TITLE PAGE

Protocol Title:	A Phase 2/3 Open-Label, Single-Arm Trial to Evaluate the Safety and Activity of Eculizumab in Pediatric Patients with Relapsing Neuromyelitis Optica Spectrum Disorder
Protocol Number:	ECU-NMO-303
Amendment Number	2.2 (Italy)
Compound:	Eculizumab
Short Title:	A Phase 2/3 Open-Label Safety and Activity Study of Eculizumab in Pediatric Patients with Relapsing Neuromyelitis Optica Spectrum Disorder
Sponsor Name	Alexion Pharmaceuticals, Inc. (Alexion)
Legal Registered Address:	121 Seaport Boulevard Boston, MA 02210, USA
Regulatory Agency Identifying Number:	IND Number: 116,207
EudraCT	2019-001829-26
Approval Date:	03 May 2021

SPONSOR SIGNATORY

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2.2 (Italy)	03 May 2021
Amendment 2.1 (Germany)	03 May 2021
Amendment 2	03 May 2021
Amendment 1.4 (Germany)	31 Aug 2020
Amendment 1.3 (Italy)	03 Jun 2020
Amendment 1.2 (Italy)	27 Apr 2020
Amendment 1.1 (Germany)	02 Apr 2020
Amendment 1	08 Jul 2019
Original Protocol	18 Apr 2019

Amendment 2.2 (Italy) 03 May 2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union due to the following key changes that are being implemented:

- 20% reduction in the number of patients to be enrolled in the study
- Addition of a washout period for immunosuppressive therapies to avoid confounding factors for efficacy assessment
- Revision of exclusion criteria related to active infections and current treatment with a biologic medication that may affect immune system functioning to enhance patient safety

Overall Rationale for the Amendment:

Protocol update necessitated from regulatory submission and update to planned number of patients. Local amendment was aligned with global amendment where possible.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Updated amendment number and approval date.	Administrative change.
Section 1.1 Synopsis, Section 4.1.1 Overall Design/Methodology, Section 9.2 Sample Size Determination	Reduced of the number of patients enrolled from 15 to 12, and reduced the number of evaluable patients for the primary analysis from 12 to 10.	Based on updated sample size calculations, total sample size was decreased for the study.
Section 1.1 Synopsis, Section 1.2 Schedule of Activities (Table 9), Section 4.1.5 Safety Follow-up Period (8 Weeks Following the Last Dose of Eculizumab)	Removed the term “commercially available” with regard to eculizumab.	Patients may transition to eculizumab through other noncommercial programs; therefore, the language was broadened.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis (Table 1), Section 4.1.3 Primary Treatment Period, Section 4.1.4 Extension Treatment Period, Section 6.1 (Table 13)	Table 1 and Table 13 footnotes: For study drug infusions given remotely, the patient's body weight from the prior study visit may be used to calculate the dose.	To allow use of the most currently recorded body weight at remote or home visits.
Section 1.2 Schedule of Activities (Table 9), Section 8.3.6 Vaccine and Antibiotic Prophylaxis	Added text to clarify that vaccination will be per local and country-specific immunization guidelines for appropriate age groups.	Clarification.
Section 2.4.2.3 Coronavirus Disease 2019, Section 10.15 COVID-19 Risk Assessment	The benefit-risk assessment related to coronavirus disease 2019 (COVID-19) was added.	To provide a clear assessment of the specific risks created by the COVID-19 pandemic as well as mitigation strategies.
Section 4.1.1 Overall Design/Methodology	Added study design schematic.	To enhance clarity.
Section 4.1.2 Screening Period (1 – 6 weeks)	Text on vaccination requirements for screened patients was removed.	To clarify that vaccination can occur at any point during the Screening Period.
Section 5.1 Inclusion Criteria, Section 6.6.1.2 Immunosuppressive Therapy	Text was added to specify that supportive immunosuppressive therapies (ISTs) must remain stable during the Screening Period.	To clarify that ISTs cannot be changed during the Screening Period.
Section 5.1 Inclusion Criteria	A washout period for ISTs was added.	To minimize any effects of recently discontinued ISTs on study patients.
Section 5.2 Exclusion Criteria	Criterion 5: Text was revised to clarify that a potential patient with active bacterial, viral, or fungal infection within 14 days prior to study drug administration would be excluded. Created a separate criterion (9) to exclude patients currently treated with a biologic medication that may affect immune system functioning.	To enhance patient safety in the study, by confirming that no patient with an active infection will start treatment with eculizumab. To clarify exclusion criteria for prior use of biologic medications that may affect immune system functioning.
Section 6.6.1.3 Treatment of On-Trial Relapse	Clarified that the treatment regimen for On-Trial Relapse would be determined by the Investigator.	To enhance clarity.
Section 6.6.2 Disallowed Medications and Therapies	Specified that biologic medications that may affect immune system functioning are not allowed.	To clarify that biologic medications that may affect immune system functioning are not allowed during the study.
Section 6.8 Intervention After the End of the Study	Removed this section.	Section not applicable, as no intervention will be performed after the end of the study.
Section 8.1 Efficacy Assessments	Corrected the name of the Pediatric Quality of Life Inventory assessment tool.	Administrative.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.4 Expanded Disability Status Scale, Section 10.9 Appendix 9 Expanded Disability Status Scale	Updated the Expanded Disability Status Scale (EDSS) used in this study from the Kurtzke EDSS to the Neurostatus EDSS.	Administrative update to correctly describe the version of the EDSS evaluation already being used in the study.
Section 9.2 Sample Size Determination	Updated sample size calculation based on data available from Study ECU-NMO-301.	Updated total sample size as data from Study ECU-NMO-301 became available.
Section 9.3 Populations for Analyses	Revised the description of the PK/PD analysis set to specify inclusion of all patients who receive at least 1 dose of eculizumab and have PK/PD assessments.	Clarification.
Section 9.4.5.2. Secondary Efficacy Analysis	Hauser Ambulation Index (HAI) added for continuous secondary efficacy endpoints.	To clarify the continuous secondary efficacy endpoints included in the secondary efficacy analyses.
Section 10.4.2 Contraception Guidance	Text was revised to define women of childbearing potential (WOCBP) and to state that WOCBP must be on hormonal contraception at least 6 weeks prior to Day 1.	In order to clearly state the time a patient must be on oral contraception prior to starting study drug.
Throughout the protocol	Minor grammatical/editorial changes, including key abbreviations.	To enhance clarity.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; PD = pharmacodynamic(s); PK = pharmacokinetic(s)

INVESTIGATOR'S AGREEMENT

I have read the ECU-NMO-303 (Amendment 2.2) study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2/3 Open-Label, Single-Arm Trial to Evaluate the Safety and Activity of Eculizumab in Pediatric Patients with Relapsing Neuromyelitis Optica Spectrum Disorder

Short Title: A Phase 2/3 Open-Label Safety and Activity Study of Eculizumab in Pediatric Patients with Relapsing Neuromyelitis Optica Spectrum Disorder

Rationale:

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an ultra-rare, severe, disabling autoimmune inflammatory disorder of the central nervous system (CNS) that predominantly affects the optic nerves and spinal cord. The prevalence of NMOSD in adults is estimated at 0.5 to 4.4/100,000. Neuromyelitis Optica Spectrum Disorder occurs even less frequently in the pediatric population, with an estimated prevalence of 0.02 to 0.03/100,000. In various pediatric populations the median age of onset has been reported as 10 to 14 years, with a range from 1.9 to 18 years. The incidence of NMOSD in patients younger than 2 years is exceedingly rare, with no cases reported in Europe or in the USA. In both the adult and pediatric populations females are much more commonly affected than males, with a female to male ratio of at least 3:1. Currently there are no approved therapies for the treatment of pediatric NMOSD.

Similarities in clinical presentation, serologic findings, and disease course strongly suggest that the pathophysiology of NMOSD in pediatric and adult patients is essentially the same. Given that eculizumab has been proven to be beneficial in adult patients, this study is being undertaken to inform on the efficacy and safety in pediatric patients.

Objectives and Endpoints

Objectives	Endpoints
Primary Treatment Period[a]: Primary: Efficacy	
• Evaluate the efficacy of eculizumab in relapsing pediatric patients with Neuromyelitis Optica Spectrum Disorder (NMOSD).	• The change from Baseline in the Annualized Relapse Rate (ARR) at 52/53 Weeks.[b] • Time to First Relapse (TFR).
Primary Treatment Period[a]: Secondary: Safety	
• Evaluate the safety and tolerability of eculizumab treatment in relapsing pediatric patients with NMOSD.	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events leading to study drug discontinuation. • Incidence of antidrug antibodies (ADA). • Changes from Baseline in vital signs, electrocardiogram (ECG) parameters, and clinical laboratory assessments. • Change from Baseline in both weight and height.

Objectives	Endpoints
Primary Treatment Period[a]: Secondary: Efficacy	
• Evaluate the efficacy of eculizumab by additional efficacy measures including:	
• Disease-related disability	• Change from Baseline in Expanded Disability Status Scale (EDSS) score at 52/53 weeks in patients ≥5 years of age. • Change from Baseline in the Hauser Ambulatory Index (HAI) score at 52/53 weeks.
• Quality of life	• Change from Baseline in Pediatric Quality of Life Inventory (PedsQL) at 52/53 weeks in patients ≥5 years of age. • Change from Baseline in Pediatric Quality of Life Inventory Parent Proxy (PedsQL Parent Proxy) at 52/53 weeks in patients < 5 years of age.
• Change in ophthalmologic examination findings	• Change from Baseline in Visual Acuity (VA) as measured by the Snellen or LEA symbols Eye Chart examination at 52/53 weeks in all patients. • Change from Baseline in Confrontational Visual Fields (VF) as measured during ophthalmologic examination at 52/53 weeks in all patients. • Change from Baseline in color vision as measured during ophthalmologic examination at 52/53 weeks in all patients.
Primary Treatment Period[a]: Secondary: PK/PD	
• Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in relapsing pediatric patients with NMOSD.	• Changes in serum eculizumab concentration over time. • Changes in serum free complement protein 5 (C5) concentrations and in vitro hemolytic activity over time.

Objectives	Endpoints
Primary Treatment Period[a]: Tertiary Efficacy Assessment	
• Evaluate the efficacy of eculizumab by additional efficacy measures including • Quality of life	• Change from Baseline in the European Quality of Life-5 Dimensions-Youth (EQ-5D-Y) score for patients ≥8 years of age and EQ-5D-Y Proxy score for patients aged between 5-7 years, at 52/53 weeks.
Extension Treatment Period[c]: Secondary Safety and Efficacy	
• Characterize long-term safety of eculizumab treatment in pediatric patients with NMOSD. • Characterize long-term efficacy of eculizumab treatment in pediatric patients with NMOSD.	• The safety and efficacy endpoints of the Primary Treatment Period will be evaluated during the Extension Treatment Period.

[a] Open-label eculizumab intravenous (IV) infusion, for a total of 52/53 weeks.
[b] For patients who start in weight cohort 10 to <20 kg, the one-year evaluation will occur on Week 53, an odd-numbered week, because maintenance dosing, which is administered every 2 weeks, begins on Week 1. For all other cohorts the one-year evaluation will occur on Week 52, because maintenance dosing begins on an even-numbered week. Hence, the end of the Primary Treatment Period is designated as Week 52/53 throughout the protocol.
[c] After completing the Primary Treatment Period, patients will continue receiving open-label eculizumab in the Extension Treatment Period for 104 weeks.
Note: Statistical analysis of the primary endpoints will be limited to the change from Baseline to Week 52/53 On-Trial ARR. TFR results will be considered descriptive; therefore, no adjustments for multiplicity will be made.

Overall Design:

This is a Phase 2/3 open-label, single-arm study to evaluate the safety and efficacy of eculizumab in pediatric patients (aged 2 to < 18 years) with relapsing NMOSD. A total of approximately 12 eligible patients will be enrolled, with a minimum target of 10 evaluable patients. Of the 10 evaluable patients, at least 3 of the patients will be aged 2 to < 12 years at the time of enrollment, and at least 5 patients will be aged 12 to < 18 years at the time of enrollment.

There are 4 periods in this study: the Screening Period, the Primary Treatment Period, the Extension Treatment Period, and the Safety Follow-up Period.

Patients who withdraw or discontinue from the study at any time, for any reason after receiving any amount of eculizumab, will be required to complete an Early Termination (ET) Visit at the time of withdrawal and a Safety Follow-up Visit at 8 weeks from the date of the patient's last dose of eculizumab. Adverse events (AEs) leading to patient discontinuation from the study will be followed until the AE has resolved or the patient's condition is medically stable, in the opinion of the Investigator.

Patients who complete the study without transitioning to uninterrupted treatment with eculizumab must complete both an End of Study Visit at the time of study completion and a Safety Follow-up Visit, which will occur 8 weeks from the date the patient's last dose of eculizumab was administered. Patients who complete the study and transition to uninterrupted treatment with eculizumab will not be required to complete the Safety Follow-up Visit at 8 weeks from the date of the last dose.

Number of Patients:

Approximately 12 patients will be enrolled to achieve the minimum of 10 evaluable patients. Of the 10 evaluable patients, at least 3 of the patients will be aged 2 to < 12 years at the time of enrollment, and at least 5 patients will be aged 12 to < 18 years at the time of enrollment.

Intervention Groups and Duration:

All patients who meet the inclusion criteria and none of the exclusion criteria, who have been vaccinated against *Neisseria meningitidis (N meningitidis)*, *Haemophilus influenzae* (Hib), and *Streptococcus pneumoniae (S pneumoniae),* in accordance with the national vaccination recommendations for each age group, and have been cleared by the Investigator, will be enrolled in the study.

All patients will receive open-label eculizumab intravenous (IV) infusion, during the Primary Treatment Period, starting on Day 1 for a total of 52/53 weeks. The dosing regimen will be based on the pediatric patient's body weight, as indicated in Table 1. Body weight is expected to change during this pediatric study and, therefore, a patient's weight cohort may change during the study.

Table 1: Weight-based Dosing Regimen of Eculizumab

Weight Cohort[a,c]	Induction Period[b]	Maintenance Phase
≥ 40 kg	900 mg weekly × 4 doses	1200 mg at Week 4; then every 2 weeks
30 to < 40 kg	600 mg weekly × 2 doses	900 mg at Week 2; then every 2 weeks
20 to < 30 kg	600 mg weekly × 2 doses	600 mg at Week 2; then every 2 weeks
10 to < 20 kg	600 mg weekly × 1 dose	300 mg at Week 1; then every 2 weeks

[a] Day 1 and maintenance period dose regimen will be based on the current visit's recorded body weight. If site/institutions policies prohibit study drug to be prepared on the day of visit, the weight from the most recent study visit should be used. If a patient is receiving an infusion at a remote facility or at home, the weight from the prior study visit may be used to calculate the dose.

[b] During the initial induction period, the dose regimen will be based on the patient's weight on Day 1 (Visit 2).

[c] All patients will remain in the same weight cohort throughout the induction period, regardless of change in weight.

Notes:

- Dosage and treatment regimen are based on results of a modelling and simulation study.
- Eculizumab will be administered by intravenous (IV) infusion.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will conduct interim monitoring of safety data.

The DMC will have access to all safety data. The DMC may make recommendations to the Sponsor regarding safety issues, study conduct, and modifying, extending, or stopping the study.

In addition, the DMC will receive reports concerning patients who have discontinued. Notification of study discontinuation and reason for the discontinuation will be sent to the DMC according to the schedule defined in the Charter. The DMC will also review summaries of all relapses.

A separate DMC Charter will document all DMC procedures for this study.

Relapse Adjudication Committee

The role of the Relapse Adjudication Committee (RAC) will be to determine whether an Investigator-Reported On-Trial Relapse meets the protocol definition of a relapse by rendering a Yes/No decision through the adjudication process. The RAC will be comprised of 3 members: a Chair and 2 additional individuals, all of whom will have expertise in NMOSD. A separate Charter will define the structure, responsibilities, and membership of the RAC, outline the process for RAC review of study data, and outline the procedures for adjudication of an Investigator-Reported Relapse.

1.2. Schedule of Activities

Table 2: Schedule of Assessments Part I: Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg

Period /Phase	**Screening[1]**	**Primary Treatment Period**															
Visit Location[Δ]	**In Clinic**	**In Clinic**									**In Clinic or Remote**						**In Clinic**
Study Visit	**Screening Visit (1)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Week	**-1 to -6 weeks**	**D1**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**
Window (Days)			**±2**														
Informed Consent[2]	X																
Medical History	X																
NMOSD History[3]	X																
NMOSD diagnosis via 2015 IPND Criteria[4]	X																
Neurologic Examination	X	X								X							X
Ophthalmological Examination	X	X								X							X
Snellen or LEA Symbols Chart[35]	X	X								X							X
Weight[6,7,29]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[8]	X	X								X							X
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[10]	X									X							X
12-Lead ECG[11]	X	X															X
Concomitant Medication[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT[14]	X																
MRI (contrast optional)[14]	X																
Expanded Disability Status Scale (EDSS)[5]	X	X								X							X
Hauser Ambulation Index (HAI)	X	X								X							X
Optic Spinal Impairment Score (OSIS)		X															
EQ-5D-Y/EQ-5D-Y Proxy[15]		X								X							X
Pediatric Quality of Life Inventory (PedsQL)/PedsQL Proxy[32]		X								X							X

Table 2: Schedule of Assessments Part I: Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg

Period /Phase	**Screening**[1]	**Primary Treatment Period**															
Visit Location[Δ]	**In Clinic**	**In Clinic**									**In Clinic or Remote**						**In Clinic**
Study Visit	**Screening Visit (1)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Week	**-1 to -6 weeks**	**D1**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**
Window (Days)			**±2**														
anti-AQP4 Ab-positive (Serum)[16,18,34]	X									X							X
Clinical Laboratory Tests[16]	X	X								X							X
Serum Pregnancy Test[17]	X																
Urine Pregnancy Test[17]		X				X		X		X		X		X		X	
PK, Hemolysis, Free C5[18]		B/P 24h	T/P			T/P				T/P							T/P
Exploratory biomarkers		B				T				T							T
ADA[18]		B								T							T
Enrollment[19]		X															
N meningitidis Vaccination[20]	X																
H influenzae Vaccination[21]	X																
S pneumonia Vaccination[21]	X																
Patient Safety Information Cards[22]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion (mg) 10 to < 20 kg[23,25,29,30]				300	N/A	300	300	300	300	300	300	300	300	300	300	300	300
Study Drug Infusion (mg) 20 to < 30 kg[7,23,25,29]		600	600	600	N/A	600	600	600	600	600	600	600	600	600	600	600	600
Study Drug Infusion (mg) 30 to < 40 kg[7,23,25,29]		600	600	900	N/A	900	900	900	900	900	900	900	900	900	900	900	900
Study Drug Infusion (mg) ≥ 40 kg[7,23,25,29]		900	900	900	900	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200

Table 3: Schedule of Assessments Part II: Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg

Period /Phase	**Primary Treatment Period Continued**														
Visit Location [Δ]	**In Clinic or Remote**						**In Clinic**	**In Clinic or Remote**					**In Clinic**		
Study Visit	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**ET[28]**	**F/U[26]**
Study Weeks	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**		**+W8**
Window (Days)	**±2**														**±2**
Weight[6,7,29]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[8]							X						X	X	
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[10]							X						X	X	
Neurologic Examination							X						X	X	
Ophthalmological Examination							X						X	X	
Snellen or LEA Symbols Chart[35]							X						X	X	
12-Lead ECG[11]													X	X	
Concomitant Medication[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Expanded Disability Status Scale (EDSS)[5]							X						X	X	
Hauser Ambulation Index (HAI)							X						X	X	
EQ-5D-Y/EQ-5D-Y Proxy[15]							X						X	X	
Pediatric Quality of Life Inventory (PedsQL)/PedsQL Proxy[32]							X						X	X	
anti-AQP4 Ab-positive (Serum)[16,18,34]							X						X	X	
Clinical Laboratory Tests[16]							X						X	X	
Serum Pregnancy Test[17]														X	
Urine Pregnancy Test[17]	X		X		X		X		X		X		X		X
PK, Hemolysis, Free C5[18]							T/P						T/P	X	
Exploratory biomarkers													T	X	
ADA[18]							T						T	X	
Patient Safety Information Cards[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion (mg) 10 to < 20 kg[23,25,29,30]	300	300	300	300	300	300	300	300	300	300	300	300	300		
Study Drug Infusion (mg) 20 to < 30 kg[7,23,25,29]	600	600	600	600	600	600	600	600	600	600	600	600	600		
Study Drug Infusion (mg) 30 to < 40 kg[7,23,25,29]	900	900	900	900	900	900	900	900	900	900	900	900	900		

Period /Phase	**Primary Treatment Period Continued**														
Visit Location [Δ]	**In Clinic or Remote**						**In Clinic**	**In Clinic or Remote**					**In Clinic**		
Study Visit	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**ET**[28]	**F/U**[26]
Study Weeks	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**		**+W8**
Window (Days)	**±2**														**±2**
Study Drug Infusion (mg) ≥40 kg[7,23,25,29]	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200		
Transition follow-up call[31]														X	

Table 4: Schedule of Assessments Part I: Weight Cohort 10 to < 20 kg

Period /Phase	**Screening[1]**	**Primary Treatment Period**														
Visit Location Δ	**In Clinic**	**In Clinic**								**In Clinic or Remote**						**In Clinic**
Study Visit	**Screening Visit (1)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Weeks	**-1 to -6 weeks**	**D1**	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W15**	**W17**	**W19**	**W21**	**W23**	**W25**	**W27**
Window (Days)			**±2**													
Informed Consent[2]	X															
Medical History	X															
NMOSD History[3]	X															
NMOSD diagnosis via 2015 IPND Criteria[4]	X															
Neurologic Examination	X	X							X							X
Ophthalmological Examination	X	X							X							X
Snellen or LEA Symbols Chart[35]	X	X							X							X
Weight[6,7,29]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[8]	X	X							X							X
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[10]	X								X							X
12-Lead ECG[11]	X	X														X
Concomitant Medication[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT[14]	X															
MRI (contrast optional)[14]	X															
Expanded Disability Status Scale (EDSS)[5]	X	X							X							X
Hauser Ambulation Index (HAI)	X	X							X							X
Optic Spinal Impairment Score (OSIS)		X														
EQ-5D-Y/EQ-5D-Y Proxy[15]		X							X							X
Pediatric Quality of Life Inventory (PedsQL)/PedsQL Proxy[32]		X							X							X
anti-AQP4 Ab-positive (Serum)[16,18,34]	X								X							X
Clinical Laboratory Tests[16]	X	X							X							X
Serum Pregnancy Test[17]	X															
Urine Pregnancy Test[17]		X			X		X		X		X		X		X	
PK, Hemolysis, Free C5[18]		B/P/24h	T/P			T/P			T/P							T/P

Table 4: Schedule of Assessments Part I: Weight Cohort 10 to < 20 kg

Period /Phase	**Screening[1]**	**Primary Treatment Period**														
Visit Location Δ	**In Clinic**	**In Clinic**								**In Clinic or Remote**						**In Clinic**
Study Visit	**Screening Visit (1)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Weeks	**-1 to -6 weeks**	**D1**	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W15**	**W17**	**W19**	**W21**	**W23**	**W25**	**W27**
Window (Days)			**±2**													
Exploratory biomarkers		B				T										T
ADA[18]		B							T							T
Enrollment[19]		X														
N meningitidis Vaccination[20]	X															
H influenzae Vaccination[21]	X															
S pneumonia Vaccination[21]	X															
Patient Safety Information Cards[22]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion (mg) 10 to < 20 kg[7,23,25,29]		600	300	300	300	300	300	300	300	300	300	300	300	300	300	300
Study Drug Infusion (mg) 20 to < 30 kg[23,25,33]			600	600	600	600	600	600	600	600	600	600	600	600	600	600
Study Drug Infusion (mg) 30 to < 40 kg[23,25,33]			900	900	900	900	900	900	900	900	900	900	900	900	900	900
Study Drug Infusion (mg) ≥ 40 kg[23,25,33]			1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200

Table 5: Schedule of Assessments Part II: Weight Cohort 10 to < 20 kg

Period /Phase	**Primary Treatment Period Continued**														
Visit Location [Δ]	**In Clinic/Remote**						**In Clinic**	**In Clinic/Remote**					**In Clinic**		
Study Visit	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**ET[28*]**	**F/U[26]**
Study Weeks	**W29**	**W31**	**W33**	**W35**	**W37**	**W39**	**W41**	**W43**	**W45**	**W47**	**W49**	**W51**	**W53**		**+W8**
Window (Days)	**±2**														**±2**
Weight[6,7,29]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[8]							X						X	X	
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[10]							X						X	X	
Neurologic Examination							X						X	X	
Ophthalmological Examination							X						X	X	
Snellen or LEA Symbols Chart[35]							X						X	X	
12-Lead ECG[11]													X	X	
Concomitant Medication[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Expanded Disability Status Scale (EDSS)[5]							X						X	X	
Hauser Ambulation Index (HAI)							X						X	X	
EQ-5D-Y/EQ-5D-Y Proxy[15]							X						X	X	
Pediatric Quality of Life Inventory (PedsQL)/ PedsQL Proxy[32]							X						X	X	
anti-AQP4 Ab-positive (Serum)[16,18,34]							X						X	X	
Clinical Laboratory Tests[16]							X						X	X	
Serum Pregnancy Test[17]														X	
Urine Pregnancy Test[17]		X		X		X		X		X		X	X		X
PK, Hemolysis, Free C5[18]							T/P						T/P	X	
Exploratory biomarkers													T	X	
ADA[18]							T						T	X	
Patient Safety Information Cards[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion (mg) 10 to < 20 kg[7,23,25,29]	300	300	300	300	300	300	300	300	300	300	300	300	300		

Table 5: Schedule of Assessments Part II: Weight Cohort 10 to < 20 kg

Period /Phase	**Primary Treatment Period Continued**														
Visit Location [Δ]	**In Clinic/Remote**						**In Clinic**	**In Clinic/Remote**					**In Clinic**		
Study Visit	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**ET**[28*]	**F/U**[26]
Study Weeks	**W29**	**W31**	**W33**	**W35**	**W37**	**W39**	**W41**	**W43**	**W45**	**W47**	**W49**	**W51**	**W53**		**+W8**
Window (Days)	**±2**														**±2**
Study Drug Infusion (mg) 20 to < 30 kg[23,25,33]	600	600	600	600	600	600	600	600	600	600	600	600	600		
Study Drug Infusion (mg) 30 to < 40 kg[23,25,33]	900	900	900	900	900	900	900	900	900	900	900	900	900		
Study Drug Infusion (mg) ≥ 40 kg[23,25,33]	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200		
Transition follow-up call[31]														X	

Table 6: Schedule of Assessments (Extension Period): Year 2 (All Weight Cohorts)

Phase	**Extension Treatment Period**								
Visit Location [Δ]	**In Clinic/Remote**						**In Clinic**	**In Clinic**	
Year 2 Visit/Week	**V31/W54 (V30/W55)**	**V32/W56 (V31/W57)**	**V33/W58 (V32/W59)**	**V34/W60 (V33/W61)**	**V35/W62 (V34/W63)**	**V36/W64 (V35/W65)**		**ET**[28]	**F/U**[26] **(+W8)**
Year 2 Visit/Week	**V37/W66 (V36/W67)**	**V38/W68 (V37/W69)**	**V39/W70 (V38/W71)**	**V40/W72 (V39/W73)**	**V41/W74 (V40/W75)**		**V42/W76 (V41/W77)**	**ET**[28]	**F/U**[26] **(+W8)**
Year 2 Visit/Week	**V43/W78 (V42/W79)**	**V44/W80 (V43/W81)**	**V45/W82 (V44/W83)**	**V46/W84 (V45/W85)**	**V47/W86 (V46/W87)**	**V48/W88 (V47/W89)**		**ET**[28]	**F/U**[26] **(+W8)**
Year 2 Visit/Week	**V49/W90 (V48/W91)**	**V50/W92 (V49/W93)**	**V51/W94 (V50/W95)**	**V52/W96 (V51/W97)**	**V53/W98 (V52/W99)**		**V54/W100 (V53/W101)**	**ET**[28]	**F/U**[26] **(+W8)**
Year 2 Visit/Week	**V55/W102 (V54/W103)**	**V56/W104 (V55/W105)**						**ET**[28]	**F/U**[26] **(+W8)**
Window (Days)	**±2**								**(±2)**
Weight[6,7,29]	X	X	X	X	X	X	X	X	X
Height[8]							X	X	
Vital Signs[9]	X	X	X	X	X	X	X	X	X
Physical Examination[10]							X	X	
Neurologic Examination							X	X	
Ophthalmological Examination							X	X	
Snellen or LEA Symbols Chart[35]							X	X	
12-Lead ECG[11]							X	X	
Concomitant Medication[12]	X	X	X	X	X	X	X	X	X
Adverse Event[13]	X	X	X	X	X	X	X	X	X
Expanded Disability Status Scale (EDSS)[5]							X	X	
Hauser Ambulation Index (HAI)							X	X	
EQ-5D-Y/EQ-5D-Y Proxy[15]							X	X	
Pediatric Quality of Life Inventory (PedsQL)/PedsQL Proxy[32]							X	X	
anti-AQP4 Ab-positive (Serum)[16,18,34]							X	X	
Clinical Laboratory Tests[16]							X	X	
Serum Pregnancy Test[17]								X	

Table 6: Schedule of Assessments (Extension Period): Year 2 (All Weight Cohorts)

Phase	**Extension Treatment Period**								
Visit Location [Δ]	**In Clinic/Remote**						**In Clinic**	**In Clinic**	
Year 2 Visit/Week	**V31/W54 (V30/W55)**	**V32/W56 (V31/W57)**	**V33/W58 (V32/W59)**	**V34/W60 (V33/W61)**	**V35/W62 (V34/W63)**	**V36/W64 (V35/W65)**		**ET**[28]	**F/U**[26] **(+W8)**
Year 2 Visit/Week	**V37/W66 (V36/W67)**	**V38/W68 (V37/W69)**	**V39/W70 (V38/W71)**	**V40/W72 (V39/W73)**	**V41/W74 (V40/W75)**		**V42/W76 (V41/W77)**	**ET**[28]	**F/U**[26] **(+W8)**
Year 2 Visit/Week	**V43/W78 (V42/W79)**	**V44/W80 (V43/W81)**	**V45/W82 (V44/W83)**	**V46/W84 (V45/W85)**	**V47/W86 (V46/W87)**	**V48/W88 (V47/W89)**		**ET**[28]	**F/U**[26] **(+W8)**
Year 2 Visit/Week	**V49/W90 (V48/W91)**	**V50/W92 (V49/W93)**	**V51/W94 (V50/W95)**	**V52/W96 (V51/W97)**	**V53/W98 (V52/W99)**		**V54/W100 (V53/W101)**	**ET**[28]	**F/U**[26] **(+W8)**
Year 2 Visit/Week	**V55/W102 (V54/W103)**	**V56/W104 (V55/W105)**						**ET**[28]	**F/U**[26] **(+W8)**
Window (Days)	**±2**								**(±2)**
Urine Pregnancy Test[17]	X		X		X		X		X
PK, Hemolysis, Free C5[18]	*Only to be collected in the event of a relapse or an ET*							X	
Exploratory biomarkers	*Only to be collected in the event of a relapse or an ET*							X	
ADA[18]	*Only to be collected in the event of a relapse or an ET*							X	
Patient Safety Information Cards[22]	X	X	X	X	X	X	X	X	X
Study Drug Infusion (mg) 10 to < 20 kg [7,23,25,29]	300	300	300	300	300	300	300		
Study Drug Infusion (mg) 20 to < 30 kg [7,23,25,29]	600	600	600	600	600	600	600		
Study Drug Infusion (mg) 30 to < 40 kg [7,23,25,29]	900	900	900	900	900	900	900		
Study Drug Infusion (mg) ≥ 40 kg [7,23,25,29]	1200	1200	1200	1200	1200	1200	1200		
Transition follow-up call[31]								X	

Table 7: Schedule of Assessments (Extension Period): Year 3 (All Weight Cohorts)

Phase	**Extension Treatment Period**								
Visit Location [Δ]	**In Clinic/Remote**						**In Clinic**	**In Clinic**	
Year 3 Visit/Week			**V57/W106 (V56/W107)**	**V58/W108 (V57/W109)**	**V59/W110 (V58/W111)**	**V60/W112 (V59/W113)**		**ET**[28]	**F/U**[26] **(+W8)**
Year 3 Visit/Week	**V61/W114 (V60/W115)**	**V62/W116 (V61/W117)**	**V63/W118 (V62/W119)**	**V64/W120 (V63/W121)**	**V65/W122 (V64/W123)**		**V66/W124 (V65/W125)**	**ET**[28]	**F/U**[26] **(+W8)**
Year 3 Visit/Week	**V67/W126 (V66/W127)**	**V68/W128 (V67/W129)**	**V69/W130 (V68/W131)**	**V70/W132 (V69/W133)**	**V71/W134 (V70/W135)**	**V72/W136 (V71/W137)**		**ET**[28]	**F/U**[26] **(+W8)**
Year 3 Visit/Week	**V73/W138 (V72/W139)**	**V74/W140 (V73/W141)**	**V75/W142 (V74/W143)**	**V76/W144 (V75/W145)**	**V77/W146 (V76/W147)**		**V78/W148 (V77/W149)**	**ET**[28]	**F/U**[26] **(+W8)**
Year 3 Visit/Week	**V79/W150 (V78/W151)**	**V80/W152 (V79/W153)**	**V81/W154 (V80/W155)**					**ET/EOS**[27,28,*] **/ V82/W156 (V81/W157)**	**F/U**[26] **(+W8)**
Window (Days)	**±2**								**(±2)**
Weight[6,7,29]	X	X	X	X	X	X	X	X	X
Height[8]							X	X	
Vital Signs[9]	X	X	X	X	X	X	X	X	X
Physical Examination[10]							X	X	
Neurologic Examination							X	X	
Ophthalmological Examination							X	X	
Snellen or LEA Symbols Chart[35]							X	X	
12-Lead ECG[11]							X	X	
Concomitant Medication[12]	X	X	X	X	X	X	X	X	X
Adverse Event[13]	X	X	X	X	X	X	X	X	X
Expanded Disability Status Scale (EDSS)[5]							X	X	
Hauser Ambulation Index (HAI)							X	X	
EQ-5D-Y/EQ-5D-Y Proxy[15]							X	X	
Pediatric Quality of Life Inventory (PedsQL)/PedsQL Proxy[32]							X	X	
anti-AQP4 Ab-positive (Serum)[16,18,34]							X	X	
Clinical Laboratory Tests[16]							X	X	

Table 7: Schedule of Assessments (Extension Period): Year 3 (All Weight Cohorts)

Phase	**Extension Treatment Period**								
Visit Location [Δ]	**In Clinic/Remote**						**In Clinic**	**In Clinic**	
Year 3 Visit/Week			**V57/W106 (V56/W107)**	**V58/W108 (V57/W109)**	**V59/W110 (V58/W111)**	**V60/W112 (V59/W113)**		**ET**[28]	**F/U**[26] **(+W8)**
Year 3 Visit/Week	**V61/W114 (V60/W115)**	**V62/W116 (V61/W117)**	**V63/W118 (V62/W119)**	**V64/W120 (V63/W121)**	**V65/W122 (V64/W123)**		**V66/W124 (V65/W125)**	**ET**[28]	**F/U**[26] **(+W8)**
Year 3 Visit/Week	**V67/W126 (V66/W127)**	**V68/W128 (V67/W129)**	**V69/W130 (V68/W131)**	**V70/W132 (V69/W133)**	**V71/W134 (V70/W135)**	**V72/W136 (V71/W137)**		**ET**[28]	**F/U**[26] **(+W8)**
Year 3 Visit/Week	**V73/W138 (V72/W139)**	**V74/W140 (V73/W141)**	**V75/W142 (V74/W143)**	**V76/W144 (V75/W145)**	**V77/W146 (V76/W147)**		**V78/W148 (V77/W149)**	**ET**[28]	**F/U**[26] **(+W8)**
Year 3 Visit/Week	**V79/W150 (V78/W151)**	**V80/W152 (V79/W153)**	**V81/W154 (V80/W155)**					**ET/EOS**[27,28,*] **/ V82/W156 (V81/W157)**	**F/U**[26] **(+W8)**
Window (Days)	**±2**								**(±2)**
Serum Pregnancy Test[17]								X	
Urine Pregnancy Test[16]	X		X		X		X		X
PK, Hemolysis, Free C5[18]	*Only to be collected in the event of a relapse or an ET*							X	
Exploratory biomarkers	*Only to be collected in the event of a relapse or an ET*							X	
ADA[18]	*Only to be collected in the event of a relapse or an ET*							X	
Patient Safety Information Cards[22]	X	X	X	X	X	X	X	X	X
Study Drug Infusion (mg) 10 to < 20 kg [7,23,25,29]	300	300	300	300	300	300	300		
Study Drug Infusion (mg) 20 to < 30 kg [7,23,25,29]	600	600	600	600	600	600	600		
Study Drug Infusion (mg) 30 to < 40 kg [7,23,25,29]	900	900	900	900	900	900	900		
Study Drug Infusion (mg) ≥ 40 kg [7,23,25,29]	1200	1200	1200	1200	1200	1200	1200		
Transition follow-up call[31]								X	

Table 8: Schedule of Assessments – Relapse Evaluation Period

Assessment	Relapse Evaluation Visit[24]	Follow- Up Relapse Evaluation Visits[24]			
Study Week	Within 24-48 hours	+W1	+W4	+W6	Unscheduled
Window (Days)	--	±2			--
Weight[6,7,29]	--	--	--	X	Procedures, tests, and assessments will be performed at the discretion of the Investigator. Refer to Section 4.2.4 and Table 11 for further details.
Vital Signs[9]	X	X	X	X	
Physical Examination[10]	--	--	--	X	
Neurologic Examination	X	X	X	X	
Ophthalmological Examination	X	X	X	X	
Snellen or LEA Symbols Chart[35]	X	X	X	X	
Electrocardiogram (ECG)[11]	--	--	--	X	
Concomitant Medication[12]	X	X	X	X	
Adverse Events (AEs)[13]	X	X	X	X	
OCT[14]	X	--	--	--	
MRI with or w/o contrast[14]	X	--	--	--	
Expanded Disability Status Scale (EDSS)[5]	X	X	X	X	
Hauser Ambulation Index (HAI)	X	X	X	X	
Optic Spinal Impairment Score (OSIS)	X	X	X	X	
EQ-5D-Y/EQ-5D-Y Proxy[15]	--	--	--	X	
Pediatric Quality of Life Inventory (PedsQL)/PedsQL Proxy[32]	--	--	--	X	
anti-AQP4 Ab-positive (serum)[16,18,34]	X	--	--	X	
Clinical Laboratory Tests[16]	X	--	--	X	
Pregnancy test (serum)[17]	--	--	--	--	
Pregnancy Test (urine)[17]	X	--	--	X	
PK/PD/Free C5 (serum)[18]	T/P	T/P	T/P	T/P	
Exploratory biomarkers	T	T	T	T	
ADA[18]	--	--	--	X	
Patient Safety Information Cards[22]	X	X	X	X	
Study drug Infusion[7,23,25,29]	Continue every 1 to 2 weeks (±2 days) as scheduled				

Table 9: Schedule of Assessments – Footnotes

Footnote	Description
1.	All Screening procedures must be completed within 1-6 weeks prior to the enrollment at Baseline (Visit 2 [Day 1]). Patients who experience a relapse during the Screening Period will be considered a Screening failure. Such patients may be rescreened for enrollment into the study. Re-Screening procedures should be confirmed with the Sponsor to determine if all Screening procedures are necessary.
2.	The patient's signed and dated informed consent form (ICF) must be obtained before conducting any study procedures.
3.	The Investigator will review the patient's history and diagnosis and document the following at the Screening Visit: NMOSD diagnosis date as well as prior Magnetic Resonance Imaging (MRI) imaging that contributed to the diagnosis; the number of relapses (onset dates), and the clinical presentation of each relapse (eg, optic neuritis (ON), transverse myelitis (TM), longitudinally extensive transverse myelitis (LETM), brainstem, area postrema, or other).
4.	All available information about relapses that meet the protocol definition of Historical Relapse, which have occurred within the 2 years prior to Screening, including relapse onset date, clinical presentation, acute and maintenance treatments, dosing regimens, any disability measurements such as the Expanded Disability Status Scale (EDSS) scores, will be recorded.
5.	The blinded EDSS Rater will perform the Kurtzke neurological assessment and document the Functional Systems Score (FSS) and EDSS score. EDSS will not be performed on patients aged 2-4 years.
6.	Collect weight with minimal clothing.
7.	During the induction period, the dosing regimen will be based on the patient's weight at Day 1 (Visit 2).
8.	Collect height with no shoes or footwear.
9.	Vital signs include assessments of systolic and diastolic blood pressure (BP), temperature, respiratory rate (RR) and heart rate (HR). Vital signs will be obtained after the patient has been supine or seated for at least 5 minutes. Ideally, each patient's BP should be measured using the same arm.
10.	Additional Physical Examinations can be performed as medically indicated during the study at the Investigator's discretion.
11.	Additional ECGs may be performed if the Investigator feels it is clinically warranted.
12.	Concomitant medications will be recorded at the Screening Visit as described in the protocol. Use of concomitant medication will be evaluated during the study and all new medications or changes to concomitant medications will be recorded.
13.	Serious adverse events and nonserious adverse events are recorded from time of signed consent.
14.	Baseline MRI with or without contrast and Optical Coherence Tomography Examinations should be performed. Follow-up assessments should be performed promptly after relapse if Investigator decides these are indicated. Exceptions may be granted (eg, based on a recent historical result being available for the study) if approved by the Alexion Medical Monitor.
15.	The QoL self- assessments (EQ-5D-Y), or Proxy version if patient is aged 5-7 years old, will be performed by the patient or parent/caregiver before any other study procedures at all study visits. This test will not be performed in patients aged 2-4 years old.
16.	Clinical laboratory tests (chemistry, hematology and urinalysis) will be performed by a central laboratory. Refer to the study protocol for a summary of the clinical laboratory tests to be measured.
17.	Pregnancy test must be performed on all women of childbearing potential at specified timepoints. Pregnancy test (urine or serum) may also be performed at any time during the study at the Investigator's discretion. Patients must practice an effective, reliable and medically approved contraceptive regimen during the study and for up to 5 months following discontinuation of treatment. If a patient or a patient's partner becomes or is found pregnant while in the study, the Sponsor will be notified in accordance with the study protocol.
18.	Obtain Baseline and trough blood samples for anti-AQP4 Ab, PK, hemolysis, free C5, and ADA tests 5 – 90 minutes before study drug infusion. Obtain peak blood samples for PK, hemolysis, and free C5 tests 60-120 minutes after the completion of study drug infusion. Obtain 24-hour post-dose blood samples for PK, hemolysis, and free C5 after study drug infusion at Visit 2 (Day 1). For the sample collected at 24 hours, there will be a window of ±1 hour for collecting the sample.

Table 9: Schedule of Assessments – Footnotes

Footnote	Description
19.	Both the Investigator and the Sponsor must approve patient eligibility prior to enrollment. Enrollment will be done by using an IXRS system on Day 1.
20.	To reduce the risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within the 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement-inhibitors (eg, eculizumab).
21.	Vaccinate patients against *H influenzae* and *S pneumoniae*, as per local and country-specific immunization guidelines for the appropriate age group if not already vaccinated, at least 2 weeks prior to receiving the first eculizumab infusion.
22.	Patients and their parents/guardians will receive information about signs and symptoms of an NMOSD relapse. Patients and their parents/guardians will also receive a separate safety card providing information about the risk of meningococcal infection.
23.	During the Study Period, study drug will be administered IV over approximately 1 to 4 hours in pediatric patients. For patients who reach ≥ 18 years of age during the study, the study drug should be administered IV over approximately 35 (± 10) minutes. If an AE occurs during administration of the study drug, the infusion may be slowed or stopped at the discretion of the Investigator, depending upon the nature and severity of the event; however, the overall duration should not exceed 2 hours from the start of the infusion in patients aged ≥ 18 years and 4 hours from the start of infusion in pediatric patients.
24.	Patient should be evaluated within 24-48 hours of notification of the Investigator of a potential relapse, and no later than 48 hours. All potential relapses must be evaluated by both the Investigator and the blinded EDSS Rater. Follow-Up Relapse Evaluation Visits will be performed at 1, 4 and 6 weeks after the onset of relapse. Additional Relapse Evaluation Visits (Unscheduled Visits) are permitted at the discretion of the Investigator. Tests, procedures, and assessments listed under the Unscheduled Visits are to be performed at the discretion of the Investigator. All investigations/tests related to the relapse evaluation (eg, MRIs, computerized tomography (CTs), lumbar punctures, etc.) should be recorded in the source documents and in the eCRF; copies of all reports should be sent to the Sponsor.
25.	Administer study drug after completion of all other tests and procedures, excluding the peak blood sampling for PK, hemolysis, and free C5 assay.
26.	Patients who complete the study and transition to uninterrupted treatment with eculizumab will not be required to complete the 8-week Safety Follow-up Visit.
27.	The end of the Primary Treatment Period Week 52/53 (time of endpoint assessment) is differentiated from the end of the study (EOS) at Week 156/157.
28.	Early Termination (ET) is defined as any time the patient leaves the study before Week 156/157. If a patient withdraws from the study or discontinues eculizumab treatment at any time prior to Week 156/157, the patient will be required to complete an ET Visit at the time of withdrawal and a Safety Follow-up Visit 8 weeks following the last dose of study drug.
29.	All patients will remain in the same weight cohort throughout the induction period, regardless of change in weight.
30.	This dosing would be applicable only if a patient started on 20 to < 30 kg weight cohort and the patient's weight decreased to 10 to < 20 kg.
31.	The Investigator must confirm with the patient or their guardian/caregiver by telephone that the transition to eculizumab occurred within 2 weeks of the last scheduled dose during the study. In the event that treatment with eculizumab is delayed, an unscheduled Safety Follow-up Visit should occur on the day of initiating eculizumab treatment or as soon as feasible.
32.	The test is designed for self-completion in patients aged ≥5 years by respondents (with 3 age-appropriate PedsQL tests available for ages 5-7, 8-12, and 13-18 years old), and by a Proxy in patients aged ≥2 to < 5 years.
33.	This dosing would be applicable only if a patient started on 10 to < 20 kg weight cohort and the patient's weight increased to higher weight cohorts.

Table 9: Schedule of Assessments – Footnotes

Footnote	Description
34.	Patients need to be anti-AQP4 Ab-positive to be eligible for enrollment into the study. A historically positive anti-AQP4 Ab test may be acceptable if the test was performed using an acceptable, validated cell-based assay from an accredited laboratory. In this setting, the historical test result and related information need to be reviewed and approved by Alexion prior to enrollment.
35.	The Snellen eye chart will be used in patients ≥6 years and a LEA symbols eye chart will be used in patients who are aged 2-5 years.
Δ	In Clinic – visits must be conducted at the investigational sites; Remote – visits may be conducted remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.
*	EOS Visit will occur at the end of all study visits and before the Safety Follow-up Visit, while ET will occur at the time the patient withdraws.
Abbreviations	Abbreviations: ADA = anti-drug antibodies; AQP4 Ab = aquaporin 4 antibody; B = Baseline sample; C5 = complement protein 5; D = day; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; EQ-5D-5L = European Quality of Life-5 Dimensions-5L; EQ-5D-Y = European Quality of Life 5-Dimension Youth; ET = Early Termination; F/U = Follow-up; IPND = International Panel for NMO Diagnosis; IXRS = Interactive Voice/Web Response System; N/A = not applicable; NMOSD = Neuromyelitis Optica Spectrum Disorder; P = peak sample; OCT = Optical Coherence Tomography; OSIS = Optic Spinal Impairment Score; PD = pharmacodynamics; PK = pharmacokinetics; QoL = quality of life; T = trough sample; W = week

2. INTRODUCTION

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an ultra-rare, severe, disabling autoimmune inflammatory disorder of the CNS that predominantly affects the optic nerves and spinal cord, and is often characterized by a relapsing course. The prevalence of NMOSD in adults is estimated at 0.5 to 4.4/100,000. Neuromyelitis Optica Spectrum Disorder occurs even less frequently in the pediatric population, with an estimated prevalence of 0.02 to 0.03/100,000. In various pediatric populations the median age of onset has been reported as 10 to 14 years, with a range from 1.9 to 18 years (Pandit, 2015). The incidence of NMOSD in patients younger than 2 years is exceedingly rare, with no cases reported in Europe or in the USA. In both the adult and pediatric populations, females are much more commonly affected than males, with a female to male ratio of at least 3:1 (Fujioka, 1989; McKeon, 2008; Mealy, 2012; Tillema, 2012).

Currently there are no approved therapies for the treatment of pediatric patients with NMOSD.

2.1. Study Rationale

Eculizumab (h5G1.1-mAb) is a humanized monoclonal antibody (mAb) that was derived from the murine anti-human complement protein 5 (C5) antibody (Ab) m5G1.1. Eculizumab specifically binds the terminal complement protein C5, thereby inhibiting its cleavage to C5a and C5b during complement activation. This strategic blockade of the complement cascade at C5 prevents the release of proinflammatory mediators and the formation of the cytolytic pore, while preserving the early components of complement activation that are essential for the opsonization of microorganisms and clearance of immune complexes.

Similarities in clinical presentation, serologic findings, and disease course strongly suggest that the pathophysiology of NMOSD in pediatric and adult patients is essentially the same. Given that eculizumab has been proven to be beneficial in adult patients, this study is being undertaken to inform on the efficacy and safety in pediatric patients (Pittock, 2019; Pittock, 2013).

2.2. Eculizumab in Patients with Neuromyelitis Optica Spectrum Disorder

In 2013, an Investigator-initiated study designed to evaluate the safety and efficacy of eculizumab in patients with anti- aquaporin-4 (AQP4) Ab-positive NMOSD demonstrated preliminary safety and efficacy in relapsing NMOSD (Pittock, 2013). After 12 months of treatment, 12/14 (86%) patients were attack-free, and 2 had possible attacks. The median annualized relapse rate (ARR) declined from 3 (pre-eculizumab, range 2-4) to 0 (post-eculizumab, range 0-1; $p<0.0001$).

In 2018, a multinational, double-blind, parallel-group Phase 3 time-to-event study, PREVENT, reported on the efficacy and safety of eculizumab compared to placebo for the treatment of adult patients with anti- AQP4 auto Ab-positive NMOSD. Treatment with eculizumab reduced the risk of NMOSD relapse by 94.2% compared to placebo ($p<0.0001$). At 48 weeks, 97.9% of patients receiving eculizumab were free of relapse compared to 63.2% of patients receiving placebo. Treatment with eculizumab also reduced the adjudicated On-Trial ARR compared to placebo, a key secondary endpoint, by 95.5% ($p<0.0001$). Eculizumab was generally well tolerated with a safety profile consistent with that seen in previous clinical studies and real-world use in its 3 approved indications (Pittock, 2019).

2.3. Background

2.3.1. Clinical Presentation of Neuromyelitis Optica Spectrum Disorder

The most common clinical hallmarks of NMOSD are acute optic neuritis (ON) and transverse myelitis (TM) that frequently involves greater than 3 vertebral levels, described as longitudinally extensive transverse myelitis (LETM) (Oh, 2012). These clinical events can occur either simultaneously or in isolation (Wingerchuk, 2007). Signs and symptoms attributable to lesions beyond the optic nerves and spinal cord, such as brainstem or cerebral lesions, also occur in patients with NMOSD (Popescu, 2011; Poppe, 2005; Wingerchuk, 1999).

The clinical presentation of NMOSD can be quite variable and may elude diagnosis at the time of the first or even the second attack. The diagnosis of NMOSD can be even more challenging in children. Although cerebral lesions in children and in adults are detected at the same rate (~60%), children are often more symptomatic, presenting with cerebral symptoms that resemble other demyelinating disorders, and may precede the typical features of ON or TM by several months (Fardet, 2003; Fragoso, 2014; McKeon, 2008). In children, cerebral presentations are variable and can include symptoms such as encephalopathy, ophthalmoparesis, ataxia, seizures, intractable vomiting, hiccups, or vertigo (Banwell, 2008); (Chelimsky, 2004); (Chitnis, 2013); (Fardet, 2003); (McKeon, 2008).

Recent studies have shown that in more than 90% of the anti-AQP4 Ab-positive pediatric cases, NMOSD is a relapsing disease (Wingerchuk, 2008). Once a relapsing course has been established, recurrent attacks result in a stepwise accumulation of neurologic disability. In patients with NMOSD, the disability accumulation is associated with relapse (Wingerchuk, 2007). Therefore, relapse prevention is paramount for successful treatment of relapsing NMOSD (Banwell, 2008; Wingerchuk, 2007; Wingerchuk, 2008).

The prognosis of untreated NMOSD is poor. Before universal recognition of NMOSD as a disease distinct from multiple sclerosis (MS), and thus requiring a very different treatment paradigm, the 5-year mortality of NMOSD was reported to be 30%; 50% of patients sustain permanent, severe visual (blind in one or both eyes) or ambulatory (requiring a wheelchair) disability. Most deaths result from neurogenic respiratory failure secondary to a high cervical cord or brainstem lesion (Wingerchuk, 1999). A more recent 2012 investigation of the clinical outcomes and prognostic characteristics of patients who are anti-AQP4 Ab-positive from the United Kingdom and Japan showed that frequent, early relapses predict a poor prognosis. In that study, approximately 1/5 (18%) patients developed permanent visual disability; 1/3 (34%) developed permanent motor disability; approximately 1/4 (23%) became wheelchair-dependent, and nearly 1/10 (9%) of patients died after a median disease duration of 75 months (Kitley, 2012).

2.3.2. Unmet Medical Need

Currently, no therapies are approved for the treatment of NMOSD in pediatric patients. Thus, supportive treatment, including corticosteroids and other immunosuppressive therapies (ISTs), is used based on clinical experience and consensus (Trebst, 2014). Despite the use of ISTs as supportive therapy, a significant number of patients (>50%) continue to experience disease relapses that result in additional and permanent neurologic deficits and disability (Bichuetti, 2015; Bichuetti, 2010; Costanzi, 2011; Jacob, 2009; Kim, 2011).

Given the seriousness of the disease and the limitations of the small number of currently available supportive treatments, there remains a significant unmet medical need for an effective and safe treatment for NMOSD in the pediatric population.

2.3.3. Role of Complement in Neuromyelitis Optica Spectrum Disorder

Complement activation is a major determinant of disease pathogenesis in patients with NMOSD (Hinson, 2009; Nytrova, 2014; Papadopoulos, 2012; Verkman, 2012). Binding of anti-AQP4 autoantibodies to the AQP4 water channel, which is highly expressed on astrocytic surfaces in the CNS, has been shown to lead to hexameric assembly of immunoglobulin G (IgG). This in turn recruits and activates complement component 1, the first step in activation of the complement cascade (Diebolder, 2014). Complement activation initiates an inflammatory cascade that induces permeabilization of the blood brain barrier and astrocyte necrosis. Lesions that form during this process are indicative of NMOSD and are positive for anti-AQP4 antibodies and complement.

2.4. Benefit/Risk Assessment

2.4.1. Potential Benefits

Given that NMOSD is a severe, disabling disease with relapse and cumulative disability occurring in more than 90% of cases (Wingerchuk, 2008), pediatric patients with NMOSD are at risk of substantial morbidity and mortality. The efficacy and safety of eculizumab compared to placebo for the treatment of adult patients with anti-AQP4 Ab-positive NMOSD has recently been demonstrated in a multinational, double-blind, parallel-group Phase 3 time-to-event study, PREVENT, in which treatment with eculizumab reduced the risk of NMOSD relapse by 94.2% compared to placebo ($p<0.0001$) (Pittock, 2019). Given that the pathogenesis of the disease in pediatric patients is similar to that in adults, treatment with eculizumab may result in reduction of relapses in pediatric patients as well.

2.4.2. Identified and Potential Risks

2.4.2.1. Meningococcal Infection and Other Encapsulated Bacterial Infections

Eculizumab blocks terminal complement; therefore, patients may have increased susceptibility to serious infections, and in particular, *Neisseria meningitidis (N meningitidis)*. Children treated with eculizumab may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* (*S pneumoniae*) and *Haemophilus influenzae* type b (Hib). Specific risk mitigation measures in place are described in Section 8.3.6.

2.4.2.2. Immunogenicity

As with any humanized mAb, administration of eculizumab may be associated with the development of anti-drug Abs (ADA). Monitoring of immunogenicity is planned, as described in Section 8.2.4 and Section 1.2.

2.4.2.3. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) global pandemic is active at the time of this amendment in many countries. Given this unique circumstance, specific consideration has been

given to the risks and benefits of the study as they relate to COVID-19 and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.15; Appendix 15.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Treatment Period[a]: Primary: Efficacy	
• Evaluate the efficacy of eculizumab in relapsing pediatric patients with Neuromyelitis Optica Spectrum Disorder (NMOSD).	• The change from Baseline in the Annualized Relapse Rate (ARR) at 52/53 Weeks.[b] • Time to First Relapse (TFR)
Primary Treatment Period[a]: Secondary: Safety	
• Evaluate the safety and tolerability of eculizumab treatment in relapsing pediatric patients with NMOSD.	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events leading to study drug discontinuation. • Incidence of antidrug antibodies (ADAs). • Changes from Baseline in vital signs, electrocardiogram (ECG) parameters, and clinical laboratory assessments. • Change from Baseline in both weight and height.
Primary Treatment Period[a]: Secondary: Efficacy	
• Evaluate the efficacy of eculizumab by additional efficacy measures including:	
◦ Disease-related disability	• Change from Baseline in Expanded Disability Status Scale (EDSS) score at 52/53 weeks in patients ≥ 5 years of age. • Change from Baseline in the Hauser Ambulatory Index (HAI) score at 52/53 weeks.
◦ Quality of life	• Change from Baseline in Pediatric Quality of Life Inventory (PedsQL) at 52/53 weeks in patients ≥ 5 years of age. • Change from Baseline in Pediatric Quality of Life Inventory Parent Proxy (PedsQL Parent Proxy) at 52/53 weeks in patients < 5 years of age.
◦ Change in ophthalmologic examination findings	• Change from Baseline in Visual Acuity (VA) as measured by the Snellen or LEA symbols Eye Chart examination at 52/53 weeks in all patients. • Change from Baseline in Confrontational Visual Fields (VF) as measured during ophthalmologic examination at 52/53 weeks in all patients. • Change from Baseline in color vision as measured during ophthalmologic examination at 52/53 weeks in all patients.
Primary Treatment Period[a]: Secondary: PK/PD	
◦ Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in relapsing pediatric patients with NMOSD.	• Changes in serum eculizumab concentration over time. • Changes in serum free complement protein 5 (C5) concentrations and in vitro hemolytic activity over time.

Objectives	Endpoints
Primary Treatment Period[a]: Tertiary: Efficacy Assessment	
• Evaluate the efficacy of eculizumab by additional efficacy measures including • Quality of life	• Change from Baseline in the European Quality of Life-5 Dimensions-Youth (EQ-5D-Y) score for patients ≥ 8 years of age and EQ-5D-Y Proxy score for patients aged between 5-7 years, at 52/53 weeks.
Extension Treatment Period[c]: Secondary: Safety and Efficacy	
• Characterize long-term safety of eculizumab treatment in pediatric patients with NMOSD. • Characterize long-term efficacy of eculizumab treatment in pediatric patients with NMOSD.	• The safety and efficacy endpoints of the Primary Treatment Period will be evaluated during the Extension Treatment Period.

[a] Open-label eculizumab intravenous (IV) infusion, for a total of 52/53 weeks.

[b] For patients who start in weight cohort 10 to < 20 kg, the one-year evaluation will occur on Week 53, an odd numbered week, because maintenance dosing, which is administered every 2 weeks, begins on Week 1. For all other cohorts the one-year evaluation will occur on Week 52, because maintenance dosing begins on an even numbered week. Hence, the end of the Primary Treatment Period is designated as Week 52/53 throughout the protocol.

[c] After completing the Primary Treatment Period, patients will continue receiving open-label eculizumab in the Extension Treatment Period for 104 weeks.

Note: Statistical analysis of the primary endpoints will be limited to the change from Baseline to Week 52/53 On-Trial ARR. TFR results will be considered descriptive; therefore, no adjustments for multiplicity will be made.

4. STUDY DESIGN

4.1. Overall Design

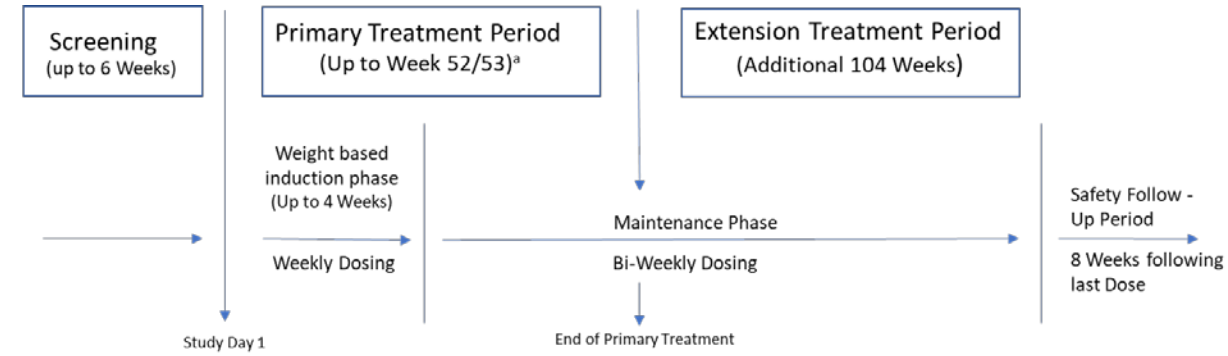
4.1.1. Overall Design/Methodology

The study design is depicted in Figure 1.

This is a Phase 2/3 open-label, single-arm study to evaluate the safety and efficacy of eculizumab in pediatric patients (aged 2 to < 18 years) with relapsing NMOSD. A total of approximately 12 eligible patients will be enrolled, with a minimum target of 10 evaluable patients. Of the 10 evaluable patients, at least 3 of the patients will be aged 2 to < 12 years at the time of enrollment, and at least 5 patients will be aged 12 to < 18 years at the time of enrollment.

There are 4 periods in this study: the Screening Period, the Primary Treatment Period, the Extension Treatment Period, and the Safety Follow-up Period.

Figure 1: Schematic Design for Study ECU-NMO-303



[a] For patients who start in weight cohort 10 to <20 kg, the one-year evaluation will occur on Week 53, an odd numbered week, because maintenance dosing, which is administered every 2 weeks, begins on Week 1. For all other cohorts the one-year evaluation will occur on Week 52, because maintenance dosing begins on an even numbered week

4.1.2. Screening Period (1 – 6 weeks)

At the Screening Visit, after obtaining the informed assent of the patient (if applicable) and the informed consent of the parent or other legal guardian, the patient will be screened for study eligibility through medical history review, demographic data, physical examination, concomitant medications, and clinical laboratory assessments (including evaluation for anti-AQP4 Ab-seropositivity). A complete neurologic assessment to include neurologic examination, Expanded Disability Status Scale (EDSS) evaluation, and other assessments, as per the schedule of activities (SoA; Section 1.2), will be performed. Baseline magnetic resonance imaging (MRI) (contrast optional) and Optical Coherence Tomography (OCT) examinations are required per the protocol; however, exceptions may be granted (eg, based on the availability of recent historical results) at the discretion of the Alexion Medical Monitor.

The medical history review will include confirmation of the NMOSD diagnosis as defined by the International Panel for NMO Diagnosis (IPND) criteria described in Wingerchuk, 2015 (Section 10.6; Appendix 6); only patients who are both anti-AQP4 Ab-positive and otherwise meet the 2015 IPND criteria will be eligible. All available information about relapses, which

occurred within the 2 years prior to Screening and that meet the protocol definition of Historical Relapse (Section 4.2.1) will be recorded, including relapse onset date, clinical presentation, acute and maintenance treatments, dosing regimens, and any disability measurements such as EDSS scores. Screening laboratory assessments will include evaluation for anti-AQP4 Ab seropositivity.

4.1.3. Primary Treatment Period (Day 1 – Week 52/53)

All eligible patients will receive open-label eculizumab IV infusion, starting on Day 1 for a total of 52/53 weeks. The dosing regimen will be based on the pediatric patient's body weight (Table 13). Weight may change for an individual patient during the study; therefore, when possible, dose regimen will be based on the current visit's recorded body weight (Section 6.1). However, all patients will remain in the same weight cohort throughout the induction period, regardless of change in weight. If site/institution policies prohibit study drug to be prepared on the day of visit, the weight from the most recent study visit should be used. Patients may have an opportunity to receive eculizumab administration remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. If a patient is receiving an infusion at a remote facility or at home, the weight from the prior study visit may be used to calculate the dose.

Clinical measures and laboratory tests, as described in Section 10.2; Appendix 2, will be routinely performed to assess safety, efficacy, neurological function, and other clinical parameters associated with physical growth and cognition for patients continuing in the Treatment Period (Section 1.2). The Primary Treatment Period ends on Week 53 for patients who were enrolled in the 10 to < 20 kg weight cohort, because for this weight cohort, the maintenance dose, administered every 2 weeks, begins on Week 1; for all other weight cohorts the Primary Treatment Period will end at Week 52 because the maintenance dosing begins on even-numbered weeks.

Identification of potential relapse is critical for patient safety and for the study. Patients and their parents/guardians will receive a Patient Education Card detailing the signs and symptoms of a potential relapse, including instructions to contact the study site at the first sign or symptom of a potential relapse. Patients should be seen within 24 to 48 hours of notification of a possible relapse so that the Investigator can evaluate the patient and determine whether or not the patient meets the definition of Investigator-Reported On-Trial Relapse as defined by this protocol (Section 4.2; Section 8.1.8).

4.1.4. Extension Treatment Period (104 weeks)

After completing the 52/53-week Primary Treatment Period, patients may continue receiving eculizumab in the Extension Treatment Period for 104 weeks. Weight may change for an individual patient during the study; therefore, when possible, dose regimen will be based on the current visit's recorded body weight (Section 6.1). If site/institution policies prohibit study drug to be prepared on the day of visit, the weight from the most recent study visit should be used. Patients may have an opportunity to receive eculizumab administration remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent

regulatory authorities. If a patient is receiving an infusion at a remote facility or at home, the weight from the prior study visit may be used to calculate the dose.

Clinical measures and laboratory tests will be routinely performed on patients to assess safety, efficacy, neurological function, and other clinical parameters associated with physical growth and cognition throughout in the Extension Treatment Period (Section 1.2).

Identification of potential relapse is critical for patient safety and for the study. Patients and their parents/guardians will receive a Patient Education Card detailing the signs and symptoms of a potential relapse, including instructions to contact the study site at the first sign or symptom of a potential relapse. Patients should be seen within 24 to 48 hours of notification of a possible relapse so that the Investigator can evaluate the patient and determine whether or not the patient meets the definition of Investigator-Reported On-Trial Relapse as defined by this protocol (Section 4.2; Section 8.1.8).

4.1.5. Safety Follow-up Period (8 Weeks Following the Last Dose of Eculizumab)

Patients who withdraw or discontinue treatment at any time and for any reason after receiving any amount of eculizumab will be required to complete both an Early Termination (ET) Visit at the time of withdrawal and a Safety Follow-up Visit at 8 weeks following the last eculizumab dose. Adverse events leading to patient discontinuation from the study are followed until resolution or are medically stable in the opinion of the Investigator.

Patients who complete the study without transitioning to uninterrupted treatment with eculizumab or ravulizumab must complete both an End of Study (EOS) Visit at the time of study completion and a Safety Follow-up Visit, which will occur 8 weeks from the date the patient's last dose of eculizumab was administered. Patients who complete the study and transition to uninterrupted treatment with eculizumab will not be required to complete the Safety Follow-up Visit at 8 weeks.

4.2. Methodology of Relapse Evaluation

4.2.1. Historical Relapse

Historical relapses are the relapses that occurred prior to the Screening Visit, including the first NMOSD attack. Please refer Section 10.5; Appendix 5 for further details.

4.2.2. On-Trial Relapse

On-Trial Relapses are acute attacks that occur during the study. Please refer Section 10.5; Appendix 5 for further details.

4.2.3. Severity of Relapse

Severity of an Investigator-Reported On-Trial Relapse will be measured by the Optic Spinal Impairment Score (OSIS) (Section 10.12; Appendix 12). The OSIS Visual Acuity (VA) Subscale Scores will be used to categorize the severity of ON. The OSIS Motor Subscale Scores and Sensory Subscale Scores will be used to categorize the severity of TM. OSIS score will be assessed by the Investigator at the time of the relapse.

Table 10: Relapse Severity as Measured by Optic Spinal Impairment Scale

Optic Neuritis		
Visual Acuity Subscale Score (taken from the eye with the largest change at the time of the event)		**Relapse Descriptor**
Pre-Relapse	**Post-Relapse**	
0-1	0-2	Minor
0-1	3+	Major
2-7	Increase by 1 point	Minor
2-7	Increase by ≥ 2 points	Major
Transverse Myelitis		
Motor Subscale Score		**Relapse Descriptor**
Pre-Relapse	**Post-Relapse**	
0-1	0-2	Minor
0-1	3+	Major
2-6	Increase by 1 point	Minor
2-6	Increase by ≥ 2 points	Major
Sensory Subscale Score		**Relapse Descriptor**
Based on proprioceptive loss only	If severe loss in ≥ 1 or more limbs with prior normal function or with mild proprioceptive loss	Major

4.2.4. Investigator

The Investigator will be responsible for the overall patient management including patient eligibility evaluation, supervision of study drug administration, recording and treating the adverse events (AEs) and monitoring of safety assessment. At the time of a relapse, the Investigator will perform a complete neurologic examination, determine if a patient experiences a relapse, and may treat the patient's relapse according to the recommended regimen for treatment of On-Trial Relapse described in Section 6.6.1.3. Treatment for relapse, as well as any changes in the ISTs following relapse, are at the discretion of the Investigator.

4.2.5. The Expanded Disability Status Scale Rater

The blinded EDSS Rater will be responsible for performing the EDSS assessments throughout the study including at the time of a relapse. The EDSS Rater must remain blinded to all other study data as well as all other patient clinical data. The EDSS Rater will perform a complete Kurtzke neurologic examination, as described in Section 10.9; Appendix 9 and document the Functional Systems Score (FSS) and the EDSS score (Kurtzke, 1983). When possible, the EDSS Rater should be a physician. If a non-physician EDSS Rater (eg, specialized nurse) will be used, the rater must be approved by the Sponsor before performing the assessments. For specific requirements for EDSS Rater qualification, refer to the training materials.

Table 11 below provides roles and responsibilities of Investigator and EDSS Rater.

Table 11: Roles and Responsibilities of the Investigator and EDSS Rater

Investigator	EDSS Rater
At protocol-specified timepoints: • Determine patient eligibility for the study • Overall patient management during the study, including study drug administration and safety assessments.	**At protocol-specified timepoints:** • Kurtzke neurological assessment • Document FSS • Record EDSS score
At the time of relapse: • Initial patient assessment • Have the EDSS Rater record Functional Systems (FS) and EDSS score[a] • Perform a complete neurologic examination • Determine if the patient has experienced an On-Trial Relapse • Determine relapse severity by OSIS • Assess VA[a], confrontational visual field, and color vision • Assess ambulation by HAI[a] • Have the patient/Proxy complete the EQ-5D-Y / EQ-5D-Y Proxy • Have the patient/Proxy complete the PedsQL/PedsQL Proxy • Treat relapse	**At the time of relapse:** • Perform the Kurtzke neurologic assessment • Document FSS • Record EDSS score

[a] Can be performed by the Investigator or a designee

Abbreviations: EDSS = Expanded Disability Status Scale; EQ 5D Y / EQ 5D-5L = Euro Quality of life-5 Dimensions-Youth; FSS = Functional Systems Score; HAI = Hauser Ambulatory Index; OSIS = Optic spinal impairment score; PedsQL = Pediatric Quality of Life Inventory; VA = Visual Acuity

4.2.6. Review of Investigator-Reported On-Trial Relapses

While Investigator-Reported On-Trial Relapses will be used to determine the primary endpoint, all relapses will be independently reviewed by the Relapse Adjudication Committee (RAC). The Committee, consisting of medical experts, who have particular expertise in NMOSD, will conduct independent reviews for all relapse events identified by the Investigators. The Committee will decide by majority vote whether each Investigator-Reported On-Trial Relapse meets the objective criteria for an On-Trial Relapse. A separate Charter will document all adjudication criteria and procedures for this study.

4.3. Scientific Rationale for Study Design

In NMOSD, the measurable, biological aspects include relapse and disability. Disability in NMOSD is a direct consequence of relapse, supporting the relevance of measuring relapses as the primary endpoint in ECU-NMO-303. During the EMEA NMO Workshop held in October

2014, a consensus was achieved regarding the use of time to first relapse (TFR) as the primary endpoint for adult pivotal studies to demonstrate efficacy of new compounds developed in NMOSD. However, no agreement regarding the primary endpoint to be used in pediatric studies has been reached, highlighting differences in clinical study methodology for the 2 populations.

In this long-term, single-arm study, the occurrence of relapses is evaluated using the co-primary endpoints ARR and TFR. The effect of eculizumab on the reduction of frequency of relapses will be measured using the ARR, with the change in On-Trial ARR compared to the Historical ARR. Time to first relapse also provides useful information regarding the efficacy of eculizumab. In clinical practice, many neurologists initiate, change, or modify treatment following a relapse. Since effectiveness of a treatment can be based on delaying and/or reducing the occurrence of relapses, TFR is an appropriate co-primary efficacy endpoint for prospectively designed studies in NMOSD (Weinshenker, 2015a; Weinshenker, 2015b). A Kaplan-Meier graphical analysis will be performed to illustrate the TFR from the start of eculizumab treatment.

4.4. Justification for Dose

The doses of eculizumab to be administered in this study have been selected based on the results of a modeling and simulation study completed to support the planned body weight-categorized dose regimens, described below.

The demonstration of pharmacokinetic (PK)-bridging between patients aged ≥ 18 years with atypical hemolytic uremic syndrome (aHUS) and NMOSD was critical to the selection of dose regimens for pediatric patients with NMOSD; while substantial data has been generated for pediatric patients with aHUS, there is no prior PK data from pediatric patients with NMOSD. The successful PK-bridging enabled extrapolation of all pediatric aHUS data and the corresponding PK model to pediatric patients with NMOSD. Simulations using the aHUS-PK model and NMOSD-PK model, respectively, demonstrated the comparability of eculizumab serum concentration time profiles between patients with aHUS and patients with NMOSD for body weight ≥ 40 kg.

Demonstrating pharmacodynamic (PD) bridging between patients aged ≥ 18 years with aHUS/paroxysmal nocturnal hemoglobinuria (PNH) and those with NMOSD was also important. Using PK and PD data from patients aged ≥ 18 years and pediatric patients with aHUS and patients aged ≥ 18 years and pediatric patients with PNH, the PK/PD (hemolysis) analysis identified an eculizumab threshold concentration range of 50-100 µg/mL to achieve complete inhibition of hemolysis.

Using PK and PD data from patients aged ≥ 18 years with NMOSD from Study ECU-NMO-301, the PK/PD analysis of hemolysis or free complement 5 (C5) identified an eculizumab threshold serum concentration of 85 µg/mL to achieve complete inhibition of hemolysis, which is within the range (50-100 µg/mL) identified above in aHUS. Therefore, the PD bridging was successfully demonstrated between the 2 indications.

In both aHUS and NMOSD-PK models, body weight was identified as the only important covariate; therefore, categorical body weight-based dosing is recommended in the pediatric population. The body weight exponent for the aHUS-PK model was used, because the aHUS-PK model leveraged the prior pediatric PK data within the weight range of interest.

The aHUS-PK model was used to simulate eculizumab concentration time profiles for pediatric patients with NMOSD. The simulation results showed that, overall, the proposed dosing regimens essentially maintained therapeutic levels of eculizumab, across the body weight categories. Hence, the proposed body weight-categorized dosing regimens are expected to achieve immediate, sustained, and complete inhibition of terminal complement in pediatric patients with NMOSD.

Complete and sustained inhibition of complement activity will be confirmed with PK/PD data derived from this study.

The dosing regimen will be based on the pediatric patient's body weight (Table 13). Body weight is expected to change during this pediatric study; therefore, a patient's weight cohort may change during the study.

4.5. End of Study Definition

A patient is considered to have completed the study if:

- The patient has completed all periods of the study including the last visit of the Extension Period and, if applicable, the Safety Follow-up Visit, *or*
- In the event the study is terminated early by the Sponsor, the patient has completed all applicable periods of the study including the EOS Visit and Safety Follow-up Visit.

The end of the study is defined as the date of the last visit of the last patient (including the Safety Follow-up, if applicable) in the study.

5. STUDY POPULATION

The study population will be comprised of pediatric patients with NMOSD who are 2 to < 18 years of age and who meet the study entry criteria listed below. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Demographic Characteristics

1. Male or female patients aged 2 years to < 18 years at time of assent/consent.
2. Male or female patients with body weight ≥ 10 kg.

Type of Participant and Disease Characteristics

3. Vaccinated against *N meningitidis* within 3 years prior to, or at the time of initiating eculizumab. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive appropriate prophylactic antibiotics until 2 weeks after the vaccination.
4. Documented vaccination against Hib and *S pneumoniae* infections at least 2 weeks prior to dosing as per local and country-specific immunization guidelines for the appropriate age group.
5. Anti-AQP4 Ab-positive and diagnosis of NMOSD as defined by the 2015 IPND criteria (Section 10.6; Appendix 6).
6. Historical Relapse Rate (as defined by protocol, Section 4.2.1) of at least 2 relapses in the last 2 years, and with at least 1 relapse in the year prior to Screening.
7. Expanded Disability Status Scale score ≤ 7 (Section 10.9; Appendix 9).
8. Patients who enter the study receiving supportive IST(s) (eg, corticosteroid, azathioprine [AZA], mycophenolate mofetil [MMF], methotrexate [MTX], tacrolimus [TAC], cyclosporin [CsA], or cyclophosphamide [CYC]) for the prevention of relapse, either in combination or monotherapy, must be on a stable dosing regimen of adequate duration prior to Screening, as follows, and remain on a stable dosing regimen during the Screening Period:
    a. If patients who enter the study are receiving AZA, they must have been on AZA for ≥ 6 months and have been on a stable dose for ≥ 2 months prior to Screening.
    b. If patients who enter the study are receiving other ISTs (eg, MMF, MTX, CsA, TAC, or CYC), they must have been on the IST for ≥ 3 months and have been on a stable dose for ≥ 4 weeks prior to Screening.
    c. If patients who enter the study are receiving oral corticosteroids, they must have been on a stable dose for ≥ 4 weeks prior to Screening.
    d. If a patient has recently discontinued any of the above medications, a period of time equal to the stable dose requirement listed above for that medication (eg, ≥ 2 months

for AZA or ≥ 4 weeks for corticosteroids) must have passed prior to the first day of the Screening Period.

9. For patients who enter the study receiving corticosteroid therapy, the daily dose of corticosteroids must not exceed 0.5 mg/kg/day of prednisone or equivalent and in no case may the dose exceed 20 mg/day.
10. Female patients of childbearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG]) at Screening (Section 10.4; Appendix 4).
11. Female patients of childbearing potential (ie, have achieved menarche) must follow protocol-specified contraception guidance for avoiding pregnancy while on treatment and for 5 months after the last dose of eculizumab (Section 10.4; Appendix 4).
12. Male patients with a female spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use double barrier contraception (male condom plus appropriate barrier method for the female partner) while on treatment and for at least 5 months after the last dose of eculizumab (Section 10.4; Appendix 4).

Informed Consent

13. Willing and capable to give informed assent (if applicable, as determined by the central Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and in accordance with local requirements) and whose parent/legal guardian are willing and able to give written informed consent, as described in Section 10.1.2; Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Demographic Characteristics

1. Parent or legal guardian is an Alexion employee.

Medical Conditions

2. Pregnant, breastfeeding, or intending to conceive during the course of the study.
3. Patients known to be human immunodeficiency virus (HIV) positive or with congenital immunodeficiency.
4. Unresolved meningococcal or other serious infection.
5. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
6. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the patient's full participation in the study, pose any additional risk for the patient, or confound the assessment of the patient or outcome of the study.
7. Hypersensitivity to murine proteins or to one of the excipients of eculizumab.

Prior/Concomitant Therapy

8. Use of rituximab within 6 months prior to Screening.
9. Patient is currently treated with a biologic medication that may affect immune system functioning, or has stopped treatment with a biologic medication that may affect immune system functioning, and 5 half-lives of the medication have not elapsed by the time of the Screening Visit, unless otherwise specified in the protocol.
10. Use of mitoxantrone within 3 months prior to Screening.
11. Use of intravenous immunoglobulin (IVIg) or plasma exchange (PE) within 3 weeks prior to Screening.
12. Use of immunomodulatory therapies for MS including: interferon beta-1b, interferon beta-1a, glatiramer acetate, natalizumab, alemtuzumab, and fingolimod within 3 months prior to Screening.

Prior/Concurrent Clinical Study Experience

13. Participation in any other investigational drug study or exposure to an investigational drug or device within 30 days of Screening or within 5 half-lives of that investigational product, whichever is greater.
14. Has previously received treatment with eculizumab or other complement inhibitors.

5.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria, and any serious adverse event (SAE).

A patient who experiences a relapse that meets the protocol definition of an On-Trial Relapse (Section 4.2) during the Screening Period will be considered a Screening failure. Such patients may be rescreened with Sponsor approval (once they are treated for relapse and considered medically stable by the Investigator). At least 30 days of clinical stability must exist prior to enrollment. The patient must meet the enrollment criteria at Re-Screening in order to enter the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor.

6. STUDY DRUG

The study drug, eculizumab, will be manufactured and supplied by Alexion or a contract manufacturing organization in single 30 mL vials as a solution concentration of 10 mg/mL. Each vial contains 300 mg of eculizumab for intravenous (IV) administration. Eculizumab will be individually packaged in kits. Both vials and kits will be labeled according to the protocol and local regulatory requirements.

Study drug orders will be released to each site upon receipt of all required documents based upon applicable regulations. Details are provided in the Pharmacy Manual.

6.1. Study Drug Administered

Eculizumab is formulated at pH 7 and each 30 mL vial contains 300 mg of eculizumab, polysorbate 80 (6.6 mg) (vegetable origin), sodium chloride (263.1 mg), sodium phosphate dibasic (53.4 mg), sodium phosphate monobasic (13.8 mg), and Water for Injection, US Pharmacopeia (USP). Additional details are provided in Table 12.

Table 12: Study Drug Administered

Product Name	Eculizumab
Dosage Form	Concentrate for solution for infusion
Unit Dose	300 mg
Route of Administration	Intravenous infusion
Physical Description	30 mL vial
Manufacturer	Alexion or a contract manufacturing organization

Study drug will be administered, according to the pediatric patient's body weight, as indicated in Table 13. Body weight is expected to change during this pediatric study; therefore, a patient's weight cohort may change during the study.

Table 13: Weight-Based Dosing Regimen of Eculizumab

Weight Cohort[a,c]	Induction Period[b]	Maintenance Phase
≥ 40 kg	900 mg weekly × 4 doses	1200 mg at Week 4; then every 2 weeks
30 to < 40 kg	600 mg weekly × 2 doses	900 mg at Week 2; then every 2 weeks
20 to < 30 kg	600 mg weekly × 2 doses	600 mg at Week 2; then every 2 weeks
10 to < 20 kg	600 mg weekly × 1 dose	300 mg at Week 1; then every 2 weeks

[a] Day 1 and maintenance period dose regimen will be based on the current visit's recorded body weight. If site/institutions policies prohibit study drug to be prepared on the day of visit, the weight from the most recent study visit should be used. If a patient is receiving an infusion at a remote facility or at home, the weight from the prior study visit may be used to calculate the dose.

[b] During the initial induction period, the dose regimen will be based on the patient's weight on Day 1 (Visit 2).

[c] All patients will remain in the same weight cohort throughout the induction period, regardless of change in weight.

Notes:

- Dosage and treatment regimen are based on results of a modelling and simulation study.
- Eculizumab will be administered by IV infusion.

Abbreviations: IV = intravenous.

6.2. Supplemental Doses

If the patient undergoes PE/plasmapheresis (PP) for an Investigator-Reported On-Trial Relapse on a day that study drug administration is not routinely scheduled, a supplemental dose of eculizumab (Table 14) must be administered, preferably within 1 to 2 hours, after each PE/PP. If PE/PP is administered on the day of regularly scheduled study drug administration, there would not be any supplemental dose given and patients will receive the regularly scheduled number of vials, preferably within 1 to 2 hours, after each PE.

If the patient receives PE/PP and study drug infusion at the Relapse Evaluation Visit, 3 blood samples for PK, PD and free C5 should be collected at the following intervals:

1. Approximately 5 to 90 minutes prior to PE/PP
2. After PE/PP and before study drug infusion
3. At least 60 minutes after the completion of study drug infusion

If a patient receives PE/PP at any visit other than the Relapse-Evaluation Visit, blood samples for PK, PD, and free C5 assays will be collected immediately before and after each session of PE/PP. A peak sample, (ie, 1 hour after completion of supplemental study drug infusion), will also be collected.

Table 14: Supplemental Dosing Regimen of Eculizumab for Plasma Exchange/Plasmapheresis

Type of Intervention	Most Recent Eculizumab Dose	Supplemental Eculizumab Dose With Each Plasma Exchange/ Plasmapheresis Intervention	Timing of Supplemental Eculizumab Dose
Plasmapheresis (PP) or Plasma Exchange (PE)	300 mg	300 mg/each PP or PE session	Within 1 to 2 hours after each PE or PP session
	600 mg or more	600 mg/each PP or PE session	

6.3. Preparation/Handling/Storage/Accountability

6.3.1. Study Drug Storage

Upon arrival at the center, the study drug should be promptly removed from the shipping cooler and stored in refrigerated conditions between 2°C to 8°C (36°F to 46°F). The study drug must be stored in a secure, limited-access storage area, and temperature must be monitored daily. On-site storage temperature excursions must be reported to the Sponsor in a timely manner.

Diluted solutions of study drug (dosing solutions) may be stored between 2°C to 8°C (36°F to 46°F) and/or at room temperature for a maximum of 24 hours. The 24-hour expiration includes preparation time, storage time, warming time, and infusion time. The solution should be allowed to warm to room temperature prior to administration. The material must not be heated (eg, by using a microwave or other heat source) other than by ambient air temperature.

Refer to the Pharmacy Manual for additional instructions.

6.3.2. Study Drug Preparation

Infusions of study drug should be prepared using aseptic technique. Each vial of study drug contains 300 mg of active ingredient in 30 mL of product solution. Withdraw the required amount of study drug from the vials. Transfer the recommended dose to an infusion bag. Dilute the study drug to a final concentration of 5 mg/mL by addition to the infusion bag of the appropriate amount (equal volume) of 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP); 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP. The final volume of a 5 mg/mL diluted study drug solution is 60 mL for 300 mg doses (1 vial), 120 mL for 600 mg doses (2 vials), 180 mL for 900 mg doses (3 vials), and 240 mL for 1200 mg doses (4 vials) as shown in Table 15.

Table 15: Study Drug Reconstitution

Study Drug	Volume of Study Drug	Volume of Diluent[a]	Total Volume of Administration
300 mg (1 vial)	30 mL	30 mL	60 mL
600 mg (2 vials)	60 mL	60 mL	120 mL
900 mg (3 vials)	90 mL	90 mL	180 mL
1200 mg (4 vials)	120 mL	120 mL	240 mL

[a] Choose one of the following diluents: 1) 0.9% sodium chloride; 2) 0.45% sodium chloride; 3) 5% dextrose in water; 4) Ringer's injection

Gently invert the infusion bag containing the diluted study drug solution to ensure thorough mixing of the product and diluents. Discard any unused portion left in a vial, as the product contains no preservatives. The diluted solution should be allowed to warm to room temperature by exposure to ambient air prior to administration.

6.3.3. Study Drug Administration

Doses of study drug must only be prepared and dispensed by qualified study personnel. Study drug is to be dispensed only to enrolled patients who are confirmed eligible for participation in this study. Once study drug is prepared for a patient, it can only be administered to that patient. Vials of study drug are for one-time use only, and any drug product remaining in the vial must not be used for another patient. Any drug remaining in the infusion tubing or infusion bag should not be used for another patient. Further details on preparation and dose administration of eculizumab, as well as disposal of the study drug, can be found in the Pharmacy Manual.

Drug must be administered at the study site during the initial 12/13 weeks of the study. Drug may be administered at a medical facility located near or at the patient's home during the Primary Treatment Period and Extension Period according to the SoA, Section 1.2. Remote visit options will be at the Investigator's discretion and oversight, in accordance with the local regulations, and conducted by a qualified medical professional. Information about AEs, concomitant medications, and signs or symptoms of NMOSD relapses will be sent to the Investigator's site for evaluation on the day of the remote visit. In case of any signs or symptoms indicating an SAE or NMOSD relapse, the patient will need to be evaluated at the study site.

Study drug should only be administered via IV infusion, using a weight-based schedule (Section 6.1). **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.**

Prior to study drug administration, the diluted solution should be allowed to warm to room temperature by exposure to ambient air. The diluted solution must not be heated in a microwave or with any heat source other than ambient air temperature. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

The diluted study drug should be IV administered over 1 to 4 hours in pediatric patients. For those patients who reach ≥ 18 years of age during the study, the study drug should be administered IV over 35 (± 10) minutes. It is not necessary to protect the infusion bags from light while study drug is being administered to the patient. The patient should be monitored for at least 1 hour following infusion.

If an AE occurs during administration of the study drug, the infusion may be slowed or stopped at the discretion of the Investigator, depending upon the nature and severity of the event; however, the overall duration should not exceed 2 hours from the start of the infusion in patients aged ≥ 18 years and 4 hours from the start of infusion in pediatric patients. The AE must be captured in the patient's source document and electronic case report form (eCRF).

The actual start and stop times of all dose administrations will be recorded in the patient's source documents and eCRF. Refer to the Pharmacy Manual for additional directions on study drug administration.

Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the infusion, and for at least 1 hour after patients have completed their infusion.

6.3.4. Study Drug Accountability

When a study drug shipment is received at the site, the pharmacist should verify the contents, sign the packing invoice provided with the shipment, and maintain the original copy for review by the study monitor. Additionally, reception of study drug (as well as reception conditions) must be reported to the Interactive Response Technology (IRT) system to allow drug randomization, resupply, estimations, and drug expiration control.

Unless notified otherwise, empty vials and vials with residual materials should be kept for inspection and accountability by the study monitor prior to their destruction or handled per local pharmacy standard operating procedures (SOPs) for clinical study drugs. Destruction of used and unused vials, either locally or centrally, must be properly documented. Drug accountability will be managed through the IRT system and detailed instructions on managing the IRT drug accountability module will be included in the IRT User Guide. The pharmacist or designee must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (patient-by-patient accounting), and accounts of any study drug accidentally or deliberately destroyed. These drug accountability records must be readily available upon request, and will be reviewed throughout the study.

Each kit will have a label and a place for the pharmacist to record the patient number and initials.

The study monitor will examine the inventory during the study. Additionally, the inventory records must be readily available to regulatory authorities, the local regulatory agency, or an independent auditor's inspection at any time.

Refer to the Pharmacy Manual for additional information.

6.3.5. Study Drug Handling and Disposal

All clinical study material provided to the Investigator will be stored in a secure place, and allocated and dispensed by appropriately trained personnel. Detailed records of the amounts of the study drug received, dispensed, and destroyed will be maintained.

To satisfy regulatory requirements regarding drug accountability, all remaining eculizumab inventory will be reconciled and destroyed or returned to Alexion at the EOS according to applicable regulations.

Refer to the Pharmacy Manual for further information.

6.4. Measures to Minimize Bias

Although this is an open-label, single arm study, the co-primary endpoint, On-Trial ARR, will be compared to the patient's Historical ARR, allowing patients to act as their own controls. Additionally, while the primary endpoint will be assessed based on Investigator reported relapses, the RAC will also adjudicate all relapses.

6.5. Study Intervention Compliance

The infusion of study drug into patients will be under the supervision of the Investigator or their designee to ensure that the patients received the appropriate dose at the appropriate timepoints during the study.

If a patient fails to return, or is otherwise unavailable, for a scheduled visit within the acceptable visit window (± 2 days), the site study staff must make a reasonable attempt to contact the patient/patient's parent or guardian to determine the reason for missing the appointment. Patients should be advised to return to the investigational site for evaluation, if relapse or an AE is suspected to have occurred. In this event, the investigational site will make a reasonable attempt to obtain all relevant medical records, and enter relevant data in the eCRF, as appropriate.

6.6. Concomitant Therapy

Prior medications (including vitamins and herbal preparations), including those discussed in the exclusion criteria (Section 5.2), and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the patient takes or undergoes within the 30 days prior to the start of Screening until the first dose of study drug, will be recorded in the patient's eCRF. In addition, history of meningococcal, Hib, and *S pneumoniae* vaccinations and ISTs (including steroids) must be collected.

All medications used and procedures undertaken during the study will be recorded in the patient's source document/medical chart and eCRF. This record will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and any other current medications. When possible, concomitant medications will be recorded from the first infusion of study drug until the patient has discontinued or completed the study. Any changes in concomitant medications also will be recorded in the patient's source document/medical chart and eCRF. Any concomitant medication deemed necessary for the patient's standard of care during the study, or for the treatment of any AE, along with any other medications, other than those listed as disallowed medications in Section 6.6.2, may be given at the discretion of the

Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full in the patient's source document/medical chart and eCRF.

6.6.1. Allowed Medication

6.6.1.1. Palliative and Supportive Care

Palliative and supportive care is permitted during the course of the study for underlying conditions.

6.6.1.2. Immunosuppressive Therapy

Patients who enter the study receiving supportive IST(s) (eg, corticosteroid, AZA, MMF, MTX, TAC, CsA, or CYC) for the prevention of relapse, either in combination or monotherapy, must be on a stable dosing regimen of adequate duration prior to Screening as follows:

a. If patients who enter the study are receiving AZA, they must have been on AZA for ≥ 6 months and have been on a stable dose for ≥ 2 months prior to Screening.

b. If patients who enter the study are receiving other ISTs (eg, MMF, MTX, CsA, TAC, or CYC), they must have been on the IST for ≥ 3 months and have been on a stable dose for ≥ 4 weeks prior to Screening.

c. If patients who enter the study are receiving oral corticosteroids, they must have been on a stable dose for ≥ 4 weeks prior to Screening.

The patient must remain on that dose regimen during the Screening Period and for the Primary Treatment Period (52/53 weeks). During the Primary Treatment Period, the patient's IST dose may be adjusted on the basis of weight/body-surface/age to account for the child's growth. No other adjustment in IST dosage and no new ISTs will be permitted, unless the patient experiences a relapse or a safety event, and a change in IST dose would be deemed necessary by the Investigator to guarantee the patient's safety.

Once the patient completes the Primary Treatment Period or experiences a relapse, there are no restrictions on ISTs used for relapse prevention; the dose and/or type of IST may be changed, supplemented, or discontinued and new medications may be added, as long as any new medications are not prohibited medications. In the event that a change in the dose or dosing regimen is considered due to a known toxicity or side-effects associated with the given IST, the Sponsor should be notified of the potential change.

The restriction on ISTs during the Primary Treatment Period is only applicable to ISTs used for relapse prevention. Concomitant use of ISTs (eg, the use of IVIg for the treatment of parvovirus B19 infection, or concurrent administration of intravenous methylprednisolone [IVMP] with antivirals for the treatment of herpes simplex virus) to treat underlying conditions, is not restricted during the study.

The choice of IST agents is at the discretion of the Investigator with the exception of disallowed medications (Section 6.6.2). Standard recommended dosing should be used for the chosen IST. Use of corticosteroids is permitted; however, the total daily dose must not exceed 0.5 mg/kg/day of prednisone or equivalent and in no case may the dose exceed 20 mg/day.

6.6.1.3. Treatment of On-Trial Relapse

During this study, the treatment of relapse is at the discretion of the Investigator. The following is an example of a standardized treatment regimen for an On-Trial Relapse, in accordance with expert opinion (Kimbrough, 2012). However, the ultimate treatment regimen and order will be determined by the Investigator:

- 30 mg/kg (not to exceed 1 gram) IVMP administered daily for 3-5 days followed by oral prednisone tapering. If the patient improves, then continue the study assessments as per schedule of this protocol.
- If there is no or minimal response to IVMP, PE/PP will be allowed at the discretion of the treating neurologist.
- If a patient undergoes PE/PP for an On-Trial Relapse during the Treatment Period, a supplemental dose of study drug should be administered after each PE/PP, preferably within 1-2 hours (Section 6.2). After receiving the supplemental dose, patients are to continue protocol-specified dosing.

6.6.2. Disallowed Medications and Therapies

The following medications and therapies, except when used in the treatment of On-Trial Relapse (Section 6.6.1.3) or when permitted by the Investigator and Sponsor, if applicable, are prohibited during the study:

- Mitoxantrone
- Rituximab or other biologicals that affect immune system functioning, such as tocilizumab
- IVIg for relapse prevention
- PE for relapse prevention
- Use of immunomodulatory therapies including: interferon beta-1b; interferon beta-1a, glatiramer acetate, natalizumab, alemtuzumab, and fingolimod.

6.7. Dose Modification

Not applicable.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A patient may withdraw from the study at any time at his/her own request, or at the request of the parent/guardian, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. If a patient discontinues treatment from the study, the Investigator will attempt to perform (if the patient agrees) assessments specified for the ET Visit, or if not possible, a Safety Follow-up phone call to be conducted 8 weeks after the last dose of study drug has been administered (SoA, Section 1.2). The Sponsor and site monitor will be notified as soon as possible. If a patient is withdrawn from the study or withdraws consent no further data will be collected. Patients who withdraw from the study will not be replaced.

Patients should be discontinued from study drug if any of the following occur during the study:

1. Serious hypersensitivity reaction (such as bronchospasm with wheezing or requiring ventilator support or symptomatic hypotension, or serum sickness-like reactions manifesting 1 to 14 days after study drug administration);
2. Use of disallowed medication as defined in Section 6.6.2;
3. Pregnancy or planned pregnancy; or
4. Sponsor deems it is in the best interest of the patient.

The Investigator should contact the Alexion Medical Monitor prior to discontinuing a patient from study drug. If a patient discontinues from treatment, the patient is required to complete an ET Visit (SoA, Section 1.2) and a Safety Follow-up Visit 8 weeks from the date the patient's last dose of study drug was administered.

The reason for the treatment discontinuation (ie, patient withdraws consent, patient withdrawal from procedures, physician decision, AE, or other reason specified in eCRF) will be recorded in the eCRF.

If a female patient is permanently discontinued from study drug due to pregnancy, the Investigator will make a reasonable attempt to follow-up, in accordance with local laws and regulations, until the outcome of the pregnancy is known (Section 10.4; Appendix 4).

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use all data collected before such a withdrawal of consent.

If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records as well as inform the site monitor and Sponsor.

7.2. Lost to Follow Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to participate in a required study visit:

1. The site must attempt to contact the patient or the patient's parent(s) and/or guardian(s) and reschedule the missed visit as soon as possible and counsel the patient or the patient's parent(s) and/or guardian(s) on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient or the patient's parent(s) and/or guardian(s) wishes to and/or should continue/allow the patient to continue in the study.
2. Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
3. Should the patient continue to be unreachable, the patient will be considered to have withdrawn consent and future missed visits will not be considered protocol deviations.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Efficacy Assessments

All efficacy assessments will be administered according to the SoA (Section 1.2). The efficacy assessments that are age-appropriate for a patient at the start of the study will be used for that patient throughout the study. Change in age during the study will not constitute a patient changing the type of survey completed (eg, for patients aged ≥ 2 years to < 5 years, the Pediatric Quality of Life Inventory [PedsQL] parent proxy will be used throughout the study).

8.1.1. Annualized Relapse Rate

Baseline ARR for all patients will be calculated using Historical Relapse data for each patient in the 2-year period prior to Screening for this study. The On-Trial ARR for the Primary Treatment Period will be calculated for the time period from the first dose of eculizumab through Week 52/53 or ET from the Primary Treatment Period. All Investigator-Reported On-Trial Relapses will additionally be adjudicated by the RAC as part of a sensitivity analysis, as described in Section 9.5.1.

8.1.2. Time to First Relapse

Time to First Relapse will be measured, in days, beginning at the time the patient's first dose of eculizumab is administered until the patient's first On-Trial Relapse is reported by the Investigator. All Investigator-Reported On-Trial Relapses will additionally be adjudicated by the RAC as part of a sensitivity analysis, as described in Section 9.5.1.

8.1.3. Neurologic Examination

A complete general neurologic examination will be performed at the appropriate visits. The complete general neurologic examination will include assessments of the following systems: mental status, fundus examination, cranial nerves, deep tendon reflexes, plantar responses, power/strength, sensation, coordination, and gait/balance. For consistency, all efforts should be made to have the neurologic examination performed by the same qualified study staff at these visits.

8.1.4. Expanded Disability Status Scale

The 10-point Kurtzke EDSS is a widely accepted clinical disability scale (Section 10.9; Appendix 9). For this study, the Neurostatus EDSS (minorly modified from the original Kurtzke EDSS) will be used.

The EDSS is considered the standard for monitoring patients with NMOSD, including those in NMOSD clinical research, although NMOSD is difficult to assess because of the differences in signs and symptoms.

The EDSS assigns a severity score to the patient's clinical status using FSS that evaluate dysfunction in the following 7 functional systems (FS):

- Pyramidal
- Cerebellar
- Brainstem
- Sensory
- Bowel and bladder
- Visual
- Cerebral

The FS are scored on a scale of 0 (low level of problems) to 5 or 6 (high level of problems) to best reflect the level of disability observed clinically.

In contrast, the total EDSS score is determined by 2 factors: gait and FS scores. EDSS scores below 4.0 are determined by the FS scores alone. People with EDSS scores of 4.0 and above may have some degree of gait impairment. Scores between 4.0 and 9.5 are determined by both gait abilities and the FS scores. For simplicity, many experts gauge the EDSS scores between 4.0 and 9.5 entirely by gait, without considering the FS scores. The EDSS is widely used and accepted as a valid tool to clinically measure and evaluate level of functioning in patients with NMOSD (Kurtzke, 1983). This assessment will be used for all patients ≥ 5 years old.

8.1.5. Hauser Ambulation Index

The Hauser Ambulation Index (HAI) is a rating scale developed to assess mobility by evaluating the time and degree of assistance required to walk 25 feet (Section 10.10; Appendix 10). Patients are asked to walk a marked 25-foot course as quickly and safely as possible. The examiner records the time and type of assistance (eg, cane, walker, crutches) needed. The rating scale also has categories for patients who are unable to walk.

Although the patient's walking is timed, the time is not used directly but is utilized in conjunction with other factors to rate the patient on an ordinal scale with 11 gradations (Bethoux, 2011). This assessment will be performed for all patients in this study.

8.1.6. Visual Acuity

Visual acuity is usually affected by ON, progressing over a period of hours to days. The Snellen chart (Section 10.13; Appendix 13) or the LEA symbols eye chart (Section 10.14; Appendix 14) will be used to assess VA. The Snellen chart quantifies ability to read letters of varying sizes at a fixed distance in relation to the distance at which a patient with normal vision could read the same letters. The test is performed at a standard distance, typically 6 meters or 20 feet. The Snellen chart is typically recorded as acuity ratio distance (6 meters or 20 feet), so for normal VA it would be recorded as 20/20 or 6/6. Sometimes this is entered as the denominator of the Snellen fraction (in US) or as a decimal (ex-US). The test should always be done with the best possible correction (ie, wearing glasses) as needed. Patients will continue to be evaluated based on the survey initially completed upon entry into the study. Note: A LEA symbols eye chart will be used in patients who are aged 2-5 years.

8.1.7. Ophthalmologic Examination

8.1.7.1. Confrontational Visual Fields

The ophthalmological examination will evaluate confrontational visual fields (VF). It is critical for these assessments that the Baseline ophthalmologic status be known so that changes in the examination can be used to evaluate prior or ongoing ON. Central scotomas are common in patients experiencing ON; however, visual field defects can present with a broad spectrum of patterns (Keltner, 1999). This assessment will be performed for all patients in this study.

8.1.7.2. Color Vision

Color vision will be assessed using Ishihara Plates. This will be assessed in all patients in this study. Loss of color vision can be a marker of ON and is therefore an important assessment tool in NMOSD.

8.1.8. Investigator-Reported On-Trial Relapse

Patients will be monitored for On-Trial Relapses throughout the study. The Investigator or a designee will review, in detail, the signs and symptoms of a potential relapse with the patient at each visit. Patients will be educated on the potential signs and symptoms of NMOSD relapse, and will be instructed to contact the study site at the first sign or symptom of a potential relapse. Patients should be evaluated within 24 hours of notification of signs or symptoms suggestive of a potential relapse, and no later than 48 hours. The evaluation of On-Trial Relapses will include:

- Complete neurological examination to determine whether the clinical signs, symptoms and examination findings meet the definition of an On-Trial Relapse (Section 4.2.2).
- Assessment of relapse severity based on the OSIS (Section 10.12; Appendix 12).
- Evaluation of the neurological FS based on the Kurtzke's FSS and the disability level based on the EDSS score (Section 10.9; Appendix 9).
- Ambulatory function assessment using the HAI (Section 10.10; Appendix 10).
- Ophthalmological examination including VA (Section 10.13; Appendix 13 and Section 10.14; Appendix 14), confrontational VF, and color vision.
- MRI +/- gadolinium and/or OCT Examinations should be performed to evaluate a potential relapse, at discretion of the Investigator.
- Additional tests are included in the SoA (Section 1.2).
- If the event is confirmed as an Investigator-Reported On-Trial Relapse, the patient will be treated at the discretion of the Investigator. An example of a standardized treatment regimen for an Investigator-Reported On-Trial Relapse Treatment regimen is included in Section 6.6.1.3.

The evolution of the relapse will be assessed during the Relapse Evaluation Period at 1, 4, and 6 weeks after the relapse onset. Additional unscheduled Relapse Evaluation Visits are

permitted at the discretion of the Investigator. Eculizumab administration will be continued as outlined in the protocol dose administration schedule.

Following the relapse, the patient may continue in the study, or may exit, based on the Investigator's discretion.

An independent RAC will review all Investigator-Reported On-Trial Relapse events using the protocol-defined criteria and a consistent process outlined in the RAC Charter. For more details refer to the RAC Section 9.5.1.

8.1.9. Optic Spinal Impairment Score

The OSIS will be used as a scoring system for the severity of a relapse. The OSIS VA Subscale Scores will be used to categorize the severity of ON. The OSIS Motor Subscale Scores and Sensory Subscale Scores will be used to categorize the severity of TM. OSIS score will be assessed by the Investigator at the time of the relapse. (Section 10.12; Appendix 12).

8.1.10. Pediatric Quality of Life Inventory

The PedsQL is a brief, standardized, generic assessment instrument that systematically assesses patients' and their parents' perceptions of health-related quality of life (HRQOL) in pediatric patients with chronic health conditions using pediatric cancer as an exemplary model. The PedsQL is based on a modular approach to measuring HRQOL and consists of a 15-item core measure of global HRQOL and 8 supplemental modules assessing specific symptom or treatment domains. The PedsQL was empirically derived from data collected from 291 pediatric cancer patients and their parents at various stages of treatment (Section 10.11; Appendix 11). Items are reverse scored and linearly transformed to a 0-100 scale, so that higher scores indicate better HRQOL. The test is designed for self-completion in patients aged ≥ 5 years by respondents (with 3 age-appropriate PedsQL tests available for ages 5-7, 8-12, and 13-18 years old), and by a Proxy in patients aged ≥ 2 to < 5 years. Attempts should be made to have the same proxy complete the evaluation at each visit.

8.1.11. Euro Quality of Life-5 Dimensions-Youth

The European Quality of Life (EuroQoL)-5D-Youth (EQ-5D-Y) is based on the EQ-5D and is designed for use in patients aged ≥ 4 to < 18 years. The EQ-5D-Y will be used in this study for self-completion in patients enrolled between the ages ≥ 8 to < 18 years by respondents, and by a Proxy in patients enrolled between the ages ≥ 5 to < 8 years. Attempts should be made to have the same proxy complete the evaluation at each visit. Children < 5 years will not have EQ-5D-Y assessed in the study.

The EQ-5D-Y consists of 2 pages: the EQ-5D-Y descriptive system (page 2) and the EQ visual analog scale (EQ VAS) (page 3). The descriptive system comprises the same 5-component scale as the EQ-5D-5L, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, but uses child-friendly wording (ie, mobility, looking after myself, doing usual activities, having pain or discomfort, feeling worried, sad, or unhappy). Each dimension has 3 levels and is rated on a scale that describes the degree of problems in that area: "no problems", "some problems", "a lot of problems" with Level 1 indicating the lowest degree of problems and Level 3 indicating the greatest degree of problems. Respondents are asked to

indicate their health state by ticking (or placing a cross) in the box that best describes their health status.

The EQ-5D VAS is an overall health scale where the rater selects a number between 0-100 to describe the condition of their health, with 100 being 'The best health you can imagine' and 0 being 'The worst health you can imagine'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. Previously published studies by EuroQoL Group members showed preliminary evidence of the instrument's feasibility, reliability and validity (Wille, 2010) (Section 10.7; Appendix 7 and Section 10.8; Appendix 8).

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.2).

8.2.1. Physical Examination

A physical examination will include assessments of the following organs/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, pulse, chest, heart, abdomen, extremities; musculoskeletal and general neurologic examination. A targeted physical examination consists of a body-system relevant examination based upon Investigator judgment and patient symptoms. For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff.

8.2.2. Vital Signs

Vital signs will be measured at every visit and will include assessments of systolic and diastolic blood pressure (BP) (mm Hg), temperature (°C or °F), respiratory rate (RR), and heart rate (HR) (beats/minute). Vital signs will be obtained after the patient has been supine or seated for at least 5 minutes. Ideally, each patient's BP should be measured using the same arm.

8.2.3. Electrocardiograms

A single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (Section 1.2) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Patients must be supine for approximately 5-10 minutes before ECG collection and remain supine but awake during ECG collection.

The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be recorded on the eCRF.

8.2.4. Clinical Safety Laboratory Assessments

Laboratory assessments will be tested at a central laboratory facility. Any clinically significant abnormal results should be followed until resolution or stabilization.

All protocol-required laboratory assessments, as defined in Section 10.2; Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.2).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Clinically significant abnormal laboratory findings associated with the underlying disease are not considered AEs unless they are judged by the Investigator to be more severe than expected for the patient's condition.

If such values do not return to normal or the Baseline level within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported to the Investigator or qualified designee by the patient (or when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative). All observed or volunteered AEs, regardless of Treatment Group or causal relationship, will be reported by the Investigator. The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study drug (Section 7). For each AE however, only the Investigator will be responsible for assessing seriousness, severity, and relationship of the AE to study drug.

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3; Appendix 3.

8.3.1. Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

All AEs will be collected from the signing of the ICF until the last visit (Safety Follow-up Visit) of the Extension Period, as specified in Table 7. In the event the patient discontinues or completes the study prior to the end of the extension period, the last visit will be considered to be the 8-week Safety Follow-up Visit.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 10.3; Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of the updated information being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3; Appendix 3.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is given in Section 10.3; Appendix 3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- The Investigator must notify the Sponsor of an SAE within 24 hours of the first awareness of the event.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- The Council for International Organizations of Medical Sciences (CIOMS) or MedWatch reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) (Section 10.3; Appendix 3) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and acknowledge the report and notify the IRB/IEC, if appropriate, according to local requirements.

8.3.5. Pregnancy

Contraception guidance that must be followed for the study duration is detailed in Section 10.4; Appendix 4.

For female patients of childbearing potential, a serum or urine pregnancy test (ie, beta-HCG) will be performed as indicated in the SoA (Section 1.2). A negative pregnancy test is required prior to administering eculizumab to patients of childbearing potential.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4; Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and should be reported as described in Section 10.3; Appendix 3.

8.3.6. Vaccine and Antibiotic Prophylaxis

As with any terminal complement antagonist, the use of eculizumab increases the patient's susceptibility to meningococcal infection (*N meningitidis*). To reduce the risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within the 3 years prior to, or at the time of, initiating study drug.

- Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
- Patients must be vaccinated against *N meningitidis* serotypes A, C, Y, W-135, and B, where available, to prevent common pathogenic meningococcal serotypes.
- Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, eculizumab).
- Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given per official guidance and local practice on the appropriate use of antibacterial agents.
- All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

In addition to meningococcal vaccination, patients must be vaccinated against Hib and *S pneumoniae* at least 2 weeks prior to initiating study drug according to local and country-specific immunization guidelines for each age group, and strictly adhere to the national vaccination recommendations for each age group.

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the patients during the course of the study patients will be provided a Patient Safety Information Card to carry with them at all times. Additional discussion and explanation of the potential risks, signs, and symptoms will occur at each visit as part of the review of the patient safety card as described in the SoA (Section 1.2).Vaccination(s) for *N meningitidis,* Hib*,* and *S pneumoniae* will be recorded on the patient's eCRF.

8.4. Pharmacokinetics

Blood samples will be obtained to assess pre- and post-treatment serum eculizumab concentrations at the timepoints and within the windows indicated in the SoA (Section 1.2). Pharmacokinetic parameters such as maximum concentration and concentration after the first dose, and during the induction and maintenance treatment phase will be obtained. Clearance and terminal half-life will be estimated.

Baseline PK samples will be collected 5-90 minutes prior to the first dose, and peak samples will be collected 60-120 minutes after the first dose and at other timepoints in the SoA. An intermediate blood sample will also be collected 24 hours after completion of the first dose.

For the sample collected at 24 hours, there will be a window of ± 1 hour for collecting the sample. The date and exact time of collection must be recorded on the eCRF and the central laboratory requisition form.

Samples obtained outside of the allotted windows will be considered protocol deviations. Unused samples may be retained for a period of up to 5 years to perform additional assessments as necessary.

Additional details on sample collection, including blood volume requirements, are provided in the Laboratory Manual.

8.5. Pharmacodynamics

Blood samples will be obtained to assess pre- and post-treatment serum hemolytic activity and, therefore, C5 complement activity inhibition at the timepoints and within the windows indicated in the SoA (Section 1.2).

Baseline PD samples will be collected 5-90 minutes prior to the first dose, and peak samples will be collected 60-120 minutes after the first dose and at other timepoints in the SoA. An intermediate blood sample will also be collected 24 hours after completion of the first dose.

For the sample collected at 24 hours, there will be a window of ± 1 hour for collecting the sample. The date and exact time of collection must be recorded on the eCRF and the central laboratory requisition form.

Samples obtained outside of the allotted windows will be considered protocol deviations. Unused samples may be retained for a period of up to 5 years to perform additional assessments as necessary.

Additional details on sample collection, including blood volume requirements, are provided in the Laboratory Manual.

8.6. Genetics

Genetics will not be evaluated in this study.

8.7. Biomarkers

Blood samples for assay of the AQP4-Ab will be collected at Screening and other timepoints as specified in the SoA (Section 1.2).

8.7.1. Exploratory biomarkers

Exploratory biomarkers of PD effect may include, but are not limited to, change from baseline in levels of markers of complement dysregulation, neuroinflammation (eg, interleukin [IL]-6), and neural injury (eg, neurofilament light chain [NfL]). Additional assessments may include biomarkers related to disease activity/progression or treatment response.

8.8. Healthcare Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, may be collected by the Investigator or designee for all patients throughout the study. Data will be recorded in the eCRF. Protocol-required procedures, tests, and encounters will be excluded.

The data collected may be used to conduct exploratory economic analyses and may include:

- Number of medical care encounters, including outpatient visits, emergency room visits, surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization

- Number and type of diagnostic and therapeutic tests and procedures

8.9. Blood Sample Volumes

Blood will be collected for clinical safety laboratory, PK, PD and biomarker assessments. In accordance with the guidance set forth by the EU, the required blood draw for all pediatric patients treated on this study will not exceed 1% of total blood volume in a single 24-hour period or 3% of total blood volume over a 4-week period.

The minimum required blood volume (in mL) to be collected by weight cohort and study visit is presented in Table 16.

Table 16: Minimum Required Blood Volumes Collected by Weight Cohort and Study Visit

Weight Cohort	Study Visit									
	Screen	**Day 1**	**Wk 1**	**Wks 4 and 7**	**Wk 12/ 13**	**Wk 26 / 27**	**Wk 40 / 41**	**Wk 52 / 53**	**Wks 76 / 77, 100 /101, 124 /125, 148 / 149**	**ET / EOS**
10 to < 20 kg	4.5	8.6	2.4	3.4	7.9	8.9	7.9	8.9	4.5	8.9
20 to > 40 kg	4.5	8.6	2.4	3.4	8.9	8.9	7.9	8.9	4.5	8.9

Note: All minimum volumes are reported in mL.
Abbreviation: ET = end of treatment; EOS = end of study; Wk = week

If a patient has an Investigator-assessed relapse, additional blood samples will be collected. The minimum required blood volume (in mL) to be collected by weight cohort and relapse evaluation visit is presented in Table 17.

Table 17: Minimum Required Blood Volumes Collected Following a Relapse by Weight Cohort and Relapse Evaluation Visit

Weight Cohort	Relapse Visit (24-48 hours)	Relapse Visit (Week 1)	Relapse Visit (Week 4)	Relapse Visit (Week 6)
10 to < 20 kg	7.9	3.4	3.4	8.9
20 to > 40 kg	7.9	3.4	3.4	8.9

Note: All minimum volumes are reported in mL.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

The primary hypothesis for this study is:

Eculizumab significantly reduces ARR as compared to Baseline ARR.

The study will be considered to have met its primary efficacy endpoint if a statistically significant p-value (<0.05) is observed for the change in ARR between the Baseline ARR and the Primary Treatment Period ARR (as reported by the Investigator) in favor of eculizumab treatment using the Wilcoxon signed rank test.

9.2. Sample Size Determination

Approximately 12 patients will be enrolled to achieve the minimum of 10 evaluable patients. Of the 10 evaluable patients, at least 3 of the patients will be aged 2 to < 12 years at the time of enrollment, and at least 5 patients will be aged 12 to < 18 years at the time of enrollment.

In this pediatric study, patients will act as their own controls. As such the Historical ARR, which will be called the Baseline ARR, will be compared with the ARR of the patient while on eculizumab during the Primary Treatment Period. A sample size of 12 patients (10 evaluable patients) will provide approximately 85% power to detect a statistically significant treatment effect of eculizumab to reduce the ARR, assuming a 2-sided significance level of 0.05, by the Wilcoxon signed rank test, and a dropout rate of 15%. The sample size calculation also assumes a Baseline ARR of at least 1 relapse/year. Likewise, the sample size calculation also assumes an eculizumab-treated ARR of 0.082 relapse/year with a standard deviation of the difference in relapse rates of 0.8 relapses/year, based on Study ECU-NMO-301, which was a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the safety and efficacy of eculizumab in patients aged ≥ 18 years with anti-AQP4 Ab-positive NMOSD.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Full Analysis Set (FAS)	The FAS includes all patients who have received at least 1 dose of eculizumab.
Safety Analysis Set	The Safety Analysis Set includes all patients who have received at least 1 dose of eculizumab.
PK/PD Analysis Set	The PK/PD Analysis Set includes all patients who have received at least 1 dose of eculizumab and have PK/PD data assessments during the study.

9.4. Statistical Analyses

Summary statistics will be computed and displayed by visit where applicable. Descriptive statistics for continuous variables will minimally include the number of patients, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. Graphical displays will be provided as appropriate. All statistical

analyses will be performed based on a 2-sided Type I error of 5% unless noted otherwise. Missing data will not be imputed.

The statistical analysis plan (SAP) will be developed and finalized prior to the primary analysis and will provide further details. The primary analysis will be conducted when all patients have completed the 52/53-week Primary Treatment Period or discontinued prior to the completion of the Primary Treatment Period. This analysis will include all efficacy, safety, and PK/PD study data for regulatory submission purpose. Another SAP will be developed and finalized prior to the completion of the entire study (including the Extension Treatment Period). Additional interim analyses during the Extension Treatment Period may be performed at the discretion of the Sponsor.

Analyses will be performed using the SAS® software Version 9.4 or higher.

9.4.1. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized for the Safety Analysis Set. Summary statistics will be presented. No formal hypothesis testing will be performed.

9.4.2. Patient Disposition

The number of patients screened and the number of patients in different analysis sets will be summarized. The number and percentage of patients discontinued will be summarized along with reasons for discontinuation in the Safety Analysis Set.

The number and percentage of patients with important protocol deviations will be summarized overall and by prespecified deviation categories.

9.4.3. Medical/Surgical History and Neuromyelitis Optica Spectrum Disorder History

The medical and surgical history will be summarized by the Medical Dictionary for Regulatory (MedDRA) Activities, Version 21.0, or later by System Organ Class (SOC) and Preferred Term. NMOSD History will also be summarized.

9.4.4. Prior and Concomitant Medications

For analysis and reporting purpose, any medication started prior to first dose of study drug will be considered as prior medications; and medications that were taken on or after the first dose of study drug will be considered as concomitant medications. Prior and concomitant medications will be summarized for all patients in the Safety Analysis Set. Medications will be coded using the World Health Organization Drug Dictionary (WHODrug; the most current version available at the time of the analyses).

9.4.5. Efficacy Analyses

Efficacy analyses will be performed on the FAS.

9.4.5.1. Primary Efficacy Analysis

Primary Treatment Period

The primary efficacy endpoint is the change from baseline in the ARR at 52/53 weeks. Baseline ARR for all patients will be calculated using Historical Relapse data for each patient in the 2-year period prior to Screening for this study. Baseline ARR will be compared to rates calculated for the On-Trial ARR, the time period from the first dose of eculizumab through Week 52/53 or ET from the Primary Treatment Period. The study will be considered to have met its primary efficacy endpoint if a statistically significant p-value (<0.05) is observed for the change in ARR between the Baseline ARR and the Primary Treatment Period ARR (as reported by the Investigator) in favor of eculizumab treatment using the Wilcoxon signed rank test.

The TFR and the percentage of patients who are relapse-free while on eculizumab treatment along with 95% confidence intervals will be computed using the Kaplan-Meier method. Time to First Relapse results will be considered descriptive; no adjustments for multiplicity will be made.

A sensitivity analysis will be performed for the change in ARR between the Baseline ARR and the adjudicated Investigator-Reported On-Trial ARR using a Wilcoxon signed rank test. The percentage of patients who are relapse-free while on eculizumab treatment in Study ECU-NMO-303 along with 95% confidence intervals will also be computed using the Kaplan-Meier method for the adjudicated On-Trial Relapses. Summaries of the primary efficacy endpoints by age subgroups (Baseline age 2 to < 12 years and age 12 to < 18 years) may be also be produced.

Extension Treatment Period

The On-Trial ARR for the final analysis of the study and any interim analyses of the Extension Treatment Period will be calculated for the On-Trial Treatment Period, the time from the first dose of eculizumab through the last dose of study drug. Further computational details will be included in the interim and/or final SAPs.

9.4.5.2. Secondary Efficacy Analysis

Secondary endpoints are as follows.

- Change from Baseline in EDSS score at 52/53 weeks in patients ≥ 5 years of age.
- Change from Baseline in the HAI score at 52/53 weeks in all patients.
- Change from Baseline in PedsQL scores at 52/53 weeks in patients ≥ 5 years of age.
- Change from Baseline in PedsQL Parent Proxy at 52/53 weeks in patients < 5 years of age.
- Change from Baseline in VA as measured by the Snellen or LEA symbols Eye Chart examination at 52/53 weeks in all patients.
- Change from Baseline in Confrontational VF as measured during ophthalmologic examination at 52/53 weeks in all patients.
- Change from Baseline in color vision as measured during ophthalmologic examination at 52/53 weeks in all patients.

Baseline is defined as the last available assessment prior to the first dose of eculizumab.

Changes from Baseline for the continuous secondary efficacy endpoints will be summarized at the Week 52/53 Visit as well as over the applicable study visits during the Primary Treatment Period and the Extension Treatment Period. Summaries will include 95% confidence intervals of the median. Continuous secondary efficacy endpoints include the EDSS, the HAI, and the PedsQL scores. Summaries will be presented by instrument (eg, Parent Proxy PedsQL, and Self-Reported PedsQL).

Visual Acuity, Confrontational VF, and Color Vision assessments will be summarized as frequencies and percentages at each applicable study visit and as shifts from Baseline to each study visit.

Further details of the summaries and analyses for these endpoints will be described in the SAP.

9.4.5.3. Tertiary Efficacy Analysis

The tertiary endpoint is as follows:

- Change from Baseline in the EQ-5D-Y/EQ-5D-Y Proxy score at 52/53 weeks.

Relapse severity is determined by OSIS score and will be summarized. Further details of the analyses of the tertiary endpoints for the analysis of the Primary Treatment Period and the Extension Treatment Period will be described in the SAP.

9.4.6. Safety Analyses

The safety and tolerability of eculizumab will be assessed based on the following:

- Incidence of treatment-emergent adverse events (TEAEs), SAEs, and AEs leading to study drug discontinuation.
- Incidence of ADA.
- Changes from Baseline in vital signs, ECG parameters, and clinical laboratory assessments.
- Growth and development: change from Baseline in both weight and height.

All safety analyses will be performed on the Safety Analysis Set.

9.4.6.1. Analysis of Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AE with onset during or after the first dose of study drug. Summary tables will include patient counts and percentages and will be presented as separate tabulations for all adverse events, SAEs, adverse events leading to treatment discontinuation or withdrawal, and adverse events leading to death.

9.4.6.2. Analysis of Clinical Laboratory Parameters, Vital Sign Measurements, and Electrocardiogram Parameters

Laboratory measurements as well as their changes from Baseline at each visit and shift from Baseline, if applicable, will be summarized descriptively. Significant ECG and vital signs will also be summarized using descriptive statistics.

9.4.6.3. Other Safety Analyses

Changes from Baseline in growth parameters (height and weight) will be summarized by visit. Immunogenicity as measured by ADA will be summarized in tabular form and in a by-patient listing.

9.4.7. Pharmacokinetics/Pharmacodynamics

Pharmacokinetic and PD assessments will be made at the timepoints indicated in the SoA. The PK, PD and biomarker exploratory analyses will be described in the SAP. The population PK analysis and PD analysis will be performed according to a separate analysis plan and the results presented separately from the main clinical study report (CSR).

The PK/PD parameters of interest for the study include:

- Maximum plasma drug concentration (C_{max})
- Terminal half-life ($t_{½}$)
- Trough (concentration at the end of the dosage interval [C_{trough}])
- Clearance
- Change in serum Free C5 concentration
- Change in the in vitro hemolytic activity

9.5. Interim Analyses

Additional interim analyses during the Extension Treatment Period may be performed at the discretion of the Sponsor.

The SAP will describe the planned interim analyses in greater detail.

9.5.1. Data Monitoring and Relapse Adjudication Committees

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will conduct interim monitoring of safety data.

The DMC will have access to all safety data. The DMC may make recommendations to the Sponsor regarding safety issues, study conduct, and modifying, extending, or stopping the study.

In addition, the DMC will receive reports concerning patients who have discontinued. Notification of study discontinuation and reason for the discontinuation will be sent to the DMC according to the schedule defined in the Charter. The DMC will also review summaries of all relapses.

A separate DMC Charter will document all DMC procedures for this study.

Relapse Adjudication Committee

The role of the Relapse Adjudication Committee (RAC) will be to determine whether an Investigator-Reported On-Trial Relapse meets the protocol definition of a relapse by rendering a Yes/No decision through the adjudication process. The RAC will be comprised of 3 members: a

Chair and 2 additional individuals, all of whom will have expertise in NMOSD. A separate Charter will define the structure, responsibilities, and membership of the RAC, outline the process for RAC review of study data, and outline the procedures for adjudication of an Investigator-Reported Relapse.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient and/or his/her legally authorized representative and answer all questions regarding the study.
- Patients and their guardians/legal representatives must be informed that the patient's participation is voluntary. Patients or their legally authorized representative [parent or other legal guardian] will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- As used in the protocol, the term "informed consent" includes all informed assent given by patients, informed permission by legally authorized representative, or, as applicable, informed consent by the patient during study participation.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the patient's legally authorized representative.
- A patient who is rescreened is not required to sign another ICF unless an updated ICF is available.

10.1.3. Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

Study-related information and study results may be posted on the US National Institutes of Health website www.clinicaltrials.gov, the EU website www.clinicaltrialsregister.eu/, or other publicly accessible websites as appropriate and in accordance with local regulations.

10.1.5. Data Quality Assurance

- All patient data relating to the study will be recorded on printed case report forms (CRFs) or eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. Study monitors will communicate with investigative sites on a regular basis regarding the study and all protocol deviations will be appropriately documented by the Investigator or designee, and study monitors.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigative site.
- The Investigator or designee will prepare and maintain adequate and accurate source documents (medical records, ECGs, AE and concomitant medication reporting, and raw data collection forms) designed to record all observations and other pertinent data for each patient.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.7. Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at their sole discretion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator

- Discontinuation of further eculizumab development

10.1.8. Publication Policy

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Study Agreement.

10.2. Appendix 2: Clinical Laboratory Tests

Chemistry Panel	**Complete Blood Count and Differential**
Sodium	White blood cell count
Potassium	White blood cell differential
Chloride	Red blood cell count (RBC)
Bicarbonate	RBC mean corpuscular volume
Blood urea nitrogen	RBC distribution width
Creatinine	Hemoglobin
Glucose	Hematocrit
Alkaline phosphatase	Platelet count
Alanine amino transferase	**Other**
Aspartate amino transferase	Human chorionic gonadotropin (urine pregnancy test)
Total bilirubin	Anti-aquaporin 4 (AQP4) antibody
Albumin	Pharmacokinetics
Total protein	Pharmacodynamics
Uric acid	Free complement component 5
Urinalysis	Anti-drug antibody
Appearance	
Specific gravity	
PH	
Protein	
Blood	
Glucose	
Ketone	
Bilirubin	
Urobilinogen	
Nitrite	

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study drug are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.

10.3.2. Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- **Results in death**
- **Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

- **Results in persistent disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.
This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**
- **Other situations:**

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

10.3.3. Suspected Unexpected Serious Adverse Reactions

Suspected Unexpected Serious Adverse Reactions Definition

Suspected unexpected serious adverse reactions are serious events that are not listed in the IB and that the Investigator identifies as related to study drug or procedure. The US 21CFR312.32 and EU Clinical Trial Directive 2001/20/EC and the associated detailed guidance documents or national regulatory requirements in participating countries require the reporting of SUSARs. Alexion has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance documents. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs/IECs where applicable.

10.3.4. Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording

- When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to Alexion or designee in lieu of completion of the AE/SAE report. If applicable, additional information such as relevant medical records, should be submitted with a signed SAE cover page to Alexion Global Pharmacovigilance (GDS) via ClinicalSAE@alexion.com or via Facsimile: + 1.203.439.9347. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before sending to Global Pharmacovigilance (GDS).
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Adverse Event and Serious Adverse Event Recording

Assessment of Event Severity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5 or higher. Each CTCAE term is a Lowest Level Term (LLT) per MedDRA. Each LLT will be coded to a MedDRA Preferred Term:

1. Grade 1: Mild (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)
2. Grade 2: Moderate (minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living [ADL])
3. Grade 3: Severe (severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL)
4. Grade 4: Life-threatening (urgent intervention indicated)
5. Grade 5: Fatal (death related to AE)

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met specific criteria for an SAE as described above.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study drug and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related (unrelated): This relationship suggests that there is no causal association between the study drug and the reported event.
  - Related: This relationship suggests that there is causal association between the investigational product and the reported event.
- The Investigator will use clinical judgment to determine the relationship to the study drug.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- This protocol will use the current IB as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor, based on the Reference Safety Document. The Investigator will also consult the IB in his/her assessment.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Alexion or designee. However, **it is very important that the Investigator always makes an assessment of causality for every event before the transmission of the SAE data to Alexion GDS.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion or designee with a copy of any postmortem findings including histopathology, if available.
- The site will enter new or updated SAE data into the electronic system as soon as it becomes available, but no later than 24 hours. The Investigator will submit any updated SAE data to the GDS within 24 hours of awareness of the information.

10.3.5. Reporting of Serious Adverse Events

Serious Adverse Event Reporting to Alexion or Designee via the RAVE Safety Gateway

All SAEs must be reported to Alexion GDS within 24 hours of the Investigator or site staff awareness. These timelines for reporting SAE information to the Sponsor need to be followed for the initial SAE report and for all follow-up SAE information.

The Investigator or designee must record the SAE data in the eCRF and verify the accuracy of the information with corresponding source documents. The SAE report should be submitted electronically via the RAVE Safety Gateway.

In the event that either the electronic data capture (EDC) or the RAVE Safety Gateway is unavailable at the site(s), the SAE must be reported on the paper SAE Contingency Form accompanied by an Investigator signed cover page. Facsimile transmission or email may be used in the event of electronic submission failure.
For all SAEs, the Investigator must provide the following:

- Appropriate and requested follow-up information in the time frame detailed below
  - Causality of the SAE(s).
  - Treatment of/intervention for the SAE(s).
  - Outcome of the SAE(s).
  - Supporting medical records and laboratory/diagnostic information.
  - The primary mechanism for reporting an SAE to Alexion or designee will be the RAVE Safety Gateway.
- If the electronic system is unavailable at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE reporting via facsimile or email. Facsimile transmission or email may be used in the event of electronic submission failure.
  Email: clinicalsae@alexion.com
  Facsimile: + 1.203.439.9347
- As soon as the EDC becomes available, the data should be entered in the eCRF and forwarded to Alexion GDS via the RAVE Safety Gateway.
- When further information becomes available, the eCRF should be updated with the new information and an updated SAE report should be submitted to Alexion GDS via the RAVE Safety Gateway.
- After the study is completed at a given site, the EDC will be taken offline to prevent the entry of new data or changes to existing data.
- If a site identifies a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form to Alexion GDS.

SAE Reporting to Alexion or Designee via Paper Contingency Case Report Form

- If applicable, additional information such as relevant medical records should be submitted to Alexion GDS via the email address or facsimile number noted above.
- All paper forms and follow-up information submitted to the Sponsor outside of the RAVE Safety Gateway (eg, discharge summary) should be kept in the appropriate section of the study file.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, secondary amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Female patients of childbearing potential and male patients with female partners of childbearing potential, pregnant, or breastfeeding, must use effective methods of contraception (as defined below), starting at Screening and continuing for at least 5 months after the last dose of study drug.

Highly effective contraceptive methods include:

1. Hormonal contraception associated with inhibition of ovulation at least 6 weeks prior to Day 1
2. Intrauterine device
3. Intrauterine hormone-releasing system
4. Bilateral tubal occlusion
5. Vasectomized partner, provided the partner is the patient's sole sexual partner
6. Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug treatment; reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

Acceptable contraceptive methods include:

7. A combination of male condom with either a cap, diaphragm, or sponge with spermicide (double barrier methods)

The above-listed method(s) of contraception chosen for an individual patient can be determined by the Investigator with consideration for the patient's medical history and concomitant medications.

10.4.3. Pregnancy Testing

Women of childbearing potential should only be included after a menstrual period and a negative highly sensitive serum pregnancy test.

Additional pregnancy testing should be performed per the timepoints specified in the SoA (Section 1.2).

10.4.4. Collection and Reporting of Pregnancy Information

1. Pregnancy data will be collected during this study for all patients and a female spouse/partner of male patients. Exposure during pregnancy (also referred to as exposure *in utero*) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.
2. If a female patient or a male patient's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be asked to provide the information.
3. Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding") and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile.

4. Pregnancy in itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs (Section 8.3.5).
5. Any female patient who becomes pregnant while participating in the study will be discontinued from study drug.

10.5. Appendix 5: Standard Protocol Definitions

Historical Relapse

Historical relapses are the relapses that occurred prior to the Screening Visit, including the first NMOSD attack. For this protocol, Historical Relapse is defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination (clinical findings or MRI findings or both) that persisted for more than 24 hours and/or the new onset of neurologic symptoms or worsening of existing neurologic symptoms that required treatment. Treatment is defined as use of high-dose IV steroids, PE, or IVIg. Events that occur within a 30-day interval are considered as 1 relapse.

On-Trial Relapse

On-Trial Relapses are acute attacks that occur during the study. For this protocol, On-Trial Relapse is defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on neurologic examination that persists for more than 24 hours as confirmed by the Investigator. The signs and symptoms must be attributed to NMOSD, ie, not caused by an identifiable cause such as infection, excessive exercise, or excessively high ambient temperature. Isolated changes on MRI or other imaging investigation with no related clinical findings is not considered an On-Trial Relapse. The relapse must be preceded by at least 30 days of clinical stability. The Investigator is not required to wait 24 hours prior to initiating treatment for the relapse.

10.6. Appendix 6: 2015 International Panel for NMO Diagnosis Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder

International Panel for NMO Diagnosis Diagnostic Criteria for NMOSD with AQP4-IgG (Wingerchuk, 2015): All 3 criteria must be met for a diagnosis of NMOSD in this study.

1. At least 1 core clinical characteristic:
    a. Optic neuritis
    b. Acute myelitis
    c. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
    d. Acute brainstem syndrome
    e. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
    f. Symptomatic cerebral syndrome with NMOSD-typical brain lesions visualized on MRI
2. Positive test for anti-AQP4 Ab using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnosis

10.7. Appendix 7: Euro Quality of Life 5 Dimensions-Youth

Describing your health TODAY

Please check the ONE box that best describes your health TODAY.

Mobility *(walking around)*

I have no problems walking around ❑

I have some problems walking around ❑

I have a lot of problems walking around ❑

Taking care of myself

I have no problems taking a bath or shower by myself or getting dressed by myself ❑

I have some problems taking a bath or shower by myself or getting dressed by myself ❑

I have a lot of problems taking a bath or shower by myself or getting dressed by myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

Feeling worried, sad, or unhappy

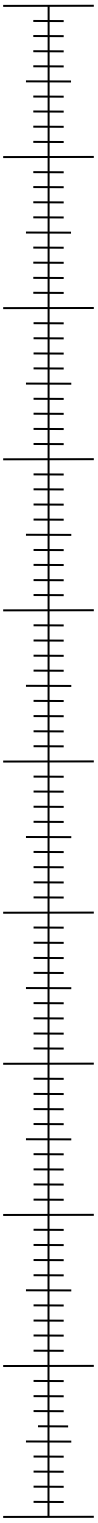
I am not worried, sad, or unhappy ❑

I am a little worried, sad, or unhappy ❑

I am very worried, sad, or unhappy ❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the line to show how good or bad your health is TODAY.



10.8. Appendix 8: Euro Quality of Life 5 Dimensions-Youth (Proxy)

Describing the child's health TODAY

Under each heading, please check the ONE box that **you think** best describes the child's health **TODAY**.

Mobility *(walking around)*

He/she has no problems walking around ❑

He/she has some problems walking around ❑

He/she has a lot of problems walking around ❑

Taking care of him/herself

He/she has no problems taking a bath or shower by him/herself or getting dressed by him/herself ❑

He/she has some problems taking a bath or shower by him/herself or getting dressed by him/herself ❑

He/she has a lot of problems taking a bath or shower by him/herself or getting dressed by him/herself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

He/she has no problems doing his/her usual activities ❑

He/she has some problems doing his/her usual activities ❑

He/she has a lot of problems doing his/her usual activities ❑

Having pain or discomfort

He/she has no pain or discomfort ❑

He/she has some pain or discomfort ❑

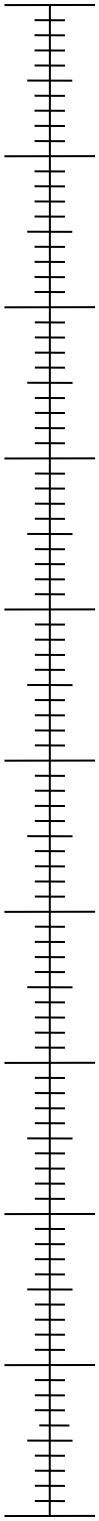
He/she has a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

He/she is not worried, sad or unhappy	❑
He/she is a little worried, sad or unhappy	❑
He/she is very worried, sad or unhappy	❑

The child's health TODAY

- We would like to know how good or bad you think the child's health is TODAY.
- This line is numbered 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the line to show how good or bad **you think** the child's health is **TODAY**.



10.9. Appendix 9: Expanded Disability Status Scale

The Neurostatus EDSS is a method of quantifying disability in MS. The EDSS replaced the previous Disability Status Scales used in MS.

The EDSS quantifies disability in 7 FS and allows neurologists to assign an FSS in each of these. The FS are:

pyramidal

cerebellar

brainstem

sensory

bowel and bladder

visual

cerebral

EDSS steps 1.0 to 4.5 refer to people with MS who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation.

Expanded Disability Status Scale	
0	Normal neurological exam (all FS grade 0)
1.0	No disability, minimal signs in one FS (one FS grade 1)
1.5	No disability, minimal signs in more than one FS (more than one FS grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three / four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one / two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1);or fully ambulatory with five FS grade 2 (others 0 or 1)
4.0	Ambulatory without aid or rest for ≥ 500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps

4.5	Ambulatory without aid or rest for ≥ 300 meters; up and about much of the day, characterized by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
5.0	Ambulatory without aid or rest for ≥ 200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5	Ambulatory without aid or rest for ≥ 100 meters
6.0	Unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting
6.5	Constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting
7.0	Unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

10.10. Appendix 10: Hauser Ambulatory Index

□ 0 = Asymptomatic; fully active.

□ 1 = Walks normally, but reports fatigue that interferes with athletic or other demanding activities.

□ 2 = Abnormal gait or episodic imbalance; gait disorder is noticed by family and friends; able to walk 25 feet (8 meters) in 10 seconds or less.

□ 3 = Walks independently; able to walk 25 feet in 20 seconds or less.

□ 4 = Requires unilateral support (cane or single crutch) to walk; walks 25 feet in 20 seconds or less.

□ 5 = Requires bilateral support (canes, crutches, or walker) and walks 25 feet in 20 seconds or less; *or* requires unilateral support but needs more than 20 seconds to walk 25 feet.

□ 6 = Requires bilateral support and more than 20 seconds to walk 25 feet; may use wheelchair[1] on occasion.

□ 7 = Walking limited to several steps with bilateral support; unable to walk 25 feet; may use wheelchair[1] for most activities.

□ 8 = Restricted to wheelchair; able to transfer self independently.

□ 9 = Restricted to wheelchair; unable to transfer self independently.

[1] The use of a wheelchair may be determined by lifestyle and motivation. It is expected that patients in Grade 7 will use a wheelchair more frequently than those in Grades 5 or 6. Assignment of a grade in the range of 5 to 7, however, is determined by the patient's ability to walk a given distance, and not by the extent to which the patient uses a wheelchair.

10.11. Appendix 11: Pediatric Quality of Life Inventory

10.11.1. Pediatric Quality of Life Inventory Child Form (Age 5 to 7-year-old)

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

YOUNG CHILD REPORT (ages 5-7)
Acute Version

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

PedsQL 2

Think about how you have been doing for the past 7 days. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PHYSICAL FUNCTIONING *(problems with...)*	Not at all	Some-times	A lot
1. Is it hard for you to walk	0	2	4
2. Is it hard for you to run	0	2	4
3. Is it hard for you to play sports or exercise	0	2	4
4. Is it hard for you to pick up big things	0	2	4
5. Is it hard for you to take a bath or shower	0	2	4
6. Is it hard for you to do chores (like pick up your toys)	0	2	4
7. Do you have hurts or aches (***Where?*** _____)	0	2	4
8. Do you ever feel too tired to play	0	2	4

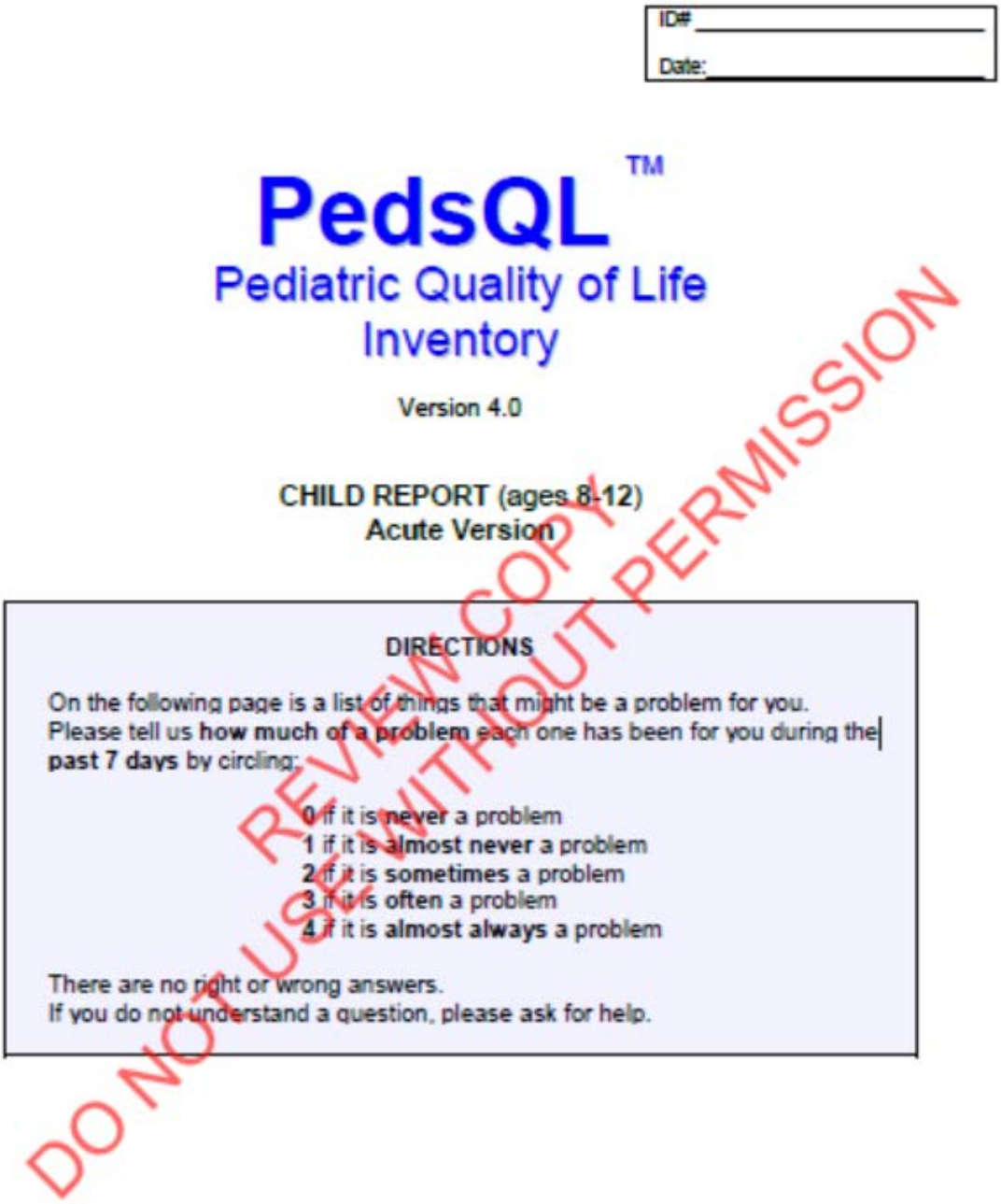
Remember, tell me how much of a problem this has been for you for the past 7 days.

EMOTIONAL FUNCTIONING *(problems with...)*	Not at all	Some-times	A lot
1. Do you feel scared	0	2	4
2. Do you feel sad	0	2	4
3. Do you feel mad	0	2	4
4. Do you have trouble sleeping	0	2	4
5. Do you worry about what will happen to you	0	2	4

SOCIAL FUNCTIONING *(problems with...)*	Not at all	Some-times	A lot
1. Is it hard for you to get along with other kids	0	2	4
2. Do other kids say they do not want to play with you	0	2	4
3. Do other kids tease you	0	2	4
4. Can other kids do things that you cannot do	0	2	4
5. Is it hard for you to keep up when you play with other kids	0	2	4

SCHOOL FUNCTIONING *(problems with...)*	Not at all	Some-times	A lot
1. Is it hard for you to pay attention in school	0	2	4
2. Do you forget things	0	2	4
3. Is it hard to keep up with schoolwork	0	2	4
4. Do you miss school because of not feeling good	0	2	4
5. Do you miss school because you have to go to the doctor's or hospital	0	2	4

10.11.2. Pediatric Quality of Life Inventory Child Form (Age 8 to 12 year-old)



ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages 8-12)
Acute Version

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **7 days**, how much of a problem has this been for you …*

About My Health and Activities *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About My Feelings *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I Get Along with Others *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

About School *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

10.11.3. Pediatric Quality of Life Inventory Child Form (Age 13 to 18 year-old)

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

TEEN REPORT (ages 13-18)
Acute Version

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **7 days**, how much of a problem has this been for you …*

About My Health and Activities *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About My Feelings *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I Get Along with Others *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

About School *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

10.11.4. Pediatric Quality of Life Inventory Parent Proxy Form (For Patients Aged ≥ 2 to < 5 years-old)

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for TODDLERS (ages 2-4)
Acute Version

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **7 days**, how much of a problem has your child had with …*

PHYSICAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Playing with other children	0	1	2	3	4
2. Other kids not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

Please complete this section if your child attends school or daycare

SCHOOL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Doing the same school activities as peers	0	1	2	3	4
2. Missing school/daycare because of not feeling well	0	1	2	3	4
3. Missing school/daycare to go to the doctor or hospital	0	1	2	3	4

10.12. Appendix 12: Optic Spinal Impairment Score

Visual Acuity (VA)

0 Normal
1 Scotoma but VA (corrected) better than 20/30
2 VA 20/30 – 20/59
3 VA 20/60 – 20/100
4 VA 20/101 – 20/200
5 VA 20/201 – 20/800
6 Count fingers only
7 Light perception only
8 No light perception

Motor Function

0 Normal
1 Abnormal signs (hyperreflexia, Babinski sign) without weakness
2 Mild weakness (Medical Research Council grade 5- or 4+) in affected limb(s)
3 Moderate weakness (grade 3 or 4) in 1 or 2 UMN muscles in affected limb(s)
4 Moderate weakness (grade 3 or 4) in 3 UMN muscles in affected limb(s)
5 Severe weakness (grade 2) in 1 or more muscles in affected limb(s)
6 Some plegia (grade 0 or 1) muscles in 1 or more limbs
7 Plegia (grade 0 or 1) of all muscles in 1 or more limbs

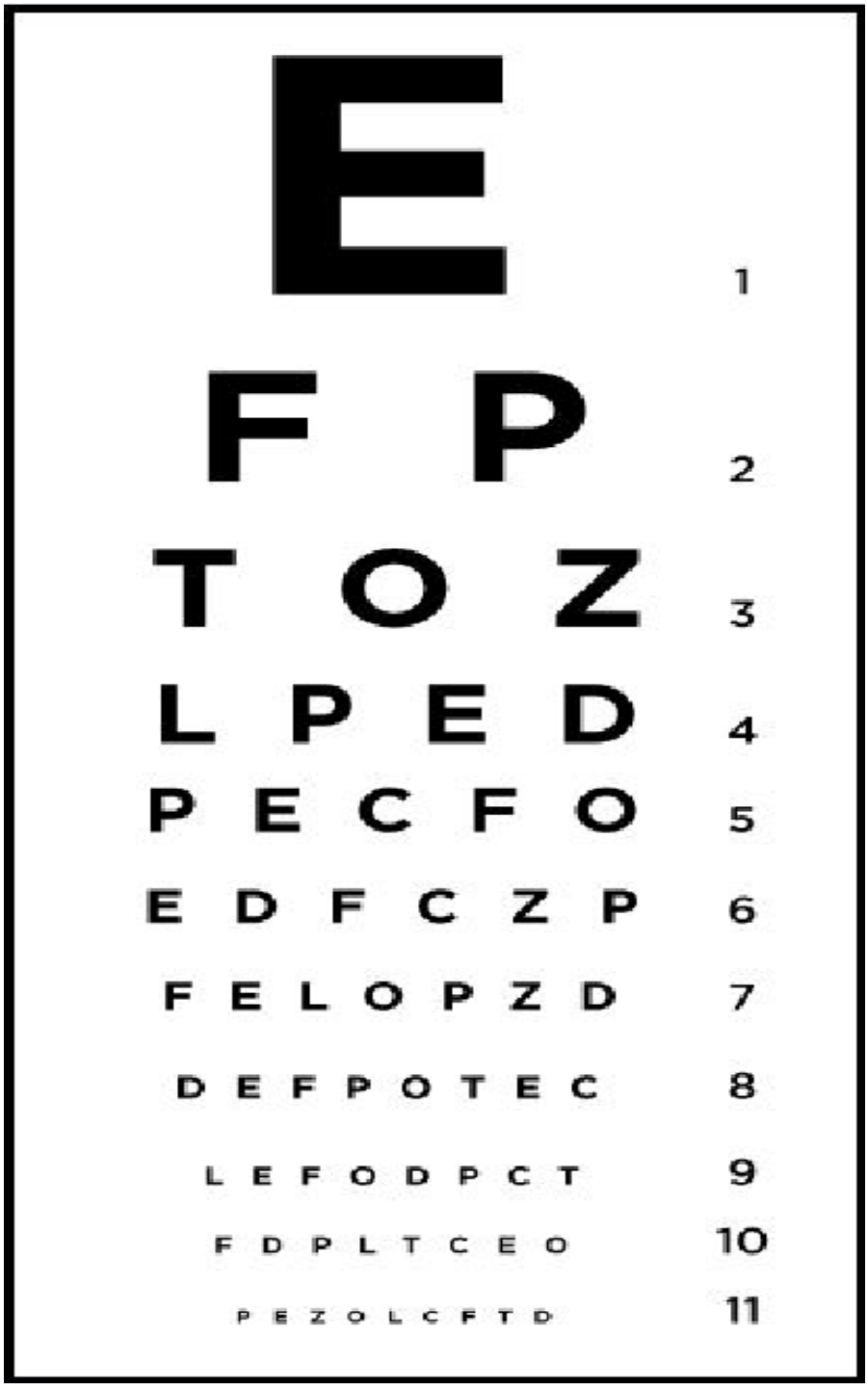
Sensory Function

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 sense
4 Loss of all sensory modalities
5 Unknown

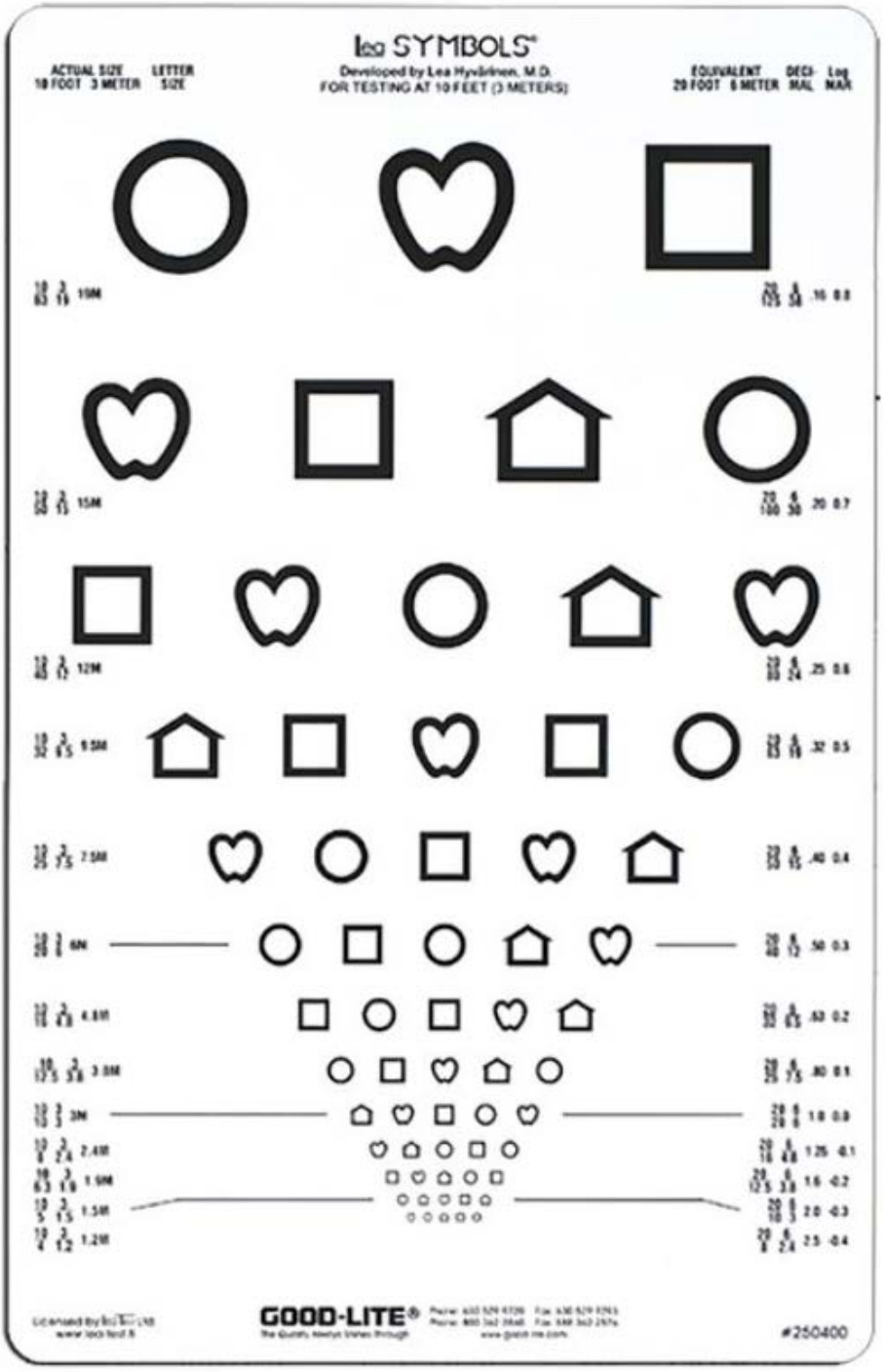
Sphincter Function

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 catheterization or aggressive (manual) bowel assistance
4 Indwelling urinary catheter or absence of sphincter control
5 Unknown

10.13. Appendix 13: Snellen Eye Chart



10.14. Appendix 14: LEA Symbols Eye Chart



10.15. Appendix 15: COVID-19 Risk Assessment

Neuromyelitis optica spectrum disorder is a severe disease that can cause irreversible morbidity, and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a patient may receive from a therapeutic study is potentially significant. In this particular case, the fact that the study is open label and every patient is treated with the study drug also contributes to the potential benefit a patient may derive from participating in the study. However, given that treatment for NMOSD does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in patients not on immunosuppression. There is no specific data to inform this risk further, however. The Principal Investigator will therefore balance the risk/benefit considerations in their patient, taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 18.

Table 18: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Potentially higher risk population for COVID-19 infection	Patients with NMOSD are at times on other immunosuppressants aside from eculizumab. It is unknown how this may impact their risk for COVID-19 infection.	During the time that the COVID-19 pandemic is active, Alexion will recommend that sites in a position to start the study and enroll patients follow the national and institutional guidance regarding prevention of COVID-19 infection. Additionally, in that time period, it is expected that Investigators and their staff will take all possible precautions in order to minimize a patient's potential exposure to COVID-19 infection. Depending on the site, this will consist of measures such as social distancing, temperature screening, enhanced cleaning, and personal protective equipment for patients, staff, and caregivers as necessary.
Healthcare institution availability for non-COVID-19 related activities	COVID-19 may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new patients at sites unless they have the resourcing and capabilities to perform the study as per protocol.

Table 18: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Data integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitoring and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study related activities. During this timeframe, site capacity will be reviewed by the Principal Investigator and the study Medical Monitor prior to screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits or participant study discontinuations due to COVID-19).

Abbreviations: COVID-19 = Coronavirus Disease 2019; eCRF = electronic case report form; NMOSD = neuromyelitis optica spectrum disorder

10.16. Appendix 16: Abbreviations

Abbreviation	Definition
Ab	antibody
ADA	antidrug antibody
ADL	Activities of Daily Living
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
AQP4	aquaporin-4
ARR	annualized relapse rate
AZA	azathioprine
BP	blood pressure
C5	complement component 5
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum plasma drug concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	concentration at the end of the dosage interval
CsA	cyclosporine
CYC	cyclophosphamide
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
EOS	end of study
EQ-5D	European Quality of Life Health 5-item questionnaire
EQ VAS	European Quality of Life Visual Analog Scale
ET	early termination
EuroQoL	European Quality of Life
FAS	full analysis set
FS	functional system(s)
FSH	follicle stimulating hormone
FSS	Functional System Scores
GCP	Good Clinical Practice
GDS	Global Pharmacovigilance
HAI	Hauser Ambulation Index
HCG	human chorionic gonadotropin
Hib	*Haemophilus influenzae* type b
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRQOL	health-related quality of life
HRT	hormonal replacement therapy
IB	Investigator's brochure
ICF	informed consent form

Abbreviation	Definition
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IPND	International Panel for NMO Diagnosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
IST	immunosuppressive therapy
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
LETM	Longitudinally extensive transverse myelitis
LLT	lowest level term
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTX	methotrexate
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorder
OCT	Optical Coherence Tomography
ON	Optic Neuritis
OSIS	Optic Spinal Impairment Score
PD	pharmacodynamic(s)
PE	plasma exchange
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PP	plasmapheresis
QoL	quality of life
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTc	corrected QT interval
RAC	Relapse Adjudication Committee
RBC	red blood cell
RR	respiration rate
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal half-life
TAC	tacrolimus
TEAE	treatment-emergent adverse event
TFR	time to first relapse
TM	transverse myelitis
USP	United States Pharmacopeia
VA	visual acuity
VF	visual field

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