

Setting the observation period

We estimated the risk of NMO relapse of both groups in the current study based on the previous reports. However, we considered the difference in the relapse risk between the current trial and the previous reports. In the previous reports the data were analyzed in patients with relapses within one year; however, patients without recent relapses and those treated with oral steroids will be enrolled in the current trial. Therefore, the disease activity and relapse risk are lower in the current study than in the previous reports. We estimated the sample size conservatively as follows. First, the annual relapse rate

in the placebo group was set to about 30% of that in the previous study. Next, calculated the required number of relapses (expected number of events) would be observed by Week 60, although the observation period was set up to Week 72. The reason why the observation period was shortened to 60 weeks in the calculation is to avoid disadvantages of patients. We can avoid the detriment of study participants due to risk of relapse in the period between Weeks 60 and 72 when the statitistical power is obtained in 60 weeks. If the expected number of events is not reached, the patient should be observed up to Week 72.

Estimated annual relapse rate and cumulative OS at Week 60 in the placebo and rituximab groups

The mean annual NMO relapse rates before and after rituximab treatment for a total of 113 NMO patients included in 7 previous reports (9-12, 15, 19, 20) were 2.65 per person-year prior to treatment and 0.29 per person-year following treatment.

Estimation of survival rate at Week 60 in the placebo group

Based on these data, the annual relapse rate in the placebo group was estimated more conservatively, assuming an annual relapse rate of 0.79 per person-year. In this instance, the cumulative survival rate at Week 60 is estimated at 40%.

Estimation of survival rate at Week 60 in the rituximab group

We expect that rituximab suppresses NMO relapse 0.11-fold because the annualized relapse rate was reduced from 2.64 to 0.29 in the previous reports. Therefore, the annual relapse rate in the active treatment group was estimated to be 0.79 x 0.11 = 0.0869 per person-year.

Based on this result, the cumulative survival rate at Week 60 was estimated at 90%.

Sample size calculation (expected number of events and required number of study participants)

The significance level of the test was calculated with α=0.05 and power of 1-β=0.8.

Hazard ratio

$$\theta = \frac{\log(0.90)}{\log(0.40)} = 0.115$$

Expected number of events e from the Freedman formula:

$$e = \left(\frac{\theta+1}{\theta-1}\right)^2 \left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)^2 = \left(\frac{1.115}{0.885}\right)^2 \times (1.960 + 0.842)^2 = 12.5 \cong 13$$

Required entry size for each group

$$n=\left(\frac{e}{2-0.90-0.40}\right) = 18.5 \cong 19$$

Number of required patients and shortening of the observation period

Based on the above, the number of patients required for enrollment was 19 patients in each group, 38 in total, with the expected number of events being 13. As previously mentioned, if the cumulative number of relapses exceeds 13 during this clinical trial, patients under observation at that time will be

observed up to Week 60, and observation will be completed after collecting the necessary data.

16.2Population for efficacy and safety analyses

The full analysis set (FAS) defined below will be used for analyses of endpoints in survival analyses. When other analytical methods are used, both the FAS and the per protocol set (PPS) will be used as analysis sets.

FAS definition: The FAS is defined as all randomized patients excluding those who were not assessed at any time after Visit 2.

PPS definition: The PPS is defined as all eligible patients, excluding those who were not assessed at any time after Visit 2 or for whom a major deviation from the protocol was identified and were withdrawn from the study, as defined below. Significant deviations include violations of eligibility criteria found after randomization, discontinuation of the administration of the investigational product, and use of prohibited concomitant drugs. For each patient, handling will be determined after the temporary database lock according to Section 16.7. Data handling will be specified separately for each endpoint.

16.3Patient classification

Eligible patients: patients who meet all of the inclusion criteria and do not meet any of the exclusion criteria

Discontinued patients: patients who were discontinued from the study due to discontinuation criteria in Section 7.6.

Dropouts: patients for whom no further observations will be performed despite not meeting discontinuation criteria in Section 7.6.

16.4Handling data from discontinued patients and dropouts

For both the FAS and PPS, actual values measured until the last observation time point regardless of the time of discontinuation or dropout will be used for evaluation.

16.5Handling of missing data

16.5.1 Handling of missing data in survival analyses

Discontinued patients will be treated as censored patients.

16.5.2 Handling of missing data in analyses other than survival analyses

For missing data for analyses except for survival analyses, the most recent prior assessment at the specified time point will be used for both the FAS and PPS.

16.6Database lock

Patients and data not specified above will be discussed and determined by the coordinating committee and principal investigators, and the database will be locked.

16.7Analysis parameters and methods

16.7.1 Breakdown of patients

The FAS, PPS, and the number of discontinued patients will be listed along with group classifications.

16.7.2 Treatment status

The status of active or placebo treatment will be summarized.

16.7.3 Summary of the data

Baseline statistics (maximum, median, minimum, 25%, 75%, mean value, standard deviation) will be calculated for all test values obtained as continuous values by treatment group at each assessment time point. Baseline statistics will also be calculated for the change from baseline, and the time course of individual patients will be shown in a graph (broken line graph) and summarized in Box-Whisker plots. In addition, the time course of data measured over time will also be summarized using Box-Whisker plots. The categories of all test values obtained as categorical data will be tabulated by treatment group and by assessment time point.

16.7.4 Significance level

Unless otherwise specified, a two-sided test of less than 5% will be considered statistically significant in both tests.

16.7.5 Analysis of the primary outcome and analysis method

Time to the first relapse will be compared between the two groups. The start day of observation will be the date of randomization and the observation period will be 72 weeks. Comparative survival analyses will be performed between the placebo and active treatment groups. The analytical method may be changed based on the statistical analysis plan prepared prior to the database lock considering the progress of this study. However, if the number of relapses reaches the expected number of events (13 events) as described in Section 16.1, observation should be completed by Week 60.

16.7.6 Analysis of secondary outcomes and analysis method

The changes in EDSS and QOSI from baseline and steroid reduction rate will be compared between the two groups. The method of analysis will be as per the statistical analysis plan.

16.7.7 Analysis of safety endpoints and analysis method (comparison of adverse events)

The frequency and severity of adverse events and adverse reactions will be summarized to determine the differences between the rituximab and placebo groups.

Severity shall be classified into Grades 1, 2, and 3 according to the "Classification Criteria for Seriousness of Adverse Drug Reactions" (Appendix 3) stipulated under the "Classification Criteria for Seriousness of Adverse Drug Reactions of Pharmaceutical Products" (Notification No. 80 of the Safety Division of the Pharmaceutical Affairs Bureau dated June 29, 1992).

Grade 1: Events considered minor adverse events

Grade 2: Non-serious adverse events but not minor adverse events

Grade 3: Events considered to be serious adverse events, in other words, depending on the patient's constitution and condition at the time of onset, there is a risk of death or permanent disability that can interfere with daily life

16.8 Adverse events

Tabulations of adverse events will be by treatment group, and Fisher's exact test will be used to perform a comparison of the incidence of each adverse event between two groups.

16.9Interim analyses

It will not be performed.

16.10 Statistical analysis plan

A statistical analysis plan will be prepared and will include technical details of the final analysis and procedures after the clinical trial protocol is finalized. A blinded review will be conducted after the final data collection, and the principal investigator will finalize the statistical analysis plan prior to the study database lock after discussion with the coordinating committee and the clinical trial statistician.

17. Completion and submission of case report forms

17.1 Data entry

For this clinical trial, an EDC system will be used for the case report forms. Data entry into the EDC system shall be performed by the principal investigator or co-investigator. The data entry method shall comply with the separately drafted manuals. Co-investigators or clinical research coordinators who can enter data into EDC shall be individuals who have been entered into the pre-prepared "list of co-investigators and clinical research coordinators." The study collaborator may enter details that do not require medical judgment, such as transcribing laboratory values, patient characteristics, and prescription status of concomitant drugs. The principal investigator will review and electronically sign the EDC system entries and notify the coordinating committee. Data entered into the EDC system based on original medical records should be consistent with the original medical records. If there are any discrepancies between the original medical records and entries, the principal investigator should prepare a record explaining the reason for the discrepancy, appropriately store the record, and promptly submit a copy to the coordinating committee.

17.2 Storage method

After completion of the data cleaning and the database lock, the revision history and EDC screens will be recorded on a CD-R and retained at the study site. The principal investigator will confirm and sign for the information stored in the CD-R.

18. Monitoring

18.1 Direct access

The heads of participating study sites and the principal investigator will accommodate monitoring visits and audits, as well as investigations by the IRB and regulatory authorities, and provide all study-related records, including source documents, for direct access. Direct access for monitoring will be performed by clinical research associates assigned to this clinical trial. In addition, direct access for audits shall be performed by the auditor.

18.2 Timing of direct access

The timing of direct access will be determined in consultation with the participating study site. In addition, in the event of serious adverse events, source documents may be accessed as necessary to ensure the safety of patients and to provide safety information to other participating study sites.

18.3 Source documents subject to direct access

1) Medical records, explanatory documents, and informed consent forms, and other medical data that can be used to check EDC entries
2) Other essential documents or records and related documents retained only at the study site

19. Quality control and assurance

The study site shall manage the quality of the clinical trial according to the standard operating procedures (SOPs) for investigator-initiated clinical studies. In addition, the auditing department will check whether the clinical trial is being properly implemented in compliance with the protocol, the investigator-initiated clinical trial SOPs, and Good Clinical Practice (GCP). In addition, confirmation that the clinical trial is being conducted appropriately and that the reliability of the data is sufficiently maintained will be obtained by visiting study sites to directly access source documents as necessary.

20. Key unlocking (unblinding)

Unblinding will be performed according to the following procedures, with the exception of emergency unblinding as specified in Section 10. After the database lock, the key code will be disclosed and unblinded.

21. Ethical considerations

21.1 Compliance with the Declaration of Helsinki and GCP

This study will be conducted in compliance with the ethical principles of the Declaration of Helsinki (partially revised in 2008) and GCP.

21.2 Institutional review board

This clinical trial will be conducted after undergoing review and obtaining approval from the IRB prior to the implementation of the clinical trial at participating study sites.

21.3 Provision of new information

The investigator shall promptly notify the heads of participating study sites and the study coordinating office of any information that may adversely affect the safety of patients, affect the conduct of the clinical trial, or change the approval status of the IRB regarding the continuation of the clinical trial. The clinical trial coordinating office shall promptly notify the coordinating committee, other principal investigators, and investigational product providers of the information.

21.4 Protection of patient human rights

In order to protect the human rights of patients, the following must be observed during the course of this clinical trial. Individuals involved in this clinical trial shall fully consider the protection of the human rights of patients when handling consent forms, case report forms, source documents, and other study-related documents, and publishing the results of the clinical trial. The discernment and identification of individual patients will be performed using a patient identification code (referred to in this study as an anonymized ID). For records that may identify patients, the privacy and confidentiality of patients should be taken into account.

22. Cost burden for the clinical trial

22.1Funding and financial relationships

This clinical trial is an investigator-initiated study, and the expenses involved in conducting the clinical trial will be subsidized by Practical Research Project for Rare/Intractable Diseases Health and Labor Science Research Grant (grant number H25/H26-Nanchi-Ippan-025) in 2013 to 2014, by the Japan Agency for Medical Research and Development (grant number 15/16/17ek0109090) from 2015 to 2017 and, from FY2018 onwards, by research funds from Zenyaku Kogyo Co., Ltd. In addition, as stated in Section 22.3 Provision of the investigational product (including transportation expenses) and some test items in Section 22.2 shall be borne by the investigation product provider. Details on reducing the burden of expenses on patients are provided in Appendix 10.

An application was filed with the Conflict of Interest Committee of the National Hospital Organization Utano National Hospital that established the clinical trial coordinating committee for approval of the status of conflict of interest occurring between the principal/co-investigator and Zenyaku Kogyo Co., Ltd., the provider of the investigational product in this clinical trial, and approval was obtained. In the future, potential for conflicts of interest regarding the conduct and outcomes of the clinical trial will be appropriately managed based on the conflict of interest management policy for each study site.

22.2Expenses related to the clinical trial

The costs of the clinical trial are covered by research grants from the Japan Agency for Medical Research and Development. In addition, clinical laboratory tests (blood tests, urinalysis, ECGs, imaging, etc.) performed during the administration of the investigational product are covered by normal medical care insurance. However, the expenses for measuring and collecting anti-AQP-4 antibodies, anti-JC virus antibodies, and HACA will be borne by the investigational product provider.

22.3 Provision of the investigational product

The investigational product will be provided by Zenyaku Kogyo Co., Ltd.

22.4 Compensation for health injuries

In the event health injuries occur in patients due to the conduct of this clinical trial, the participating study site will provide sufficient treatment and perform other appropriate measures. In addition, diseases, disabilities, etc. caused by adverse reactions, which are considered serious to a certain degree,

will be covered by the clinical trial compensation insurance. The investigational product provider will assume the responsibility for the manufacture of the investigational product in case of health injuries caused by the manufacture of the investigational product.

23. Protocol deviations

23.1 Deviations from the date of assessment

Deviations from the date of assessment exceeding the acceptable windows defined in Section 11.4 shall be reported as protocol deviations. Individual assessment should be performed as to whether values measured on the deviating assessment day should be considered missing values.

23.2 Deviations from the study protocol

The principal/co-investigator may deviate from the protocol without prior approval from the IRB if there are unavoidable medical circumstances, such as to avoid an immediate hazard to patients.

23.3 Preparation of records of protocol deviations

The principal/co-investigator will document all protocol deviations. If situations mentioned in Section 25.2 occur, the principal investigator shall prepare a record explaining the reason, submit this to the heads of participating study sites, and retain a copy.

24. Amendments to the clinical trial protocol

The principal investigator will revise the protocol as necessary whenever important new information becomes available that may be relevant to the proper conduct of the clinical trial, such as information on the quality, efficacy, and safety of the investigational product.

When revising the protocol, the principal investigator will submit the revised version of the protocol to the heads of the participating study sites in advance. The heads of the participating study sites will consult with the IRB regarding the protocol amendment.

If the protocol amendment results in revisions to the case report forms and informed consent form, the principal investigator shall also submit these documents to the heads of participating study sites as soon as possible, and the heads of the participating study sites shall consult with the IRB.

25. Study completion and early termination

25.1 Study completion

Once the clinical trial is completed, the principal investigator shall report the completion of the clinical trial to the heads of the participating study sites.

25.2 Criteria for premature termination or suspension of the entire study

The principal investigator will terminate or suspend the entire study if any of the following situations arise.

1) If ethical or medical issues, such as ensuring the safety of patients, arise

2) If the scientific validity of the clinical trial is lost

25.3 Discontinuation or suspension of the clinical trial at study sites

The principal investigator or the heads of the participating study sites may prematurely terminate or suspend the clinical trial at a participating study site if any of the following situations arise.

1) Discovery of significant or persistent noncompliance by the principal/co-investigator or study site
2) If continuation of the clinical trial is not feasible due to the transfer of the principal investigator
3) Failure of the study site to continue to meet the requirements required for the proper conduct of the clinical trial

26. Handling of study documents

26.1 Record retention

The retention period for essential documents shall be as per the policies of the participating study site. The clinical trial coordinating office shall collectively manage the case report forms.

27. Publication of study results

The publication of study results may be led by the clinical trial coordinating committee and the committee may co-author the results along with researchers recommended by the research organization who meet the authorship criteria. There are no requirements for the investigational product provider to publish results.

28. Study administrative structure

Refer to Appendix 9

29. Literature

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2. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999; 53: 1107-1114.
3. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;
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6. Interferon-beta (1b) treatment in neuromyelitis optica. Neurol. 2009;62(3):167-170.
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9. An open label study of the effects of rituximab in neuromyelitis optica. Neurology. 2005 12;64(7):1270-1272.
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11. Impact of rituximab on relapse rate and disability in neuromyelitis optica. Multiple Sclerosis Journal
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12. Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab.
Neurology. 2011;76(15):1310-1315.
13. Trial of rituximab in three patients with neuromyelitis optica. Rinsho Shinkeigaku.
2009 ;49(8):457-462.
14. EFNS guidelines on diagnosis and management of neuromyelitis optica. Eur J Neurol 2010;17:1019-1032
15. Repeated treatment with rituximab based on the assessment of peripheral circulating memory B cells in patients with relapsing neuromyelitis optica over 2 years. Arch Neurol2011;68:1412-1420
16. Prognostic factors and course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. Brain.
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17. Treatment of Neuromyelitis Optica. Jpn.J. Clin. Immunol. 2012;35:129-135
18. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol.
2011;69:292-302.
19. Variable responses to rituximab treatment in neuromyelitis optica (Devic's disease). Neurol Sci.
2007;28:209-211.
20. Rituximab reduces attacks in Chinese patients with neuromyelitis optica spectrum disorders. J. Neurol Sci. 2013;324:38-39._

Appendix 1. Investigational product administration

1. Preparation of investigational product

(1) Dose

Assuming that the investigational product would be administered at a dose of 375 mg/m2/administration, the body surface area should be calculated based on that measured at the time of definitive enrollment using the DuBOIS equation below* (rounded to the first decimal place)

* Body surface area (BSA) (m2) = weight (kg) 0.425 x height (cm) 0.725 x 0.007184

(2) Preparation method

Immediately prior to administration, dilute the investigational product (at a concentration of 10 mg/mL) with Japanese Pharmacopoeia (JP) physiological saline to prepare a 1 mg/mL concentration solution. The entire volume of prepared infusion solutions should be fully administered within 24 hours. Do not use any diluent other than JP physiological saline.

2. Premedications

To prevent infusion reactions, administer antihistamines and antipyretic analgesics as premedications 30 minutes prior to each administration of the investigational product.

- Antihistamines: d-chlorpheniramine maleate 2 mg, etc.
- Antipyretic analgesics: acetaminophen 400 mg, etc.

3. Administration of the investigational product

(1) First administration in each course

The starting dose is 50 mg/h administered for 30 minutes. In the absence of adverse reactions such as allergic symptoms or infusion reactions, the infusion rate can be increased by 50 mg/h every 30 minutes up to a maximum dose of 400 mg/h.

However, in the case that the infusion rate cannot be increased every 30 minutes due to the onset of infusion reactions or some other reasons, the reason should be recorded.

If adverse reactions are observed during administration of the investigational product, the infusion rate of the investigational product should be maintained, reduced, or temporarily interrupted, and appropriate supportive care should be provided as needed (Refer to "5. Reduction, interruption, and resumption of investigational product administration at the time of onset of adverse events" below).

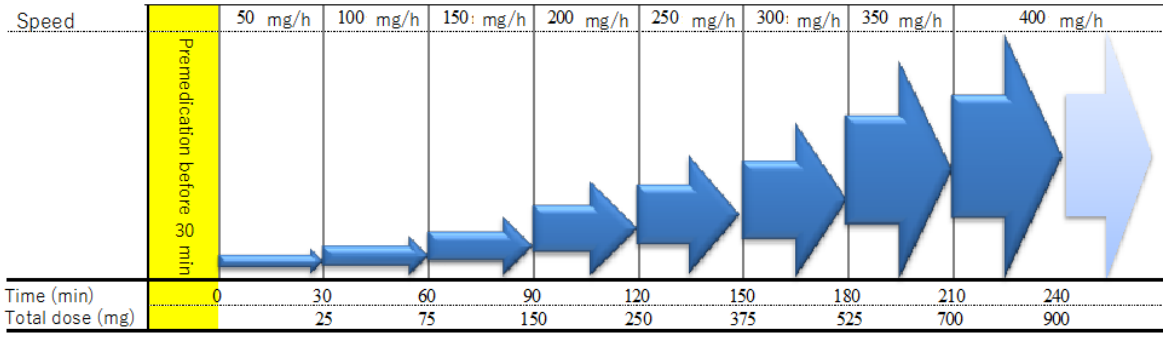


Figure 1. Infusion rate of the first administration of the investigational product in each course

(2) Second and subsequent administrations of the investigational product in each course

If adverse reactions such as allergic symptoms or infusion reactions that occurred during the previous administration of study drug are Grade 2 or lower, the second and subsequent administrations can be started at 100 mg/h and increased by 100 mg/h every 30 minutes to a maximum of 400 mg/h. If adverse reactions such as Grade 3 allergic symptoms or infusion reactions are observed during the previous administration of the investigational product, set the starting infusion rate at 50 mg/h and administer for 30 minutes and, if adverse reactions are not observed, can increase the starting infusion rate by 50 mg/h every 30 minutes up to a maximum dose of 400 mg/h. Patients should be closely monitored and extreme caution should be paid when increasing the infusion rate.

In the case that, the rate cannot be increased every 30 minutes due to the onset of infusion reactions or some other reason, the reason should be recorded.

If adverse reactions such as allergic symptoms or infusion reactions are observed during administration of the investigational product, the infusion rate of the investigational product should be maintained, reduced, or temporarily interrupted, and appropriate supportive care should be provided as needed (Refer to "5. Reduction, interruption, and resumption of study drug administration at the time of onset of adverse events" below).

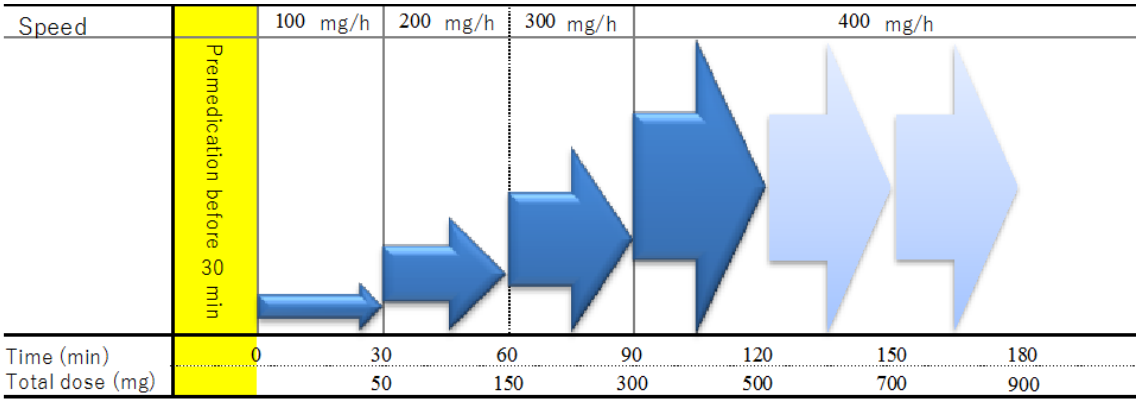


Figure 2. Infusion rate of second and subsequent administrations of the investigational product in each course

Note 1) Grade 2 infusion reaction: Requiring interruption of treatment or infusion, but responding to treatment for symptoms (e.g., antihistamines, NSAIDs, narcotics, IV fluids)

Note 2) Grade 3 infusion reaction: Causes administration delays (e.g., not responding promptly to symptomatic treatment and/or temporary interruption of infusion), relapses even after initial improvement, requires hospitalization for sequelae

4. After investigational product administration

After completion of investigational product administration, have patients rest for at least 30 minutes.

5. Reduction, interruption, and resumption of investigational product administration at the time of onset of adverse events

(1) If Grade 1 to 2 infusion reactions or other adverse reactions occur during administration of the investigational product, maintain, reduce the infusion rate, or interrupt administration at the discretion of the principal (or sub) investigator depending on the condition of the patient. Administer supportive care as needed. If the infusion rate is to be reduced, reduce the infusion rate to 1/2 or lower. After interrupting administration, administration may be resumed at the discretion of the principal (or sub) investigator. If administration is to be resumed, confirm that the reason for interruption, such as infusion reactions, have resolved and resume administration at an infusion rate that is lower than or equivalent to 1/2 of the rate at the time of interruption.

(2) If Grade 3 infusion reactions or other adverse reactions occur during administration of the study drug, immediately interrupt administration and actively treat the patient. After confirming that the reason for interruption, such as infusion reactions, have been resolved, administration may be resumed at the discretion of the principal (or sub) investigator. Resume administration at an infusion rate that is lower than or equivalent to 1/2 of the rate at the time of interruption. If the same Grade 3

event recurs within the same cycle, discontinue further investigational product administration.

(3) If increasing the infusion rate is difficult due to the onset of infusion reactions, etc., the investigational product may be administered at a low infusion rate; however, complete the administration of the entire volume of prepared investigational product within 24 hours of preparation.

6. Measurement of vital signs (body temperature, blood pressure, pulse rate) at the time of administration of the investigational product

(1) Measure vital signs prior to the start and after the completion of investigational product administration.

(2) If the infusion rate is reduced or administration is interrupted due to the onset of adverse events or for other reasons, record vital signs and subjective and objective symptoms at the time of reduction or interruption.

Appendix 2. Prohibited concomitant drugs and therapies

1. Steroid pulse therapy (500 to 1,000 mg of methylprednisolone per dose, 3 to 5 consecutive days)
2. Plasmapheresis (irrespective of type of simple plasma exchange or immunoadsorption therapy, etc.)
3. Monoclonal antibodies (natalizumab, alemtuzumab, tocilizumab, etc.)
4. High-dose immunoglobulin therapy
5. Immunosuppressive agents/anticancer drugs (cladribine, mitoxantrone, cyclophosphamide, azathioprine, tacrolimus, cyclosporine, cyclophosphamide, methotrexate, fingolimod, etc.)
6. Immunomodulators (interferon-β, glatiramer acetate, etc.)
7. Live or live-attenuated vaccines
8. Investigational product other than those used in this study

Appendix 3. Criteria for classifying the severity of adverse reactions

The severity shall be classified into Grades 1, 2, and 3 according to the "Classification Criteria for Seriousness of Adverse Drug Reactions" stipulated in the "Classification Criteria for Severity of Adverse Drug Reactions of Pharmaceutical Products" (Notification No. 80 of the Safety Division of the Pharmaceutical Affairs Bureau dated June 29, 1992).

Grade 1: Events considered minor adverse events

Grade 2: Non-serious adverse events but not minor adverse events

Grade 3: Events considered to be serious adverse events, in other words, depending on the patient's constitution and condition at the time of onset, there is a risk of death or permanent disability that can interfere with daily life.

Appendix 4. Independent Data Monitoring Committee (IDMC) Members

1） Department of Brain Pathophysiology, Graduate School of Medicine, Kyoto University, Department of Clinical Neurology (Neurology)

Professor Ryosuke Takahashi

2） Director of Clinical Research Management, Center for Clinical Research, Kyoto University Hospital

Professor Kazuo Matsubara

3） Director, Health Science Center, Health Science Division, Japan Environmental Safety Insurance Organization, Kyoto University

Professor Takashi Kawamura

4） Director, Center for Brain Function Research, Graduate School of Medicine, Kyoto University

Professor Hidenao Fukuyama

Appendix 5. EDSS and FS

From EDSS 0 to 10, evaluations are in 0.5 increments.

From EDSS 0 to 5.5, evaluations also use FS (degree of functional impairment: pyramidal function, cerebellar function, brain stem function, sensory function, bladder bowel function, visual function, mental function, etc.) in the lower part of the following table in combination.

EDSS 6 to 10 is evaluated based on ADL, and EDSS 7 is wheelchair-level ADL, where the patient cannot walk more than 5 m without assistance.

Appendix 6. QOSI (Adapted from Ref. 2)

Score	Description
Visual Acuity (V_A)	
0	Normal
1	Scotoma but visual acuity (V_A) (corrected) ≧0.7
2	V_A (corrected) ≧0.4, <0.7
3	V_A (corrected) 0.2-0.3
4	V_A (corrected) ≦0.1
5	Count fingers only
6	Light perception only
7	No light perception
8	Unknown
Motor Function	
0	Normal
1	Abnormal signs (hyperreflexia, Babinski sign) without weakness
2	Mild weakness (MRC grade 5– or 4+) in affected limb(s)
3	Moderate weakness (grade 3 or 4) in 1
4	Severe weakness (grade 2) in 1 or more muscles in affected limb(s)
5	Some plegic (grade 0 or 1) muscles in 1 or more limbs
6	Plegia (grade 0 or 1) of all muscles in 1 or more limbs
7	Unknown
Sensory Function	
0	Normal
1	Mild decrease in vibration
2	Mild decrease in pinprick/temperature/proprioception or moderate decrease in vibration
3	Moderate decrease in touch/pin/proprioception or essentially lost vibration s
4	Loss of all sensory modalities
5	Unknown
Sphincter Function	
0	Normal
1	Mild urinary urgency or hesitancy; constipation
2	Moderate urinary urgency, hesitancy, or retention of bladder or bowel, infrequent urinary incontinence (less than once/week)
3	Frequent incontinence or retention requiring intermittent bladder catheterizat or aggressive (manual) bowel assistance
4	Indwelling urinary catheter or absence of sphincter control
5	Unknown

Appendix 7. Magnetic resonance imaging

- Magnetic resonance imaging (MRI) scanners used should have a magnetic field strength of 1.5T or 3T in order to standardize the conditions between sites and scanners.
- If more than one 1.5 or 3T MRI scanner are available, only one of them should be used for imaging.
- Check for any contraindications before using contrast media.
- Perform scans using the parameters specified in the attached scanning parameter tables.
- In the case that your facility uses 1.5T or 3T scanners of different models or from different manufacturers, please develop protocols in accordance with the conditions shown in the tables.
- Do not change the protocol developed when performing MRI scans in this study.
- Perform MRI scans on the V1 brain area, as well as on the optic nerve (plain scan) for control at the time of recurrence. If a recurrence of optic neuritis is observed, use a contrast agent.
- MRI scans for suspected recurrence should only be performed with contrast enhancement with the exception of plain MRI scans using the parameters defined for this clinical trial.

<Imaging targets>

- Brain (plain → with contrast)
- Entire spinal cord (plain cervicothoracic→ plain thoracolumbar → thoracolumbar with contrast → cervicothoracic with contrast)

* Do not perform brain and entire spinal cord scans on the same day.

* Even if a scanner is available to cover the entire spinal cord in one scan, the scan for the entire spinal cord should divided into two scans to ensure that conditions between sites and scanners are met.

- Optic nerve (plain, but with contrast at the time of recurrence of optic neuritis)

* If optic neuritis is suspected during the course of the clinical trial and an MRI is performed, administer a contrast agent according to the same sequence as that used in the protocol for optic nerve imaging at the time of tentative enrollment, and start the Axial T1WI fatsat 10 minutes after the completion of administration of contrast agent.
(Perform image positioning scan and Axial T2WI fatsat within 10 minutes after completion of administration of contrast agent)

<Procedure for brain MRI>

1 Positioning

Have the patient lay on the bed so that he/she can undergo the scan in the most comfortable position

and align the eyebrows with the isocenter of the magnet.

2 Protocol

2.1 Localizer

2.2 True mid-line sagittal Localizer (mid-sagittal）

2.3 Sagittal FLAIR

2.4 Axial FLAIR

2.5 Axial T1WI

2.6 Contrast agent administration

2.7 Axial T2WI

2.8 Axial T1WI

2-1.

This is a three-section scout used for positioning for the subsequent sequence.

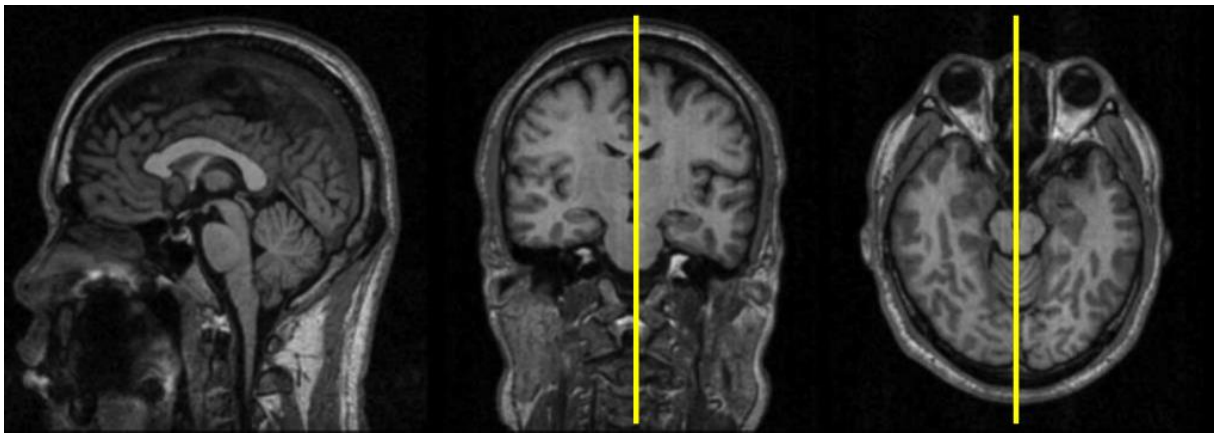
2-2

Scan the mid-sagittal plane using a sequence allowing for definitely clear AC-PC lines.

2-3

Plan scans in parallel with imaging of the mid-sagittal plane in 2-2 (Fig. 1)

Figure 1



2-4., 2-5., 2-7., 2-8.

Use the images of the midline sagittal plane taken in 2-2 for positioning so that to align with the AC-PC line (Fig. 2) and the upper edges of the slices as shown in Fig. 3.

Plan the second and subsequent images as closely as possible to the position of the first slice.

Figure 2

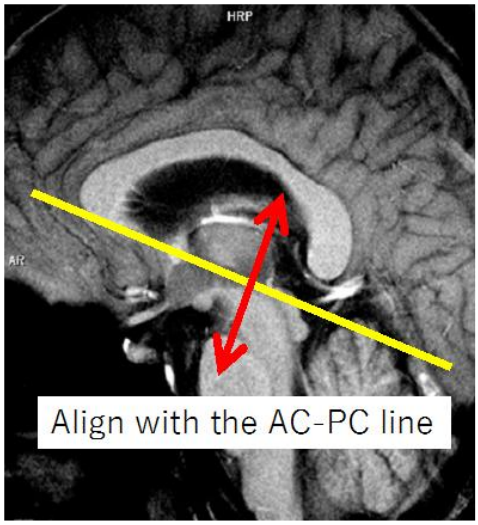
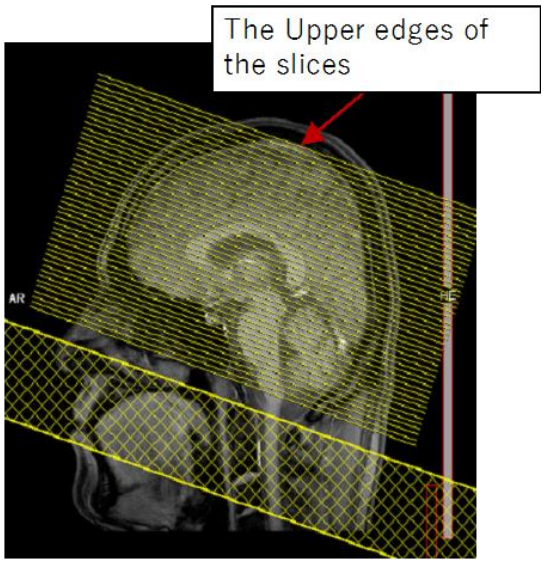


Figure3



2-6.

Administer contrast medium intravenously at a dose of 0.2 ml/kg.

For post-contrast T1WI, start imaging 10 minutes after the completion of contrast agent infusion.

Image sequences using the parameters for 2-5 T1WI plain scans.

(Image the 2-7 Axial T2WI during the 10-minute waiting period.)

* Use the same contrast medium during the entire duration of the study.

<Procedure for spinal MRI>

Divide the imaging for the entire spinal cord into two scans.

* Include the entire spinal cord because the main assessment of the spinal cord is performed on the sagittal plane.
* Position the junction between the cervicothoracic and thoracolumbar parts of spinal cord so that there is overlap in one or more vertebral bodies (Fig. 4)
* If scoliosis is severe and the entire spinal cord cannot be imaged using the specified procedure, change the angle and perform additional imaging (Fig. 5)

Figure 4

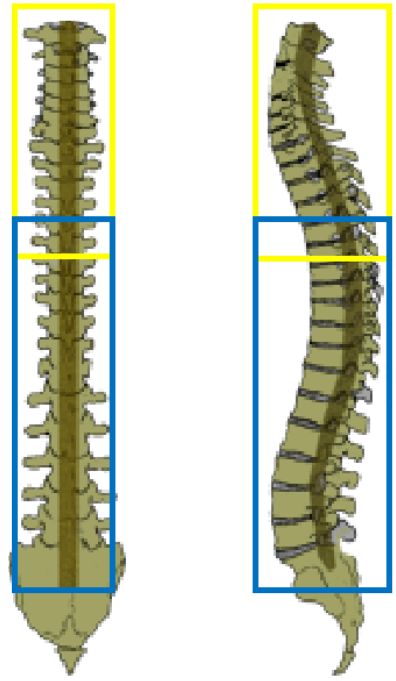
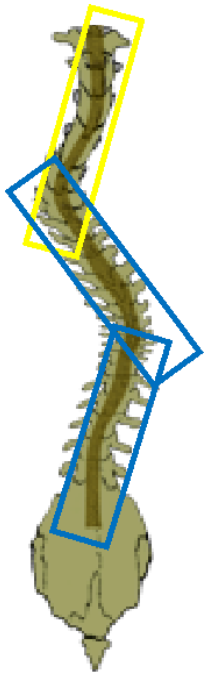


Figure 5



<Flow of imaging>

Cervicothoracic/thoracolumbar parts of spinal cord

1. Positioning

Have the patient lie straight so that their spine is straightly aligned against the bed and align the xiphoid process of the manubrium/sternum such that the inferior border is 4 fingers wide from the isocenter of the magnet. Adjust the posture as much as possible so that the spinal cord forms an identical cross-sectional image in the sagittal plane.

2. Protocol

Cervicothoracic (plain)

2-1. Localizer

2-2. Sagittal T1WI

2-3. Sagittal T2WI

Thoracolumbar (plain)

2-4. Localizer

2-5. Sagittal T1WI

2-6. Sagittal T2WI

2-7. Contrast agent administration

Cervicothoracic (with contrast)

2-8. Sagittal T1WI

2-9. Axial T1WI

2-10. Axial T2WI

Thoracolumbar (with contrast)

2-11. Localizer

2-12. Sagittal T1WI

2-13. Axial T1WI

2-14. Axial T2WI

2-1., 2-4., 2-11

This is a three-section scout used to select the position of the subsequent sequence.

2-2., 2-3.

Select positioning to sufficiently include C1 relative to the upper border of the field of view (FOV).

After imaging, proceed to plain imaging of the thoracolumbar part of spinal cord.

2-5., 2-6.

Select positioning to sufficiently include S1 relative to the upper border of the FOV.

If the FOV380 does not overlap with at least one vertebral body at the thoracic spinal junction, widen the FOV.

Ensure that the setting assures more than one vertebral body overlapping.

* If scoliosis is severe enough to make it difficult to capture the cervical thoracic spine and thoracolumbar part of spinal cord in the sagittal plane in two scans, additional imaging is taken with standardized FOV to 300.

2-7. Contrast agent administration

Administer contrast medium intravenously at a dose of 0.2 ml/kg.

For 2-8. Sagittal T1WI, start imaging 10 minutes after the completion of contrast agent infusion.

Image sequences using the parameters for 2-5. Sagittal T1WI plain scans.

* The flow of T1WI Sagittal imaging is to start 10 minutes after completion of administration of the contrast medium. However, to shorten the time, the T2WI Sagittal imaging can be started first.

* Use the same contrast medium during the entire duration of the study.

* 2-9., * 2-10.

Obtain axial images of new lesions or pre-existing lesions.

If no lesions are present, the axial view can be omitted.

2-11., 2-12., *2-13., *2-14.

After completing thoracolumbar imaging, return to the cervicothoracic part of spinal cord and use the same alignment as for plain imaging to obtain sagittal T1WI (with contrast) images.
Obtain axial images of new or pre-existing lesions, as well as the thoracolumbar part.
If no lesions are present, the axial image can be omitted.

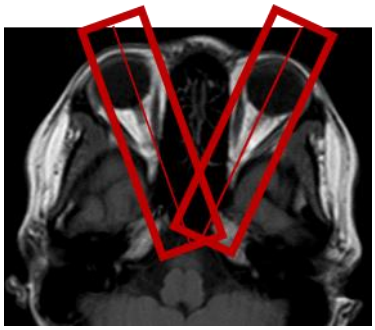
<Submission of imaging data>
Create a CD containing images in DICOM format and submit the CD.

<Procedures for MRI of optic nerves>
1 Positioning
Have the patient lay in the bed so that they can undergo the scan in the most comfortable position, align the eye socket with the isocenter of the magnet, and ask the patient to gently close their eyes and not move their eyeballs.

2 Protocol
2.1 Localizer
2.2 Sagittal Localizer (sagittal section parallel to the right and left optic nerves)
2.3 Axial T2WI fatsat
2.4 Axial T1WI fatsat
2.5 Coronal T2WI fatsat
2.6 CoronalT1WI fatsat

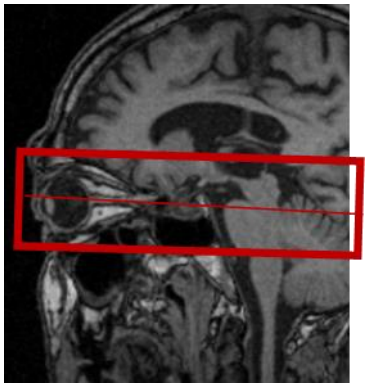
2-1
This is a three-section scout used to select the position of the subsequent sequence.

2-2
Scan sagittal sections parallel to the right and left optic nerves.



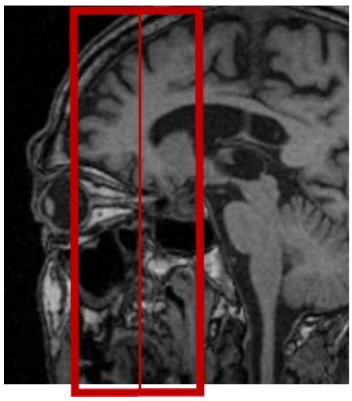
2-3., 2-4.

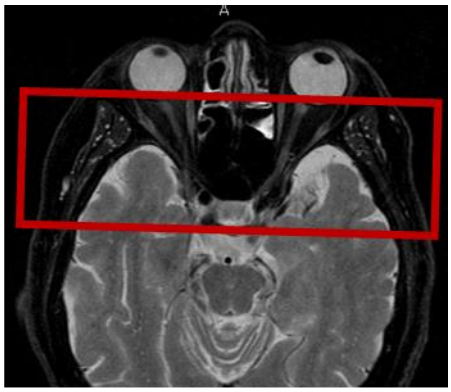
Confirm the position of the right and left optic nerves in images of the sagittal section taken in 2-2 and, as much as possible, select the position to obtain axial images of the right and left optic nerves in the same slice.



2-5., 2-6.

Plan to run directly along the optic nerve and select positioning to include the optic chiasm as much as possible.





3 Contrast agent administration (in case of recurrence of optic neuritis)

Administer contrast medium intravenously at a dose of 0.2 ml/kg.

For T1WI fatsat, start imaging 10 minutes after the completion of contrast agent infusion.

Image sequences using the parameters used during the initial tentative enrollment.

* Use the same contrast medium as that used for patients in the RIN-1 study.

<Submission of imaging data>

As with other sections, create a CD containing images in DICOM format and submit the CD.

(Precautions for brain protocol)

Do not apply a sensitivity-correction filter (normalizing filter).

Do not use parallel imaging.

Use Sequence Nos. 1 and 2 for the positioning sequence. Scan the sagittal sections using the sequence allowing for clear visualization of CD-PC

Use the values shown in yellow in the following table.

Brain Protocol (SIEMENS MAGNETOM Symphony (1.5T), CP HEAD ARRAY)							
Sequence No.	1	2	3	4	5	6	7
Sequence Name	Loc	Sag Loc	FLAIR	FLAIR	T1WI	T2WI	Contrast T1WI
Sequence type			2D TSE	2D TSE	2D SE	2D TSE	2D SE
Orientaion			Sagittal	Axial	Axial	Axial	Axial
Number of slices			40	45	45	45	45
thickness/gap[mm]			3/0	3/0	3/0	3/0	3/0
phase encoding			A-P	R-L	R-L	R-L	R-L
FOV [mm]			240	240	240	240	240
FOV PHASE [%]			100	87.5	87.5	87.5	87.5
TR [ms]			10000	10000	500	4000	500
TE [ms]			123	123	17	88	17
TI [ms]			2500	2500			
Flip angle [deg]			150	150	80	180	80
Matrix (frequency x phase)			256x256	256x256	256x256	256x256	256x256
Addition count			1	1	1	1	1
Concatenations			3	3	3	2	3
Turbo factor			31	25		9	
Flow comp			off	off	on	off	on
Multi slice mode			Interleaved	Interleaved	Interleaved	Interleaved	Interleaved
Band width			201	201	130	93	130
Imaging time			5:00	5:00	5:44	3:30	5:44

(Precautions for spinal cord protocol)

Do not apply a sensitivity-correction filter (normalizing filter).

Do not use parallel imaging.

Use presaturation for the anterior spine.

Use Sequence No. 1 for the positioning sequence.

Use the values shown in yellow and red in the following table.

Spine (Cervicothoracic parts) Protocol (SIEMENS MAGNETOM Symphony (1.5T), CP NECK/SPINE ARRAY)						
Sequence No.	1	2	3	4	5	6
Sequence Name	Loc	T2WI	T1WI	contrast T1WI	contrast T1WI	contrast T2WI
Sequence type		2D TSE	2D TSE	2D TSE	2D TSE	2D TSE
Orientaion		Sagittal	Sagittal	Sagittal	Axial	Axial
Number of slices		15	15	15	28	28
thickness/gap[mm]		3/0	3/0	3/0	5/0.5	5/0.5
phase encoding		H-F	H-F	H-F	A-P	A-P
FOV [mm]		300	300	300	180	180
FOV PHASE [%]		100	100	100	100	100
TR [ms]		3600	600	600	530	4300
TE [ms]		108	8.6	8.6	9	105
Flip angle [deg]		180	170	170	180	180
Matrix (frequency x phase)		384x269	384x269	384x269	256x256	256x256
Addition count		2	2	2	1	1
Concatenations		1	1	1	3	2
Turbo factor		17	3	3	3	17
Flow comp		on	off	off	off	on
Multi slice mode		Interleaved	Interleaved	Interleaved	Interleaved	Interleaved
Band width		150	213	213	201	130
Imaging time		3:34	3:19	3:19	3:11	3:54

Spine (thoracolumbar parts) Protocol (SIEMENS MAGNETOM Symphony (1.5T), CP SPINE ARRAY)						
Sequence No.	1	2	3	4	5	6
Sequence Name	Loc	T2WI	T1WI	contrast T1WI	contrast T1WI	contrast T2WI
Sequence type		2D TSE	2D TSE	2D TSE	2D TSE	2D TSE
Orientaion		Sagittal	Sagittal	Sagittal	Axial	Axial
Number of slices		15	15	15	28	28
thickness/gap[mm]		3/0	3/0	3/0	5/0.5	5/0.5
phase encoding		H-F	H-F	H-F	A-P	A-P
FOV [mm]		380	380	380	180	180
FOV PHASE [%]		100	100	100	100	100
TR [ms]		3200	620	620	530	4300
TE [ms]		106	9	9	9	105
Flip angle [deg]		180	170	170	180	180
Matrix (frequency x phase)		448x224	448x224	448x224	256x256	256x256
Addition count		1	2	2	1	1
Concatenations		2	1	1	3	2
Turbo factor		17	3	3	3	17
Flow comp		on	off	off	off	on
Multi slice mode		Interleaved	Interleaved	Interleaved	Interleaved	Interleaved
Band width		130	211	211	201	130
Imaging time		3:01	3:08	3:08	3:11	3:54

Optic nerve Protocol（SIEMENS MAGNETOM Symphony (1.5T), CP HEAD ARRAY）						
Sequence No.	1	2	3	4	5	6
Sequence Name	Loc	Sag Loc	T2WI fatsat	T1WI fatsat	T2WI fatsat	T1WI fatsat
Sequence type			2D TSE	2D SE	2D TSE	2D SE
Orientaion			Axial	Axial	Coronal	Coronal
Number of slices			15	15	20	20
thickness/gap[mm]			3/0.3	3/0.3	3/0.3	3/0.3
phase encoding			R-L	R-L	R-L	R-L
FOV [mm]			200	200	200	200
FOV PHASE [%]			100	100	100	100
TR [ms]			4000	480	4000	480
TE [ms]			82	12	82	12
Flip angle [deg]			170		170	
Matrix (frequency x phase)			512x256	512x256	512x256	512x256
Addition count			2	1	2	1
Concatenations			1	2	1	2
Turbo factor			9		9	
Flow comp			off		off	
Multi slice mode			Interleaved	Interleaved	Interleaved	Interleaved
Band width			110	90	110	90
Imaging time			3:58	5:14	3:58	5:14

Appendix 8. Handling of Anti-AQP-4 antibody, anti-JC virus antibody, and human anti-chimeric antibody (HACA) samples

Testing for anti AQP-4 antibodies, anti-JC virus antibodies, and human anti-chimeric antibodies (HACA) in blood in this clinical trial is outsourced. Blood sampling and sample storage should be performed according to the procedures described below.

1. Anti AQP4 antibodies and anti-JC-virus antibodies

(1) Collect 5 ml of whole blood samples in blood collection tubes at specified visits (Visit 1, Visit 5, Visit 8, Visit 11, Visit 14, Visit 17, Visit 20, and at study discontinuation for anti-AQP antibodies, and only at Visit 1 for anti-JC antibodies).

(2) Invert and mix the blood collection tubes five times and allow the tubes to stand still for 30 minutes (room temperature).

(3) Subsequently centrifuge immediately at room temperature (3,000 x g for 20 minutes).

(4) Aspirate and dispense the supernatant into the appropriate storage tube.

(5) Store storage tubes filled with the supernatant frozen at -20°C or below.

2. HACA

(1) Collect 10 ml of whole blood samples into blood collection tubes for HACA measurement at specified visits (Visit 1, Visit 5, Visit 8, Visit 11, Visit 14, Visit 17, Visit 20, and at study discontinuation).

(2) Invert and mix the blood collection tubes five times and allow the tubes to stand still for 30 minutes (room temperature).

(3) Subsequently centrifuge immediately at room temperature (3,000 x g for 20 minutes).

(4) Aspirate and dispense equal volumes (minimum: 2 mL) of supernatant into two specified storage tubes*.

(5) Store storage tubes filled with the supernatant frozen at -20°C or below.

The individual in charge of collection will collect the samples and request the designated contract laboratory to conduct tests.

Appendix 9. Study administrative structure

1. List of those conducting the clinical trial (principal investigators) and clinical trial sites

1) Department of Clinical Research Center, National Hospital Organization Utano National Hospital
Department of Neurology/Rehabilitation Medical Officer Masayuki Tahara (Principal Investigator (PI))
Vice-President Hideyuki Sawada
Director of Clinical Research Center Tomoko Oeda
Address 8 Ontoyama-cho, Kitaki-ku, Right-kyo-ku, Kyoto 616-8255
Phone 075-461-5121

2) Department of Neurology, Tokyo Women's Medical University
Specially Appointed Professor Yuko Shimizu (PI)
Address 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666
Phone 03-3353-8111

3) Department of Neurology, University of Occupational and Environmental Health
Associate Professor Kazumasa Okada (PI)
Address 1-1 Medical Sugaoka, Yahatanishi-ku, Kitakyushu 807-8555
Phone 093-603-1611

4) Department of Neurology and Sensory Diseases, Graduate School of Medicine, Tohoku University
Lecturer Tatsuro Misu (PI)
Ichiro Nakashima (former PI)
Kazuo Fujihara
Address: 1-1, Seiryo-cho, Aoba-ku, Sendai 980-8574
Phone 022-717-7189

5) Departmentof Applied Life Sciences, Faculty of Medical, Dental and Pharmaceutical Health Sciences, Hiroshima University
Professor Hirofumi Maruyama (PI)
Medical Lecturer Kazuhide Ochi (former PI)
Address 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
Phone 082-257-5555

6) Department of Neurology, Saitama Medical University Medical Center
Professor Kyoichi Nomura (PI)

Associate Professor Hikoaki Fukaura

Address 1981 Kamoda, Kawagoe-shi, Saitama350-8550

Phone 049-228-3400

7) Department of Neurology, Nara Medical University

Lecturer Takao Kiriyama (PI)

Address 840 Shijo-cho, Kashihara, Nara 634-8521, Japan

Phone 0744-22-3051

8) Department of Neurology, Graduate school of Medicine, Ciba University

Associate Professor Masahiro Mori (PI)

Address 1-8-1inohana, Chuo-ku, Chiba, Chiba 260-8670, Japan

Phone 043-222-7171

[Responsibilities]

1) Developing and amending the clinical trial protocol
2) Developing and revising explanatory documents and informed consent forms
3) Selecting study participants and obtaining their informed consent
4) Guiding and supervising sub-investigators and study coordinators
5) Providing materials and information, and providing help to monitoring and audits
6) Handling deviations from or changes to the clinical trial protocol
7) Reporting adverse events
8) Preparing case report forms
9) Storing study-related documents or records
10) Other activities specified under Good Clinical Practice (GCP)

2. Clinical trial coordination committee

National Hospital Organaization Utano Hosipital Clinical Research Center

Chief Masayuki Tahara

Vice President Hideyuki Sawada

Director Tomoko Oeda

Address 8 Ondoyma-cho, Narutaki, Ukyo-ku, Kyoto, Kyoto 616-8255, Japan

Tel: 075-461-5121

[Responsibilities]

1) Developing and amending the clinical trial protocol
2) Developing and revising explanatory documents and informed consent forms
3) Coordination and implementation of the details in the contents of the clinical trial Protocol and

queries occurred during the trial at each facility, specified in the "Standard Operating Procedures of the clinical trial coordination committee".

3. Clinical trial Statistician

Department of Internal Medicine, Kyoto Medical Center, National Hospital Organization

Masashi Goto, MD, PhD

Address 1-1 Fukasa-mukaihata-cho, Fushimi-ku, Kyoto 612-8555

Phone 075-641-9161

[Responsibilities]

From a biostatistical point of view, advising all statistical aspects of this trial, such as the design of clinical trials, the calculation of the number of required cases, the duration of clinical trials and analysis methods.

4. Clinical trial coordination office

Clinical trial management office, Clinical Research Center, National Hospital Organization Utano National Hospital

Address 8 Ontoyama-cho, Narutaki, Ukyo-ku, Kyoto 616-8255

Phone 075-461-5121

[Responsibilities]

Under the direction of the clinical trial coordination committee, supporting the work conducted by the clinical trial coordination committee.

5. Clinical trial drug provider

Zenyaku kogyo Co., Ltd

Address 5-6-15 Otsuka, Bunkyo-ku, Tokyo 112-8650

Phone 03-3946-1113

Fax: 03-3946-1202

[Responsibilities]

Provide clinical trial drugs, clinical trial drug outline, materials or information necessary for the preparation of clinical trial protocol, etc., in an appropriate manner. In addition, provide information on the safety of the clinical trial drugs provided, and information on the approval of manufacturing and sales approval matters partly change approval application, etc., and other necessary information in an appropriate manner.

6. Person in charge of assigning investigational drugs of clinical trial

DOT International Co., Ltd.

Masato Nakata

Address 2-14-1 Higashi-Shimbashi, Minato-ku, Tokyo105-0021

Phone 03-3433-6060 / Fax:03-3433-6161

[Responsibilities]

1. Create, store, and manage key codes and key code tables
2. Create, store, and manage emergency key codes
3. Attaching drug numbers to clinical trials
4. Confirmation of inability to identify clinical trials
5. Check the seal status of the recovery trial drug before the key is opened
6. Check the status of the emergency key code when opening and open the key code
7. Check the seal status of the investigational drug after the key is opened

7. Person in charge of delivery of investigational drugs of clinical trial

Zenyaku kogyo Co., Ltd

Kazuhiro Endo

Masato Watanabe

Address 5-6-15 Otsuka, Bunkyo-ku, Tokyo 112-8650

Phone 03-3946-1113 / Fax: 03-3946-1202

[Responsibilities]

Appropriately manage investigational drugs and deliver them to medical institutions

8. Registration Center

DOT International Co., Ltd.

Masato Nakata

Address 2-14-1 Higashi-Shimbashi, Minato-ku, Tokyo105-0021

Phone 03-3433-6060 / Fax:03-3433-6161

[Responsibilities]

Central assignment is performed in a predetermined manner.

9. Data Management

DOT International Co., Ltd.

Hiroko Iijima

Address 2-14-1 Higashi-Shimbashi, Minato-ku, Tokyo105-0021

Phone 03-3433-6060 / Fax: 03-3433-6161

[Responsibilities]

Entering, inspecting, and fixing CRF data into the database

Data validation and validation

10. Statistical analysis

DOT International Co., Ltd.

Tomonori Kimura

Address 2-14-1 Higashi-Shimbashi, Minato-ku, Tokyo105-0021

Phone 03-3433-6060 / Fax:03-3433-6161

[Responsibilities]

Preparation of statistical analysis plan, execution of analysis based on statistical analysis plan, preparation of analysis report

11. Monitoring

DOT International Co., Ltd.

Namiko Murao

Address 2-14-1 Higashi-Shimbashi, Minato-ku, Tokyo105-0021

Phone 03-3433-6060 / Fax:03-3433-6161

[Responsibilities]

Collection and provision of information by visiting medical institutions, procedures for contracts, collection of clinical trial investigational drugs, confirmation of clinical trial implementation status, collection and investigation of case reports form, implementation of direct browsing, confirmation of preservation of documents, etc., eligibility survey of medical institutions and clinical trial responsible physicians, Monitoring regularly implemented medical institutions

12. Medical Writing

None

13. Audit

DOT International Co., Ltd.

Harutoshi Kon

Address 2-14-1 Higashi-Shimbashi, Minato-ku, Tokyo105-0021

Phone 03-3433-6060 / Fax:03-3433-6161

[Responsibilities]

Investigate whether the clinical trial is conducted in compliance with the clinical trial protocol, standard operating procedure and GCP by the principal investigator and the clinical trial coordinating committee (including the clinical trial coordination office), includeing consistency with the original material by direct viewing.

14. Management of clinical trials

DOT International Co., Ltd.

Tetsuya Orido

Address 2-14-1 Higashi-Shimbashi, Minato-ku, Tokyo105-0021

Phone 03-3433-6060 / Fax: 03-3433-6161

[Responsibilities]

Based on the instructions of the clinical trial Coordinating Committee, supporting the clinical trial coordination office.

15. Doctor-led clinical trial insurance

Mitsui Sumitomo Insurance Co., Ltd.

Liability claim Insurance amount: 100 million yen per person/accident, limit 300 million yen

No deductible

Liability insurance insurance amount Death 20 million yen (livelihood maintainer)

7 million yen (other than the livelihood maintainer)

disability grade (*)

1st class 30 million yen (livelihood maintainer) 20 million yen (non-livelihood maintainer)

2nd class 24 million yen (livelihood maintainer) 16 million yen (non-livelihood maintainer)

*Pharmaceutical Side Effects Damage Relief System Standards

No deductible

Total payment limit 300 million yen

[Responsibilities]

1. Payment of insurance for damages incurred by the subject of this trial due to the disability of the subject of this trial and the insured person (the subject of insurance) is liable for legal liability.

2. Payment of insurance claims for "compensation liability" required by the Ethical Guidelines for Clinical Research.

3. Liability insurance: Damages, dispute expenses (litigation fees, attorney's compensation, etc.)

Liability insurance: Death and disability 1st and 2nd grade

Table 1. Schedule

	Screenig for eligibility	allocation and drug administration				period of efficay and safety					drug administration		period of efficay and safety						
Visit	V1	V2-1 (*)	V2-2	V2-3	V2-4	V3	V4	V5	V6	V7	V8-1 (*)	V8-2	V9	V10	V11	V12	V13		
Week	-35D~-1D	0W	1W	2W	3W	4W	8W	12W	16W	20W	24W	(V8-1 +2W)	28W	32W	36W	40W	44W		
Visit											V14-1 (*)	V14-2	V15	V16	V17	V18	V19	V20	at relapse/ termination
Week											48W	(V14-1 +2W)	52W	56W	60W	64W	68W	72W	
Physical Exam	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎
Neurological Exam (EDSS、QOSI)	◎	◎				◎	◎	◎	◎	◎	◎		◎	◎	◎	◎	◎	◎	◎
Brain MRI (plain, gadlinium)	◎							◎			◎				◎			◎	◎
Spine MRI (plain, gadlinium)	◎										◎							◎	◎
Ophthalmological Exam	◎							◎			◎				◎			◎	◎
VEP	◎							◎			◎				◎			◎	◎
SEP	◎																		◎
CSF Exam	◎																		◎
Labolatory Exam	◎	◎				◎	◎	◎			◎				◎			◎	◎
Infection	◎										◎							◎	
Subset of lymphocyte (blind)		◎				◎	◎	◎			◎				◎			◎	◎
Anti-aquaporin-4 antibody	◎							◎			◎				◎			◎	◎
HACA	◎							◎			◎				◎			◎	◎
Urine Exam (pregnancy test)	◎										◎							◎	◎
Vital sign	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎	◎
Body wight & Height	◎	◎									◎							◎	◎
ECG	◎										◎							◎	◎
Chest x-ray	◎										◎							◎	◎

(*) performed before administration of drug

CSF, cerebrospinal fluid; D, day; ECG, electrocardiogram; EDSS, expanded disability status scale; Exam, examination; HACA, human anti-chimeric antibody
MRI, magnetic resonance imaging; QOSI, quantification of optic nerve and spinal impairment; SEP somatic evoked potential; V,visit; VEP, visual evoked potential