30 March 2023
EMA/182657/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ultomiris

International non-proprietary name: ravulizumab

Procedure No. EMEA/H/C/004954/II/0032

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Antidrug Antibody
(S)AE	(Serious) Adverse Event
aHUS	atypical Hemolytic Uremic Syndrome
AQP4	Anti-aquaporin-4
ARR	Annualized Relapse Rate
AUCss	Area under the serum concentration-time curve at steady state
BLQ	Below the limit of quantitation
BMI	Body Mass Index
C(3)(5)	Complement Component (3) (5)
C5b-9	terminal complement complex
CI	Confidence Interval
CL	Linear Clearance
CNS	Central Nervous System
Cmax,(ss)	maximum observed serum concentration (under steady-state conditions)
Ctrough, (ss)	Concentration at the end of the dosage interval (under steady-state conditions)
COVID-19	coronavirus disease 2019
EDSS	Expanded Disability Status Scale
EQ-5D	European Quality of Life Health 5-dimension Questionnaire
FAS	Full Analysis Set
HAI	Hauser ambulation index
Ig(G)	Immunoglobulin (G)
IST	Immunosuppressive Therapy
IV	Intravenous(ly)
IVIg	Intravenous immunoglobulin
gMG	generalized Myasthenia Gravis
LLOQ	lower limit of quantitation
MAC	Membrane Attack Complex
MedDRA	Medical Dictionary for Regulatory Activities
NMOSD	Neuromyelitis optica spectrum disorder
Q8W	once every 8 weeks
Q	intercompartmental clearance
PE	Plasma Exchange
PD	Pharmacodynamic
(pop)PK	(Population) Pharmacokinetic
PNH	Paroxysmal Nocturnal Hemoglobinuria
pcVPC	prediction-corrected visual predictive check
PIP	Paediatric Investigation Plan
PPS	Per Protocol Set
PP	Plasmapheresis
RAC	Relapse Adjudication Committee
SD	Standard Deviation
sIPTW	stabilized inverse probability of treatment weights
SMD	standardized mean difference
SOC	System Organ Class
RSE	Robust Standard Error
TE(S)AE	Treatment-Emergent (Serious) Adverse Event
t½	elimination half-life
Vc / p	Volume of distribution in the Central / Peripheral compartment

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Alexion Europe SAS submitted to the European Medicines Agency on 30 August 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody-positive for Ultomiris, based on interim results from study ALXN1210-NMO-307; this is a phase 3, external placebo-controlled, open-label, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with NMOSD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0474/2021on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0474/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Derogation of market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application submitted a claim addressing the following derogation laid down in Article 8.3 of the same Regulation; the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the MAH.

Scientific advice

The MAH received Scientific Advice from the CHMP on 10 January 2020 (EMA/CHMP/SAWP/209064/2007)30 August 2019 (EMA/CHMP/SAWP/545125/2019). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: Robert Porszasz

Timetable	Actual dates
Submission date	30 August 2022
Start of procedure:	17 September 2022
CHMP Rapporteur Assessment Report	24 November 2022
PRAC Rapporteur Assessment Report	18 November 2022
CHMP Co-Rapporteur Assessment	5 December 2022
PRAC members comments	23 November 2022
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	1 December 2022
CHMP members comments	5 December 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 December 2022
Request for supplementary information (RSI)	15 December 2022
CHMP Rapporteur Assessment Report	1 March 2023
PRAC Rapporteur Assessment Report	n/a
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	24 March 2023
CHMP Opinion	30 March 2023
The CHMP adopted a report on similarity of Ultomiris with Soliris and Enspryng on date (Appendix 1)	30 March 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, severely disabling, complement-mediated autoimmune neuroinflammatory disease of the central nervous system (CNS) characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord [1,2].NMOSD is typically characterized by relapses (also known as attacks). Disease generally progresses in a stepwise fashion due to neurologic disability that may accumulate with each relapse, with relative stability in between relapses[3].

Epidemiology

The prevalence of NMOSD among Whites/Caucasians is ~1/100,000 population, with an annual incidence of 0.5-0.8/million population. Among East Asians, the prevalence is higher, at ~3.5/100,000 population, while the prevalence in Blacks may be up to 10/100,000 population. In AQP4-antibody-positive NMOSD, female preponderance is definite (up to 90%) and the majority of the cases are adults[4].

Aetiology and pathogenesis

Complement activation is a major determinant of disease pathogenesis in patients with NMOSD who are AQP4 antibody positive[5]. AQP4 is a water channel that is predominantly expressed on the cell membrane of astrocytic end-feet, forming part of the blood–brain barrier. Binding of antibody downregulates AQP4 and causes astrocytic injury through activation of the classical complement pathway. Antibody-complement complex formation results in chemotaxis of T and B lymphocytes, macrophages, neutrophils and eosinophils, principally through activation of NFκB. Demyelination and oligodendrocyte injury occur as a secondary effect of this immune response[6] .

Clinical presentation, diagnosis

The condition is characterized by attacks of predominantly optic neuritis and/or longitudinally extensive transverse myelitis. Brainstem signs have also been described, which predominant manifestations described are vomiting and hiccups, occurring mainly at disease onset[7]. Attacks tend to be severe and recurrent, often with incomplete recovery and morbidity and mortality are substantial[8].

In 2015 the International Panel for NMO Diagnosis unified the concept of NMO and NMOSD and developed the revised diagnostic criteria, based on AQP4-IgG status. The core clinical characteristics required for

[1] Wingerchuk DM et al. Neurol Ther 2022; 11:123–135
[2] Stellmann JP et al. J Neurol Neurosurg Psychiatry 2017;88(8):639-647.
[3] Wingerchuk DM et al. Neurology 2006; 66(10): 1485-1489.
[4] Hor JY et al. Front Neurol. 2020;11:501.
[5]Nytrova et al. J Neuroimmunol 2014; 274(1-2):185-191.
[6]Broadley S, Khalili E, Heshmat S, Clarke L, ACNR 2017;17(1):11-14
[7] Kremer L et al. Multiple Sclerosis Journal 2014, Vol. 20(7) 843–847
[8] Kitley J et al. Brain 2012: 135; 1834-1849

patients with NMOSD with AQP4-IgG include clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral presentations. More stringent clinical criteria, with additional neuroimaging findings, are required for diagnosis of NMOSD when AQP4 antibodies are absent or where serologic testing is unavailable[9].

Management

Treatment of NMOSD is comprised of both acute treatment of relapses and long-term relapse prevention therapy. Acute treatment of NMOSD relapses consists primarily of high-dose corticosteroids and plasmapheresis[10]. The goal of long-term treatment is to prevent the occurrence of relapses.

Before approved therapies were available, preventative treatment for NMOSD included the use of off-label immunosuppressive therapies (ISTs) based on clinical experience and consensus. Rituximab, mycophenolate mofetil, prednisolone and azathioprine are ISTs that have been used off-label for the prevention of NMOSD relapses, with rituximab showing the strongest evidence to support relapse risk reduction[11].

Three treatment options have been approved through the centralized procedure since 2019 for the treatment of NMOSD in adult patients who are anti-AQP4 antibody-positive. Eculizumab, inebilizumab, and satralizumab are all monoclonal antibodies that target different components of the immune system (C5, CD19, and interleukin-6 receptor [IL-6r], respectively) with the aim of preventing NMOSD relapses.

2.1.2. About the product

Ravulizumab (Ultomiris®; ALXN1210) is a humanized monoclonal antibody that binds to complement component 5 (C5) and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin C5a and the formation of the terminal complement complex via C5b.Complement activation is a major determinant of disease pathogenesis in patients with NMOSD who are AQP4 antibody positive (Hinson, 2009; Nytrova, 2014; Papadopoulos, 2012).

Ravulizumab was initially approved in the EU on 02 Jul 2019 under the trade name Ultomiris for the treatment of Paroxysmal nocturnal hemoglobinuria (PNH) in adult patients. Subsequently, the indication for ravulizumab was extended and it is currently approved in the EU for the treatment of PNH and atypical hemolytic uremic syndrome (aHUS) both in adult and paediatric patients and for the treatment of generalized myasthenia gravis (gMG) in adult patients.

The proposed indication for ravulizumab is:

> *The treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.*

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development program for NMOSD in adult patients consists of an ongoing phase 3, external placebo-controlled, open-label, multicenter clinical study (ALXN1210-NMO-307) designed to evaluate the efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD), and immunogenicity of ravulizumab in adult patients with NMOSD who areAQP4 antibody-positive. There is no CHMP Guideline

[9]Wingerchuk DM et al. Neurology 2015;85:177-189.
[10]Mealy MA et al. Mult Scler Relat Disord. 2019;28:64-68.
[11]Levy M et al. Lancet Neurol 2021;20(1): 60-67.

on the treatment of NMOSD currently available. The clinical program as well as the design and outcomes of study ALXN1210-NMO-307 were discussed during a scientific advice in October 2019 (EMA/CHMP/SAWP/545125/2019) and during a follow-up procedure in February 2020 (EMEA/H/SA/3331/5/FU/1/2020/II). The MAH has overall followed the recommendations received.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

A non-clinical information package was included in the original electronic CTD for Ultomiris (ravulizumab), presented in 2018. Direct testing of ravulizumab in non-clinical models of NMOSD is precluded by ravulizumab being a highly specific monoclonal antibody that binds only to human C5; ravulizumab has not been shown to bind to C5 from any other mammalian species tested.

Complement activation lead to the cleavage of C3 into C3b. C3b is also a critical structural subunit of C5 convertase, which activates terminal complement by cleaving C5 into its active metabolites C5a and C5b. C5b recruits the terminal complement components C6, C7, C8 and C9 to form the terminal complement complex (C5b-9) or membrane attack complex (MAC).

NMOSD is an ultra-rare, severe, disabling autoimmune inflammatory disorder of the CNS that predominately affects the optic nerves and spinal cord, and is typically characterized by a relapsing course. Complement activation is a major determinant of disease pathogenesis in patients with AQP4 antibody-positive NMOSD (Hinson, 2009; Papadopoulos, 2012; Verkman, 2012; Nytrova, 2014). 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. This in turn recruits and activates the complement cascade (Diebolder, 2014).

2.2.2. Pharmacology

Primary pharmacodynamic studies

In vitro models

In vitro model of inflammation that consisted of human astrocyte line, NMOSD serum, and allogenic peripheral blood neutrophils from healthy individuals, the evidence of pathogenicity of NMOSD serum was shown, which by consecutive action of anti-AQP4 antibodies, complement system, and neutrophils affected astrocyte function (Piatek, 2018). Anti-AQP4 antibodies binding astrocytes initiated two parallel complementary reactions. The first one was dependent on the complement cytotoxicity via C5b-9 complex formation, and the second one on the reverse of astrocyte glutamate pump into extracellular space by C5a-preactivated neutrophils. As a consequence, astrocytes were partially destroyed.

Animal models

In addition, animal experiment in mice showed that injection of anti-AQP4 antibodies directly into the brain, either intracerebrally or as a continuous infusion into the cerebrospinal fluid, does not cause disease by itself. However, in the presence of abundant complement, animals develop NMOSD-like pathology (Wu, 2019). Similarly, addition of anti-AQP4 antibodies to cultured astrocytes causes no

cellular destruction unless exogenous complement is added (Alexopoulos, 2015). In mice, inactivation of CD59 glycoprotein, also known as MAC-inhibitory protein, or knockout of the gene that encodes this protein increased the extent of NMOSD pathology caused by co-injection of anti-AQP4 antibodies and complement (Yao, 2017).

Moreover, evidence of complement involvement in anti-AQP4 antibody-positive NMOSD was characterized in postmortem studies of anti-AQP4 antibody-positive NMOSD patients which showed; abundant complement deposition at sites of pathology, and markers of complement activation (C5a and soluble MAC) detected in the plasma and cerebrospinal fluid during active disease (Wang, 2014), and astrocyte lysis stage in histopathological analyses (Takai, 2021).

2.2.3. Ecotoxicity/environmental risk assessment

According CHMP guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) with effective date of December 2006, states that vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted of environmental risk assessment because, due to their nature they are unlikely to result in significant risk to the environment. Due to the fact that ravulizumab is a monoclonal antibody and thus a protein, no Environmental Risk Assessment is provided for this Type II variation.

2.2.4. Discussion on non-clinical aspects

For a new indication, a proof of concept based on nonclinical data is usually required. The dose and administration route proposed for this new indication is the same that were previously approved for aHUS and PNH indications; no new concerns are raised. Thus, no additional nonclinical toxicity studies are required.

The existing nonclinical package of ravulizumab already supports the potency of ravulizumab to inhibit terminal complement activation. On that basis, complement cascade inhibition mediated by C5 protein block with ravulizumab provides the therapeutic rationale for NMOSD indication. For the proof of concept, no additional nonclinical data with ravulizumab have been generated for this new indication NMOSD. The nonclinical overview summarizes results from several published studies including *in vitro* and *in vivo* models that evaluated the role of complement to develop NMOSD-like pathology in mice in presence of anti-AQP4, which constituted the rationale for evaluating ravulizumab in NMOSD. Direct testing of ravulizumab in non-clinical models of NMOSD is precluded by ravulizumab being a highly specific monoclonal antibody that binds only to human C5; ravulizumab has not been shown to bind to C5 from any other mammalian species tested.

Eculizumab, a similar monoclonal antibody previously approved, is also indicated for the treatment of NMOSD in patients who are AQP4 antibody-positive. Despite ravulizumab was derived from eculizumab by introducing 4 unique amino acid substitutions to the CDR and Fc regions, these mutations are not expected to impact in the mechanism of action, and both antibodies recognize and bind to the same epitope of the target (C5). Thus, the therapeutic rationale and proof of concept provided by the Applicant are considered adequate.

2.2.5. Conclusion on the non-clinical aspects

A full nonclinical package was included in the original MAA for Ultomiris presented in 2018. With the exception of the published studies discussed above, no additional non-clinical data have been generated. This is considered acceptable.

Considering the above data, ravulizumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

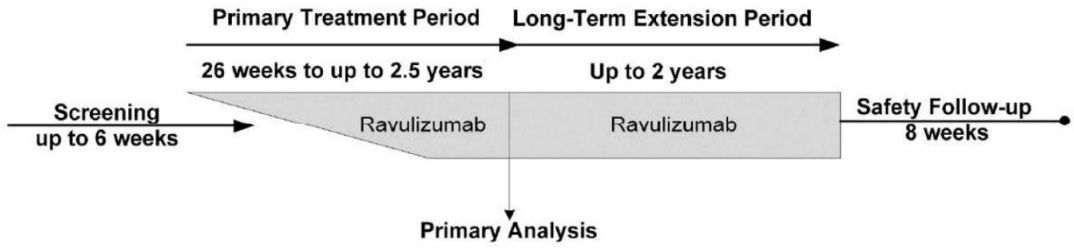
Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s);** **Dosage Regimen;** **Route of Administration**	**Number of Patients (Planned/ Treated)[c,d]**	**Diagnosis of Patients**	**Duration of Treatment**	**Study Status;** **Type of Report**
Efficacy, safety, PK, PD, and immuno-genicity	ALXN1210-NMO-307	M5.3.5.1	To evaluate the effect of ravulizumab on adjudicated On-trial Relapses[a] in adult patients with NMOSD	Phase 3, external placebo-controlled[b], open-label, multicenter study in adult patients with NMOSD	**Primary Treatment Period:** Ravulizumab IV weight-based loading[c] dose on Day 1 and weight-based maintenance[d] dose starting on Day 15 and q8w thereafter **Long-term Extension Period**: Ravulizumab IV weight-based maintenance dose[d] q8w	Rav: 55/58	Adult patients with NMOSD who are anti-AQP4 Ab positive	**Primary Treatment Period:** between 13.7 and 117.7 weeks **Long-term Extension Period:** Up to 2 years	Ongoing in Long-term Extension Period (Primary Treatment Period Completed) Primary Analysis CSR

a On-trial Relapses refer to relapses as determined by the Treating Physician that occurred during the study treatment period. All On-trial relapses were adjudicated by a separate relapse adjudication committee (RAC). The term "Adjudicated On-trial Relapse" is used to reflect only those events that were adjudicated positively by the RAC.
b The placebo group data (N = 47) were collected as part of Study ECU-NMO-301 (conducted from 2014 to 2018).
c Ravulizumab loading dose: 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg.
d Ravulizumab maintenance dose: 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg.
Abbreviations: AQP4 Ab= aquaporin 4 antibody; CSR = clinical study report; IV = intravenous; NMOSD = neuromyelitis optica spectrum disorder; PD = pharmacodynamics; PK = pharmacokinetics; q8w = once every 8 weeks

2.3.2. Pharmacokinetics

The population PK (popPK), PK/PD and exposure-response analyses of ravulizumab were performed based on patients with NMOSD who received ravulizumab in study ALXN1210-NMO-307.

Figure 1: Schematic Overview of Study ALXN1210- NMO-307



Ravulizumab dosage regimen:

Loading Dose (Day 1):
2400 mg for patients weighing ≥ 40 kg to < 60 kg
2700 mg for patients weighing ≥ 60 kg to < 100 kg
3000 mg for patients weighing ≥ 100 kg

Maintenance Dose (Day 15 and every 8 weeks [q8w] thereafter):
3000 mg for patients weighing ≥ 40 kg to < 60 kg
3300 mg for patients weighing ≥ 60 kg to < 100 kg
3600 mg for patients weighing ≥ 100 kg

Table 1: Summary of PK, PD, and Immunogenicity Data for the Ravulizumab NMOSD Development Program

Study Identifier: (Population Studied)	Study Description	Number of Patients	Duration of PK, PD, and Immunogenicity Data Coverage
ALXN1210-NMO-307 (Adult complement inhibitor treatment-naive patients with anti-AQP4 antibody-positive NMOSD)	Phase 3, external placebo-controlled, open-label multicenter study to evaluate the efficacy, PK, PD, immunogenicity, and safety of ravulizumab IV	58	Up to Week 50[a]

a Descriptive statistics for the PK and PD results presented in Section 2 of this Module are based on data obtained through the data cutoff date of 15 Feb 2022.
Abbreviations: AQP4 = aquaporin-4; IV = intravenous; NMOSD = neuromyelitis optica spectrum disorder; PD = pharmacodynamics; PK = pharmacokinetics

Table 2: Dosing and Sampling Schedules for Study ALXN1210-NMO-307 Primary Treatment Period

Parameter	Dosing and Sampling Schedules
Dosing regimen	Ravulizumab IV 10 mg/mL body weight-based dosing, loading dose on Day 1 and maintenance doses on Day 15 and then every 8 weeks through Day 1639. • Patients weighing ≥ 40 to < 60 kg: loading dose 2400 mg, maintenance dose 3000 mg • Patients weighing ≥ 60 to < 100 kg: loading dose 2700 mg, maintenance dose 3300 mg • Patients weighing ≥ 100 kg: loading dose 3000 mg, maintenance dose 3600 mg
Serum PK and PD (free C5)	• Serum samples for PK and PD were obtained within 90 minutes before start of infusion (predose) and within 60 minutes after completion of infusion (post dose) on Days 1, 15, 71, 127, 183, 239, 351, 463, 573, 743, 911, 1135, 1359, and 1583, as well as at EOT/ED. Serum samples for PK and PD were obtained anytime on Day 43. • In the event of an On-trial Relapse, serum samples were to be obtained for PK and PD at any time during a Relapse Evaluation Visit. • If a patient received PE/PP/IVIg, serum samples for PK and PD were to be obtained immediately before and after each session of PE/PP/IVIg and within 1 hour after completion of supplemental study drug infusion (in those situations where supplemental study drug was administered).
Immunogenicity (ADA)	Serum samples for ADAs were obtained within 5 to 90 minutes before start of infusion (predose) on Days 1, 183, 351, 575, 743, 911, 1135, 1359, and 1583, as well as at EOT/ED.

Note: Day 1 refers to start of dosing. Abbreviations: ADA = antidrug antibody; C5 = complement component 5; ED = early discontinuation; EOT = end of treatment; IV = intravenous; IVIg = intravenous immunoglobulin; PD = pharmacodynamics; PE = plasma exchange; PK = pharmacokinetics; PP = plasmapheresis

Absorption

Ravulizumab IV doses are 100% bioavailable resulting from IV administration. The time to maximum observed serum concentration is expected at the end of infusion or soon after end of infusion. Over the studied dose and regimen range, ravulizumab exhibited dose proportional and time linear PK.

Distribution

The mean (SD) volume of distribution at steady state in adult patients with NMOSD is 4.77 (0.819) L.

Elimination

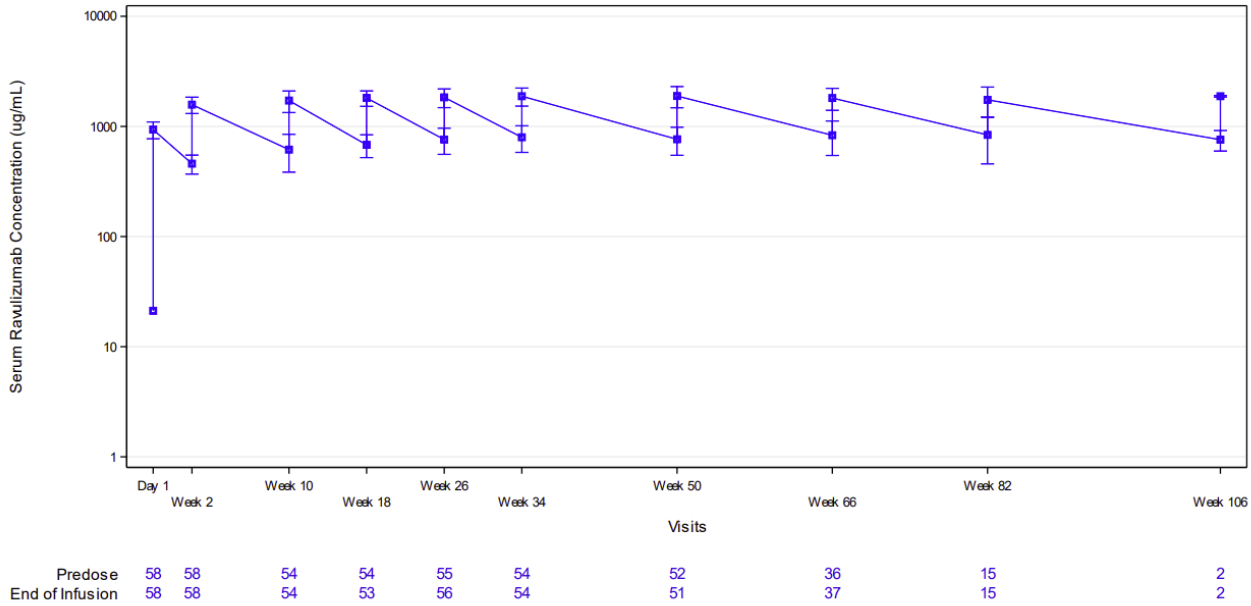
As an immunoglobulin G (IgG) monoclonal antibody, ravulizumab is expected to be metabolized in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination. Ravulizumab contains only natural occurring amino acids and has no known active metabolites. The mean (SD) elimination half-life (t½) and linear clearance (CL) of ravulizumab in adult patients with NMOSD is 64.3 (11.0) days and 0.00228 (0.000662) L/h, respectively.

Target population

Exploratory PK data

The mean (SD) ravulizumab serum concentration versus time profile is presented in Figure 2.

Figure 2: Mean (SD) Ravulizumab Serum Concentration Over Time, Semi-log Scale (Study ALXN1210-NMO-307 PK/PD Set)



Numbers below the x-axis represent the number of samples contributing to the predose and end of infusion data at the given timepoint.
For ravulizumab concentrations BLQ (1.00 µg/mL), the LLOQ divided by 2 (ie, 0.5 µg/mL) is summarized.
BLQ = below the limit of quantitation; LLOQ = lower limit of quantitation; PD = pharmacodynamic; PK = pharmacokinetic; SD = standard deviation

PK parameters for ravulizumab are summarized by body weight categories in Table 3 and Table 4 following the loading dose and following maintenance dosing, respectively.

Table 3: Ravulizumab PK Parameters Following the First (Loading) Dose (Study ALXN1210-NMO-307 PK/PD Set)

Parameter	Statistics	All Patients	≥ 40 to < 60 kg	≥ 60 to < 100 kg	≥ 100 kg
C_{max} (µg/mL)	n	58	22	31	5
	Mean (SD)	935.3 (162.25)	941.9 (167.63)	953.0 (159.85)	796.8 (96.49)
	Median (min, max)	933.5 (575, 1280)	941.5 (578, 1250)	989.0 (575, 1280)	780.0 (664, 918)
C_{trough} (µg/mL)	n	58	22	31	5
	Mean (SD)	459.1 (90.34)	475.0 (86.67)	466.5 (86.56)	343.2 (45.40)
	Median (min, max)	447.0 (282, 643)	453.5 (312, 639)	463.0 (302, 643)	341.0 (282, 409)

C_{max} = maximum observed serum concentration; C_{trough} = concentration at the end of the dosage interval; max = maximum; min = minimum; PD = pharmacodynamic; PK = pharmacokinetic; SD = standard deviation

Table 4: Ravulizumab PK Parameters Following Maintenance Dosing (Study ALXN1210-NMO-307 PK/PD Set)

Parameter	Statistics	All Patients	≥ 40 to < 60 kg	≥ 60 to < 100 kg	≥ 100 kg
C_{max} (µg/mL)	n	56	22	29	5
	Mean (SD)	1836.4 (355.39)	1899.5 (396.25)	1878.3 (271.43)	1316.0 (153.07)
	Median (min, max)	1905.0 (759, 2650)	1925.0 (759, 2650)	1940.0 (1130, 2290)	1340.0 (1090, 1480)
C_{trough} (µg/mL)	n	54	20	30	4
	Mean (SD)	796.9 (216.04)	877.9 (213.78)	778.7 (196.30)	528.3 (138.98)
	Median (min, max)	808.5 (360, 1280)	885.5 (435, 1280)	785.0 (371, 1220)	534.0 (360, 685)

Note: For this table, the Week 26 post dose sample was used for Cmax and the Week 34 predose sample was used for C_{trough}.
Abbreviations: C_{max} = maximum observed serum concentration; C_{trough} = concentration at the end of the dosage interval; max = maximum; min = minimum; PD = pharmacodynamic; PK = pharmacokinetic; SD = standard deviation

Population PK model development

The PK population consisted of 58 patients who received a least one dose of ravulizumab and at least one post-dose measurable concentration up to Week 50 (i.e., Day 351 ±7) in study ALXN1210-NMO-307. Descriptive statistics of baseline characteristics are presented in Table 5.

Table 5: Baseline Characteristics of Ravulizumab PK Population

Characteristics	ALXN1210-NMO-307 (N=58)
Sex	
Female	52 (89.7%)
Male	6 (10.3%)
Race	
White	22 (37.9%)
Black or African American	6 (10.3%)
Asian	21 (36.2%)
Hispanic or Latino	9 (15.5%)
Japanese Population[a]	
Non-Japanese	49 (84.5%)
Japanese	9 (15.5%)
Ethnicity	
Not Hispanic or Latino	45 (77.6%)
Hispanic or Latino	9 (15.5%)
Not reported	4 (6.9%)
Age (years)	
Mean (SD)	47.4 (13.9)
Median [Min, Max]	46.0 [18.0, 74.0]
Body Weight (kg)	
Mean (SD)	69.8 (19.3)
Median [Min, Max]	63.8 [41.0, 125]
Height (cm)	
Mean (SD)	162 (8.16)
Median [Min, Max]	160 [148, 193]
Missing	2 (3.4%)
BMI (kg/m^2)	
Mean (SD)	26.7 (6.50)
Median [Min, Max]	25.6 [17.7, 45.8]
Missing	2 (3.4%)
Free C5 (µg/mL)	
Mean (SD)	120 (42.4)
Median [Min, Max]	115 [0.0264, 212]
Missing	1 (1.7%)
Baseline ADA	
Negative	53 (91.4%)
Positive	5 (8.6%)

ADA = Antidrug antibody; BMI = body mass index; CV = coefficient of variation; Min = minimum; Max = maximum; SD = standard deviation. a Patients enrolled in Japan were considered as Japanese while patients enrolled in other countries were considered as non-Japanese

Table 6: Number of Patients/Observations Included in the Analysis

Endpoint	PK Data	Free C5 Data	ADA Data
Number of patients	58	58	58
Number of samples analyzed	853	851	165
Number of samples included in the analysis	792[a]	819[b]	165

a Based on a total of 853 samples, 792 (92.8%) were included in the population PK analysis.
b Based on a total of 851 samples assayed, 32 (3.8%) samples had no measurable concentrations of free C5 and, therefore, were excluded from the PK/PD analysis. As a result, a total of 819 (96.2%) were included in the PK/PD analysis.
ADA = antidrug antibodies; C5 = complement component 5; PD = pharmacodynamic; PK = pharmacokinetic

Prior modelling experience

A popPK analysis was previously performed to assess concentration-time profiles of ravulizumab following IV administration in healthy volunteers and patients with PNH (PopPK and PD Analysis to Support Ravulizumab Dosing in Patients with PNH, 1 June 2018). A 2-compartment model with CL adequately characterized the concentration-time profiles of ravulizumab. The popPK analysis included 38 (12.7%) healthy subjects and 261 (87.3%) patients with PNH. The popPK model in PNH patients included the effect of body weight on all clearance and volume parameters (CL, intercompartmental clearance [Q], volume of distribution in the central compartment [Vc], and volume of distribution in the peripheral compartment [Vp]). The popPK model also included the effect of body mass index (BMI) on volume of distribution parameters (Vc and Vp). Finally, the model included the effect of hemoglobin on central parameters (CL and Vc).

In addition, a popPK analysis was previously performed to assess concentration-time profiles of ravulizumab following IV administration in patients with gMG (PopPK and PD Analysis to Support Ravulizumab Dosing in Patients with gMG, 6 October 2021). A 2-compartment model with first-order elimination and estimated allometric exponents for body weight on CL/Q and Vc/Vp resulted in an adequate goodness-of-fit based on peak/trough concentrations collected in patients with gMG. PK parameters of peripheral compartments (Q and Vp) were fixed to those originally observed in patients with PNH**.**

Rescue therapy (e.g, high-dose corticosteroid, PP/PE, or IVIg) was allowed for patient with gMG who experienced Clinical Deterioration. The effect of PP/PE or IVIg on CL were investigated as part of the base model development. Based on 2 patients with at least one PP/PE intervention and corresponding PK data, the CL of ravulizumab during a PP/PE intervention was estimated to be 0.793 L/h, which translated into a $t_{1/2}$ of 3.6 days. Based on 5 patients with at least one IVIg intervention and corresponding PK data, the CL of ravulizumab during an IVIg intervention was 0.0108 L/h, which translated into a t1/2 of 14.7 days.

For patients with NMOSD enrolled in study ALXN1210-NMO-307, PP/PE or IVIg interventions may have been administered along with supplemental doses of ravulizumab Overall, the above 2-compartment model with PP/PE or IVIg was used as a starting point. All covariates were re-evaluated as part of the final analysis.

Base PopPK Model

The starting point for model development was a 2-compartment model with first-order elimination, as well as estimated allometric exponents for body weight on CL/Q and Vc/Vp. The effect of PP/PE or IVIg on the CL of ravulizumab was investigated as part of the base model development. A single patient had 5 PP/PE interventions with corresponding PK data and a single patient had one IVIg intervention with corresponding PK data.

Table 7: Base Population PK Model Parameter Estimates

Parameter	Model Term	Parameter Scale (θ)		Transformation	Back-Transformed		
		Estimate	RSE (%)		Estimate	RSE (%)	95% CI
CL (L/h)	exp(θ)	-6.10	0.402	log	0.00225	2.45	0.00215 – 0.00236
PP/PE Event	× exp(θ) if PP/PE	7.27	0.0605	log	1442	0.440	1430 – 1455
Body Weight (kg)	× (WTBL/70)$^{\theta}$	0.771	12.9	identity	0.771	12.9	0.577 – 0.966
Q (L/h)	exp(θ)	-4.15	NA	log	0.0158	NA	NA – NA
Body Weight (kg)	× (WTBL/70)$^{\theta}$	0.771[a]	12.9	identity	0.771	12.9	0.577 – 0.966
Vc (L)	exp(θ)	1.07	1.89	log	2.91	2.02	2.80 – 3.03
Body Weight (kg)	× (WTBL/70)$^{\theta}$	0.575	11.2	identity	0.575	11.2	0.449 – 0.702
Vp (L)	exp(θ)	0.663	NA	log	1.94	NA	NA – NA
Body Weight (kg)	× (WTBL/70)$^{\theta}$	0.575[a]	11.2	identity	0.575	11.2	0.449 – 0.702
Assay Conversion							
Residual Error							
Proportional Error (%)							
PPD	θ if PPD	0.0988	3.80	%	9.88	3.80	9.15 – 10.6
Additive Error (µg/mL)							
Between Subject Variability							
Parameter	**Model Term**	**Estimate**	**RSE (%)**	**95% CI**		**CV (%)**	**Shrinkage (%)**
On CL	$\omega = SD(\eta_{Vc,i})$	0.178	9.15	0.146 – 0.210		17.9	1.95
On Vc	$\omega = SD(\eta_{Vc,i})$	0.141	14.6	0.100 – 0.181		14.2	5.34
On Vp	$\omega = SD(\eta_{Vp,i})$	0	NA	NA – NA		0	

CI = confidence interval; CL = clearance; Q = peripheral clearance; RSE = relative standard error; Vc=volume of distribution in the central compartment; Vp=volume of distribution in the peripheral compartment; WTBL = body weight at baseline (kg). a Effect of body weight on Q equal to effect on CL; effect of body weight on Vp equal to effect on Vc; effect of BMI on Vp equal to effect on Vc.

Covariate analysis

Graphical exploration of the relationship between baseline covariates and individual random effects (ETAs) on CL and Vc was performed to explore sources of variability.

A formal covariate analysis was performed using a stepwise forward addition (p-value = 0.01) followed by backward elimination (p-value = 0.001). The following covariates were formally tested on CL and Vc: BMI, age, sex, race, markers of renal function (estimated glomerular filtration rate and creatinine clearance), markers of liver function (alanine aminotransferase, aspartate aminotransferase alkaline phosphatase, and bilirubin), haematocrit, hemoglobin, albumin, and ADA (baseline and time-varying), concomitant medications (anabolic agents for systemic use, antithrombotic agents, antianemia preparations, antihypertensives, antibacterial for systemic use, antimycotics for systemic use, corticosteroids for systemic use, immunosuppressants).

A summary of covariates included in the model as part of the forward inclusion step is presented in Table 8

Table 8: Stepwise Covariate Analysis: Forward Inclusion

Step	Covariates	MOF	ΔMOF	df	P-Value
0	Base Model	8413.184	--	--	--
1	BMI on Vc,Vp	8401.929	-11.255	1	0.001
2	ALT on Vc	8394.219	-7.710	1	0.005

CL = clearance; MOF = minimum objective function, AMOF = maximum change in objective function, confidence interval, level of significance for 1 degree of freedom = 6.63 (p<0.01), Vc = volume of distribution of the central compartment.

The effect of alanine aminotransferase on Vc was removed as part of the backward elimination due to not meeting the p-value threshold of 0.001.

Final PopPK Model

PopPK parameter of ravulizumab as well as between-subjects and residual error parameters derived with the final model are presented in Table 9.

Table 9: Final Population PK Model: Parameter Estimates

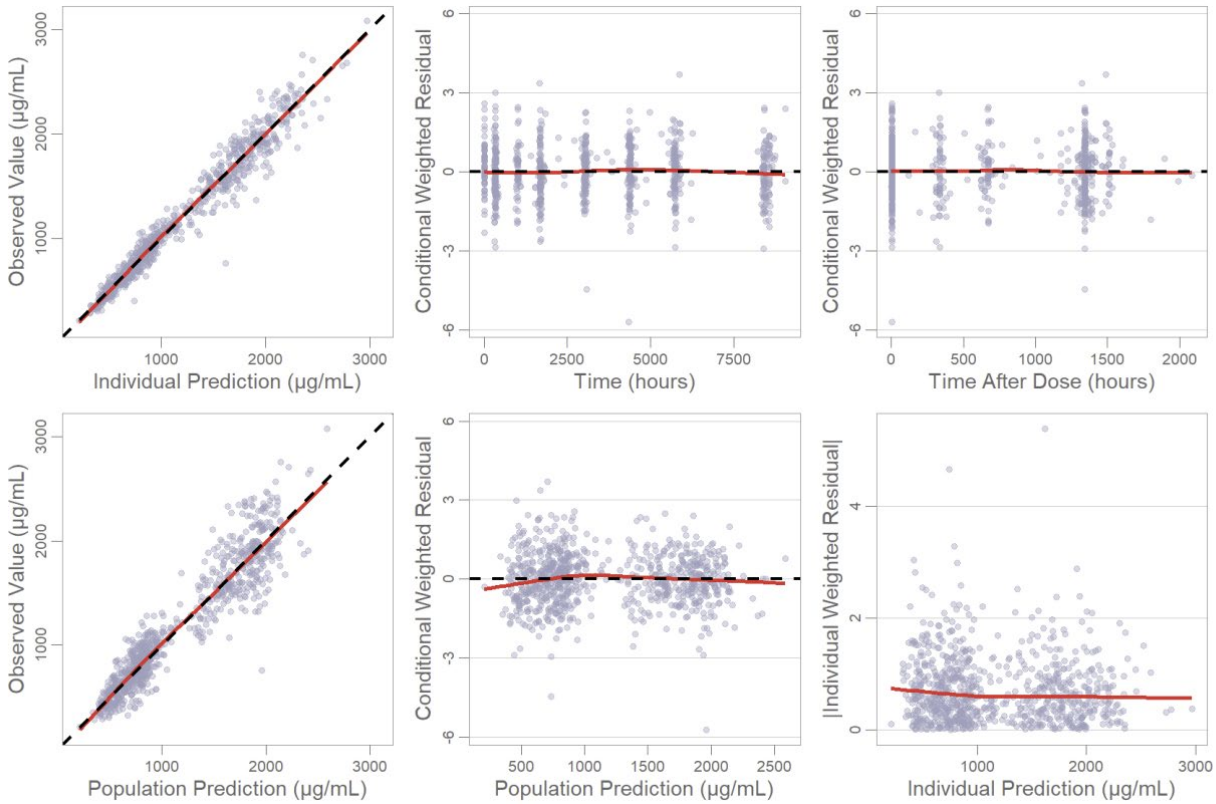
Parameter	Estimates[a]	RSE (%)	BSV[b] (%)	Shrinkage (%)
CL (L/h)	**0.00226** (without PE/PP intervention)	2.45	17.9	1.84
	× 1437 during PE/PP intervention	0.407	NA	NA
	× $(WT/70)^{0.772}$	12.7	NA	NA
Q (L/h)	**0.0158, Fixed**	NA	NA	NA
	× $(WT/70)^{0.772}$	12.7	NA	NA
Vc (L)	**3.01**	2.09	12.9	6.46
	× $(WT/70)^{1.01}$	13.8	NA	NA
	× $(BMI/25.1)^{-0.546}$	31.9	NA	NA
Vp (L)	**1.94, Fixed**	NA	NA	NA
	× $(WT/70)^{1.01}$	13.8	NA	NA
	× $(BMI/25.1)^{-0.546}$	31.9	NA	NA
Error model				
Proportional error (%)	**9.86**	3.80	NA	NA

Note: The reference patient was a 70-kg male patient with NMOSD with a BMI of 25.1 kg/m2. Peripheral compartment parameters (ie, Q and Vp) were fixed to population estimates originally identified in patients with PNH and no random effects were estimated for these parameters.
a Parameter estimates are back-transformed from the log-transformed domain.
b BSV is presented as the standard deviation of the random effect (ηi), with the % coefficient of variation (100 × (exp(ω2)-1)0.5) in parentheses.
BMI = body mass index; BSV = between-subject variability; CI = confidence interval; CL = central clearance; NA = not applicable; NMOSD = neuromyelitis optica spectrum disorder; PE = plasma exchange; PK = pharmacokinetic; PP = plasmapheresis; Q = intercompartmental clearance; RSE = relative standard error; Vc = volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment; WT = body weight

Population estimates of CL and Vc of ravulizumab were 0.00226 L/h and 3.01 L in a typical 70-kg patient with a BMI of 25.1 kg/m2, respectively. The CL and Vc were robustly estimated with robust standard error (RSE) values less than 5%. The between-subject variability of CL and Vc were 17.9% and 12.9%, respectively. The mean $t_{1/2}$ was 64.3 days.

The goodness-of-fit derived with the final popPK model is presented in Figure 3.

*Figure 3**:** Final Population PK Model of Ravulizumab: Goodness-of-Fit*

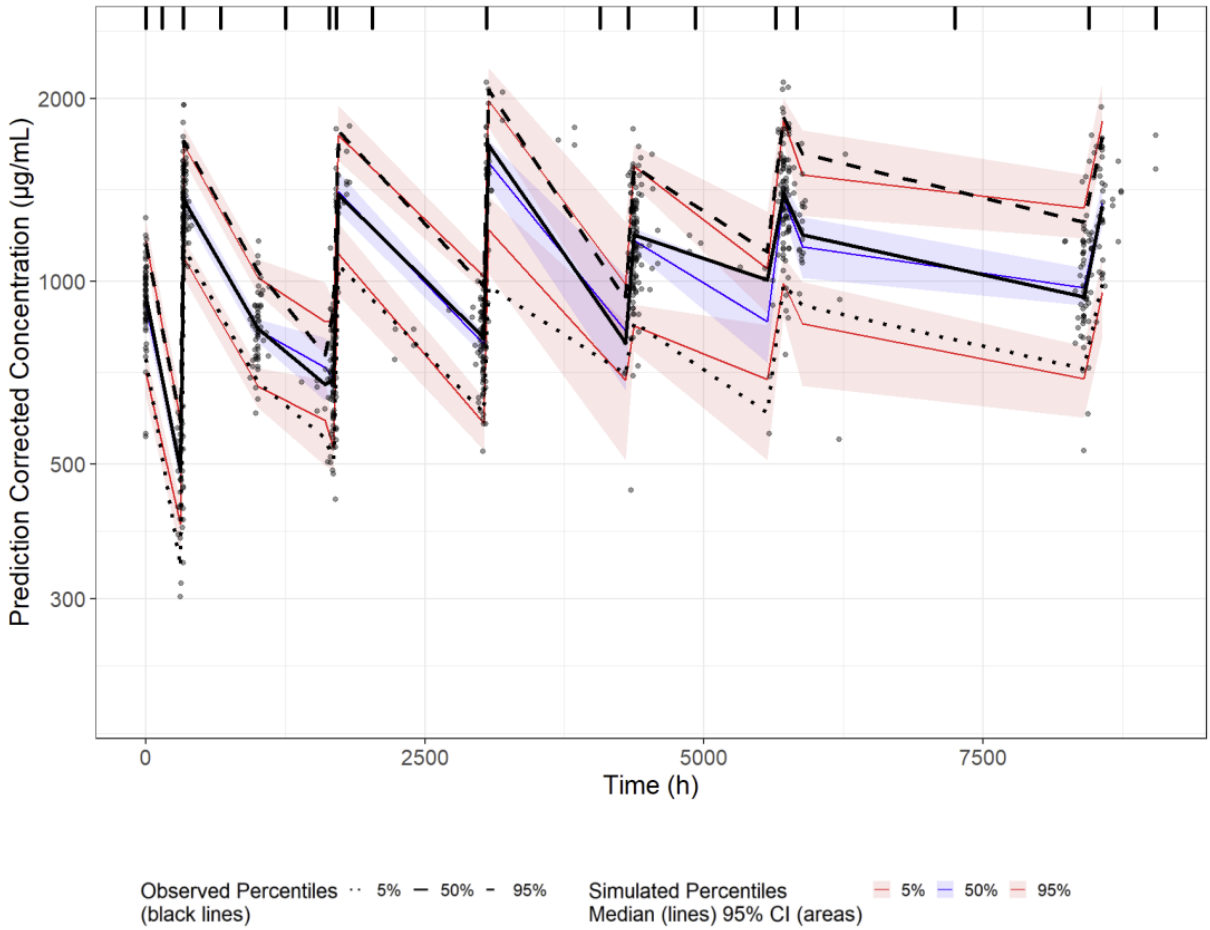


Thick line on all plots is the LOESS line. Dashed line is the line of identity. Observed and individual/population predicted values are ravulizumab concentrations (µg/mL). Abbreviations: LOESS = locally weighted scatter-plot smoothing; PK = pharmacokinetic

A bootstrap resampling analysis was performed. PopPK parameters and covariate effects derived with bootstrap analysis were within 1% of those derived in the original analysis.

The final model was evaluated by performing a prediction-corrected visual predictive check (pcVPC). Results of the pcVPC (time after dose) on a semi-log scale is presented in Figure 4.

*Figure 4**:** Final Population PK Model of Ravulizumab: Prediction-corrected Visual Predictive Check*



Covariate effects

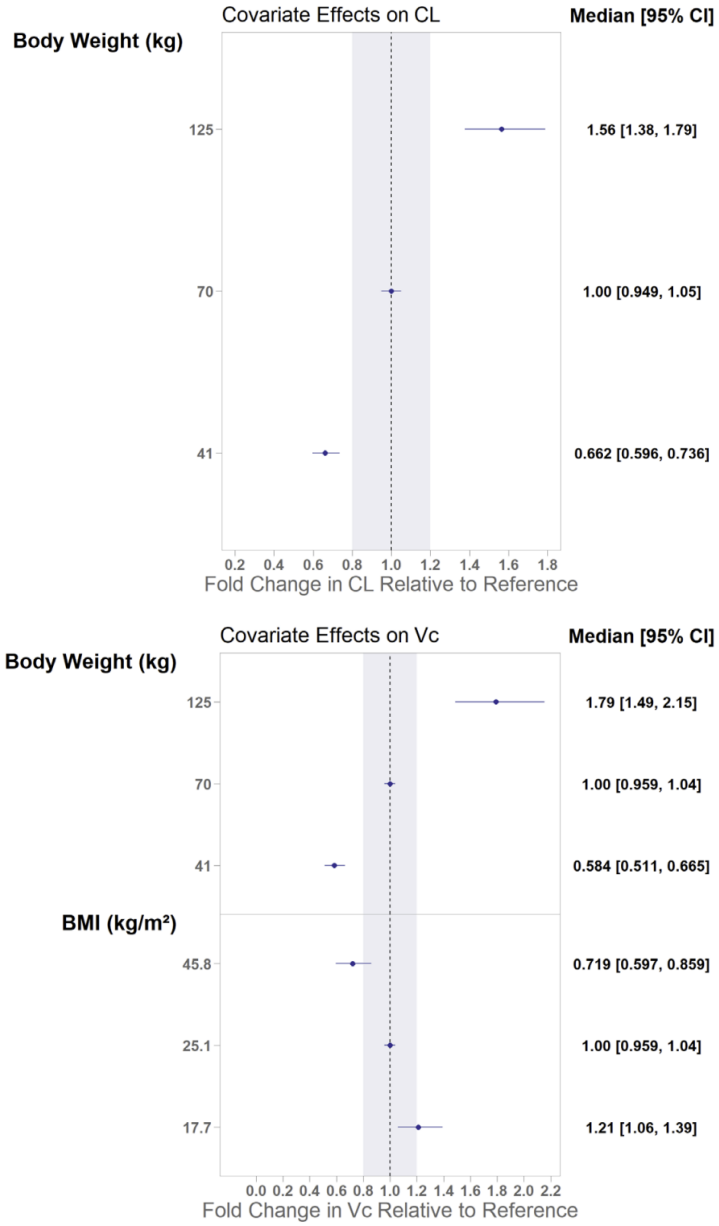
- The CL of ravulizumab was dependent on body weight. The exponent for the effect of weight on CL was 0.772 [(Body Weight/70)$^{0.772}$] suggesting higher CL values in patients with higher body weight. For example, typical patients with body weight values of 41.0 and 125.0 kg are expected to have CL values 34% slower and 57% faster (0.00150 and 0.00354 L/h, respectively) relative to a typical patient with a body weight of 70 kg.
- A single patient presented with a single IVIg intervention. Due to the limited data available, adding IVIg intervention as a covariate did not show a statistically significant improvement in the objective function. IVIg intervention was not included as a covariate.
- The CL of ravulizumab during PP/PE interventions was 3.24 L/h. The effect of PP/PE intervention on the CL of ravulizumab was robustly estimated (RSE <5%) despite the fact that a single patient received PP/PE interventions. Based on *post hoc* estimates, the faster CL of ravulizumab during the PP/PE interventions (CL = 0.00186 L/h× 1437) corresponded to a $t_{1/2}$ of 3.4 days. The $t_{1/2}$ of ravulizumab without PP/PE in this patient was 61.7 days.
- The Q of ravulizumab was dependent on body weight. Similar to CL, the exponent for the effect of weight on Q was 0.772 [(Body Weight/70)$^{0.772}$]. The effect of weight on Q had therefore the same magnitude of effect as that presented for CL.
- The Vc of ravulizumab was dependent on body weight. The exponent for the effect of weight on Vc was 1.01 [(Body Weight/70)$^{1.01}$] suggesting higher Vc values in patients with higher body weight. For example, typical patients with body weight values of 41.0 and 125.0 kg (corresponding to minimum and maximum values in the PK population) are expected to have Vc

values 42% smaller and 80% greater (1.75 and 5.40 L, respectively) relative to a typical patient with a body weight of 70 kg.

- The Vc of ravulizumab was also dependent on BMI. The exponent for the effect of BMI on Vc was -0.548 [(BMI/25.1)-0.548] suggesting lower Vc values in patients with higher BMI. For example, typical patients with BMI values of 17.7 and 45.8 kg/m2 (corresponding to minimum and maximum values in the PK population) are expected to have Vc values 21% greater and 28% smaller (3.64 and 2.16 L), respectively, relative to a typical patient with a BMI of 25.1 kg/m2.
- The Vp of ravulizumab was dependent on body weight and BMI. The effect of weight on Vp had the same magnitude as that presented for Vc.

The effect of body weight and BMI on PK parameters of ravulizumab relative to the reference population is presented in Figure 5.

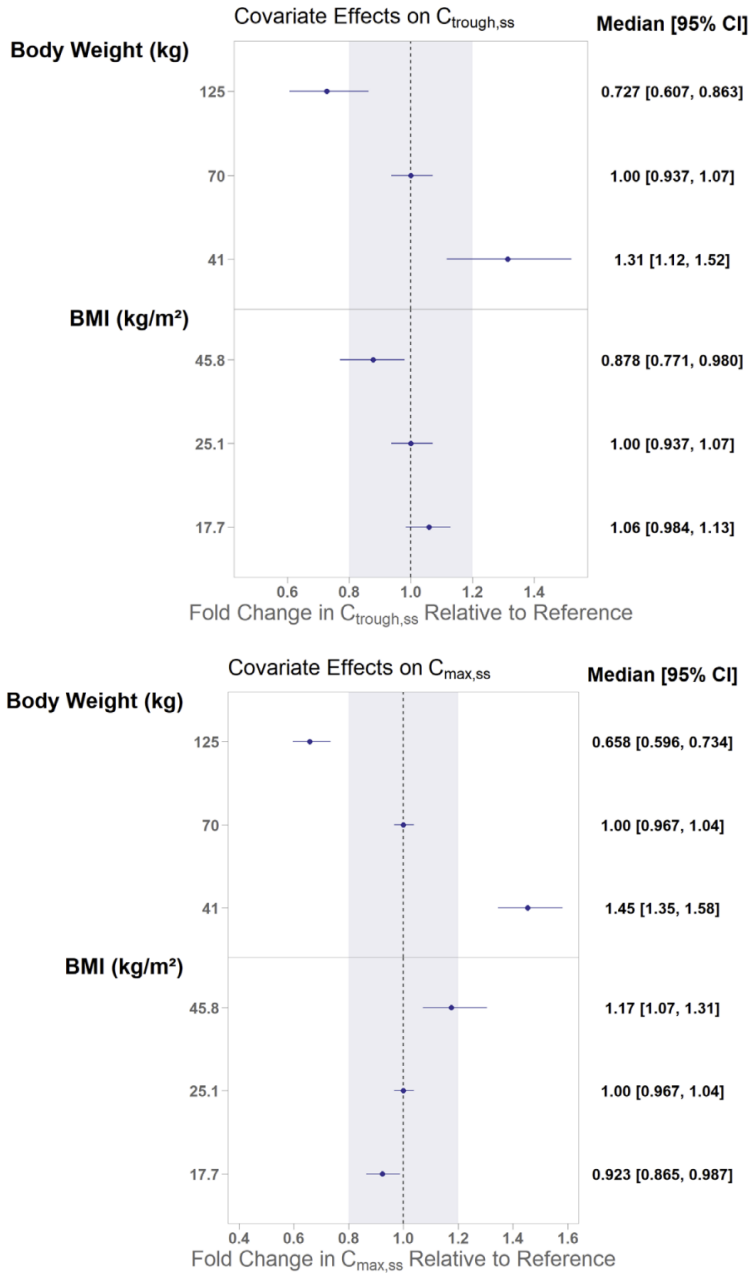
Figure 5: Forest Plot: Impact of Covariates on the CL and Vc of Ravulizumab



The reference patient was a typical 70-kg male patient with NMOSD. Abbreviations: BMI = body mass index; CI = confidence interval; CL = central clearance; NMOSD = neuromyelitis optica spectrum disorder; Vc = volume of distribution in the central compartment

The effect of specific covariates on the $C_{trough,ss}$ and $C_{max,ss}$ of ravulizumab relative to the reference population is presented in Figure 6.

Figure 6: Forest Plot: Impact of Covariates on the $C_{trough,ss}$ and $C_{max,ss}$ of Ravulizumab



Note The reference patient was a typical 70-kg male patient with NMOSD

Comparison across indications- Patients with NMOSD vs Patients with gMG

Exposure parameters of ravulizumab in patients with NMOSD were compared to patients with gMG, a disease characterized by uncontrolled terminal complement activation at the neural or muscle surface. The comparison was conducted using patient data from the following two trials: NMOSD (ALXN1210-NMO-307) and gMG (ALXN1210-MG-306).

Descriptive statistics of exposure parameters of ravulizumab by body weight group in patients with NMOSD and gMG are presented in Table 10.

Table 10: Descriptive Statistics of Steady State Exposure Parameters of Ravulizumab by Body Weight Group in Patients with NMOSD and gMG

Parameter (Units)	Indication	Mean (SD) Median [2.5th – 97.5th Percentile]			
		≥ 40 to < 60 kg	≥ 60 to < 100 kg	≥ 100 kg	All Patients
$C_{trough,ss}$ (µg/mL)	NMOSD	N = 22 867 (236) 877 [463 – 1330]	N = 31 789 (191) 831 [468 – 1070]	N = 5 540 (178) 454 [352 – 742]	N = 58 797 (223) 834 [443 – 1270]
	gMG	N = 7 922 (305) 823 [625 – 1430]	N = 47 635 (160) 625 [305 – 865]	N = 32 473 (118) 482 [254 – 667]	N = 86 598 (202) 569 [268 – 1060]
$C_{max,ss}$ (µg/mL)	NMOSD	N = 22 2020 (340) 2030 [1560 – 2670]	N = 31 1930 (305) 1960 [1430 – 2450]	N = 5 1450 (210) 1480 [1160 – 1680]	N = 58 1930 (343) 1940 [1330 – 2560]
	gMG	N = 7 2280 (485) 2080 [1860 – 3040]	N = 47 1700 (297) 1750 [1220 – 2230]	N = 32 1360 (215) 1390 [881 – 1770]	N = 86 1620 (382) 1580 [1130 – 2540]
AUC_{ss} (µg.h/mL)	NMOSD	N = 22 1610000 (357000) 1630000 [1030000 – 2300000]	N = 31 1490000 (293000) 1540000 [969000 – 1890000]	N = 5 1070000 (258000) 980000 [771000 – 1360000]	N = 58 1500000 (344000) 1540000 [954000 – 2180000]
	gMG	N = 7 1750000 (480000) 1570000 [1280000 – 2530000]	N = 47 1240000 (260000) 1250000 [722000 – 1620000]	N = 32 958000 (188000) 972000 [569000 – 1250000]	N = 86 1180000 (336000) 1120000 [664000 – 1940000]

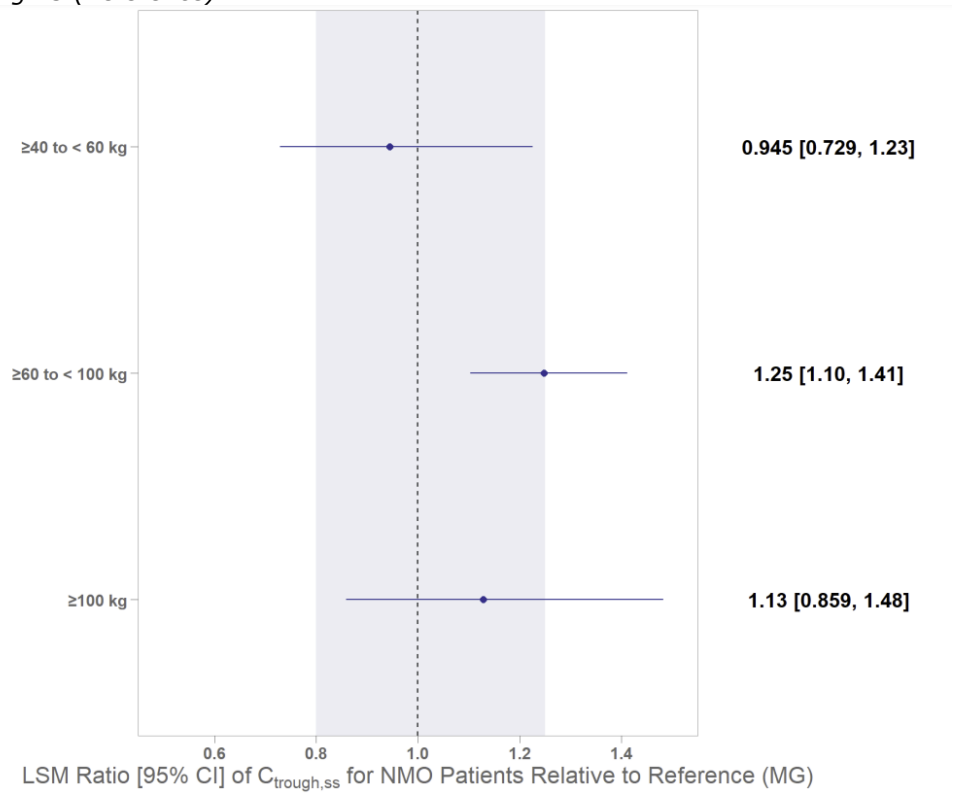
AUCss = area under the serum concentration-time curve at steady state; Cmax,ss = maximum serum concentration under steady-state conditions; Ctrough,ss = concentration at the end of the dosage interval under steady-state conditions; gMG = generalized myasthenia gravis; NMOSD = neuromyelitis optica spectrum disorder; SD = standard deviation
Ravulizumab dosing in patients with body weight ≥ 40 to <60kg (2400mg LD/3000mg MD q8w), ≥60 to < 100kg (2700mg LD/3300mg MD q8w) and ≥ 100kg (3000 mg LD / 3600mg MD q8w).

$C_{trough,ss}$ were similar across indications with the exception of the ≥60 to <100 kg group, whereby the median $C_{trough,ss}$ in patients with NMOSD was 33% higher than patients with gMG. This is likely due to the different body weight distributions <100 kg group.

Consequently, additional comparisons were performed by stratifying across different body weight groups. Ratios of least-squares mean along with 95% confidence interval (CI) were derived for exposure parameters in patients with NMOSD relative to patients with gMG within each body weight group.

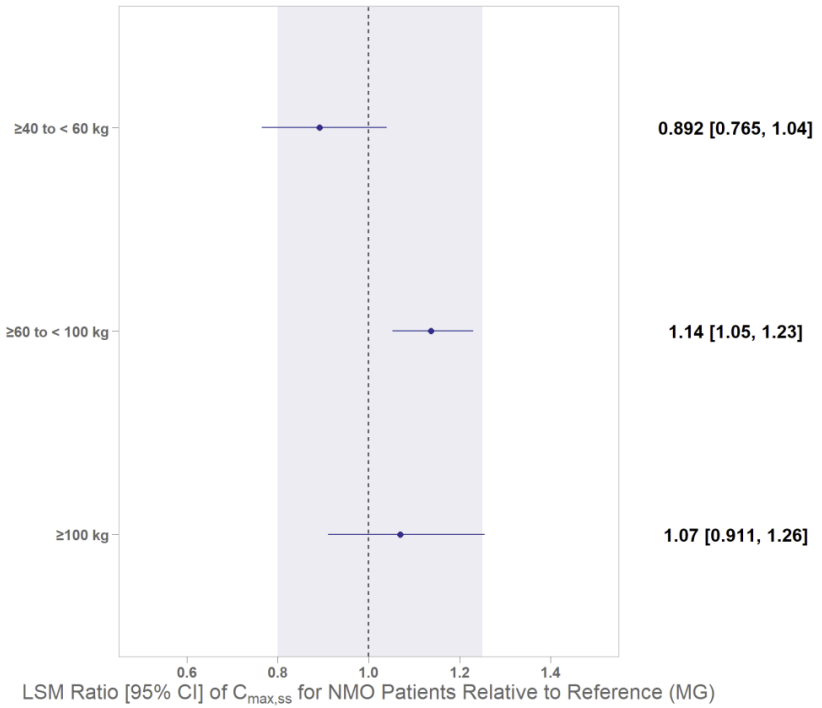
The ratio of least-squares mean with 95% CI of $C_{trough,ss}$ in patients with NMOSD (Test) vs. patients with gMG (Reference) is presented in Figure 7.

Figure 7: Ratio of least-squares mean with 95% CI of $C_{trough,ss}$ Patients with NMOSD (Test) vs. Patients with gMG (Reference)



Ravulizumab dosing in patients with body weight ≥ 40 to < 60 kg (2400 mg LD/3000 mg MD q8w), ≥ 60 to < 100 kg (2700 mg LD/3300 mg MD q8w), and ≥ 100 kg (3000 mg LD/3600 mg MD q8w) in patients with NMOSD or gMG.
CI = confidence interval; Ctrough,ss = concentration at the end of the dosage interval under steady-state conditions; gMG = generalized myasthenia gravis; LD = loading dose; LSM = least squares mean; MD = maintenance dose; MG = myasthenia gravis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; q8w = once every 8 weeks

Figure 8: Ratio of LSM with 95% CI of $C_{max,ss}$ Patients with NMOSD (Test) vs. Patients with gMG (Reference)



Ravulizumab dosing in patients with body weight ≥ 40 to < 60 kg (2400 mg LD/3000 mg MD q8w), ≥ 60 to < 100 kg (2700 mg LD/3300 mg MD q8w), and ≥ 100 kg (3000 mg LD/3600 mg MD q8w) in patients with NMOSD or gMG.

CI = confidence interval; Cmax,ss = maximum serum concentration under steady-state conditions; gMG = generalized myasthenia gravis; LD = loading dose; LSM = least squares mean; MD = maintenance dose; MG = myasthenia gravis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; q8w = once every 8 weeks

Impact of PP/PE or IVIG and Supplemental Doses

As defined in study protocol of ALXN1210-NMO-307, use of PP/PE was allowed as acute therapy.

For patients who received PE/PP, supplemental doses of ravulizumab were to be administered within 4 hours after the PE/PP session completed according to the patient's body weight as described below:

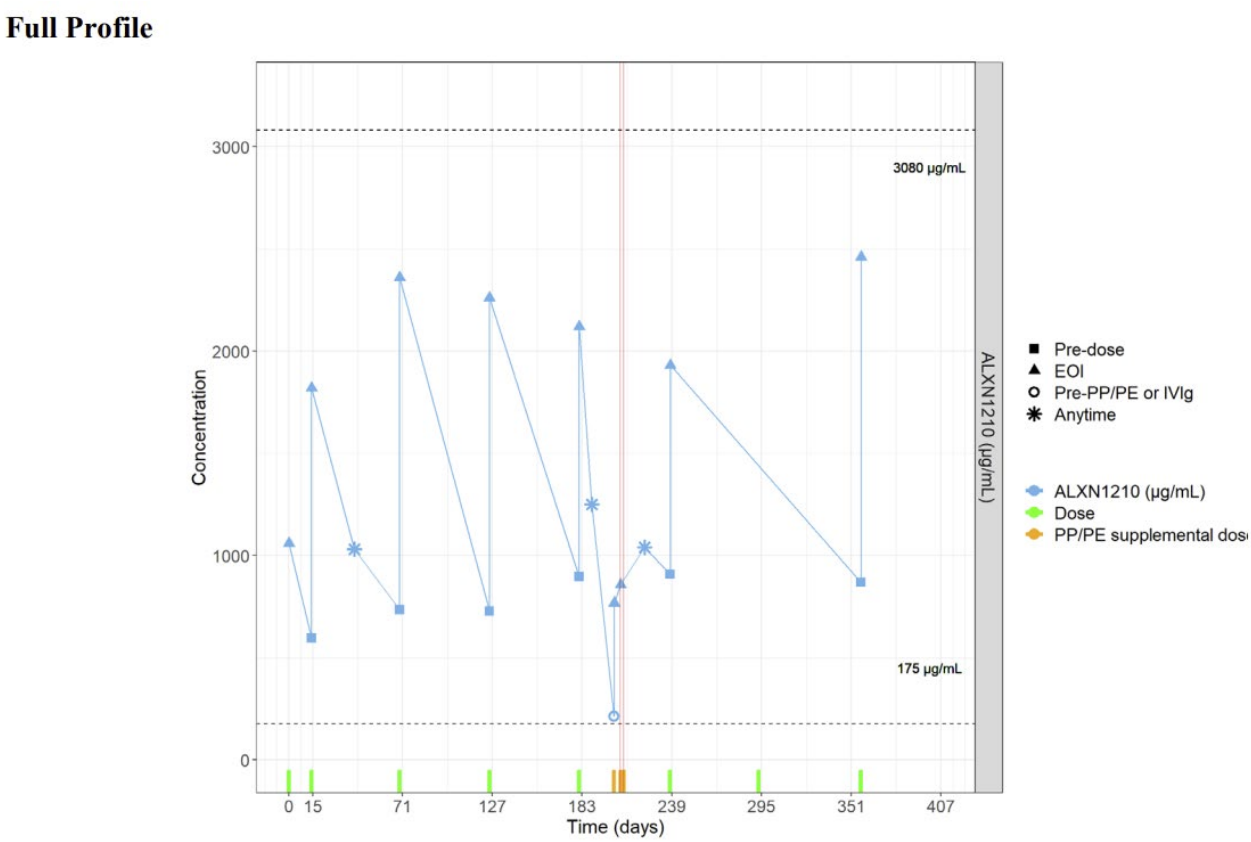
• For a PE/PP intervention during the loading dose phase, patients with body weight ≥ 40 to < 60, ≥ 60 to < 100, or ≥ 100 kg were prescribed supplemental doses of 1200, 1500, or 1500 mg, respectively.

• For a PE/PP intervention during the maintenance dose phase, patients with body weight ≥ 40 to < 60, ≥ 60 to < 100, or ≥ 100 kg were prescribed supplemental doses of 1500, 1800, or 1800 mg, respectively.

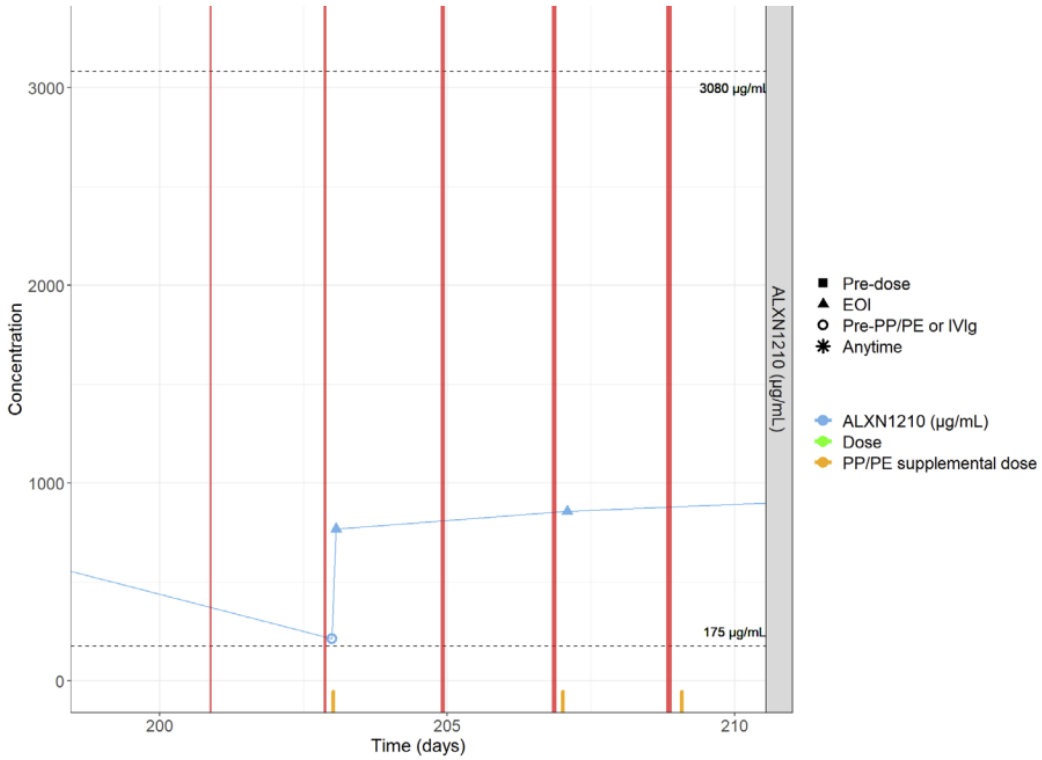
For patients who received IVIg, for all body weight groups, supplemental ravulizumab doses of 600 mg were to be administered within 4 hours after the last session(s) of the IVIg course was completed.

A single patient required 5 PP/PE interventions (of 0.75, 1.03, 1.58, 1.90 and 2.28 hours duration each). The supplemental doses during the maintenance phase (body weight) were 1500mg (59.4kg) except for the last intervention (2.28 hours) that was followed by a supplemental dose of 3000mg (59.9kg).

Figure 9: Impact of PP/PE Interventions and Supplemental Doses on Concentration-Time Profile of Ravulizumab Full Profile (Top Panel) and Days of PP/PE Interventions (Bottom Panel) – single patient.



PE/PP Intervention Event Periods Only

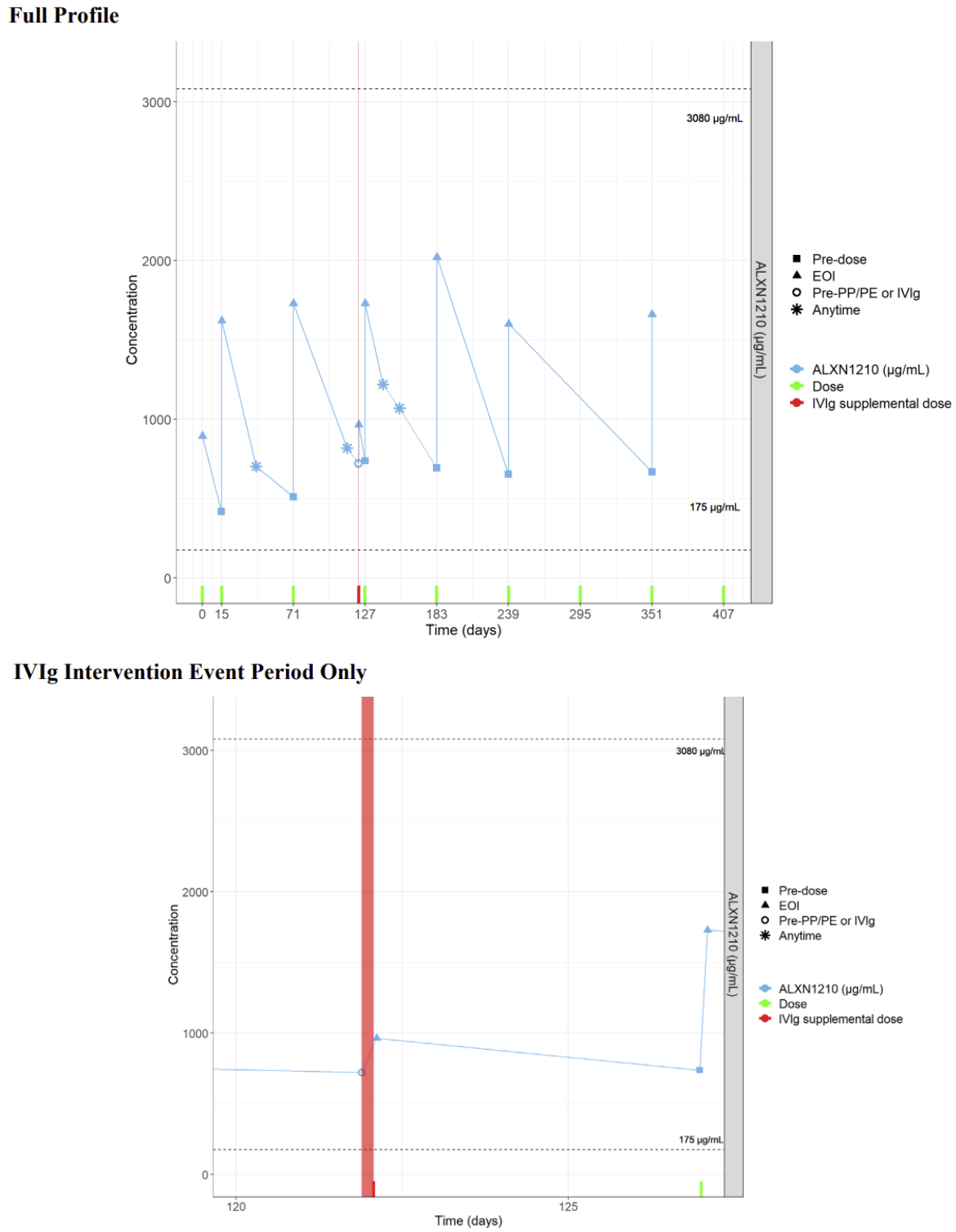


The upper dashed line represents the greatest ravulizumab concentration observed during a clinical study and the lower dashed line represents the PK therapeutic target threshold. Vertical red lines indicate PE/PP intervention.
ALXN1210 = ravulizumab; EOI = end of infusion; IVIg = intravenous immunoglobulin; PE = plasma exchange; PK = pharmacokinetic; PP = plasmapheresis

As defined in study protocol of ALXN1210-NMO-307, use of IVIg was also allowed for patients as acute therapy following an On-trial Relapse. Only one patient required a single IVIg intervention with 4.4 hours of duration of PK impact (derived as the time from that start of IVIg dosing to next PK sample). The patient received a supplemental dose (maintenance) of 600mg.

The impact of each IVIg intervention and the corresponding supplemental dose on individual concentration-time profiles of ravulizumab are presented in Figure 10.

Figure 10: Impact of IVIg Intervention and Supplemental Dose - Concentration-Time Profile of Ravulizumab Full Profile (Top Panel) and Days of IVIg Intervention (Bottom Panel) – single patient



The upper dashed line represents the greatest ravulizumab concentration observed during a clinical study and the lower dashed line represents the PK therapeutic target threshold. Vertical red lines indicate IVIg intervention
ALXN1210 = ravulizumab; EOI = end of infusion; IVIg = intravenous immunoglobulin; PE = plasma exchange; PK = pharmacokinetic; PP = plasmapheresis

Immunogenicity

A total of 53 (91.4%) patients presented with negative ADA at baseline and 5 (9.3%) presented with positive ADA at baseline. All post-dose samples were associated with a negative ADA status, with the

exception of single patient who presented an ADA positive sample at Week 26. This patient also presented a positive ADA sample at baseline. All pre- and post-dose positive samples in patients who received ravulizumab were tested to be negative for neutralising antibodies.

Similar concentration-time profiles of ravulizumab were observed in patients with positive and negative ADA status at baseline

Special populations

Body weight

Mean (SD) estimates of CL and Vc in all patients were 0.00228 L/h (0.000662) and 2.91 L (0.571), respectively. The mean (SD) CL and Vc of ravulizumab increased as a function of body weight. The mean (SD) t ½ of ravulizumab in all patients with NMOSD was 64.3 (11.0) days.

Table 11: Descriptive Statistics of Population PK Parameters of Ravulizumab in Study ALXN1210-NMO-307

Parameters	≥40 to < 60 kg (N=22)	≥60 to < 100 kg (N=31)	≥100 kg (N=5)	All Patients (N=58)
CL (L/h)				
Mean (SD)	0.00195 (0.000455)	0.00231 (0.000493)	0.00354 (0.000877)	0.00228 (0.000662)
Median [2.5th – 97.5th percentile]	0.00184 [0.00131 – 0.00290]	0.00215 [0.00176 – 0.00341]	0.00368 [0.00264 – 0.00469]	0.00213 [0.00141 – 0.00376]
Q (L/h)				
Mean (SD)	0.0128 (0.000925)	0.0165 (0.00202)	0.0229 (0.00152)	0.0156 (0.00329)
Median [2.5th – 97.5th percentile]	0.0131 [0.0106 – 0.0137]	0.0160 [0.0141 – 0.0205]	0.0219 [0.0216 – 0.0246]	0.0147 [0.0111 – 0.0234]
Vc (L)				
Mean (SD)	2.62 (0.350)	2.94 (0.522)	3.95 (0.377)	2.91 (0.571)
Median [2.5th – 97.5th percentile]	2.59 [2.05 – 3.26]	2.89 [2.31 – 4.29]	3.85 [3.51 – 4.44]	2.79 [2.18 – 4.34]
Vp (L)				
Mean (SD)	1.63 (0.126)	1.93 (0.206)	2.48 (0.170)	1.86 (0.296)
Median [2.5th – 97.5th percentile]	1.63 [1.38 – 1.81]	1.88 [1.63 – 2.29]	2.50 [2.30 – 2.71]	1.81 [1.45 – 2.61]
Vss (L)				
Mean (SD)	4.25 (0.441)	4.87 (0.655)	6.43 (0.544)	4.77 (0.819)
Median [2.5th – 97.5th percentile]	4.22 [3.48 – 4.98]	4.76 [4.00 – 6.47]	6.35 [5.81 – 7.15]	4.64 [3.72 – 6.70]
$t_{1/2\beta}$ (days)				
Mean (SD)	66.6 (11.4)	64.0 (10.2)	56.0 (12.7)	64.3 (11.0)
Median [2.5th – 97.5th percentile]	66.2 [44.2 – 85.8]	64.8 [44.6 – 82.8]	49.2 [44.9 – 70.5]	65.1 [44.4 – 83.9]

CL = clearance; Q = intercompartmental clearance; t ½ = terminal elimination half-life; Vc = volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment. Vss = apparent volume of distribution at equilibrium, SD = standard deviation
Ravulizumab dosing in patients with body weight ≥ 40 to <60kg (2400mg LD/3000mg MD q8w), ≥60 to < 100kg (2700mg LD/3300mg MD q8w) and ≥ 100kg (3000 mg LD / 3600mg MD q8w).

Table 12: Descriptive Statistics of Steady State Exposure Parameters of Ravulizumab in Study ALXN1210-NMO-307

Parameters	≥40 to < 60 kg (N=22)	≥60 to < 100 kg (N=31)	≥100 kg (N=5)	All Patients (N=58)
$C_{trough,ss}$ (µg/mL)				
Mean (SD)	867 (236)	789 (191)	540 (178)	797 (223)
Median [2.5th – 97.5th percentile]	877 [463 – 1330]	831 [468 – 1070]	454 [352 – 742]	834 [443 – 1270]
$C_{max,ss}$ (µg/mL)				
Mean (SD)	2020 (340)	1930 (305)	1450 (210)	1930 (343)
Median [2.5th – 97.5th percentile]	2030 [1560 – 2670]	1960 [1430 – 2450]	1480 [1160 – 1680]	1940 [1330 – 2560]
$C_{avg,ss}$ (µg/mL)				
Mean (SD)	1200 (266)	1110 (218)	795 (192)	1120 (256)
Median [2.5th – 97.5th percentile]	1210 [769 – 1710]	1140 [721 – 1410]	729 [573 – 1010]	1150 [710 – 1620]
AUC_{ss} (µg.h/mL)				
Mean (SD)	1610000 (357000)	1490000 (293000)	1070000 (258000)	1500000 (344000)
Median [2.5th – 97.5th percentile]	1630000 [1030000 – 2300000]	1540000 [969000 – 1890000]	980000 [771000 – 1360000]	1540000 [954000 – 2180000]

AUCss = area under the curve over the dosing interval under steady state conditions (ie, 8 weeks); $C_{avg,ss}$ = average concentrations under steady state conditions; $C_{max,ss}$ = maximum concentrations under steady state conditions; $C_{trough,ss}$ = minimum concentrations under steady state conditions
Ravulizumab dosing in patients with body weight ≥ 40 to <60kg (2400mg LD/3000mg MD q8w), ≥60 to < 100kg (2700mg LD/3300mg MD q8w) and ≥ 100kg (3000 mg LD / 3600mg MD q8w).

Patients with body weight ≥40 kg to <60 kg treated with a 3000-mg MD q8w presented median Ctrough,ss, $C_{max,ss,}$ and $C_{avg,ss}$ values 5.5%, 3.5%, and 6.1% higher than patients with body weight ≥ 60 to < 100 kg treated with a 3300-mg MD q8w, respectively.

Patients with body weight ≥100 kg treated with a 3600-mg MD q8w presented median $C_{trough,ss,}$ $C_{max,ss,}$ and $C_{avg,ss}$ values 45%, 25%, and 36% lower than patients with body weight ≥ 60 to < 100 kg treated with a 3300-mg MD q8w, respectively.

Japanese vs non-Japanese patients

Table 13: Descriptive Statistics of PK and Steady State Exposure Parameters of Ravulizumab in Study ALXN1210-NMO-307 Japanese and Non-Japanese Patients

Parameters	Japanese (N=9)	Non-Japanese (N=49)	All Patients (N=58)
CL (L/h)			
Mean (SD)	0.00186 (0.000429)	0.00235 (0.000672)	0.00228 (0.000662)
Median [2.5th – 97.5th percentile]	0.00174 [0.00154 – 0.00274]	0.00218 [0.00139 – 0.00379]	0.00213 [0.00141 – 0.00376]
Q (L/h)			
Mean (SD)	0.0131 (0.00147)	0.0161 (0.00331)	0.0156 (0.00329)
Median [2.5th – 97.5th percentile]	0.0127 [0.0110 – 0.0155]	0.0149 [0.0118 – 0.0239]	0.0147 [0.0111 – 0.0234]
Vc (L)			
Mean (SD)	2.54 (0.403)	2.97 (0.574)	2.91 (0.571)
Median [2.5th – 97.5th percentile]	2.39 [2.16 – 3.33]	2.89 [2.26 – 4.38]	2.79 [2.18 – 4.34]
Vp (L)			
Mean (SD)	1.63 (0.138)	1.91 (0.298)	1.86 (0.296)
Median [2.5th – 97.5th percentile]	1.63 [1.43 – 1.82]	1.82 [1.53 – 2.63]	1.81 [1.45 – 2.61]
Vss (L)			
Mean (SD)	4.17 (0.446)	4.88 (0.826)	4.77 (0.819)
Median [2.5th – 97.5th percentile]	4.16 [3.69 – 4.97]	4.72 [3.85 – 6.70]	4.64 [3.72 – 6.70]
$t_{1/2\beta}$ (days)			
Mean (SD)	67.9 (10.6)	63.6 (11.1)	64.3 (11.0)
Median [2.5th – 97.5th percentile]	68.8 [48.0 – 80.1]	64.8 [44.6 – 84.6]	65.1 [44.4 – 83.9]
$C_{trough,ss}$ (µg/mL)			
Mean (SD)	922 (205)	774 (220)	797 (223)
Median [2.5th – 97.5th percentile]	956 [542 – 1190]	746 [441 – 1270]	834 [443 – 1270]
$C_{max,ss}$ (µg/mL)			
Mean (SD)	2140 (323)	1880 (334)	1930 (343)
Median [2.5th – 97.5th percentile]	2140 [1620 – 2590]	1890 [1320 – 2440]	1940 [1330 – 2560]
$C_{avg,ss}$ (µg/mL)			
Mean (SD)	1270 (230)	1090 (252)	1120 (256)
Median [2.5th – 97.5th percentile]	1280 [841 – 1570]	1060 [705 – 1610]	1150 [710 – 1620]
AUC_{ss} (µg.h/mL)			
Mean (SD)	1710000 (310000)	1460000 (339000)	1500000 (344000)
Median [2.5th – 97.5th percentile]	1730000 [1130000 – 2110000]	1420000 [948000 – 2160000]	1540000 [954000 – 2180000]

CL = clearance; Q = intercompartmental clearance; $t_{1/2}$ = terminal elimination half-life; Vc = volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment. Vss = apparent volume of distribution at equilibrium, SD = standard deviation; AUC_{ss} = area under the curve over the dosing interval under steady state conditions (ie, 8 weeks); $C_{avg,ss}$ = average concentrations under steady state conditions; $C_{max,ss}$ = maximum concentrations under steady state conditions; $C_{trough,ss}$ = minimum concentrations under steady state conditions

In Japanese patients ≥40 to < 60 kg, the median $C_{trough,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ of ravulizumab were 13%, 23%, and 8.5% higher than those observed in non-Japanese patients, respectively (Table 14).

In Japanese patients ≥60 to 100 kg, the median $C_{trough,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ of ravulizumab were 29%, 24%, and 25% higher than those observed in non-Japanese patients, respectively (Table 14).

Table 14: Descriptive Statistics of Steady State Exposure Parameters of Ravulizumab in Study ALXN1210-NMO-307 - Japanese and Non-Japanese Patients by Body Weight Groups

Parameters	≥40 to < 60 kg		≥60 to < 100 kg		≥100 kg
	Japanese (N=7)	Non-Japanese (N=15)	Japanese (N=2)	Non-Japanese (N=29)	Non-Japanese (N=5)
$C_{trough,ss}$ (µg/mL)					
Mean (SD)	884 (194)	859 (259)	1050 (NA)	771 (177)	540 (178)
Median [2.5th – 97.5th percentile]	956 [522 – 1010]	844 [495 – 1350]	1050 [886 – 1220]	816 [466 – 1010]	454 [352 – 742]
$C_{max,ss}$ (µg/mL)					
Mean (SD)	2080 (306)	2000 (362)	2390 (NA)	1900 (282)	1450 (210)
Median [2.5th – 97.5th percentile]	2140 [1620 – 2390]	1950 [1560 – 2750]	2390 [2150 – 2620]	1930 [1420 – 2350]	1480 [1160 – 1680]
$C_{avg,ss}$ (µg/mL)					
Mean (SD)	1230 (220)	1190 (291)	1420 (NA)	1090 (202)	795 (192)
Median [2.5th – 97.5th percentile]	1280 [821 – 1390]	1180 [793 – 1750]	1420 [1240 – 1610]	1140 [721 – 1340]	729 [573 – 1010]
AUC_{ss} (µg.h/mL)					
Mean (SD)	1650000 (296000)	1600000 (391000)	1910000 (NA)	1460000 (271000)	1070000 (258000)
Median [2.5th – 97.5th percentile]	1730000 [1100000 – 1870000]	1590000 [1070000 – 2350000]	1910000 [1660000 – 2160000]	1530000 [969000 – 1800000]	980000 [771000 – 1360000]

AUC_{ss} = area under the curve over the dosing interval under steady state conditions (ie, 8 weeks); $C_{avg,ss}$ = average concentrations under steady state conditions; $C_{max,ss}$ = maximum concentrations under steady state conditions; $C_{trough,ss}$ = minimum concentrations under steady state conditions; NA = not applicable. Note: a standard deviation was not derived for a sample size less than three

2.3.3. Pharmacodynamics

Mechanism of action

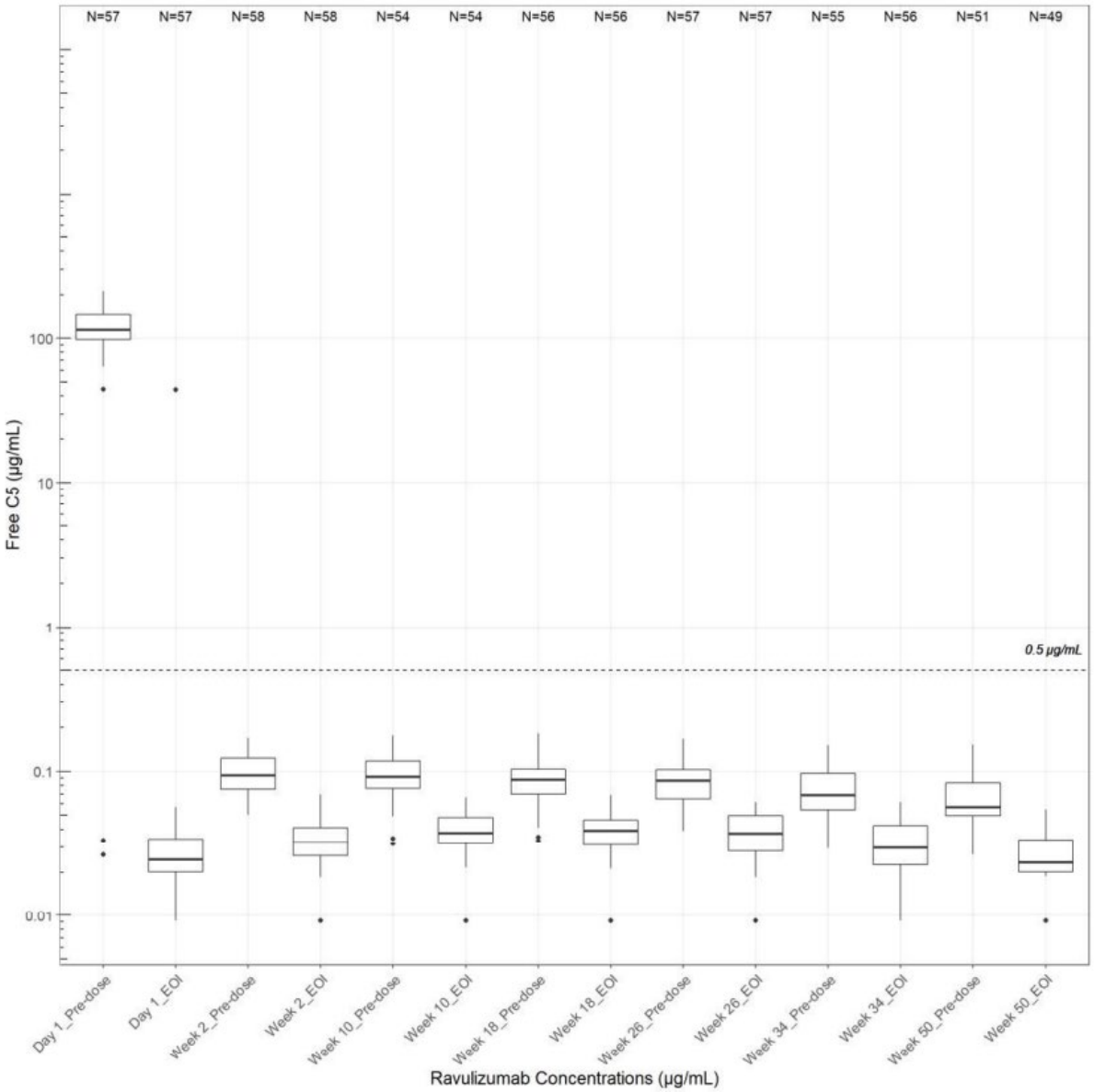
Ravulizumab is a terminal complement inhibitor that specifically binds to C5 with high affinity. This action inhibits the enzymatic cleavage of C5 and thereby prevents the generation of the proinflammatory/prothrombotic complement activation product, C5a, and the MAC, formed by C5b-9, which are responsible for the Ab-mediated destruction of astrocytes associated with anti-AQP4 antibody-positive NMOSD. By binding specifically to C5, ravulizumab antagonizes terminal complement-mediated inflammation, cell activation, and cell lysis. This mechanism of action provides a therapeutic rationale for the use of ravulizumab in NMOSD.

2.3.4. PK/PD modelling

Exploratory Analysis of PK and PD

Longitudinal concentrations of free C5 (semi-log scale) in patients during the primary treatment period in study ALXN1210-NMO-307 are presented in Figure 11.

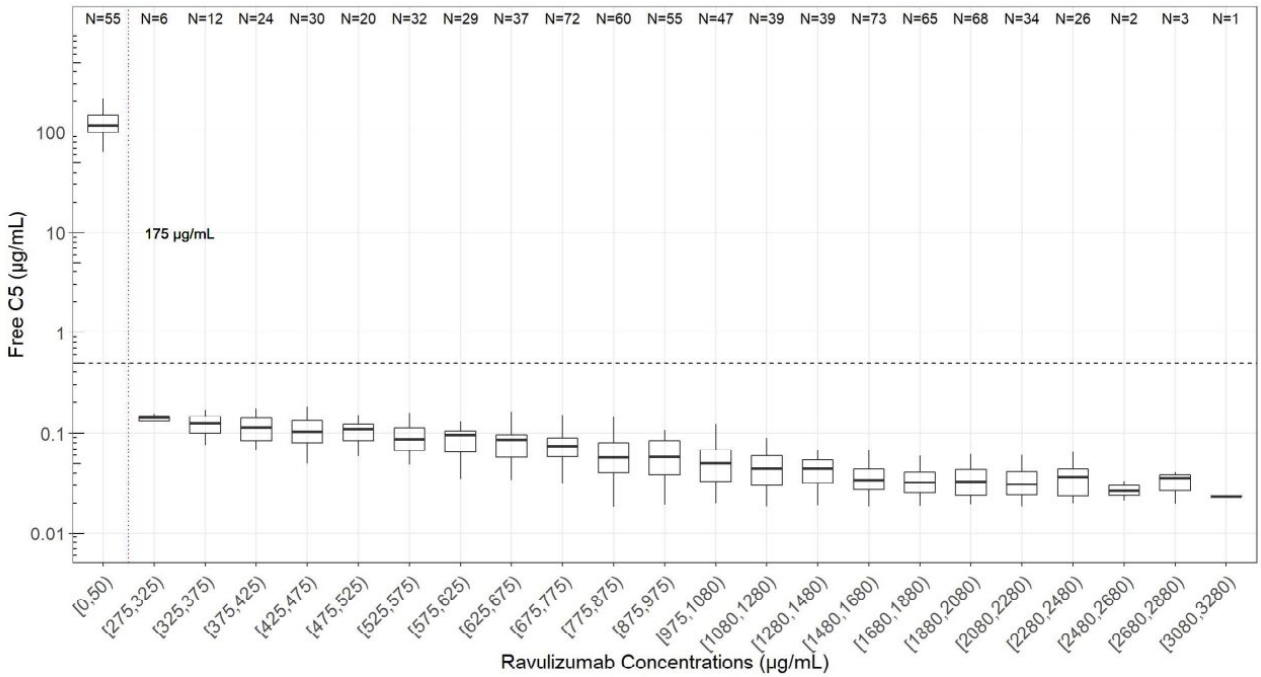
Figure 11: Longitudinal Profiles of Free C5 in the Primary Treatment Period Study ALXN1210-NMO-307



Note 1: On Day 1_Pre-dose, two outlier samples were observed: one patient presented a free C5 concentration of 0.0264 µg/mL and a ravulizumab BLQ concentration, and another patient presented a free C5 concentration of 0.0335 µg/mL and a ravulizumab concentration of 1200 µg/mL
Note 2: On Day1_EOI, an outlier sample was observed: one patient presented a free C5 concentration of 44.1 µg/mL and a ravulizumab concentration at EOI of 972 µg/mL. There is a possibility of a sample switch/mislabel between the "on day 1_predose" and "on day 1_EOI"sample in this subject.

A total of 58 patients with at least one measurable concentration of ravulizumab and a corresponding measurable concentration of free C5 was included in the PK/PD analysis. Based on a total of 851 samples, 819 (96.2%) were included in the exploratory PK/PD analysis.

Figure 12: PK/PD Relationship Ravulizumab and Free C5 Concentrations in the Primary Treatment Period Study ALXN1210-NMO-307



Note: Only samples with PK and a corresponding PD measurements are presented in the above figure. For graphical presentation, ravulizumab concentrations that were BLQ prior to dosing on Day 1 were set to 0 µg/mL. No ravulizumab concentration was observed between 50 and 275 µg/mL.

Figure 13: Summary of Serum Ravulizumab and Free C5 Concentrations within Thresholds of Interest

Study Drug	Serum Drug Concentration		Serum Free C5 Concentration	
	All Concentrations > Threshold* n (%)	≥ 1 Concentration ≤ Threshold* n (%)	All Concentrations < 0.5 µg/mL n (%)	≥ 1 Concentration ≥ 0.5 µg/mL n (%)
Ravulizumab (N = 58)	57 (98.3)	1 (1.7%)	57 (98.3%)	1 (1.7%)

* Threshold for serum concentration of ravulizumab is 175 µg/mL

Exposure-Safety relationship

The probability of a TEAE observed as a function of Cmax,ss and AUCss are presented in Table 15 and Table 16, respectively.

Table 15: Probability of TEAEs as a Function of Ravulizumab Maximum Concentration at Steady State in Study ALXN1210-NMO-307

TEAE	$C_{max,ss}$ 1st Quartile 1139 – 1691 µg/mL (N = 15)	2nd Quartile 1711 – 1935 µg/mL (N = 14)	3rd Quartile 1951 – 2100 µg/mL (N = 14)	4th Quartile 2138 – 2909 µg/mL (N = 15)	Overall (N = 58)
Any TEAE					
n	14	14	11	12	51
%	93.3%	100.0%	78.6%	80.0%	87.9%
95% CI	[68.1% – 99.8%]	[76.8% – 100.0%]	[49.2% – 95.3%]	[51.9% – 95.7%]	[76.7% – 95.0%]
Headache					
n	4	2	3	4	13
%	26.7%	14.3%	21.4%	26.7%	22.4%
95% CI	[7.8% – 55.1%]	[1.8% – 42.8%]	[4.7% – 50.8%]	[7.8% – 55.1%]	[12.5% – 35.3%]
COVID-19					
n	2	4	1	0	7
%	13.3%	28.6%	7.1%	0.0%	12.1%
95% CI	[1.7% – 40.5%]	[8.4% – 58.1%]	[0.2% – 33.9%]	[0.0% – 21.8%]	[5.0% – 23.3%]
Back pain					
n	3	2	0	1	6
%	20.0%	14.3%	0.0%	6.7%	10.3%
95% CI	[4.3% – 48.1%]	[1.8% – 42.8%]	[0.0% – 23.2%]	[0.2% – 31.9%]	[3.9% – 21.2%]
Cystitis					
n	0	3	0	2	5
%	0.0%	21.4%	0.0%	13.3%	8.6%
95% CI	[0.0% – 21.8%]	[4.7% – 50.8%]	[0.0% – 23.2%]	[1.7% – 40.5%]	[2.9% – 19.0%]
Pyrexia					
n	1	3	0	1	5
%	6.7%	21.4%	0.0%	6.7%	8.6%
95% CI	[0.2% – 31.9%]	[4.7% – 50.8%]	[0.0% – 23.2%]	[0.2% – 31.9%]	[2.9% – 19.0%]
Upper respiratory tract infection					
n	1	2	1	1	5
%	6.7%	14.3%	7.1%	6.7%	8.6%
95% CI	[0.2% – 31.9%]	[1.8% – 42.8%]	[0.2% – 33.9%]	[0.2% – 31.9%]	[2.9% – 19.0%]
Urinary tract infection					
n	1	3	1	0	5
%	6.7%	21.4%	7.1%	0.0%	8.6%
95% CI	[0.2% – 31.9%]	[4.7% – 50.8%]	[0.2% – 33.9%]	[0.0% – 21.8%]	[2.9% – 19.0%]
Arthralgia					
n	0	2	1	1	4
%	0.0%	14.3%	7.1%	6.7%	6.9%
95% CI	[0.0% – 21.8%]	[1.8% – 42.8%]	[0.2% – 33.9%]	[0.2% – 31.9%]	[1.9% – 16.7%]
Dizziness					
n	1	1	0	2	4
%	6.7%	7.1%	0.0%	13.3%	6.9%
95% CI	[0.2% – 31.9%]	[0.2% – 33.9%]	[0.0% – 23.2%]	[1.7% – 40.5%]	[1.9% – 16.7%]
Infusion related reaction					
n	3	1	0	0	4
%	20.0%	7.1%	0.0%	0.0%	6.9%
95% CI	[4.3% – 48.1%]	[0.2% – 33.9%]	[0.0% – 23.2%]	[0.0% – 21.8%]	[1.9% – 16.7%]
Chills					
n	0	2	1	0	3
%	0.0%	14.3%	7.1%	0.0%	5.2%
95% CI	[0.0% – 21.8%]	[1.8% – 42.8%]	[0.2% – 33.9%]	[0.0% – 21.8%]	[1.1% – 14.4%]

Constipation					
n	0	1	1	1	3
%	0.0%	7.1%	7.1%	6.7%	5.2%
95% CI	[0.0% – 21.8%]	[0.2% – 33.9%]	[0.2% – 33.9%]	[0.2% – 31.9%]	[1.1% – 14.4%]
Cough					
n	1	1	1	0	3
%	6.7%	7.1%	7.1%	0.0%	5.2%
95% CI	[0.2% – 31.9%]	[0.2% – 33.9%]	[0.2% – 33.9%]	[0.0% – 21.8%]	[1.1% – 14.4%]
Fatigue					
n	1	0	0	2	3
%	6.7%	0.0%	0.0%	13.3%	5.2%
95% CI	[0.2% – 31.9%]	[0.0% – 23.2%]	[0.0% – 23.2%]	[1.7% – 40.5%]	[1.1% – 14.4%]
Malaise					
n	0	2	1	0	3
%	0.0%	14.3%	7.1%	0.0%	5.2%
95% CI	[0.0% – 21.8%]	[1.8% – 42.8%]	[0.2% – 33.9%]	[0.0% – 21.8%]	[1.1% – 14.4%]
Migraine					
n	2	1	0	0	3
%	13.3%	7.1%	0.0%	0.0%	5.2%
95% CI	[1.7% – 40.5%]	[0.2% – 33.9%]	[0.0% – 23.2%]	[0.0% – 21.8%]	[1.1% – 14.4%]
Sinusitis					
n	3	0	0	0	3
%	20.0%	0.0%	0.0%	0.0%	5.2%
95% CI	[4.3% – 48.1%]	[0.0% – 23.2%]	[0.0% – 23.2%]	[0.0% – 21.8%]	[1.1% – 14.4%]
Vomiting					
n	1	1	0	1	3
%	6.7%	7.1%	0.0%	6.7%	5.2%
95% CI	[0.2% – 31.9%]	[0.2% – 33.9%]	[0.0% – 23.2%]	[0.2% – 31.9%]	[1.1% – 14.4%]

TEAE = treatment emergent adverse effect; COVID-19 = coronavirus disease; Cmax,ss = maximum concentrations under steady state conditions; CI = confidence interval Note: 95% CI are calculated using the Clopper and Pearson method.

Table 16: Probability of TEAEs as a Function of Ravulizumab Area Under the Curve at Steady State in Study ALXN1210-NMO-307

TEAE	AUC_{ss}				Overall (N = 58)
	1st Quartile 751445 – 1273522 µg.h/mL (N = 15)	2nd Quartile 1294308 – 1537803 µg.h/mL (N = 14)	3rd Quartile 1545971 – 1734214 µg.h/mL (N = 14)	4th Quartile 1759706 – 2437742 µg.h/mL (N = 15)	
Any TEAE					
n	14	13	12	12	51
%	93.3%	92.9%	85.7%	80.0%	87.9%
95% CI	[68.1% – 99.8%]	[66.1% – 99.8%]	[57.2% – 98.2%]	[51.9% – 95.7%]	[76.7% – 95.0%]
Headache					
n	4	2	4	3	13
%	26.7%	14.3%	28.6%	20.0%	22.4%
95% CI	[7.8% – 55.1%]	[1.8% – 42.8%]	[8.4% – 58.1%]	[4.3% – 48.1%]	[12.5% – 35.3%]
COVID-19					
n	2	4	1	0	7
%	13.3%	28.6%	7.1%	0.0%	12.1%
95% CI	[1.7% – 40.5%]	[8.4% – 58.1%]	[0.2% – 33.9%]	[0.0% – 21.8%]	[5.0% – 23.3%]
Back pain					
n	4	1	1	0	6
%	26.7%	7.1%	7.1%	0.0%	10.3%
95% CI	[7.8% – 55.1%]	[0.2% – 33.9%]	[0.2% – 33.9%]	[0.0% – 21.8%]	[3.9% – 21.2%]
Cystitis					
n	1	1	2	1	5
%	6.7%	7.1%	14.3%	6.7%	8.6%
95% CI	[0.2% – 31.9%]	[0.2% – 33.9%]	[1.8% – 42.8%]	[0.2% – 31.9%]	[2.9% – 19.0%]
Pyrexia					
n	1	3	0	1	5
%	6.7%	21.4%	0.0%	6.7%	8.6%
95% CI	[0.2% – 31.9%]	[4.7% – 50.8%]	[0.0% – 23.2%]	[0.2% – 31.9%]	[2.9% – 19.0%]

Upper respiratory tract infection					
n	0	2	2	1	5
%	0.0%	14.3%	14.3%	6.7%	8.6%
95% CI	[0.0% – 21.8%]	[1.8% – 42.8%]	[1.8% – 42.8%]	[0.2% – 31.9%]	[2.9% – 19.0%]
Urinary tract infection					
n	1	2	1	1	5
%	6.7%	14.3%	7.1%	6.7%	8.6%
95% CI	[0.2% – 31.9%]	[1.8% – 42.8%]	[0.2% – 33.9%]	[0.2% – 31.9%]	[2.9% – 19.0%]
Arthralgia					
n	1	1	2	0	4
%	6.7%	7.1%	14.3%	0.0%	6.9%
95% CI	[0.2% – 31.9%]	[0.2% – 33.9%]	[1.8% – 42.8%]	[0.0% – 21.8%]	[1.9% – 16.7%]
Dizziness					
n	1	1	1	1	4
%	6.7%	7.1%	7.1%	6.7%	6.9%
95% CI	[0.2% – 31.9%]	[0.2% – 33.9%]	[0.2% – 33.9%]	[0.2% – 31.9%]	[1.9% – 16.7%]
Infusion related reaction					
n	4	0	0	0	4
%	26.7%	0.0%	0.0%	0.0%	6.9%
95% CI	[7.8% – 55.1%]	[0.0% – 23.2%]	[0.0% – 23.2%]	[0.0% – 21.8%]	[1.9% – 16.7%]
Chills					
n	0	2	1	0	3
%	0.0%	14.3%	7.1%	0.0%	5.2%
95% CI	[0.0% – 21.8%]	[1.8% – 42.8%]	[0.2% – 33.9%]	[0.0% – 21.8%]	[1.1% – 14.4%]
Constipation					
n	0	1	0	2	3
%	0.0%	7.1%	0.0%	13.3%	5.2%
95% CI	[0.0% – 21.8%]	[0.2% – 33.9%]	[0.0% – 23.2%]	[1.7% – 40.5%]	[1.1% – 14.4%]
Cough					
n	1	1	1	0	3
%	6.7%	7.1%	7.1%	0.0%	5.2%
95% CI	[0.2% – 31.9%]	[0.2% – 33.9%]	[0.2% – 33.9%]	[0.0% – 21.8%]	[1.1% – 14.4%]
Fatigue					
n	1	0	1	1	3
%	6.7%	0.0%	7.1%	6.7%	5.2%
95% CI	[0.2% – 31.9%]	[0.0% – 23.2%]	[0.2% – 33.9%]	[0.2% – 31.9%]	[1.1% – 14.4%]
Malaise					
n	0	2	1	0	3
%	0.0%	14.3%	7.1%	0.0%	5.2%
95% CI	[0.0% – 21.8%]	[1.8% – 42.8%]	[0.2% – 33.9%]	[0.0% – 21.8%]	[1.1% – 14.4%]
Migraine					
n	2	1	0	0	3
%	13.3%	7.1%	0.0%	0.0%	5.2%
95% CI	[1.7% – 40.5%]	[0.2% – 33.9%]	[0.0% – 23.2%]	[0.0% – 21.8%]	[1.1% – 14.4%]
Sinusitis					
n	2	1	0	0	3
%	13.3%	7.1%	0.0%	0.0%	5.2%
95% CI	[1.7% – 40.5%]	[0.2% – 33.9%]	[0.0% – 23.2%]	[0.0% – 21.8%]	[1.1% – 14.4%]
Vomiting					
n	1	1	0	1	3
%	6.7%	7.1%	0.0%	6.7%	5.2%
95% CI	[0.2% – 31.9%]	[0.2% – 33.9%]	[0.0% – 23.2%]	[0.2% – 31.9%]	[1.1% – 14.4%]

TEAE = treatment emergent adverse effect; COVID-19 = coronavirus disease; CI = confidence interval 95% CI are calculated using the Clopper and Pearson method

2.3.5. Discussion on clinical pharmacology

Ravulizumab as monotherapy for the treatment of adult patients with NMOSD who are AQP4 antibody-positive is being evaluated in the pivotal phase 3 study ALXN1210-NMO-307 (ongoing). The clinical pharmacology update includes data from the ALXN1210-NMO-307 study (primary treatment period, up

to week 50), which includes PK, PD and immunogenicity observations in 58 patients receiving ravulizumab.

The final dataset for the current popPK model development included 792 observation records from 58 patients with NMOSD treated with ravulizumab in the primary treatment period of the pivotal study ALXN1210-NMO-307.

A popPK analysis was previously performed in healthy volunteers and patients with PNH. Ravulizumab PK was described using a 2-compartment model with linear clearance and included the effect of body weight on clearance and volume parameters. Subsequently, a population PK analysis was developed in patients with gMG. A 2-compartment model with first-order elimination and estimated allometric exponents for body weight on clearance and volume parameters resulted in an adequate description of the data. In this case, PK parameters of the peripheral compartment (Q and Vp) were fixed to the value obtained in patients with PNH and healthy subjects, which could be adequate based on the experimental evidence collected. The estimated allometric exponents for body weight on CL/Q and central/peripheral compartment volume (Vc/Vp) (0,772 and 1.01 respectively), which are close to the standard allometric exponents for clearance (0.75) and apparent volume of distribution (1). Rescue therapy was allowed for patient with gMG in the pivotal study and therefore the effect of PP/PE or IVIg on CL were investigated as part of the base model development. Finally, the effect of PP/PE and IVIg therapy were incorporated on CL. Overall, the modelling strategy and evaluation is endorsed.

Residuals were described by proportional error model. IIV was included on CL, Vc and the percentage of coefficient of variation was moderate (17.9% and 12.9%, respectively). Structural model parameters were estimated with good precision (RSE values of 2.45% and 2.09% for CL and Vc respectively). The RSE of PK parameters were below 15%, except for the effect of BMI on volume parameters (RSE=31.9%) showing the adequacy of the final parameter estimates.

The covariate analysis revealed a clinically relevant effect of body weight on $C_{trough,ss}$ and $C_{max,ss,}$ showing that differences >20% are expected in patients with body weight <41 and >125 kg compared to the reference patient (70 kg).

Model performance evaluation of the final popPK through the pcVPC suggests the adequacy of the current model to describe the overall data of the ALXN1210-NMO-307 study.

The exposure comparison across the different indications (NMOSD and gMG) suggested similar exposure levels for each sub-group of body weight patients evaluated (40-60, 60-100, ≥100 kg). In general, slightly higher exposure levels were predicted in NMOSD patients compared to gMG patients. The overall trend suggests lower exposure for high body weight patients (≥100 kg) for both indications compared to patients with lower body weight, despite the different dosing regimens based on body weight. However, based on the PK/PD threshold (175 µg/mL) and the range of exposure levels in patients with body weight ≥100 kg, no efficacy concern is expected with the proposed dosing regimen.

In Japanese patients ≥60 to 100 kg, the median $C_{trough,ss,}$ $C_{max,ss,}$ and $C_{avg,ss}$ of ravulizumab were 29%, 24%, and 25% higher than those observed in non-Japanese patients, respectively. However, it seems premature to establish any conclusion since only 2 Japanese patients were enrolled in this body weight group. Based on these results, additional experimental evidence is required in order to support the dosing regimen in Japanese patients.

Immunogenicity was assessed in Study ALXN1210-NMO-307. The impact of immunogenicity after ravulizumab treatment showed no relevant concerns.

The PK/PD relationship was empirically established through the graphical representation of experimental PK (serum ravulizumab concentration) and PD (free C5 concentration) observations and no model-based approach has been conducted. Based on experimental evidence, concentrations of ravulizumab greater

than 175 µg/mL were associated with free C5 concentrations below 0.5 µg/mL. The exploratory PK/PD analysis showed that 57 patients presented all ravulizumab concentrations above the threshold and also presented values of free C5 below 0.5 µg/mL. Only 1 patient had concentrations of ravulizumab post dose below the threshold.

The exposure-safety evaluation revealed no clinically relevant relationship of ravulizumab quartiles and the incidence/probability of adverse events (AE).

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology properties of ravulizumab as monotherapy for the treatment of adult patients with NMOSD who are AQP4 antibody-positive has been adequately characterized. A previously developed popPK model has been updated based on the clinical evidence collected in ALXN1210-NMO-307 study. The results suggest similar exposure across the different sub-groups of body weight patients and the adequacy of the proposed dosing regimen based on the PD target levels (free C5).

2.4. Clinical efficacy

The ravulizumab clinical development program in NMOSD includes 2 clinical studies:

• An ongoing phase 3 randomized, external placebo-controlled, open-label, multicenter study (Study ALXN1210-NMO-307; submitted)

• A phase 2/3, open-label, historical-controlled, multicenter extension study of children and adolescents (Study ALXN1210-NMO-317; initiated on 23 Jun 2022)

2.4.1. Dose response study

No specific dose response study has been submitted for this extension of the indication. The recommended body weight-based ravulizumab treatment regimen for adult patients with NMOSD is identical to the approved dosing for adult patients in other indications.

2.4.2. Main study

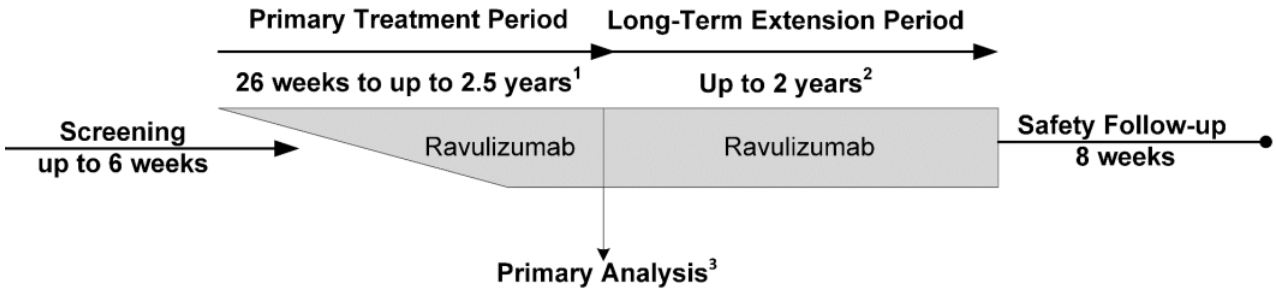
Title of Study: A Phase 3, External Placebo-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD)

Methods

Study ALXN1210-NMO-307 is an ongoing Phase 3, external placebo-controlled, open-label, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with NMOSD.

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

Figure 14: Study ALXN1210-NMO-307 Schematic



1All eligible patients received open-label ravulizumab during the Primary Treatment Period. The end of the Primary Treatment Period was triggered when all patients had completed, or discontinued prior to, 50 weeks on study.
Patients who completed 50 weeks on study prior to this point remained in the Primary Treatment Period until it was completed for all patients.
2 The Primary Treatment Period ended and the Long-Term Extension Period started when all patients completed their EOPT Visit. Patients continue to receive ravulizumab during the Long-Term Extension Period for up to approximately 2 years, or until ravulizumab is approved for the studied indication and/or available (in accordance with country-specific regulations), whichever occurs first.
3The primary analysis for regulatory submission was conducted at the end of the Primary Treatment Period, and included all available efficacy, safety, and PK/PD/ADA data collected from the Primary Treatment Period.
ADA = antidrug antibody; EOPT = End of Primary Treatment; PD = pharmacodynamics; PK = pharmacokinetics

Study participants

Key inclusion criteria:

• Male or female patients ≥ 18 years of age who were anti-AQP4 Ab-positive and had a diagnosis of NMOSD as defined by the 2015 international consensus diagnostic criteria. A historically positive anti-AQP4 Ab test was acceptable if the test was performed using an acceptable, validated cell-based assay from an accredited laboratory.

• At least 1 relapse in the last 12 months prior to the Screening Period.

• Expanded Disability Status Scale (EDSS) score ≤ 7

• Vaccinated against Neisseria meningitidis within 3 years prior to, or at the time of, initiating ravulizumab

• Stable doses of background immunosuppressive therapies were permitted, but not required

Key exclusion criteria:

• Participation in Study ECU-NMO-301, regardless of the study drug received (eculizumab or placebo)

• History of unexplained infections

• Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1

• Use of rituximab or mitoxantrone within 3 months prior to Screening, use of IVIg within 3 weeks prior to Screening, or previous or current treatment with a complement inhibitor.

Patients were to be discontinued from study drug in the case of serious hypersensitivity reactions, severe uncontrolled infection, use of disallowed medication, pregnancy or planned pregnancy, or if the Sponsor or the Investigator deemed it to be in the best interest of the patient.

The external control is the placebo arm of Study ECU-NMO-301.

Treatments

Patients received open-label ravulizumab, supplied as a 10 mg/mL solution during the Primary Treatment Period. All doses, including the loading dose on Day 1 and maintenance doses on Day 15 and q8w thereafter, were administered by IV infusion. Dosages were based on the patient's body weight:

Table 17: Loading and maintenance dose based on body weight (kg)

	Body Weight (kg)[a]	Dose (mg)
Loading dose	≥ 40 to < 60	2400
	≥ 60 to < 100	2700
	≥ 100	3000
Maintenance dose	≥ 40 to < 60	3000
	≥ 60 to < 100	3300
	≥ 100	3600

a Dose regimen was based on the last recorded study visit body weight. This was commonly the current visit as weight was measured prior to dose preparation on the day of the visit. If the study drug was prepared the night before a visit, the weight from the most recent prior study visit was used.

During the Long-Term Extension Period, patients were changed from the 10 mg/mL formulation to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen.

As per the study design, the end of the Primary Treatment Period was to be triggered when 2 patients had an adjudicated On-trial Relapse and all patients had completed, or discontinued prior to, 26 weeks on study. If 2 patients had not had an adjudicated On-trial Relapse by the time all patients had completed, or discontinued prior to, 50 weeks on study, the end of the Primary Treatment Period was to be triggered at that time.

Patients who entered the study receiving supportive IST (including corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, or cyclophosphamide) for the prevention of relapse, either in combination or monotherapy, must have been on a stable dosing regimen of adequate duration prior to Screening with no plan to change the dose during the initial study period (starting from the Screening Visit). Changes were allowed per protocol after 106 weeks in the study.

Supplemental Doses: During the study, PE/ PP or IVIg was allowed at the discretion of the treating physician for treatment of an On-trial Relapse. If PE/PP was administered for On-trial Relapse, a supplemental dose of ravulizumab was administered within 4 hours after each session of PE/PP was completed, and was based on the most recently administered ravulizumab dose. If PE/PP was administered on a day of scheduled dosing visit, patients received the regularly-scheduled dose of ravulizumab within 1 to 2 hours after the PE/PP session. If IVIg was administered, a ravulizumab supplemental dose was administered after the last dose of IVIg in the series.

Objectives / Endpoints

Table 18: Objectives and endpoints for Study ALXN1210-NMO-307

Objectives	Endpoints
Primary	
• To evaluate the effect of ravulizumab on adjudicated On-trial[a] Relapses in adult patients with NMOSD	• Time to first adjudicated On-trial Relapse and relapse risk reduction (1)
Secondary	
• To evaluate the effect of ravulizumab on adjudicated ARR in adult patients with NMOSD	• Adjudicated On-trial ARR (2)
• To evaluate the effect of ravulizumab on neurologic function in adult patients with NMOSD	• Clinically important change from baseline in HAI (3)
• To evaluate the effect of ravulizumab on QoL in adult patients with NMOSD	• Change from baseline in EQ-5D Index Score (4) and EQ-5D VAS Score (5)
• To evaluate the effect of ravulizumab on disease-related disability in adult patients with NMOSD	• Clinically important worsening from baseline in EDSS (6)
• To evaluate the safety of ravulizumab in adult patients with NMOSD	• Incidence of TEAEs, TESAEs, and TEAEs leading to study drug discontinuation
• To characterize the PK of ravulizumab in adult patients with NMOSD	• Change in serum ravulizumab concentration over the study duration
• To characterize the PD of ravulizumab in adult patients with NMOSD	• Change in serum free C5 concentration over the study duration
• To characterize the immunogenicity of ravulizumab in adult patients with NMOSD	• Presence and titer of ADAs over the study duration

Primary and secondary efficacy endpoints were tested in a hierarchical approach (numbers included for rank order of analyses).
a On-trial Relapses refer to relapses as determined by the Treating Physician that occurred during the study treatment period. All On-trial Relapses were adjudicated by a separate Adjudication Committee. The term "Adjudicated On-trial Relapse" is used to reflect only those events that were adjudicated positively by the RAC.
ADA = antidrug antibody; AQP4 Ab = aquaporin-4 antibody; ARR = annualized relapse rate; C5 = complement component 5; CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; EQ-5D = European Quality of Life Health 5-dimension Questionnaire; HAI = Hauser ambulation index; Ig = immunoglobulin; NMOSD = neuromyelitis optica spectrum disorder; PD = pharmacodynamics; PK = pharmacokinetics; QoL = quality of life; RAC = Relapse Adjudication Committee; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; VAS = Visual Analogue Scale.

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 Treating Physician.

Adjudicated On-trial Relapse reflected only those events that were adjudicated positively by the RAC. The RAC consisted of physicians with particular expertise in NMOSD and conducted independent reviews of all On-trial Relapses. They evaluated each On-trial Relapse as reported by the Treating Physician and confirmed whether it met the protocol defined criteria for an NMOSD relapse.

A Case of Interest was an event judged by the Treating Physician to not be an On-trial Relapse (ie, it is not an Investigator confirmed On-trial Relapse), but which met criteria to be submitted to the RAC for adjudication.

Sample size

The sample size and power calculation assumptions using the primary endpoint were as follows:

- Log-rank test for comparison of ravulizumab to placebo

- 47 patients in the placebo treatment group
- Power 90%
- Two-sided 5% level of significance
- Drop-out rate 2-10%
- Relapse-free rate of 92% for the ravulizumab arm at 12 months
- Relapse-free rate of 63% for the placebo arm at 12 months

With these assumptions, a maximum sample size of approximately 55 patients in the ravulizumab treatment group provides at least 90% power to detect a treatment difference in time to first positively adjudicated relapse.

Randomisation

This study employs a single-arm treatment design.

Blinding (masking)

This is a single-arm, open-label study. All study patients, site personnel, Sponsor staff, Sponsor designees, and all staff directly associated with the conduct of the study were unblinded to patient treatment assignments

To minimize potential for bias in this open-label study, operational measures were employed regarding the efficacy endpoints and adjudication process.

The study database was monitored according to prespecified guidelines in order to confirm that all potential relapses were collected and analyzed. An independent RAC evaluated each On-trial Relapse as reported by the Treating Physician and confirmed whether it met the protocol defined criteria for an NMOSD relapse. An "adjudicated On-trial Relapse" is a relapse that was confirmed following evaluation by the RAC. Additionally, while the EDSS Raters were aware that all patients are on ravulizumab, the EDSS Raters were blinded to all study data when making their assessments.

As already stated, the external control is the placebo arm of Study ECU-NMO-301. In order to ensure a valid comparison, constancy with Study ECU-NMO-301 was tried to be maintained in Study ALXN1210-NMO-307, including with regards to the inclusion of similar patient populations, permitted concomitant medications, adjudication procedures, and endpoints. To address any biases arising from slight differences in study designs and unforeseen enrolment differences, sensitivity analyses using propensity scores and tipping point analyses (E-value) (VanderWeele, 2017) were performed.

Statistical methods

Populations for Analysis

- Full Analysis Set (FAS): All patients who have received at least 1 dose of study drug (ravulizumab or placebo.
- Safety Set: All patients who receive at least 1 dose of study drug (ravulizumab or placebo).
- Per Protocol Set (PPS): All patients who:
    - Have no important protocol deviations or key inclusion/exclusion criteria deviations that might potentially affect efficacy
    - Patients who took at least 80% of the required treatment doses while they were in the Treatment Period.

The SAP Version 3.0 was finalized on 09 Jul 2021 before the CSR database lock date (25 Apr 2022).

The primary analysis of efficacy was to be performed on the FAS. The primary efficacy analysis of time to first adjudicated On-Trial Relapse and some sensitivity analyses were to be also performed on the PPS. Baseline was defined as the last available assessment prior to treatment for all patients regardless of treatment group.

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint was time to first adjudicated On-Trial Relapse. The time to first adjudicated On-Trial Relapse was to be evaluated using the log-rank test; the null hypothesis was that there is no difference in the survival curves of the ravulizumab and the placebo treatment groups. The alternative hypothesis was that there is a difference between the two survival curves, and ravulizumab is superior to placebo.

The study was considered to have met its primary efficacy objective if a statistically significant difference (i.e., 2-sided p-value 0.05) was observed between the ravulizumab treatment group and the placebo group for the primary endpoint of the time to first adjudicated On-Trial Relapse. The comparison of the treatment groups for the primary endpoint was to use a log-rank test. Hazard ratio and risk reduction were to be summarized from a Cox proportional hazards model including treatment group as a factor. In absence of observed event in a treatment arm, Firth's Penalized Likelihood (Heinze, 2001) was to be used to estimate the hazard ratio, risk reduction, and the profile likelihood 95% CIs. The Kaplan-Meier estimates of proportion of patients with no adjudicated On-Trial Relapse were to be presented for various time points (e.g, Week 24, Week 48) with a 95% CI based on the complementary log-log transformation. A figure showing the Kaplan-Meier curves of the time to first adjudicated On-Trial Relapse for each treatment group was to be produced.

<u>Sensitivity Analyses of the Primary Endpoint</u>

The following sensitivity analyses will be performed (among others):

- A sensitivity analysis of the primary analysis described above for the FAS was to be performed using the PPS.
- A sensitivity analysis of the primary analysis described above for the FAS was to be performed in which patients who were diagnosed with COVID-19 and had not relapsed prior to COVID-19 infection were censored on the start date of the first COVID-19 related AE.
- A sensitivity analysis for the comparison of the treatment groups for the primary endpoint was to be performed as described above but stratified using propensity score strata. The propensity score is the probability of being assigned to the placebo arm vs. the ravulizumab arm and was to be estimated from a logistic regression that includes observed baseline characteristics as predictors of the treatment assignment. In lieu of having a randomized study, the propensity score serves to balance treatment groups on the baseline characteristics. (Austin, 2011). A propensity score was to be estimated for each patient and categorized into two strata, such that each patient is identified as having low (≤median) or high (> median) probability of being in the placebo treatment group. The analysis was to be performed using a log-rank test, stratified on propensity score strata. Hazard ratio and risk reduction was to be summarized from a Cox proportional hazards model, also stratified using propensity score strata. This was to be performed for the FAS and the PPS.
- A sensitivity analysis of the comparison of the treatment groups for the primary endpoint was to be performed as described above, but weighted using the stabilized inverse probability of treatment weights (sIPTW), which are calculated using the propensity score. The analysis was

to be performed using a weighted log-rank test and Kaplan-Meier curves were to be presented using weighted Kaplan-Meier estimates (Xie, 2005); the hazard ratio and risk reduction were to be summarized from a weighted Cox proportional hazards model. Estimates of the hazard ratios from the weighted Cox proportional hazards model represent the average treatment effect. This was to be performed using the FAS, and the PPS.

- A tipping point analysis using the E-value approach proposed by Vanderweele, 2017 was to be conducted. The E-value, constructed as a risk ratio, quantifies the level of confounding which could compensate the estimated treatment effect; the smallest E-value of 1 represents no confounding. The E-value was to be calculated using the hazard ratio from the Cox proportional hazards model using both the unstratified model described for the primary analysis and the model stratified using propensity score strata. This value was to be calculated for both the estimate and the upper 95% confidence limit using the FAS, and the PPS.

Propensity Scores for Baseline Covariates

Propensity scores were utilized to account for any differences in baseline characteristics between the Study ALXN1210-NMO-307 ravulizumab group and the Study ECU-NMO-301 placebo treatment group. The variables in the propensity score calculation included region, gender, age at first dose, background IST use, baseline EDSS, and historical ARR within the 24 months prior to Screening. Sensitivity analyses for the efficacy endpoints stratifying by propensity score strata were performed to balance these baseline covariates between treatment groups and further reduce potential bias introduced through an external control.

The median propensity scores were 0.675 for the ravulizumab group and 0.425 for the placebo group. Following stratification on median propensity score, 70.7% of patients in the ravulizumab group and 23.4% of patients in the placebo group had a propensity score that was above the median. This is considered by the Applicant as indicating that selected baseline characteristics included in the propensity score calculation had a higher probability of occurring in the ravulizumab group than the placebo group.

The analysis of baseline characteristics by strata is provided in Table 19. According to the Applicant, while some differences between treatment groups in baseline characteristics were still observed across the propensity score strata, the majority of covariates included in the propensity score calculation had a standardized mean difference (SMD) $< \pm 0.25$, indicating that these covariates were balanced within strata (Stuart, 2010).

Table 19: Baseline Covariates by Propensity Score Strata and Treatment Group (Full Analysis Set)

Variable	Statistic	≤ Median Propensity Score			> Median Propensity Score		
		ECU-NMO-301 Placebo (N = 36)	ALXN1210-NMO-307 Ravulizumab (N = 17)	SMD	ECU-NMO-301 Placebo (N = 11)	ALXN1210-NMO-307 Ravulizumab (N = 41)	SMD
Americas region[a]	n (%)	9 (25.0)	7 (41.2)	0.35	6 (54.5)	14 (34.1)	-0.42
European region	n (%)	17 (47.2)	6 (35.3)	-0.24	2 (18.2)	11 (26.8)	0.21
Asia-Pacific region	n (%)	10 (27.8)	4 (23.5)	-0.10	3 (27.3)	16 (39.0)	0.25
Age at first dose (years) [a]	Mean (SD)	46.1 (14.05)	42.3 (10.56)	-0.30	41.5 (10.23)	49.6 (14.57)	0.64
	Median	47.0	41.0		39.0	49.0	
	Min, max	21, 75	27, 68		29, 58	18, 74	
Male[a]	n (%)	4 (11.1)	1 (5.9)	-0.19	1 (9.1)	5 (12.2)	0.10
Female	n (%)	32 (88.9)	16 (94.1)	0.19	10 (90.9)	36 (87.8)	-0.10
No IST usage (monotherapy)[a]	n (%)	5 (13.9)	4 (23.5)	0.25	8 (72.7)	26 (63.4)	-0.20
Baseline EDSS Score[a]	Mean (SD)	4.56 (1.388)	4.35 (1.529)	-0.14	3.27 (1.539)	2.87 (1.405)	-0.28
	Median	4.50	4.00		3.50	3.00	
	Min, max	1.5, 6.5	2.0, 7.0		1.0, 6.0	0.0, 6.5	
Historical ARR (within the 24 months prior to Screening)[a]	Mean (SD)	2.2 (1.07)	2.3 (1.83)	0.05	1.7 (0.86)	1.7 (1.48)	0.03
	Median	1.9	1.4		1.4	1.4	
	Min, max	1, 6	0, 7		1, 4	0, 7	
Baseline HAI Score	Mean (SD)	2.3 (1.52)	1.9 (2.06)	-0.22	1.7 (0.79)	0.9 (0.94)	-1.01
	Median	2.0	1.0		2.0	1.0	
	Min, max	0, 6	0, 7		0, 3	0, 3	
Baseline EQ-5D Index	Mean (SD)	0.7 (0.20)	0.6 (0.31)	-0.06	0.7 (0.17)	0.8 (0.15)	0.48
	Median	0.7	0.8		0.8	0.8	
	Min, max	0, 1	0, 1		0, 1	0, 1	
Baseline EQ-5D VAS	Mean (SD)	58.4 (20.56)	72.6 (13.85)	0.81	61.4 (20.63)	74.0 (15.33)	0.70
	Median	60.0	76.0		60.0	78.0	
	Min, max	0, 95	41, 90		30, 95	30, 97	

Note: The placebo group data were collected as part of Study ECU-NMO-301. Propensity Score is the predicted probability of being in the ravulizumab treatment group. Americas: Argentina, Canada, and the United States; Europe: Germany, Denmark, Spain, the United Kingdom, Croatia, Italy, Poland, Russia, and Turkey; Asia-Pacific: Australia, Hong Kong, Japan, the Republic of Korea, and Taiwan. a Variables included in the propensity score calculation.
ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; EQ-5D = European Quality of Life Health 5-dimension Questionnaire; HAI = Hauser Ambulation Index; IST = immunosuppressive therapy; max = maximum; min = minimum; SD = standard deviation; SMD = standardized mean difference; VAS = visual analogue scale

As another approach to balance the baseline covariates between treatment groups and more closely match the patients between treatment groups, standardized inverse probability treatment weights, derived from propensity scores, were applied in the summary of baseline characteristics. Following this method of weighting, the SMD for all covariates included in the propensity score calculation was < ± 0.25. The Applicant considers this indicates that the objective of balancing the baseline characteristics between treatment groups was achieved (Stuart, 2010) (Table 20). This method of weighting also balanced on covariates not included in the propensity score calculation, including HAI score and EQ-5D index.

Table 20: SIPTW Weighted Summary of Baseline Covariates Included in the Propensity Score by Treatment Group (Full Analysis Set)

Covariate	Statistic	ECU-NMO-301 Placebo (N = 47)	ALXN1210-NMO-307 Ravulizumab (N = 58)	SMD
sIPTW Weighted N	N	43.7	62.7	NA
Americas region [a]	n (%)	15.9 (36.3)	20.0 (31.9)	-0.09
European region	n (%)	14.7 (33.7)	25.0 (39.8)	0.13
Asia-Pacific region	n (%)	13.1 (30.0)	17.7 (28.3)	-0.04
Age at first dose (years)	Mean (SD)	44.0 (12.81)	46.0 (12.52)	0.16
	Median	43.0	46.0	
	Min, max	21, 75	18, 74	
Male	n (%)	3.8 (8.6)	4.8 (7.7)	-0.03
Female	n (%)	39.9 (91.4)	57.8 (92.3)	0.03
No IST usage (monotherapy)	n (%)	17.4 (39.8)	24.0 (38.2)	-0.03
Baseline EDSS Score	Mean (SD)	3.86 (1.545)	4.04 (1.859)	0.10
	Median	3.50	4.00	
	Min, max	1.0, 6.5	0.0, 7.0	
Historical ARR (within the 24 months prior to Screening)	Mean (SD)	2.0 (1.00)	1.8 (1.57)	-0.15
	Median	1.9	1.4	
	Min, max	1, 6	0, 7	
Baseline HAI Score	Mean (SD)	2.0 (1.24)	2.0 (2.24)	0.03
	Median	2.0	1.0	
	Min, max	0, 6	0, 7	
Baseline EQ-5D Index	Mean (SD)	0.7 (0.19)	0.6 (0.33)	-0.23
	Median	0.8	0.8	
	Min, max	0, 1	0, 1	
Baseline EQ-5D VAS	Mean (SD)	61.0 (20.10)	72.0 (15.56)	0.61
	Median	60.0	78.0	
	Min, max	0, 95	30, 97	

The placebo group data were collected as part of Study ECU-NMO-301. Propensity Score is the predicted probability of being in the ravulizumab treatment group. sIPTW is calculated using the propensity score. Summary statistics are provided using weighted observations. a Americas: Argentina, Canada, and the United States; Europe: Germany, Denmark, Spain, the United Kingdom, Croatia, Italy, Poland, Russia, and Turkey; Asia-Pacific: Australia, Hong Kong, Japan, the Republic of Korea, and Taiwan.
ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; EQ-5D = European Quality of Life Health 5-dimension Questionnaire; HAI = Hauser Ambulation Index; IST = immunosuppressive therapy; max = maximum; min = minimum; NA = not applicable; sIPTW = stabilized Inverse Probability Treatment Weights; SD = standard deviation; SMD = standard mean difference; VAS = visual analogue scale

As part of the responses the Applicant provided the following table to complement the initially submitted data.

Table 21: Comparative Information on All Baseline Data Including Raw SMDs and Hazard Ratios

Parameter	Placebo mean (SD), n (%)	Ravulizumab mean (SD), n (%)	Treatment Difference (Raw SMD)	Prognostic Influence (Hazard Ratio)	Pre-specified Propensity Score		Newly Derived Propensity Score		
					Included in Original PS	SMD after sIPTW	Met PS Criterion (SMD, HR, Prognostic) [a]	Included in Updated PS	SMD after sIPTW
Age at first dose (years), 10-year increment	45.0 (13.29)	47.4 (13.84)	0.18	0.814	Yes	0.16	S		0.10
Age group (< 45)	24 (51.1)	25 (43.1)	-0.16	2.574		-0.25	S,H,P [b]	Yes	0.02
Age group (< 65)	44 (93.6)	51 (87.9)	-0.20	4.276		-0.15	S,H [b]		-0.33
Age at initial presentation (years), 10-year increment	38.5 (14.98)	42.3 (15.15)	0.25	0.888		0.08	S		0.09
Age at diagnosis (years), 10-year increment	41.1 (14.36)	44.2 (14.48)	0.21	0.807		0.13	S		0.10
Sex (male)	5 (10.6)	6 (10.3)	-0.01	4.52	Yes	-0.03			-0.10
Ethnicity (Hispanic or Latino)	3 (6.4)	9 (15.5)	0.3	1.255		0.21	S,H [c]		0.24
Race									
Asian	15 (31.9)	21 (36.2)	0.09	0.778		-0.11	H		-0.03
Black or African American	8 (17.0)	6 (10.3)	-0.2	0.443		-0.31	S,H [d]		-0.08
White	24 (51.1)	29 (50.0)	-0.02	1.873		0.28	H		0.03
Japanese subject	5 (10.6)	9 (15.5)	0.15	1.137		0.07	S		-0.07
Region					Yes		S,H,P	Yes	
Europe	19 (40.4)	17 (29.3)	-0.23	2.589		0.13			-0.09
Asia-Pacific	13 (27.7)	20 (34.5)	0.15	0.866		-0.04			0.00
Americas	15 (31.9)	21 (36.2)	0.09	0.32		-0.09			0.09
Baseline height, 10-cm increments	164.50 (8.147)	161.86 (8.157)	-0.32	1.475		-0.08	S,H [e]		-0.35
Baseline weight, 5 kg increments	69.65 (16.441)	69.85 (19.343)	0.01	0.969		0.13			0.08
Baseline BMI, 5-unit increments	25.65 (5.240)	26.68 (6.501)	0.18	0.823		0.21	S		0.25
Baseline HAI, 1-point increment	2.1 (1.40)	1.2 (1.42)	-0.7	0.736		0.03	S,H,P	Yes	-0.17
Baseline EQ5D index, 0.1-unit increments	0.680 (0.1961)	0.766 (0.2203)	0.41	1.02		-0.23	S		0.07
Baseline EQ5D VAS, 10-unit increments	59.1 (20.39)	73.6 (14.81)	0.81	0.953		0.61	S		0.77
Baseline EDSS, 1-point increments	4.26 (1.510)	3.30 (1.584)	-0.62	0.804	Yes	0.10	S,P [f]		-0.24
Baseline EDSS (≥ 4)	30 (63.8)	20 (34.5)	0.61	0.61		0.04	S,H,P	Yes	-0.19
Time from initial presentation to first dose (years), 10-year increments	6.601 (6.5863)	5.189 (6.3762)	-0.22	0.73		0.11	S,H,P [g]	No	-0.03
Time from initial presentation to diagnosis (months), 1-year increments	32.067 (58.1952)	23.093 (47.9133)	-0.17	0.816		0.14	S [g]		0.01
Time from diagnosis to first dose (years), 10-year increments	3.932 (4.4804)	3.267 (4.3616)	-0.15	1.55		0.02	S,H [g]		-0.05
Total number of historical relapses	6.3 (4.58)	3.6 (4.00)	-0.62	1.032		-0.15	S		-0.32
Historical Relapses in the 12 months prior to Screening	2.1 (0.78)	1.4 (0.68)	-1.01	1.553		-0.97	S,H [h]		-0.84
Historical ARR (within the 12 months prior to Screening)	2.23 (1.088)	2.04 (1.533)	-0.15	1.318		-0.15	S,H,P [h]	Yes	-0.09
Historical relapses in the 24 months prior to Screening	3.2 (0.97)	1.7 (0.87)	-1.59	1.343		-1.50	S,H [h]		-1.19
Historical ARR (within the 24 months prior to Screening)	2.07 (1.037)	1.87 (1.594)	-0.15	1.328	Yes	-0.15	S,H,P [h]	No	-0.06
Optic neuritis (within the 24 months prior to Screening)	22 (46.8)	25 (43.1)	-0.07	2.44		0.20	H	No	-0.17
Transverse myelitis (within the 24 months prior to Screening)	42 (89.4)	34 (58.6)	-0.75	2.962		-0.86	S,H,P	Yes	-0.14
Brainstem symptoms (within the 24 months prior to Screening)	15 (31.9)	9 (15.5)	-0.39	1.433		-0.31	S,H,P	Yes	-0.07
Cerebral symptoms (within the 24 months prior to Screening)	5 (10.6)	6 (10.3)	-0.01	0.339		-0.07	H		0.03
Any IST usage	34 (72.3)	28 (48.3)	-0.51	0.589	Yes	0.03	S,H,P	Yes	-0.17
Steroids alone	11 (23.4)	12 (20.7)	-0.07	0.587		0.29	H		0.05
Azathioprine subgroup	13 (27.7)	7 (12.1)	-0.40	1.206		-0.25	S,H [i]		-0.25
Mycophenolate mofetil subgroup	8 (17.0)	6 (10.3)	-0.20	0.688		-0.20	S,H [i]		-0.10
Other ISTs	2 (4.3)	3 (5.2)	0.04	1.16		0.22			0.16

Note: Negative SMDs represent a lower proportion or a lower mean in the ravulizumab arm.

[a] Denotes whether the covariate met any of the criteria for consideration in the updated propensity score model. S = met criteria for standard mean difference; H = met criteria for hazard ratio; P = prognostic indicator. All prognostic indicators were considered in the updated propensity score model. To be a prognostic indicator, the covariate must have met both criteria for standard mean difference (≥ |0.10|) and hazard ratio (< 0.8 or > 1.25).

[b] Both age group < 45 and age group < 65 appear to be meaningful, however the 65-year dichotomy results were based on small sample sizes. For this reason, the 45-year dichotomy was chosen for consideration in the analysis.

[c] There were too few Hispanic patients in the placebo arm for results to be considered reliable.

[d] This finding suggests that black patients are less likely to relapse, however this is contrary to known literature and understanding of NMOSD. This is considered a spurious finding as a result of the small number of black patients in the placebo arm.

[e] Although the data suggest that height could be a prognostic factor, there is no medical reason and it is believed to be associated with other variables.

[f] Although the HR criterion is not technically met, literature suggests that baseline EDSS is a prognostic factor.

[g] Among these covariates, the time from initial presentation to first dose was considered to be the more meaningful prognostic factor.

[h] Historical ARR was considered to be a meaningful prognostic factor because it accounts for disease duration.
[I] Individual subcategories of ISTs used were not considered prognostic factors, due to smaller sample sizes.
ARR = annualized relapse rate; BMI = body mass index; EDSS = expanded disability status scale; EQ5D = European Quality of Life Five Dimension; HAI = hauser ambulation index; HR = hazard ratio; IST = immunosuppressant therapy; PS = propensity score; sIPTW = stabilized Inverse Probability Treatment Weights; SMD = standardized mean difference; VAS = visual analog scale.

Results

Participant flow

Of the 78 screened patients, 20 (25.6%) were screen failures. The most common (⩾ 5%) reason for screen failure was not meeting the inclusion criteria of being anti-AQP4 antibody-positive at screening and having a diagnosis of NMOSD (n = 9; 11.5%).

A total of 58 patients were treated with ravulizumab in Study ALXN1210-NMO-307. As of the clinical data cut-off date, 56 of the 58 patients completed the Primary Treatment Period and are ongoing in the Long-Term Extension Period. Two (3.4%) patients were reported as discontinued from the Primary Treatment Period due to adverse events. Fifty-seven (98.3%) patients were reported as continuing the study; 1 patient who discontinued from the Primary Treatment Period due to an AE had not yet completed the Safety Follow Up visit at the time of the clinical cut-off date and was listed as ongoing in the database. However, this patient subsequently discontinued the study after the data cut-off.

As of the data cutoff date, no patients discontinued from Study ALXN1210-NMO-307 due to COVID-19.

Approximately one third of patients overall were enrolled from each of the following regions, as specified per protocol: America, Europe, and Asia Pacific.

Table 22: Patient Disposition (All Treated Patients)

Variable Category	ALXN1210-NMO-307 Ravulizumab (N = 58) n (%)
Treated	58
Completed the Primary Treatment Period	56 (96.6)
Discontinued Primary Treatment Period	2 (3.4)
Adverse event	2 (3.4) [a]
Continuing in the study	57 (98.3)
Discontinued the study	1 (1.7)
Adverse event	1 (1.7) [a]
COVID-19 - related	0 (0.0)

Percentages were based on the number of patients in the treatment group.
a One patient who discontinued the Primary Treatment Period had not completed the Safety Follow-up Visit at the time of data cutoff date; for this reason, there was no end of study disposition for this patient.
COVID-19 = coronavirus disease 2019

Recruitment

This study was conducted at 36 sites that enrolled 58 patients across 11 countries (Australia, Canada, Denmark, Germany, Italy, Japan, the Republic of Korea, Poland, Spain, the United Kingdom, and the United States).

Date first patient enrolled: 13 Dec 2019

End of the Primary Treatment Period: 15 Mar 2022

Clinical Data cut-off date: 15 Mar 2022

Conduct of the study

Because no patients had an adjudicated On-trial Relapse during the study, the end of the Primary Treatment Period was triggered when all patients completed, or discontinued prior to, 50 weeks on study. Patients who completed 50 weeks on study prior to this point remained in the Primary Treatment Period until it was completed for all patients. Therefore, the overall treatment duration for an individual patient varied and was dependent upon when they enrolled in the study. Based on the estimated enrollment rate, the duration of the Primary Treatment Period for each patient was initially expected to be between 26 weeks (or 50 weeks if < 2 patients had an adjudicated On-trial Relapse) (plus 2 weeks for the EOPT visit window) and approximately 2.5 years.

Per protocol, all patients who entered the Long-Term Extension Period will continue to receive ravulizumab for up to approximately 2 years, or until ravulizumab is approved for the studied indication and/or available (in accordance with country-specific regulations), whichever occurs first. Based on the estimated enrolment rate of NMOSD patients, the total treatment duration for each patient is anticipated to be up to approximately 4.5 years. After the last dose of study drug or ED, patients will be followed for 8 weeks. The total study duration for each patient will be up to approximately 4.75 years.

The study duration for an individual patient as of the cut-off date ranged between 13.7 and 117.7 weeks.

All results presented in this report are based on the clinical database cut-off date of 15 Mar 2022, with the exception of clinical laboratory, PK, PD, and ADA data which are based on a cut-off date of 15 Feb 2022. All analyses presented in this report are based on a database lock date of 25 Apr 2022.

Changes in Planned Analyses Prior to Database Lock

Changes made after the final SAP and before database lock (25 Apr 2022) are described here.

• A summary and analysis of On-trial Relapses were added.

• To address the possibility that no adjudicated On-trial Relapses would be observed, an analysis was added to arrive at a p-value and the upper limit of the 95% CI.

• CSF samples were not available at the time of submission and this analysis has not yet been performed as part of the Pharmacokinetic and Pharmacodynamic Analyses.

Changes Following Database Lock and Post-hoc Analyses

Histograms showing the distribution of the change from baseline to End of Study Period inEQ-5D index and EQ-5D VAS were added.

Baseline data

Demographic Characteristics

The majority of patients in both the ravulizumab and placebo groups, respectively, were female (89.7% and 89.4%), not Hispanic or Latino (77.6% and 87.2%), and were White (50.0% and 51.1%) or Asian (36.2% and 31.9%).

Table 23: Demographics and Baseline Characteristics (Safety Set)

Variable **Variable**	**ECU-NMO-301** **Placebo** **(N = 47)**	**ALXN1210-NMO-307** **Ravulizumab** **(N = 58)**
Age at first dose (years), n	47	58
Mean (SD)	45.0 (13.29)	47.4 (13.84)
Median	44.0	46.0
Min, max	21, 75	18, 74
Age (years) category, n (%)		
< 45 years	24 (51.1)	25 (43.1)
≥ 45 years	23 (48.9)	33 (56.9)
Age (years) category, n (%)		
18 to < 65 years	44 (93.6)	51 (87.9)
≥ 65 years	3 (6.4)	7 (12.1)
Sex, n (%)		
Male	5 (10.6)	6 (10.3)
Female	42 (89.4)	52 (89.7)
Ethnicity, n (%)		
Hispanic or Latino	3 (6.4)	9 (15.5)
Not Hispanic or Latino	41 (87.2)	45 (77.6)
Not reported	1 (2.1)	4 (6.9)
Unknown	2 (4.3)	0 (0.0)
Race, n (%)		
Asian	15 (31.9)	21 (36.2)
Black or African American	8 (17.0)	6 (10.3)
White	24 (51.1)	29 (50.0)
Unknown	0 (0.0)	2 (3.4)
Japanese patient, n (%)		
Yes	5 (10.6)	9 (15.5)
No	42 (89.4)	49 (84.5)
Region[a], n (%)		
Americas	15 (31.9)	21 (36.2)
Europe	19 (40.4)	17 (29.3)
Asia-Pacific	13 (27.7)	20 (34.5)
Weight (kg), n	47	58
Mean (SD)	69.65 (16.441)	69.85 (19.343)

Median	67.00	63.80
Min, max	46.1, 116.0	41.0, 124.7
Height (cm), n	47	56
Mean (SD)	164.50 (8.147)	161.86 (8.157)
Median	163.50	160.00
Min, max	149.9, 193.0	148.0, 193.0
BMI (kg/m^2), n	47	56
Mean (SD)	25.65 (5.240)	26.68 (6.501)
Median	24.73	25.65
Min, max	17.7, 38.5	17.7, 45.8

Note: The placebo group data were collected as part of Study ECU-NMO-301. a Americas: Argentina, Canada, and the United States; Europe: Germany, Denmark, Spain, the United Kingdom, Croatia, Italy, Poland, Russia, and Turkey; Asia-Pacific: Australia, Hong Kong, Japan, the Republic of Korea, and Taiwan.
BMI = body mass index; max = maximum; min = minimum; SD = standard deviation

Baseline Disease Characteristics

Table 24: Baseline NMOSD Disease Characteristics by Treatment Group (Safety Set)

Variable	Statistic	ECU-NMO-301 Placebo (N = 47)	ALXN1210-NMO-307 Ravulizumab (N = 58)
Baseline HAI Score	Mean (SD)	2.1 (1.40)	1.2 (1.42)
	Median	2.0	1.0
	Min, max	0, 6	0, 7
Baseline EQ-5D Index Score	Mean (SD)	0.680 (0.1961)	0.766 (0.2203)
	Median	0.706	0.815
	Min, max	0.27, 1.00	0.04, 1.00
Baseline EQ-5D VAS	Mean (SD)	59.1 (20.39)	73.6 (14.81)
	Median	60.0	77.5
	Min, max	0, 95	30, 97
Baseline EDSS Score	Mean (SD)	4.26 (1.510)	3.30 (1.584)
	Median	4.00	3.25
	Min, max	1.0, 6.5	0.0, 7.0
Age at NMOSD initial clinical presentation (years)	Mean (SD)	38.5 (14.98)	42.3 (15.15)
	Median	38.0	42.5
	Min, max	12, 73	16, 73
Age at NMOSD diagnosis (years)	Mean (SD)	41.1 (14.36)	44.2 (14.48)
	Median	42.0	44.0
	Min, max	14, 73	17, 73

Time from initial clinical presentation to first IP dose (years)	Mean (SD)	6.601 (6.5863)	5.189 (6.3762)
	Median	3.760	1.955
	Min, max	0.51, 29.10	0.19, 24.49
Time from NMOSD diagnosis to first IP dose (years)	Mean (SD)	3.932 (4.4804)	3.267 (4.3616)
	Median	2.030	0.935
	Min, max	0.23, 23.78	0.08, 24.13
Time from initial clinical presentation to NMOSD diagnosis (months)	Mean (SD)	32.067 (58.1952)	23.093 (47.9133)
	Median	9.510	1.960
	Min, max	0.00, 269.24	0.00, 202.20

The placebo group data were collected as part of Study ECU-NMO-301. For HAI and EDSS higher scores represent more disability. For EQ-5D Index and VAS, higher scores represent a better state.
EDSS = Expanded Disability Status Scale; EQ-5D = European Quality of Life Health 5-dimension Questionnaire; HAI = Hauser Ambulation Index; IP = investigational product; max = maximum; min = minimum; NMOSD = neuromyelitis optica spectrum disorder; SD = standard deviation; VAS = visual analogue scale

NMOSD History

The mean (SD) historical ARR within the 24 months prior to Screening was 1.87 (1.594) in the ravulizumab group and 2.07 (1.037) in the placebo group. Differences in NMOSD history between the ravulizumab and placebo groups were not expected to meaningfully affect the results of the primary analysis.

Table 25: History of Prior NMOSD Relapses by Treatment Group (Safety Set)

Variable	Statistic	ECU-NMO-301 Placebo (N = 47)	ALXN1210-NMO-307 Ravulizumab (N = 58)
Total number of historical relapses	Mean (SD)	6.3 (4.58)	3.6 (4.00)
	Median	4.0	2.0
	Min, max	2, 20	1, 22
Number of relapses (within the 12 months prior to screening)	Mean (SD)	2.1 (0.78)	1.4 (0.68)
	Median	2.0	1.0
	Min, max	1, 4	1, 4
Historical ARR (within the 12 months prior to screening)	Mean (SD)	2.23 (1.088)	2.04 (1.533)
	Median	1.85	1.75
	Min, max	0.9, 6.4	0.9, 6.9
Number of relapses (within the 24 months prior to screening)	Mean (SD)	3.2 (0.97)	1.7 (0.87)
	Median	3.0	1.5
	Min, max	2, 6	1, 4
Historical ARR (within the 24 months prior to screening)	Mean (SD)	2.07 (1.037)	1.87 (1.594)
	Median	1.92	1.44
	Min, max	1.0, 6.4	0.5, 6.9

The placebo group data were collected as part of Study ECU-NMO-301.
Abbreviations: ARR = annualized relapse rate; max = maximum; min = minimum; NMOSD = neuromyelitis optica spectrum disorder; SD = standard deviation

In both the ravulizumab and placebo groups, the most common clinical presentations for historical relapses within 24 months prior to screening were optic neuritis (43.1% and 46.8%, respectively) and transverse myelitis (58.6% and 89.4%, respectively)

Table 26: Type of Historical NMOSD Relapse (Safety Set)

	ECU-NMO-301 Placebo (N = 47)		ALXN1210-NMO-307 Ravulizumab (N = 58)	
Historical Relapses 24 Months Prior to Screening	**E**	**n (%)**	**E**	**n (%)**
Optic neuritis	35	22 (46.8)	32	25 (43.1)
Unilateral left	16	10 (21.3)	14	13 (22.4)
Unilateral right	12	11 (23.4)	9	8 (13.8)
Bilateral	7	5 (10.6)	9	6 (10.3)
Transverse myelitis	105	42 (89.4)	59	34 (58.6)
Partial	52	24 (51.1)	23	14 (24.1)
Complete	6	4 (8.5)	10	8 (13.8)
Partial longitudinally extensive	32	19 (40.4)	20	17 (29.3)
Complete longitudinally extensive	15	10 (21.3)	6	5 (8.6)
Brain stem symptoms	18	15 (31.9)	13	9 (15.5)
Cerebral symptoms	9	5 (10.6)	6	6 (10.3)
Other symptoms	18	10 (21.3)	0	0 (0.0)

The placebo group data were collected as part of Study ECU-NMO-301. Percentages are based on the total number of patients in each treatment group.
E = number of events; NMOSD = neuromyelitis optica spectrum disorder

Most patients in both the ravulizumab (n = 50; 86.2%) and placebo (n = 45; 95.7%) groups used supportive therapy for NMOSD prior to study treatment. The most common therapies used for NMOSD prior to study treatment were corticosteroids, rituximab, and azathioprine.

A greater percentage of patients in the placebo group were on ISTs at baseline compared with the ravulizumab group (72.3% and 48.3%, respectively). Two (3.4%) patients in the ravulizumab group and 1 (2.1%) patient in the placebo group had a concomitant important IST change that resulted in exclusion from the PPS.

Table 27: Supportive IST Use at Baseline by IST Subgroup (Safety Set)

IST Categorization Statistic	ECU-NMO-301 Placebo (N = 47) n (%)	ALXN1210-NMO-307 Ravulizumab (N = 58) n (%)
Any IST usage	34 (72.3)	28 (48.3)
Steroids alone	11 (23.4)	12 (20.7)
Azathioprine subgroup	13 (27.7)	7 (12.1)
Azathioprine alone	6 (12.8)	3 (5.2)
Azathioprine + steroids	7 (14.9)	4 (6.9)
Mycophenolate mofetil subgroup	8 (17.0)	6 (10.3)
Mycophenolate mofetil alone	5 (10.6)	2 (3.4)
Mycophenolate mofetil + steroids	3 (6.4)	4 (6.9)
Other ISTs	2 (4.3)	3 (5.2)
Other ISTs alone	0 (0.0)	2 (3.4)
Other ISTs + steroids	2 (4.3)	1 (1.7)
No IST usage (monotherapy)	13 (27.7)	30 (51.7)

The placebo group data were collected as part of Study ECU-NMO-301.
Abbreviations: IST = immunosuppressive therapy

Exposure

Median (min, max) study duration was 73.50 (13.7, 117.7) weeks in the ravulizumab group and 43.14 (8.0, 208.6) weeks in the placebo group. As of the data cut-off, 55 (94.8%) ravulizumab-treated patients were followed for > 12 months, with 21 (36.2%) patients followed for > 18 months.

The median (min, max) number of ravulizumab infusions was 11.0 (2, 18). Two patients received supplemental infusions of ravulizumab, 1 supplemental infusion in1 patient and 3 supplemental infusions in the other patient. No patients in the ravulizumab treatment group had any missed doses during the Primary Treatment Period.

Delayed doses, defined as doses that occurred outside of the protocol-specified window, were identified for 20 (34.5%) patients in the ravulizumab group. Delayed doses that occurred> 14 days after the protocol-specified time point were identified in 9 of these 20 patients; however, no patients had a dose delayed > 35 days.

Numbers analysed

The definitions of analysis populations for Study ALXN1210-NMO-307 were similar to the definitions used in Study ECU-NMO-301, with any differences stemming from study design as described in Appendix 16.1.9 Statistical Methods Section 9.6. In total, all 47 (100%) patients randomized to placebo in Study ECU-NMO-301 were eligible for inclusion in the comparator group in the analysis sets for Study ALXN1210-NMO-307.

All 58 treated patients in the ravulizumab group and all 47 treated patients in the placebo group were included in the Full Analysis Set, Safety Set, and PK/PD Set.

The PPS excluded 3 patients in the ravulizumab group for major IST changes, including 1 patient who stopped background steroids on Day 1, 1 patient who stopped background steroids on Day 2, and 1

patient who stopped prednisolone on Day 42; 3 patients in the placebo group were excluded from the PPS, 1 each due to major IST change (initiation of prednisone after randomization), key inclusion/ exclusion criteria (IC/EC) eligibility violation (daily corticosteroid dose more than prednisone 20 mg/day [or equivalent] after Screening), and emergency unblinding.

Table 28: Analysis Sets (All Treated Patients)

Variable Category	ECU-NMO-301 Placebo (N = 47) n (%)	ALXN1210-NMO-307 Ravulizumab (N = 58) n (%)
Number of patients in the Full Analysis Set	47 (100.0)	58 (100.0)
Number of patients in the PPS	44 (93.6)	55 (94.8)
Number of patients excluded from the PPS	3 (6.4)	3 (5.2)
Major IST change	1 (2.1)	3 (5.2)
Prohibited plasma exchange/plasmapheresis	0 (0.0)	0 (0.0)
Key inclusion/exclusion eligibility violation	1 (2.1)	0 (0.0)
Prohibited medication	0 (0.0)	0 (0.0)
Treatment compliance < 80%	0 (0.0)	0 (0.0)
Emergency unblinding	1 (2.1)	0 (0.0)
Number of patients in the SS	47 (100.0)	58 (100.0)
Number of Patients in the PK/PD Set	47 (100.0)	58 (100.0)

The placebo group data were collected as part of Study ECU-NMO-301. Percentages were based on the number of patients in the respective treatment group. A patient may have had more than 1 reason for exclusion from the PPS.
IST = immunosuppressive therapy; PD = pharmacodynamic; PK = pharmacokinetic; PPS = Per-Protocol Set; SS = Safety Set

Outcomes and estimation

Primary Efficacy Endpoint: Time to First Adjudicated On-trial Relapse

Primary Analysis

The study met its primary objective by demonstrating the efficacy of ravulizumab for the treatment of adult patients with NMOSD. No patients in the ravulizumab group had an adjudicated On-trial Relapse during the Primary Treatment Period of Study ALXN1210-NMO-307, compared with 20 patients (42.6%) in the placebo group from Study ECU-NMO-301 (Table 29).

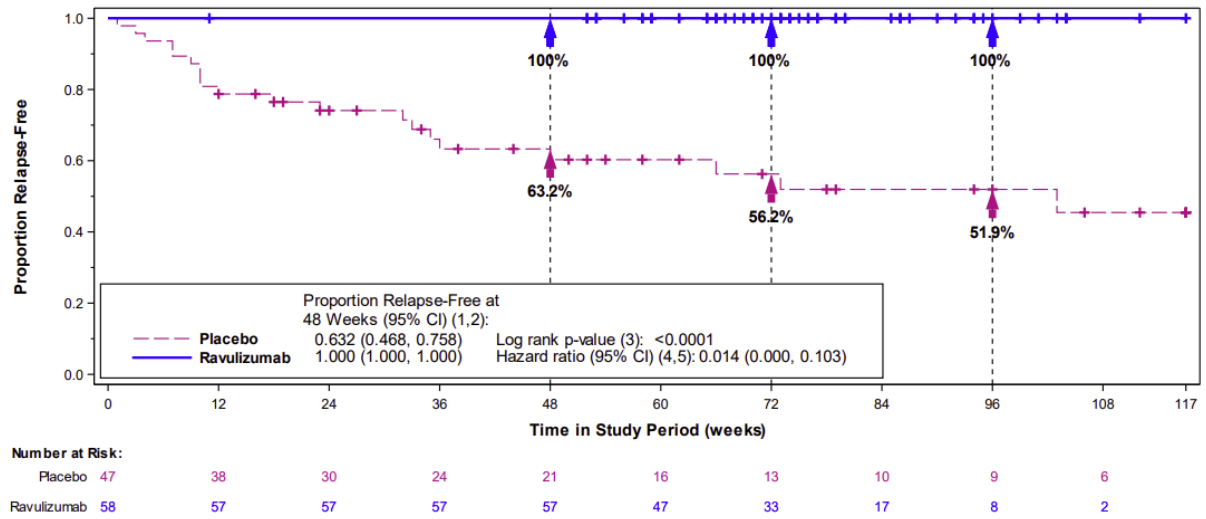
Table 29: Time to First Adjudicated On-trial Relapse (Full Analysis Set)

Variable	Statistic	ECU-NMO-301 Placebo (N = 47)	ALXN1210-NMO-307 Ravulizumab (N = 58)
Patients with an adjudicated On-trial Relapse	n (%)	20 (42.6)	0 (0.0)
Follow-up time (weeks)	Median (min, max)	36.00 (1.86, 117.71)	73.50 (11.00, 117.71)
Estimated proportion of patients relapse-free at:			
24 weeks	Cumulative probability[a] (95% CI[b])	0.740 (0.587, 0.843)	1.000 (1.000, 1.000)
48 weeks		0.632 (0.468, 0.758)	1.000 (1.000, 1.000)
72 weeks		0.562 (0.389, 0.703)	1.000 (1.000, 1.000)
96 weeks		0.519 (0.341, 0.670)	1.000 (1.000, 1.000)
120 weeks		NA (NA, NA)	NA (NA, NA)
144 weeks		NA (NA, NA)	NA (NA, NA)
Relapse-free time (weeks)	Percentile[a]		
	10th	7.71	NA
	25th	23.71	NA
	50th	103.14	NA
Treatment effect	p-value[c]	< 0.0001	
	Hazard ratio[d] (ravulizumab/placebo)	0.014	
	95% CI[e]	0.000, 0.103	
	% reduction[d] (ravulizumab/placebo)	98.6	
	95% CI[e]	89.7, 100.0	
	E-value		
	For estimate	24.68	
	For upper 95% CL[f]	8.33	

The placebo group data were collected as part of Study ECU-NMO-301.
Patients who did not experience an adjudicated on-trial relapse were censored at the end of the study period. If a patient in the placebo group was followed longer than any of the patients in the ravulizumab arm, then that patient was censored at the longest ravulizumab follow-up time.
a Based on the Kaplan-Meier product limit method.
b Based on the complementary log-log transformation.
c Based on a log-rank test.
d Based on a Cox proportional hazards model, with Firth's adjustment.
e Wald confidence interval or Profile Likelihood Confidence Limits.
f Constructed as a risk ratio: A tipping point analysis quantifying the level of confounding which could account for the estimated treatment effect.
CI = confidence interval; CL = confidence limit; max = maximum; min = minimum; NA = not applicable.

A significant effect on the time to first adjudicated On-trial Relapse and relapse risk reduction was observed with ravulizumab treatment compared to placebo during the Primary Treatment Period ($p < 0.0001$;Figure 15).

Figure 15: Kaplan-Meier Survival Estimates for Time to First Adjudicated On-trial Relapse (Full Analysis Set)



The placebo group data were collected as part of Study ECU-NMO-301.
Patients who did not experience an adjudicated On-trial Relapse were censored at the end of the study period. If a patient in the placebo group was followed longer than any of the patients in the ravulizumab arm, then that patient was censored at the longest ravulizumab follow-up time.
1 Based on the Kaplan-Meier product limit method.
2 Based on the complementary log-log transformation.
3 Based on a log-rank test.
4 Based on a Cox proportional hazards model, with Firth's adjustment.
5 Wald confidence interval or Profile Likelihood Confidence Limits.
CI = confidence interval

The hazard ratio (95% CI) for ravulizumab compared with placebo was 0.014 (0.000, 0.103),representing a 98.6% reduction in the risk of relapse. At Week 48, all patients in the ravulizumab group were relapse free (versus 63.2% in placebo-treated patients). This effect was sustained through the end of the Primary Treatment Period, at which point all patients in the ravulizumab group remained relapse free. The median (min, max) analysis follow-up time was 73.50 (11.00,117.71) weeks for the ravulizumab group and 36.00 (1.86, 117.71) weeks for the placebo group.

The E-value presented in Table 29 quantifies the level of confounding which could account for the estimated treatment effect observed in the primary analysis. The E-value of the upper confidence limit (8.33) indicates that only an unmeasured confounder that is associated with an 8.33 times greater risk of an adjudicated On-trial Relapse and that occurs 8.33 times more in patients in the placebo group would result in a non-significant treatment effect. Therefore, any unmeasured confounder is unlikely to have a large enough impact on the results of the primary analysis to account for the observed treatment effect.

Sensitivity Analyses

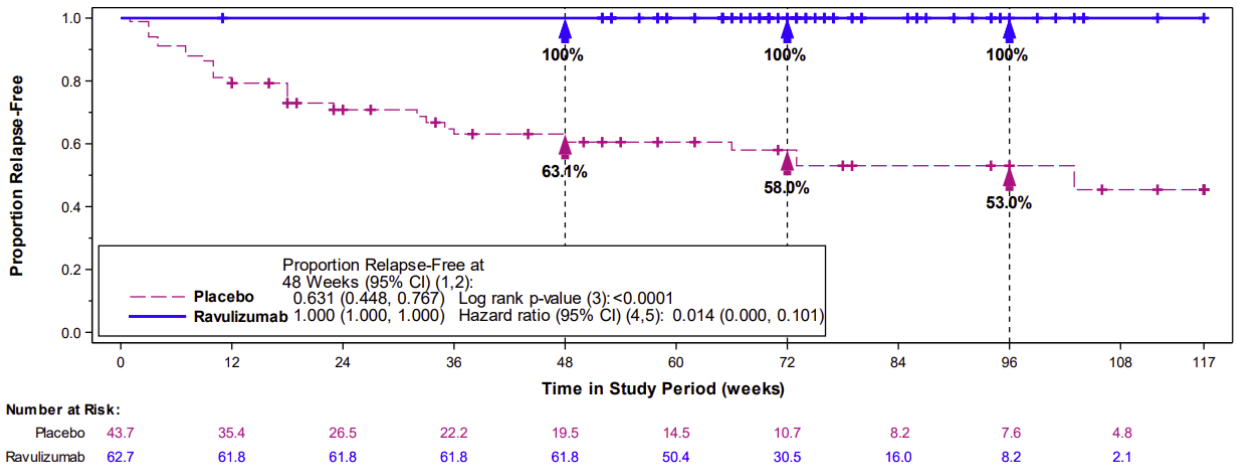
- Time to First Adjudicated On-trial Relapse Stratified by Propensity Score

When stratifying by propensity score, the significant effect of ravulizumab compared to placebo on the time to first adjudicated On-trial Relapse and relapse risk reduction during the Primary Treatment Period was maintained ($p < 0.0001$); the hazard ratio (95% CI) for ravulizumab compared with placebo was 0.019 (0.000, 0.153), representing a 98.1% reduction in the risk of relapse.

- Time to First Adjudicated On-trial Relapse Using Propensity Scores in a Weighted Analysis

Using propensity scores in a weighted analysis, the hazard ratio (95% CI) for ravulizumab compared with placebo was 0.014 (0.000, 0.101), representing a 98.6% reduction in the risk of relapse (Figure 16), which is highly consistent with that of the main analysis.

Figure 16: Kaplan-Meier Survival Estimates for Time to First Adjudicated On-trial Relapse Using Weighted Analysis (Full Analysis Set)

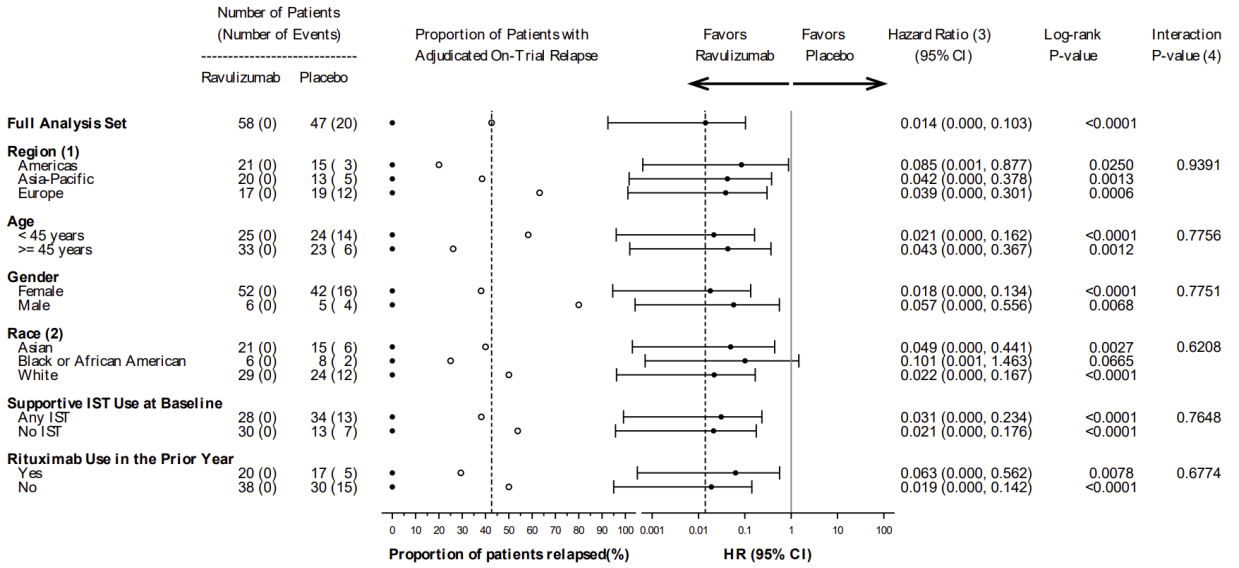


The placebo group data were collected as part of Study ECU-NMO-301. Patients who did not experience an adjudicated on-trial relapse were censored at the end of the study period. If a patient in the placebo group was followed longer than any of the patients in the ravulizumab arm, then that patient was censored at the longest ravulizumab follow-up. Analysis was weighted using sIPTW, which are calculated using the propensity score.
1 Based on a weighted Kaplan-Meier product limit method.
2 Based on the complementary log-log transformation.
3 Based on the weighted log-rank test.
4 Based on a weighted Cox proportional hazards model, with Firth's adjustment if no relapses observed in a treatment arm.
5 Wald confidence interval or Profile Likelihood Confidence Limits, if no relapses observed in a treatment arm.
CI = confidence interval; sIPTW = stabilized Inverse Probability Treatment Weights

Subgroup Analyses

A consistent effect on the time to first adjudicated On-trial Relapse and relapse risk reduction was observed for ravulizumab compared with placebo across all pre-specified subgroups, including region, age group, gender, race (Asian, White), use of concomitant IST at baseline, and prior rituximab use. The treatment effect was notably observed in the subgroup with no IST use at baseline (ie, patients on ravulizumab monotherapy or placebo alone during the Primary Treatment Period); the hazard ratio for the subgroup of patients with no IST use at baseline was 0.021 (0.000, 0.176), representing a 97.9% reduction in the risk of relapse.

Figure 17: Prespecified Subgroups for Time to First Adjudicated On-trial Relapse (Full Analysis Set)



The placebo group data were collected as part of Study ECU-NMO-301.
Dotted vertical lines show the overall placebo proportion with a relapse and the overall hazard ratio for the Full Analysis Set; open circles represent placebo and closed circles represent ravulizumab.
1 Americas: Argentina, Canada, and the United States; Europe: Germany, Denmark, Spain, the United Kingdom, Croatia, Italy, Poland, Russia, and Turkey; Asia-Pacific: Australia, Hong Kong, Japan, the Republic of Korea, and Taiwan.
2 Unknown race excluded from forest plot and interaction effect model.
3 Based on a Cox proportional hazards model with treatment covariate. Firth's adjustment with profile likelihood confidence limits applied.
4 Based on a Cox proportional hazards model with interaction term.
CI = confidence interval; HR = hazard ratio; IST = immunosuppressive therapy

Supportive Analyses

- On-trial Relapses as Determined by the Treating Physician and Cases of Interest

Two patients in the ravulizumab group had an On-trial Relapse as determined by the Treating Physician that was adjudicated negatively by the RAC. The results for time to first On-trial Relapse as determined by the Treating Physician were consistent with the results of the primary analysis. A significant effect on the time to first On-trial Relapse as determined by the Treating Physician was observed for ravulizumab compared with placebo ($p < 0.0001$). The hazard ratio (95% CI) for ravulizumab compared with placebo was 0.039 (0.009, 0.164), representing a 96.1% reduction in the risk of relapse.

Overall, 11 cases of interest in the ravulizumab group and 12 cases of interest in the placebo group were identified. All 11 (100%) cases of interest in the ravulizumab group were adjudicated negatively by the RAC. One case of interest in the placebo group was adjudicated positively by the RAC.

Secondary Efficacy Endpoints

The study met the first 2 of the 5 secondary endpoints according to the prespecified rank order: Adjudicated On-trial ARR (Table 31) and clinically important changes from baseline in HAI (Table 32). Since the treatment effect did not reach statistical significance for the EQ-5D Index Score assessment ($p = 0.0567$), nominal p-values are presented for change from baseline in EQ-5D VAS Score and clinically important worsening in EDSS score.

Adjudicated On-trial ARR

The adjudicated On-trial ARR (95% CI) was 0.00 (NA, 0.044) in the ravulizumab group, representing a statistically significant lower ARR than 0.25 (1 adjudicated On-trial annualized relapse per 4 patient-years) ($p < 0.0001$). The results of sensitivity analyses, including a comparison with the placebo group from Study ECU-NMO-301, were statistically significant and consistent with the results of the main analysis.

Table 30: Adjudicated On-trial Annualized Relapse Rate (Full Analysis Set)

Variable	Statistic	Ravulizumab (N = 58)
Total number of relapses	Sum	0
Total number of PY in study period	Sum	84.01
Unadjusted ARR[a] (2) [b]	Rate	0.000
	95% CI	(NA, NA)
	Exact Method[c]	
	95% CI	(NA, 0.044)
	P-value	< 0.0001
Adjusted adjudicated ARR[d]	Rate	0.000
	Poisson Model	
	95% CI	(NA, NA)
	P-value	NA

a Calculated as the total number of relapses during the study period for all patients, divided by the total number of patient-years in the study period. Confidence interval, based on a Poisson regression, could not be estimated.
b Primary and secondary efficacy endpoints were tested in a hierarchical approach (number included for rank order of analysis).
c Upper 95% confidence limit using exact methods is based on the chi-square distribution with 1 degree of freedom, divided by patient-years; the lower confidence limit is not defined for 0 relapses. The p-value is based on the Poisson distribution with 0 relapses and patient-years.
d Based on a Poisson regression centered on the mean historical ARR in the 24 months prior to screening; p-value tests the significance of the difference from 0.25 relapses/patient-year. The model results could not be estimated when the relapse rate was 0.
ARR = annualized relapse rate; CI = confidence interval; NA = not applicable

Clinically important change from baseline in ambulatory function, as measured by the HAI score, was selected as the next hierarchical secondary endpoint to capture the effect of ravulizumab on progressive worsening of gait, a key manifestation of neurologic disability in patients with NMOSD.

HAI Score

Patients in the ravulizumab group were less likely to experience worsening in mobility-related neurologic disability, as measured by HAI score, compared with patients in the placebo group (Odds ratio [95% CI]; p-value: 0.155 [0.031, 0.771]; p = 0.0228). Clinically important worsening from baseline in HAI score was reported for 2 (3.4%) patients in the ravulizumab group and 11 (23.4%) patients in the placebo group (Table 31). The treatment effect of clinically important worsening from baseline in HAI score stratifying by propensity score strata, while not statistically significant, was numerically consistent with the results of the main analysis.

ED-5D Index Score and ED-5D VAS

While not statistically significant, similar trends favoring ravulizumab were observed for the analyses of EQ-5D Index Score (p = 0.0567) and EQ-5D VAS (nominal p = 0.0297). Since the treatment effect did not reach statistical significance for the EQ-5D Index Score assessment, nominal p-values are presented for change from baseline in EQ-5D VAS Score.

EDSS

The treatment effect did not reach statistical significance for the EDSS score, clinically important worsening in EDSS score are presented in Table 31.

Table 31: Other Secondary Endpoints Results (Full Analysis Set)

Variable	Statistic	ECU-NMO-301 Placebo (N = 47)	ALXN1210-NMO-307 Ravulizumab (N = 58)	Comparison	Treatment Effect (95% CI)	P-value
Secondary Efficacy Endpoints (ALXN1210-NMO-307 CSR Section 5.1.2)						
EDSS (3)	No clinically important worsening; n (%)	36 (76.6)	52 (89.7)	Odds Ratio (rav/placebo)	0.332 (0.106, 1.042)	0.0588
	Clinically important worsening; n (%)	11 (23.4)	6 (10.3)			
HAI (4)	No clinically important worsening; n (%)	36 (76.6)	56 (96.6)	Odds Ratio (rav/placebo)	0.155 (0.031, 0.771)	0.0228[a]
	Clinically important worsening; n (%)	11 (23.4)	2 (3.4)			
EQ-5D Index (5)	Median Change from Baseline (min, max)	0.000 (-0.67, 0.41)	0.000 (-0.33, 0.50)	Difference in LS Means[b]	11.15 (-0.32, 22.62)	0.0567[a]
EQ-5D VAS (6)	Median Change from Baseline (min, max)	0.0 (-28, 40)	0.5 (-45, 40)	Difference in LS Means[b]	13.38 (1.35, 25.41)	0.0297[a]

The placebo group data were collected as part of Study ECU-NMO-301.
Primary and secondary efficacy endpoints were tested in a hierarchical approach (number included for rank order of analysis)
a The treatment effect represents the difference between treatment groups in the ranked values.
b Nominal p-value.
EDSS = Expanded Disability Status Scale; EQ-5D = European Quality of Life Health 5-item Questionnaire; HAI = Hauser Ambulation Index; LS = least square; max = maximum; min = minimum; rav = ravulizumab; VAS = visual analog scale

Other Clinically-Relevant Efficacy Results

Table 32: Relapse-Related Hospital and Acute Therapy Use for All Physician Determined Relapses (Full Analysis Set)

Annualized Relapse-Related	Statistic	ECU-NMO-301 Placebo (n = 47) PY = 46.93)	ALXN1210-NMO-307 Ravulizumab (n = 58) PY = 81.42	P-value
Hospitalizations	Events	16	0	< 0.0001
	Rate (95% CI)	0.34 (0.21, 0.56)	0.0 (NA, NA)	
High-dose oral steroids	Events	6	0	0.0005
	Rate (95% CI)	0.13 (0.06, 0.28)	0.0 (NA, NA)	
IV methylprednisolone	Events	22	0	< 0.0001
	Rate (95% CI)	0.47 (0.31, 0.71)	0.0 (NA, NA)	
Plasma exchange	Events	10	1	0.0002
	Rate (95% CI)	0.21 (0.11, 0.40)	0.01 (0.00, 0.9)	
IVIg	Events	0	1	NC
	Rate (95% CI)	0.00 (0.00, 0.00)	0.01 (0.00, 0.09)	

The placebo group data were collected as part of Study ECU-NMO-301.
CI = confidence interval; IV = intravenous; IVIg = intravenous immunoglobulin; NA = not applicable; NC = not calculated; PY = patient-years

Summary of main study(ies)

The following table summarises the efficacy results from the main studies supporting the present

application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33: Summary of Efficacy for trial ALXN1210-NMO-307

Title: A Phase 3, External Placebo-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD)			
Study identifier	ALXN1210-NMO-307, EudraCT 2019-003352-37, NCT04201262		
Design	External placebo-controlled, open label, multicenter study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Variable per patient, from 50 weeks to approximately 2.5 years Up to 6 weeks Up to 2 years
Hypothesis	Superiority		
Treatments groups	Ravulizumab		Open-label ravulizumab IV body weight-based loading dose on Day 1, followed by maintenance doses on Day 15 and every 8 weeks thereafter N = 58 patients
	Placebo (external control from Study ECU-NMO-301)		Placebo IV every week for the first 4 weeks, followed by maintenance doses on Week 5 and every 2 weeks thereafter N = 47 patients
Endpoints and definitions	Primary endpoint	Time to first adjudicated On-trial Relapse	The time to first adjudicated On-trial Relapse is compared between treatment groups using the log-rank test. Hazard ratio and risk reduction are summarized from a Cox proportional hazards model including treatment group as a factor.
	First secondary endpoint	Adjudicated On-trial annualized Relapse Rate (ARR)	The adjudicated On-trial ARR is tested against the null hypothesis of 0.25(1 relapse in 4 patient-years). This comparison was selected, as opposed to a comparison to placebo, because of differences in study design between Studies ALXN1210-NMO-307 andECU-NMO-301 that result indifferences in follow-up time for patients following a relapse. The comparator rate was chosen to represent a conservative ARR that maybe experienced in the NMOSD patient population.
	Secondary endpoint		Clinically important change from baseline in HAI
	Secondary endpoint		Change from baseline in EQ-5D Index Score
	Secondary endpoint		Change from baseline in EQ-5D VAS Score
	Secondary endpoint		Clinically important worsening from baseline in EDSS
Database lock	25 Apr 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat End of the Primary Treatment defined as when all patients completed, or discontinued prior to, 50 weeks on study		
Descriptive statistics and estimate variability	Treatment groups	Ravulizumab	External placebo
	Number of subjects	58	47

	Patients with an adjudicated On-trial Relapse n (%)	0 (0.0)	20 (42.6)
Effect estimate per comparison	Time to first adjudicated On-trial Relapse	Comparison groups	Ravulizumab versus external placebo
		Reduction in the risk of relapse	98.6%
		Hazard ratio (95% CI)	0.014 (0.000, 0.103)
		P-value based on a log-rank test	< 0.0001
Analysis description	**Secondary analysis**		
Analysis population and time point description	Intent to treat End of the Primary Treatment defined as when all patients completed, or discontinued prior to, 50 weeks on study		
Descriptive statistics and estimate variability	Treatment group	Ravulizumab	
	Number of subjects	58	
	Patients with an adjudicated On-trial Relapse n (%)	0 (0.0)	
	Total number of patient-years in study period	84.01	
Effect estimate per comparison	Adjudicated On-trial ARR	Comparison groups	Ravulizumab versus a rate of 0.25 (1 relapse per 4 patient-years)
		Rate	0.000
		95% CI	NA, 0.044
		P-value based on a Poisson distribution	< 0.0001

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The evidence of the efficacy of Ultomiris (ravulizumab) in the treatment of NMOSD patients with AQP4 antibodies is provided by one phase 3 clinical trial, study ALXN1210-NMO-307, still ongoing.

The use of ravulizumab in this condition is based on the role of the complement activation in the pathogenesis of NMOSD. When AQP4-antibody binds to AQP4 channels on astrocytes the classical complement cascade is activated causing granulocyte, eosinophil, and lymphocyte infiltration, culminating in injury first to astrocyte, then oligodendrocytes, followed by demyelination and neuronal loss[12],[13]. Ravulizumab blocks the formation of terminal complement complex by selectively preventing the enzymatic cleavage of C5.

Study design

[12] Lucchinetti CF et al. Brain Pathol. 2014 January ; 24(1): 83–97
[13]Mader S, Brimberg L. Cells 2019, 8, 90

Study ALXN1210-NMO-307 is a phase 3, single arm, open-label, multicentre study in adult patients with NMOSD with ravulizumab on top of the background therapy. In general, a single pivotal study could be acceptable considering the rarity and the progressive nature of the condition if the observed effects are sufficiently compelling. The clinical program as well as the design of the Study NMO-307 was discussed during a scientific advice in October 2019 (EMA/CHMP/SAWP/545125/2019) and a follow-up procedure in February 2020 (EMEA/H/SA/3331/5/FU/1/2020/II).

The study was a single arm study. The efficacy of a new treatment would normally be demonstrated in double-blind, randomized, controlled clinical trial(s). Three monoclonal antibodies have been approved for adults with NMOSD: eculizumab, satralizumab and inebilizumab. All have been tested in randomized, double-blind, placebo-controlled studies. During the discussion with SAWP in 2019 the Applicant argued that the use of a placebo arm as control was ethically unacceptable when other therapies for NMOSD were to be available during the conduct of the study, including eculizumab, already available in a number of countries. In addition, the comparison to eculizumab under a non-inferiority hypothesis was considered unfeasible in terms of required sample size in a rare condition. All considered, it was concluded that a single arm uncontrolled study could be considered acceptable in these exceptional circumstances.

For comparison purposes, the Applicant has used external data, i.e. from the placebo arm of study ECU-NMO-301 trial. This was a randomised (2:1) and double-blind trial using a time-to-event primary endpoint, time-to-first adjudicated relapse. As outlined above, this approach of using a retrospective placebo-arm as control arm was addressed during the scientific advice procedures. As discussed during the first advice in 2019, the fact that the efficacy and safety of eculizumab in NMOSD had been previously demonstrated, that ravulizumab and eculizumab only slightly differs in their molecular structure and have the same mechanism of action, that the biological rationale for C5 inhibition to prevent complement-mediated damage is established and that the non-inferiority of ravulizumab versus eculizumab was demonstrated in two phase 3 pivotal trials in PNH (considered supportive even if the indication is different), are considered to provide a reasonable framework for exceptionally accepting the proposed approach. In addition, it was noted that to be acceptable it was important that ravulizumab study included similar population, operational procedures and endpoints in order to get results as comparable as possible.

The study was conducted between December 2019 and March 2022 (End of the Primary Treatment Period). One of the main concerns is the comparability of two non-contemporary groups (study ECU-NMO-301 was conducted between 2014 and 2018) and the intrinsic differences between a group of patients prospectively studied (ravulizumab group) and a retrospectively selected placebo group without the protection from bias of randomisation.

Patient population

Adult patients with confirmed diagnosis of NMOSD (based on the 2015 international consensus diagnostic criteria[14]) who were positive for AQP4 antibodies were eligible for the study. Additionally, patients were required to have had at least 1 relapse in the last 12 months prior to the Screening Period and an EDSS score ≤ 7.

Patients enrolled in the external placebo arm (Study ECU-NMO-301), were selected according NMO 2006 diagnostic criteria with the requirement of the presence of AQP4-Abs. (NMO 2006/NMOSD 2007). The revision performed in 2015 led to broaden the clinical and neuroimaging spectrum of NMO for including new clinical entities and better defining brain and spinal cord MRI findings. It could be that differences in diagnostic criteria may result in dissimilar selected populations, limiting the interpretation of the

[14] Wingerchuk DM et al. Neurology® 2015;85:177–189

results. In this case, seropositive patients fulfil either or both criteria from 2006 and 2015. [15] Thus, it may be considered that patients recruited according to the Study ECU-NMO-301 selection criteria also meet the 2015 NMOSD criteria.

Patients with active, relapsing disease were recruited. Whereas patients in ravulizumab study were required to have had at least 1 relapse in the last 12 months prior to entry, at least two relapses in the last year (or three in the last 2 years) were required in eculizumab study. In this regard more severe patients could be expected in the control group favouring ravulizumab.

Both on treatment and untreated patients were allowed, provided that immunosuppressive agents were administered at stable doses at entry. At the time of starting the study only eculizumab was approved in some countries. However, immunosuppressants were recommended for the prevention of relapses based on available data. In an active population with previous relapses it would be expected that a relevant number of patients were on treatment.

A total of 78 patients were screened for this study, of which 58 patients were finally included and treated. Most of them (n=56; 96.6%) completed the Primary Treatment Period and 57 were on the study at the time of the data cut-off date (15 Mar 2022).

The population included had a mean age of 47.4 years (ranging from 18 to 74 years). A total of 7 patients (12.1%) were ≥65 year-old. Most patients were female (90%), and predominantly white (50%). There were 29.3% of patients from Europe, 36.2% from America and 34.5% from Asia-Pacific.

Mean age for first relapse was 42.3 year, and patients had had mean 3.6 historical relapses, with a mean of 1.4 relapses within the year prior to screening (historical ARR 2.04) and 1.7 within the two years prior to screening (historical ARR 1.87). The most frequent relapses were transverse myelitis (58.6%) and optic neuritis (43.1%). 86.2% had therapy for NMOSD in the past: mainly corticosteroids (50%), rituximab (36%) and azathioprine (22%). At baseline the majority of patients (51.7%) were not on treatment and 13.8% had not received any prior supportive IST for NMOSD. Most of the patients using ISTs during the study were on monotherapy (32.7%), mainly corticosteroids 20.7% and azathioprine 5.2%. Since any relapse can result in the accumulation of neurological disability, prevention of relapse is the principal goal of NMOSD management[16,17]. For this reason and considering the history of patients it would have not been expected that such a relevant number of patients had entered the study without background therapy.

The overall mean baseline EDSS score was 3.30 (fully ambulatory patients) and the mean HAI Score was 1.2 (walking patients)

Baseline demographic characteristics were in general well balanced when the two groups (ravulizumab treated patients and external placebo group) were compared although patients on placebo were younger (47.4 vs 45.0 vs; with no elderly patients in placebo group) and European patients are less represented in the ravulizumab group (29.3% vs 40.4%). More Black patients (10.3% vs17.0%) were included in placebo arm. Ethnic differences have been reported in relation to age of onset (younger onset age in Afro-American/Afro-European patients than Caucasian patients), severity of the attacks (more severe attacks in Afro-descendent patients than Caucasian or Asian patients) and mortality (higher rates reported in Afro-descencent patients compared to Caucasian patients).[18,19]

In line with what was expected with respect to baseline disease status placebo patients showed more disability than ravulizumab group: higher mean HAI Score (2.1 vs. 1.2) and mean EDSS Score (4.26 vs

[15] McCreary M, Mealy MA, Wingerchuk DM, Levy M, DeSena A, GreenbergBM. Mult Scler J Exp Transl Clin. 2018;4(4): 2055217318815925
[16]Wingerchuk D et al. Neurol Ther (2022) 11:123–135
[17]Wingerchuk D et al. N Engl J Med (2022)387:631-9.
[18] Kim SH et al. Neurology Nov 2018, 91 (22) e2089-e2099,
[19] Mealey M. Neurol Neuroimmunol Neuroinflamm. 2018 Jul; 5(4): e468.

3.30), and higher disease activity with 6.3 vs 3.6 total historical relapses (ARR 1y: 2.23 vs 2.04; ARR 2y: 2.07 vs. 1.87). The distribution of nature of the relapses shows a higher number of transverse myelitis (89.4% vs 58.6%) and brain stem symptoms (31.9% vs 15.5%) in patients on placebo. More patients in placebo group had been previously treated (95.7% vs 86.2%) and were on treatment during the study (72.3% vs 48.3%).

Importantly, these differences between the placebo and the ravulizumab groups could have a significant impact on the primary and key secondary endpoints.

In Study ALXN1210-NMO-307 the end of the Primary Treatment Period was to be triggered when 2 patients had an adjudicated On-trial Relapse and all patients had completed, or discontinued prior to, 26 weeks on study. If 2 patients had not had an adjudicated On-trial Relapse by the time all patients had completed, or discontinued prior to, 50 weeks on study, the end of the Primary Treatment Period was to be triggered at that time. As no on-trial relapse was adjudicated, the primary period of study was completed (50 weeks). It resulted in differences in exposure between the two arms when they were compared; i.e. 43.14 (8.0, 208.6) weeks in the placebo group vs 73.50 (13.7, 117.7) weeks in the ravulizumab group.

Treatment regimen

No specific dose-response studies have been conducted for this indication. The selected dosing regimen is a loading dose of 2400-3000 mg followed by maintenance doses of 3000-3600 mg on Day 15 and then q8w. This dosing regimen is identical to that already approved for the treatment of PNH aHUS and gMG and based on the inhibition of terminal complement activation achieved by >90% of patients (see clinical pharmacology section).

During the primary treatment period ravulizumab was administered in a 10 mg/mL formulation. During the long-term extension period patients were treated with the 100 mg/ml formulation, approved at that time, on the same weight-based dose regimen.

Endpoints

Given the relapsing course of the condition and that accrual of neurological impairment is mainly NMO relapses-related the main objective of reducing the risk of relapses is adequate. The primary efficacy endpoint is time to first adjudicated On-Trial Relapse.

Additionally, the effect on neurologic disability was evaluated by as secondary endpoints measuring changes on Hauser Ambulation Index and EDSS score. Quality of life was also evaluated with Euro-QoL-5D.

The study has included validated scales and the primary and secondary endpoints have been tested in clinical developments of medicinal products for the treatment of NMOSD. In general, they are considered to measure relevant aspects of the condition and are in line with the variables assessed in study ECU-NMO-301 as recommended in the scientific advice. The inclusion of an independent committee of adjudication provides robustness to the adjudication of events although the unblinded nature of the study cannot preclude the risk of bias.

MRI was not included among the selected biomarkers. In case of relapse, additional tests (e.g., MRI, OCT, laboratory tests) could be performed at the discretion of the Investigator.

Statistical analysis

A sample size of 55 patients was estimated, which is a limited number of patients integrating an efficacy database. Of note, one of the assumptions refers to the size of the placebo control group (47 patients

from Study ECU-NMO-301) but it should be taken into account that a randomisation ratio of 2:1 was followed in the original study, resulting in a total of 96 patients in the active arm.

The MAH has implemented a number of measures in order to reduce the potential bias related to the fact that study ALXN1210-NMO-307 is open label. These measures include the evaluation of the primary efficacy measure by an independent committee, and the blindness to all the study data. However, the fact that both the investigator and the expert members of the committee were aware of the treatment and the lack of objective measures does not dissipate the concerns on the risk of bias.

It is also noted that both the baseline data and outcome results from the external-control arm were available during the planning phase before the start of the single arm trial. Thus, it is challenging to rule out any potential influence to the actual single arm trial patients' characteristics and results. In response to this, the MAH provided a description of the measures taken to ensure that the prior knowledge of the external-control data had not affected the conduction of the analyses.

The main analysis for the primary endpoint, time to first adjudicated on-trial relapse in the FAS population, was analysed using the log-rank test with a two-sided 5% alpha level. Hazard ratio and risk reduction was summarised from a Cox proportional hazards model including treatment group as a factor.

This is considered as a standard procedure in randomised trials and *per se* might be considered adequate, with or without stratification, in those designs. However, the two treatment arms do not come from a randomised design and comparability at baseline is far from being guaranteed. The proposed strategy may be considered adequate as an additional sensitivity analyses, but not as the main strategy for the main analysis given the risk of bias.

The MAH has followed the guidance provided in the scientific advice (EMA/CHMP/SAWP/545125/2019) and efforts have been made to address the concerns of possible hidden effects of confounding factors due to the comparison of the treatment arm against an external control. To tackle this issue, a propensity score method has been conducted to investigate both sources of patients' data with similar baseline characteristics. The assessment of the sequential steps taken by the MAH are crucial in the assessment to contextualise the final results presented in this procedure.

The probability of being in the treatment arm compared to the placebo arm, the PS, has been modelled by a logistic regression using baseline covariates as predictors. The variables considered in this analysis were the following: (a) region (Americas, Europe, Asia-Pacific), (b) gender, (c) age at first dose (continuous), (d) background IST (yes/no), (e) baseline EDSS (continuous) and (f) historical ARR the 24 months prior to screening.

The MAH has considered the following strategies to analyse the data based on the PS: stratification by the median PS and sIPTW. In principle, sIPTW is normally preferred but both are considered valid and results are provided using both strategies. However, there is a number of concerns that was addressed by the Applicant:

Initially the Applicant provided the baseline covariates by propensity score strata and treatment group which are above or below the median scores with the SMDs. However, comparative information on all baseline data including raw SMDs and after the sIPTW with no stratification was not initially provided (only initially provided for selected baseline data) and was considered key to judge the baseline comparability of the proposed main (raw/unadjusted) analysis. These tables were provided during the procedure. Additionally, descriptive statistics and SMDs for all baseline variables for the raw and the sIPTW analyses were presented upon request.

Furthermore, although there is no universal consensus on a specific threshold for a standardised difference to indicate a substantial imbalance, there are many publications where a value of |0.10| has been proposed as the "imbalance" criterion. The Applicant justified in their responses the reasons why a

|0.25| threshold was used instead, mainly based on sample size limitations. This can be acknowledged. Further, additional (sensitivity) analyses have been provided supporting the originally estimated treatment effect.

The potential role of all covariates and their impact on the outcome efficacy results was also discussed by the Applicant. The provided discussion can be followed. Lastly, the Applicant has performed an additional *post hoc* propensity score model using most of the baseline characteristics. The results showed a HR of 0.014 (0.000, 0.105) and a risk reduction of 98.6% (89.5%, 100.0%). These results are consistent with those initially provided.

Efficacy data and additional analyses

During the study On-Trial Relapses were determined by the Treating Physicians once patients contacted them with sign/symptom of a potential relapse. If confirmed by the clinical evaluation, the treatment for the relapse and changes in the background therapy was at his/her discretion. According to the study protocol, the recommended treatment included one gram of IV methylprednisolone administered daily for 3-5 days followed by an oral prednisone tapering. PE was recommended in case of insufficient response to methylprednisolone. Once the relapse was over the patient may continue in the study if considered appropriate. The RAC reviewed the On-Trial Relapses in order to decide whether the adjudication criteria established had been met.

No patients in the ravulizumab group had an adjudicated On-trial Relapse. In the external placebo control a total of 20 relapses were adjudicated by the external adjudication committee. The primary endpoint was met. The hazard ratio (95% CI) for ravulizumab compared with placebo was 0.014 (0.000, 0.103), representing a 98.6% reduction in the risk of relapse. All patients on ravulizumab were relapse-free at the end of the Primary Treatment Period (versus 63.2% in placebo-treated patients).

This analysis however, did not take into account the lack of randomisation and no SMDs on the raw data were provided to support the baseline similarity of this main unadjusted analysis. There is no information either on the similarity of both arms once applied the sIPTW analysis since SMDs are missing and it is difficult to assess the similarity in the PS stratified analysis. However, descriptive statistics and SMDs for all baseline variables for the raw and the sIPTW analyses were presented upon request during the review procedure. Regarding the testing of the secondary endpoints, once the primary endpoint was statistically significant, a closed testing procedure was performed with a pre-specified rank order. In the hierarchy, the Adjudicated On-Trial ARR and Clinically important changes from baseline in ambulatory function were met (p-values: <0.0001 and 0.0228 respectively).

As supportive analysis, the E-value has been provided by the Applicant. This is welcome as it provides some reassurance that it is unlikely that the results would have changed the direction of the primary outcome (i.e., to be no longer statistically significant), even in the presence of unmeasured confounder biases.

Overall, the efficacy of ravulizumab appears evidenced but there is a risk of overestimation of the treatment effect, particularly as the profile of patients according to the baseline covariates appears to be better in the active arm.

For comparison, in the original Study ECU-NMO-301, 3 adjudicated on-trial relapses were reported in the eculizumab group. The fact that no relapses were adjudicated for ravulizumab in spite of the differences in exposure between the groups may be related to the less severity of patients included in ravulizumab study, to the differences in sample size (eculizumab n=96, ravulizumab n=58) and/or the lack of "power" of the open label design to detect one relapse. Also, it could be related to a higher efficacy of ravulizumab compared to eculizumab although no relevant differences have been observed

in the rest of indications so far. It is uncertain how many relapses would have occurred (in the placebo arm) of a randomized, placebo controlled study, so including two truly comparable arms. At this stage the actual effect (size) of ravulizumab cannot be considered convincingly established.

Two patients receiving ravulizumab had a relapse as determined by the treating physician but not adjudicated as such by the RAC. In addition, 11 cases of interest in the ravulizumab group and 12 cases of interest in the placebo group were identified. All 11 (100%) cases of interest in the ravulizumab group were adjudicated negatively by the RAC. One case of interest in the placebo group was adjudicated positively by the RAC.

As for the clinical (secondary) endpoints, mainly related with disability, the lack of relapses in ravulizumab treated patients makes that no relevant improvement is observed in this group given that worsening of visual and motor function is directly related to relapses. This is also the case for QoL where no relevant changes are expected with respect to baseline except for the safety profile of ravulizumab. In any case, the interpretation of any change is challenging in these circumstances, given the absence of a concomitant comparator, the limited number of patients treated and the differences in exposure between the active treatment and the external placebo.

2.4.4. Conclusions on the clinical efficacy

The efficacy of ravulizumab on prevention of disease activity (relapses) has been established in a single pivotal open label study (ALXN1210-NMO-307). No patients in the ravulizumab group had an adjudicated On-trial Relapse during the Primary Treatment Period of Study ALXN1210-NMO-307. The study met its primary endpoint of time to first adjudicated On-trial Relapse and relapse risk reduction, and some of the secondary endpoints tested (i.e. Adjudicated On-Trial ARR, and reduction of clinical worsening in ambulatory function as measured by the HAI score).

Instead of a concurrent control arm, an external placebo control (i.e. the placebo group from study ECU-NMO-301) has been used for interpretation of the data, that diminishes the strength of the efficacy results presented. Even if the particularities of both the disease and the drug are acknowledged, the risk of overestimation of the treatment effect cannot be ruled out in an uncontrolled open label study. In this context, the Applicant explained the measures implemented during the study to reduce the potential bias and provided additional sensitivity analyses. These efforts are acknowledged and although the uncertainties are not fully addressed, there is sufficient evidence to confirm the effect of ravulizumab in the intended indication.

2.5. Clinical safety

Introduction

The safety evaluation supporting the use of ravulizumab administered intravenously for the treatment of adult patients with NMOSD is based on the Primary Treatment Period of the pivotal clinical study ALXN1210-NMO-307, a Phase 3, external placebo-controlled, open-label, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with NMOSD.

Based on the protocol-defined criteria for ending the Primary Treatment Period and because no patients had an adjudicated On-trial Relapse during the study, the end of the Primary Treatment Period was triggered when all patients completed, or discontinued prior to, 50 weeks on study. Patients who completed 50 weeks on study prior to this point remained in the Primary Treatment Period until it was

completed for all patients. Therefore, the overall treatment duration for an individual patient varied and was dependent upon when they enrolled in the study.

Safety analyses were performed on the Safety Set, which included all patients who received at least one dose of ravulizumab.

Subgroup analyses were based on age at first study drug infusion, gender, race, and region.

Patient exposure

A total of 58 adult patients with documented diagnosis of anti-AQP4 antibody-positive NMOSD were randomized and treated in Study ALXN1210-NMO-307. As of the clinical data cutoff date, 56 of the 58 patients had completed the Primary Treatment Period and were ongoing in the Long-term Extension Period. Two (3.4%) patients discontinued from the Primary Treatment Period due to AEs.

The median (min, max) study duration was 73.50 (13.7, 117.7) weeks in the ravulizumab group (Study ALXN1210-NMO-307). As of the data cut-off, 55 (94.8%) ravulizumab-treated patients were followed for > 12 months, with 21 (36.2%) patients followed for > 18 months. Overall, treatment exposure was 84.1 patient-years for ravulizumab.

Treatment compliance (defined as receiving the full intended amount of study drug) was 100% in all 58 patients treated with ravulizumab.

The majority of patients in Study ALXN1210-NMO-307 were female (89.7%), not Hispanic or Latino (77.6%), and White (50.0%) or Asian (36.2%). The mean age at first dose was 47.4 years. Most patients (n = 50; 86.2%) used ISTs for NMOSD relapse prevention prior to study treatment. The most common ISTs prior to Study ALXN1210-NMO-307 treatment were corticosteroids, rituximab, and azathioprine. 48.3% of the patients in Study ALXN1210-NMO-307 were on ISTs at baseline

Adverse events

Overall, TEAEs were reported in 53 (91.4%) patients (Table 34) in Study ALXN1210-NMO-307. Most TEAEs were not related to study drug and were mild in severity. Severe TEAEs were reported in 9 (15.5%) patients. Severe TEAEs were most common in the System Organ Class (SOC) of Infections and infestations (1 [1.7%] patient each with encephalitis meningococcal, intervertebral discitis, meningococcal sepsis, pneumonia, and upper respiratory tract infection). There were no severe TEAEs of COVID-19. In addition, 2 (3.4%) patients experienced severe TEAEs in the SOC of Musculoskeletal and connective tissue disorders (back pain and rheumatoid arthritis). Other severe TEAEs included 1 (1.7%) patient each in the SOCs of General disorders and administration site conditions (fatigue); Injury, poisoning and procedural complications (alcohol poisoning); Neoplasms benign, malignant and unspecified (incl cysts and polyps) (invasive lobular breast carcinoma); Nervous system disorders (dizziness); Psychiatric disorders (suicidal ideation); and Renal and urinary disorders (acute kidney injury).

AEs considered related to the study drug were reported in 26 (44.8%) patients in the ravulizumab group. Related TEAEs were most common in the SOCs of Infections and infestations (9 [15.5%] patients) and Injury, poisoning and procedural complications (4 [6.9%] patients). Related TEAEs in the Infections and infestations SOC included cystitis, urinary tract infection, and upper respiratory tract infection (2 [3.4%] patients each) and nasopharyngitis, sinusitis, encephalitis meningococcal, meningococcal sepsis, and pneumonia (1 [1.7%] patient each). Related TEAEs in the Injury, poisoning and procedural complications SOC included 7 events of infusion related reaction in 4 (6.9%) patients.

TESAEs were reported in 8 (13.8%) patients. Two (3.4%) patients each experienced 1 event of meningococcal infection. Both patients were promptly treated and recovered with no sequelae. The TESAE of encephalitis meningococcal, along with 2 non-serious TEAEs (bronchitis and stenotrophomonas infection), led to withdrawal of the study drug in one (1.7%) of these patients.

No patients in the ravulizumab group died during the study and, overall, ravulizumab was well tolerated.

Table 34: Overview of All Treatment-Emergent Adverse Events (TEAEs) in the Ravulizumab Group (Safety Set)

Adverse Event Category	**Ravulizumab (N = 58) Patient-Years (PY) = 84.1**		
	Events n	**Rate per 100 PY**	**Patients n (%)**
Events and patients with events	328	390.2	53 (91.4)
Deaths	-	-	0 (0.0)
TEAEs	328	390.2	53 (91.4)
Related	38	45.2	26 (44.8)
Not related	290	345.0	52 (89.7)
Mild	244	290.3	48 (82.8)
Moderate	71	84.5	29 (50.0)
Severe	13	15.5	9 (15.5)
TEAEs leading to withdrawal from study drug[a]	3	3.6	1 (1.7)
TESAEs	8	9.5	8 (13.8)
Related	3	3.6	3 (5.2)
Not related	5	5.9	5 (8.6)
TESAEs leading to withdrawal from study drug[a]	1	1.2	1 (1.7)

TEAEs are AEs with a start date on or after the date of the first dose of study drug. For the ravulizumab treatment group, AEs reported as Grade 1 were mapped to mild, Grade 2 to moderate, and Grades 3 to 5 to severe. Percentages are based on the total number of patients in the Safety Set in the ravulizumab treatment group. If a patient had multiple events for a particular relationship or severity category, he/she is counted only once for that relationship or severity. In the events column, all events are included. Patient-years for a treatment group = sum of study duration (years) of all patients in the treatment group; rate per 100 PY = 100*the number of events/patient-years.

[a] For one patient, the reason for discontinuing was 'Adverse Event'; this event (invasive lobular breast carcinoma) is not included in this row, because it was reported as dose not changed. The patient remained on study for approximately 6 months after AE onset.

AEs = adverse events; PY = patient-years; TEAEs = treatment-emergent adverse events; TESAEs = treatment-emergent serious adverse events

The overall rate of TEAEs did not increase with increased exposure to ravulizumab and no trends were observed in the rates of individual TEAEs with increased exposure to ravulizumab (Table 35).

Table 35: Treatment-emergent Adverse Events (TEAEs) in the Ravulizumab Group by 6 Month Study Periods (Safety Set)

	Ravulizumab N=58									
	0 to 6 months (N = 58)		> 6 to 12 months (N = 57)		> 12 to 18 months (N=55)		> 18 to 24 months (N=21)		> 24 to 30 months (N=4)	
Events and Patients with Events	Events n 128	Patients n (%) 41 (70.7)	Events n 109	Patients n (%) 40 (70.2)	Events n 73	Patients n (%) 31 (56.4)	Events n 15	Patients n (%) 8 (38.1)	Events n 3	Patients n (%) 2 (50.0)

A total of 15 (25.9%) patients in the ravulizumab group experienced 16 AEs of COVID-19 during the study. Fourteen patients had events coded to the Preferred Term of COVID-19, and 1 patient had an event coded to the Preferred Term of SARS-CoV-2 test positive. The patient with 2 events had 1 event each coded to the Preferred Terms of COVID-19 and post-acute COVID-19 syndrome. No patients died of COVID-19 during the study, and none of the TEAEs related to COVID-19 were serious or considered related to the study drug. All cases of COVID-19 resolved, including the 1 case of post-acute COVID-19 syndrome.

Common AEs

The most common TEAEs (occurring in ≥ 10% of patients) included COVID-19 (14 [24.1%] patients), headache (14 [24.1%] patients), back pain (7 [12.1%] patients), arthralgia (6 [10.3%] patients), and urinary tract infection (6 [10.3%] patients). Of note, Study ALXN1210-NMO-307 was initiated on 13 Dec 2019, and approximately 90% of patients were enrolled during the COVID-19 pandemic (ie, Mar 2020 or after).

Table 36: Treatment-emergent Adverse Events (TEAEs) by Preferred Term for Events Occurring in ≥ 5% of Patients in the Ravulizumab Group (Safety Set)

Preferred Term	Ravulizumab (N = 58) Patient-Years (PY) = 84.1		
	Events n	Rate per 100 PY	Patients n (%)
Events and patients with events	328	390.2	53 (91.4)
COVID-19	14	16.7	14 (24.1)
Headache	24	28.6	14 (24.1)
Back pain	8	9.5	7 (12.1)
Arthralgia	6	7.1	6 (10.3)
Urinary tract infection	7	8.3	6 (10.3)
Cystitis	7	8.3	5 (8.6)
Pyrexia	6	7.1	5 (8.6)

Preferred Term	Ravulizumab (N = 58) Patient-Years (PY) = 84.1		
	Events n	Rate per 100 PY	Patients n (%)
Upper respiratory tract infection	5	5.9	5 (8.6)
Constipation	5	5.9	4 (6.9)
Dizziness	4	4.8	4 (6.9)
Infusion related reaction	7	8.3	4 (6.9)
Vomiting	5	5.9	4 (6.9)
Chills	5	5.9	3 (5.2)
Cough	3	3.6	3 (5.2)
Diarrhoea	3	3.6	3 (5.2)
Fatigue	3	3.6	3 (5.2)
Gastrooesophageal reflux disease	4	4.8	3 (5.2)
Lymphadenopathy	3	3.6	3 (5.2)
Malaise	3	3.6	3 (5.2)
Migraine	4	4.8	3 (5.2)
Myalgia	3	3.6	3 (5.2)
Nasopharyngitis	3	3.6	3 (5.2)
Non-cardiac chest pain	3	3.6	3 (5.2)
Sinusitis	3	3.6	3 (5.2)
Vaccination site pain	3	3.6	3 (5.2)

Adverse events are coded using MedDRA Version 25.0. TEAEs are AEs with a start date on or after the date of the first dose of study drug. Percentages are based on the total number of patients in the Safety Set in the ravulizumab treatment group. If a patient had multiple events for a particular PT, he/she is counted only once for that PT. PTs are in the order of descending frequency. Patient-years for a treatment group = sum of study duration (years) of all patients in the treatment group; rate per 100 PY = 100*the number of events/patient-years.
AE = adverse event; COVID 19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; PY = patient-years

Serious adverse event/deaths/other significant events

Deaths

No deaths occurred during Study ALXN1210-NMO-307.

Other Serious AE (SAE)

Eight (13.8%) patients each reported a single TESAE during the study. The only System Organ Class (SOC) with TESAEs reported by more than 1 patient in the ravulizumab group was Infections and infestations (5 [8.6%] patients). These TESAEs included infection (not otherwise specified), intervertebral discitis, pneumonia, meningococcal sepsis, and encephalitis meningococcal (1 [1.7%] patient each). Other TESAEs included spinal osteoarthritis, invasive lobular breast carcinoma, and suicidal ideation (1 event each in 1 [1.7%] patient).

Table 37: Treatment-emergent Serious Adverse Events (TESAEs) by MedDRA System Organ Class/Preferred Term in the Ravulizumab Group (Safety Set)

System Organ Class Preferred Term	ALXN1210-NMO-307 Ravulizumab (N = 58) Patient-Years (PY) = 84.1		
	Events n	Rate per 100 PY	Patients n (%)
Events and patients with events	8	9.5	8 (13.8)
Infections and infestations	5	5.9	5 (8.6)
Encephalitis meningococcal	1	1.2	1 (1.7)
Infection	1	1.2	1 (1.7)
Intervertebral discitis	1	1.2	1 (1.7)
Meningococcal sepsis	1	1.2	1 (1.7)
Pneumonia	1	1.2	1 (1.7)
Musculoskeletal and connective tissue disorders	1	1.2	1 (1.7)
Spinal osteoarthritis	1	1.2	1 (1.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1.2	1 (1.7)
Invasive lobular breast carcinoma	1	1.2	1 (1.7)
Psychiatric disorders	1	1.2	1 (1.7)
Suicidal ideation	1	1.2	1 (1.7)

Adverse events are coded using MedDRA Version 25.0. TEAEs are AEs with a start date on or after the date of the first dose of study drug. Percentages are based on the total number of patients in the Safety Set in the ravulizumab treatment group. If a patient had multiple events for a particular SOC or PT, he/she is counted only once for that SOC or PT. SOCs are presented in alphabetic order. PTs are in the order of descending frequency in the ravulizumab column. Patient-Years for a treatment group = sum of Study Duration (years) of all patients in the treatment group; Rate per 100 PY = 100*the number of events/Patient-Years.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; PY = patient-years; SOC = System Organ Class; TEAE = treatment emergent adverse event

Three (5.2%) ravulizumab-treated patients reported TESAEs that were considered related to study drug, including encephalitis meningococcal, meningococcal sepsis, and pneumonia (1 [1.7%] patient each). There were no COVID-19-related TESAEs.

The overall rate of TESAEs did not increase with increased exposure to ravulizumab, and no TESAEs were reported in the ravulizumab group in the 21 patients treated beyond 18 months.

Table 38: Treatment-emergent Serious Adverse Events (TESAEs) by MedDRA SOC/Preferred Term by 6-month Study Periods (Safety Set)

	ALXN1210-NMO-307 Ravulizumab (N = 58)									
	0-6 Months (N = 58)		> 6 to 12 Months (N = 57)		> 12 to 18 Months (N = 55)		> 18 to 24 Months (N = 21)		> 24 to 30 Months (N = 4)	
System Organ Class Preferred Term	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
Events and patients with events	2	2 (3.4)	4	4 (7.0)	2	2 (3.6)	0	0 (0.0)	0	0 (0.0)
Infections and infestations	1	1 (1.7)	2	2 (3.5)	2	2 (3.6)	0	0 (0.0)	0	0 (0.0)
Encephalitis meningococcal	1	1 (1.7)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Infection	0	0 (0.0)	0	0 (0.0)	1	1 (1.8)	0	0 (0.0)	0	0 (0.0)
Intervertebral discitis	0	0 (0.0)	1	1 (1.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Meningococcal sepsis	0	0 (0.0)	0	0 (0.0)	1	1 (1.8)	0	0 (0.0)	0	0 (0.0)
Pneumonia	0	0 (0.0)	1	1 (1.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Musculoskeletal and connective tissue disorders	0	0 (0.0)	1	1 (1.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Spinal osteoarthritis	0	0 (0.0)	1	1 (1.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (1.7)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Invasive lobular breast carcinoma	1	1 (1.7)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Psychiatric disorders	0	0 (0.0)	1	1 (1.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Suicidal ideation	0	0 (0.0)	1	1 (1.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Adverse events are coded using MedDRA Dictionary Version 25.0. TEAEs are AEs with a start date on or after the date of the first dose of study drug. Percentages are based on the total number of patients in the Safety Set in the 6-month study period. If a patient had multiple events for a particular SOC or PT, he/she is counted only once for that SOC or PT. SOCs are presented in alphabetic order. PTs are in the order of descending frequency in the 0-6 month study period.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAEs = treatment-emergent adverse events

Adverse Events of Special Interest

Meningococcal infection was the only AE of special interest in Study ALXN1210-NMO-307. Two (3.4%) patients in the ravulizumab group experienced 1 TESAE each of meningococcal infection (Preferred Terms: meningococcal sepsis and encephalitis meningococcal). Both patients were treated promptly with antibiotics and recovered with no sequelae. One patient discontinued the study drug and study as a result of this event, and the other patient was continuing to receive ravulizumab in the study as of the data cutoff date.

Infusion Reactions

Preferred terms indicating local (infusion site or injection site reactions), systemic (infusion-associated/infusion-related reactions within 24 hours of infusion start), and in the Anaphylactic reaction (Narrow) and Hypersensitivity (Narrow) SMQs were evaluated.

Table 39: Definitions for Infusion Reactions

Local Administration Reaction	Systemic Reaction	Immune-mediated Reactions
Infusion site/injection site reactions	Infusion-associated/Infusion-related reactions	Hypersensitivity
AEs localized to the site of study drug administration[a]	Systemic AEs occurring during or within 24 hours of the start of infusion (eg, fever and/or shaking chills, flushing and/or itching, etc.)[b]	AEs with Preferred Terms in the narrow SMQ of Anaphylactic reaction and the narrow SMQ of Hypersensitivity

a Includes PTs containing "infusion site" (eg, "infusion site reaction", "infusion site hypersensitivity"). b Includes selected PTs indicating potential systemic reactions occurring within 24 hours of the start of the infusion.
AE = adverse event; PT = preferred term; SMQ = Standardised MedDRA (Medical Dictionary for Regulatory Activities) Query

Using these search criteria, 20 (34.5%) patients had 1 or more TEAEs identified as potential infusion reactions. None of these events were serious, and none resulted in withdrawal of ravulizumab.

Four (6.9%) patients in the ravulizumab group had infusion reactions that led to study drug interruption during a total of 5 infusions. In three patients (Preferred Term of infusion related reaction), the events were described by the Investigators as rigors and abdominal pain (1 patient each) and muscle spasms and back pain (occurring during 2 infusions in 1 patient). One patient experienced vomiting requiring interruption of the infusion. None of these infusion reactions were serious, and the total infusion volume was subsequently administered in each case. No patients experienced an anaphylactic reaction.

Table 40: Infusion Reactions by MedDRA System Organ Class/Preferred Term in the Ravulizumab Group (Safety Set)

Infusion Reactions **System Organ Class** **Preferred Term**	**ALXN1210-NMO-307 Ravulizumab (N = 58)** **Patient-Years (PY) = 84.1**		
	Events n	**Rate per 100 PY**	**Patients n (%)**
Infusion reactions	41	48.8	20 (34.5)
Eye disorders	1	1.2	1 (1.7)
Conjunctivitis allergic	1	1.2	1 (1.7)
Gastrointestinal disorders	3	3.6	3 (5.2)
Vomiting	2	2.4	2 (3.4)
Diarrhea	1	1.2	1 (1.7)
General disorders and administration site conditions	13	15.5	10 (17.2)
Vaccination site pain	3	3.6	3 (5.2)
Pyrexia	2	2.4	2 (3.4)
Asthenia	1	1.2	1 (1.7)
Chills	2	2.4	1 (1.7)
Fatigue	1	1.2	1 (1.7)
Injection site reaction	1	1.2	1 (1.7)
Pain	1	1.2	1 (1.7)
Swelling face	1	1.2	1 (1.7)
Vaccination site pruritus	1	1.2	1 (1.7)
Injury, poisoning and procedural complications	7	8.3	4 (6.9)
Infusion related reaction	7	8.3	4 (6.9)
Musculoskeletal and connective tissue disorders	1	1.2	1 (1.7)
Myalgia	1	1.2	1 (1.7)

Nervous system disorders	8	9.5	6 (10.3)
Headache	6	7.1	5 (8.6)
Dizziness	2	2.4	2 (3.4)
Respiratory, thoracic and mediastinal disorders	1	1.2	1 (1.7)
Rhinitis allergic	1	1.2	1 (1.7)
Skin and subcutaneous tissue disorders	5	5.9	5 (8.6)
Rash	2	2.4	2 (3.4)
Dermatitis	1	1.2	1 (1.7)
Eczema	1	1.2	1 (1.7)
Urticaria	1	1.2	1 (1.7)
Vascular disorders	2	2.4	2 (3.4)
Hypertension	2	2.4	2 (3.4)

Adverse events are coded using MedDRA Dictionary Version 25.0. Infusion Reactions are derived from the Narrow SMQ of Hypersensitivity and Anaphylactic reaction, and the special categories of Infusion Site Reactions and Infusion Reactions (within 24 hours). TEAEs are AEs with a start date on or after the date of the first dose of study drug. Percentages are based on the total number of patients in the Safety Set in the ravulizumab treatment group. If a patient had multiple events for a particular SOC or PT, he/she is counted only once for that SOC or PT. SOCs are presented in alphabetic order. PTs are in the order of descending frequency in the ravulizumab column.
Patient-Years for a treatment group = sum of Study Duration (years) of all patients in the treatment group; Rate per 100 PY = 100*the number of events/Patient-Years.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PY = patient-years; SMQ = standardized MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event

Adverse events related to COVID-19

A total of 15 (25.9%) patients with 16 adverse events indicating COVID-19 infection, positive test for SARS-CoV-2, and/or complications of COVID-19 infection were identified. Fourteen patients had events coded to the preferred term of COVID-19, and 1 patient had an event coded to the preferred term of SARS-CoV-2 test positive. The patient with 2 events had 1 event each coded to the preferred terms of COVID-19 and post-acute COVID-19 syndrome. Five of the 15 patients (33.3%) developed COVID-19 infection before their first COVID-19 vaccination, 7 of 15 (46.7%) patients developed COVID-19 after at least 1 vaccination, and 3 of 15 (20.0%) patients did not receive a COVID-19 vaccination. The median (min, max) time between the first dose of ravulizumab and COVID-19 onset was 378.0 (40, 740) days. No patients died of COVID-19 during the study, and none of the TEAEs related to COVID-19 were serious or considered related to the study drug. All cases of COVID-19 resolved, including the 1 case of post-acute COVID-19 syndrome.

Laboratory findings

Chemistry and haematology parameters

No clinically significant trends were observed in any chemistry and haematology parameters over time in Study ALXN1210-NMO-307.Of the reported TEAEs that were associated with a laboratory finding, the majority were mild in severity, not considered related to the study drug, and resolved without interruption of the study drug. No patients in the ravulizumab group had a TEAE associated with a laboratory finding that was considered serious.

Vital signs, physical findings and other observations related to safety

No clinically significant trends were observed in any vital sign parameters, body weight or ECG results over time. No safety signals were identified through physical examination.

One (1.7%) patient with a history of depression (ongoing) experienced 2 events of suicidal ideation during treatment with ravulizumab. One of the events was considered non-serious and of Grade 2 and the other event was reported as a TESAE (suicidal ideation) and of Grade 4. This TESAE resolved and no action was taken with the study drug in response to this event. Both events of suicidal ideation were considered not related to study drug by the Investigator.

No pregnancies were reported in Study ALXN1210-NMO-307.

Immunogenicity

Five (8.6%) of 58 patients in the ravulizumab group were classified as having pre-existing immunoreactivity (ie, an ADA-positive response at baseline, with either all post-first-dose ADA results negative or all post-first-dose ADA responses less than 4-fold over the baseline titer level). One of these 5 patients was ADA positive at Week 26 with a low titer of 1:3. The baseline titer of this patient could not be determined. Based on the definition of pre-existing immunoreactivity and given that the only ADA positive sample (Week 26) during the treatment phase was at a low titer, this patient was categorized as exhibiting pre-existing immunoreactivity. None of the samples that were positive in the ADA assay exhibited any neutralizing activity in the neutralizing antibody assay.

No treatment-emergent immunogenicity (ie, an ADA-positive response post first dose when baseline results are negative or missing) was observed following ravulizumab administration to patients with NMOSD during the Primary Treatment Period of Study ALXN1210-NMO-307.

Safety in special populations

Intrinsic factors

Analyses of the safety profile by intrinsic factors (ie, age, gender, race, geographic region) were performed based on TEAEs and TESAEs. No notable trends were observed in any subgroup; however, some subgroups included a small number of patients, which limits interpretation of these results.

Extrinsic factors

No subgroup analyses were performed based on extrinsic factors.

Use in pregnancy and lactation

Ravulizumab has not been studied in pregnant or lactating females.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted with ravulizumab IV.

Discontinuation due to adverse events

Two (3.4%) patients discontinued from the Primary Treatment Period due to adverse events. One (1.7%) patient experienced 3 TEAEs (bronchitis, encephalitis meningococcal, and stenotrophomonas infection) that resulted in withdrawal from the study drug. One additional patient in the ravulizumab group discontinued the Primary Treatment Period due to an AE of invasive lobular breast carcinoma. The patient

remained on treatment for approximately 6 months following the diagnosis, but eventually discontinued the study due to the ongoing cancer and need for additional treatment. This patient is not included in Table 41, as the action taken with study drug due to the TEAE was "dose not changed".

Table 41: Treatment-emergent Adverse Events (TEAEs) Resulting in Interruption of or Withdrawal from Study Drug in the Ravulizumab Group (Safety Set)

Preferred Term	ALXN1210-NMO-307 Ravulizumab (N = 58) n (%)
Patients with events resulting in interruption of the study drug	5 (8.6)
Infusion related reaction	3 (5.2)
Pneumonia	1 (1.7)
Vomiting	1 (1.7)
Patients with events resulting in withdrawal from the study drug	1 (1.7)
Bronchitis	1 (1.7)
Encephalitis meningococcal	1 (1.7)
Stenotrophomonas infection	1 (1.7)

Adverse events are coded using MedDRA Version 25.0. TEAEs are AEs with a start date on or after the date of the first dose of study drug. Percentages are based on the total number of patients in the Safety Set in the ravulizumab treatment group. If a patient had multiple events for a particular PT, he/she is counted only once for that PT. PTs are in the order of descending frequency in the ravulizumab column. Additional TEAEs resulting in study drug interruption (ie, delayed infusions) were identified after clinical database lock. These TEAEs are discussed in text but are not reflected in the table above. For one patient, the reason for discontinuing was 'Adverse Event'; this event (invasive lobular breast carcinoma) is not included in this row, because it was reported as dose not changed. The patient remained on study for approximately 6 months after AE onset.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAEs = treatment-emergent adverse events

Post marketing experience

The estimated postmarketing exposure to ravulizumab IV since the first Marketing Authorization (21 Dec 2018) through 31 Dec 2021 was 5733.9 PY for PNH and aHUS indications.

Meningococcal infection remains an important identified risk for ravulizumab IV based on the mechanism of action, findings from the ravulizumab clinical studies, and long-term experience with eculizumab (SOLIRIS®), another approved C5 inhibitor.

The cumulative postmarketing reporting rate for meningococcal infections is approximately 0.05 cases per 100 PY (3 cases per 5733.9 PY). The understanding and characterization of this risk remain unchanged based on the cumulative data as of 31 Dec 2021. Mitigation measures for the risk of meningococcal infections already in place for ravulizumab remain appropriate and effective and will be applied similarly for patients with NMOSD.

Additionally, hypersensitivity reaction was confirmed as an identified risk based on a cumulative data review of the Standardised MedDRA Query hypersensitivity.

2.5.1. Discussion on clinical safety

Ravulizumab is currently approved for the treatment of adult and paediatric patients with PNH and aHUS, and for the treatment of adult patients with gMG. From the first Marketing Authorization (21 Dec 2018) to 31 Dec 2021, the cumulative postmarketing exposure to ravulizumab was 5733.9 patient-years. The

safety profile of ravulizumab is already known. Ravulizumab is derived from eculizumab and the safety profile of eculizumab is also taken into consideration.

The safety analyses for ravulizumab for the treatment of NMOSD are based on the pivotal phase 3 Study ALXN1210-NMO-307, an external placebo-controlled, open-label, multicenter study.

The ravulizumab clinical development programme for NMOSD includes results from 58 patients treated with ravulizumab from study ALXN1210-NMO-307 and 47 patients treated with placebo from study ECU-NMO-301 as the external control group.

A total of 58 patients were exposed to ravulizumab as of the clinical cut-off date (84.1 patient-years of exposure). These patients were treated with the proposed dosing regimen for a median duration of 73.14 weeks. The median (min, max) number of ravulizumab infusions was 11.0 (2, 18). Only 21 patients have been followed for more than 18 months so far (study still ongoing). This is a rather limited safety database for the global analysis. Given the low prevalence of NMOSD, drug exposure can be considered acceptable for the short-term safety assessment of ravulizumab. The available safety information of ravulizumab in the already authorised indications (PNH, aHUS, gMG) can be taken as supportive considering that patients have been treated with the same dosing regimen. Nevertheless, long-term safety profile is at present uncertain for the intended population. During the procedure the MAH submitted an update of the safety results. As of the data cut-off date (15 Jun 2022), 81% of the patients (47) were followed for > 18 months, with 24% (14) followed for > 24 months.

With regard to baseline demographic characteristics, about half of the patients were white and approximately 90% of the patients were women. The mean age at first dose was 47.4 years (ranging from 18 to 74 years). Seven (12.1%) elderly patients were included in study ALXN1210-NMO-307. European patients represent 29.3% of the patients treated with ravulizumab, 36.2% were from the Americas, and 34.5% were from the Asia-Pacific Region.

Most patients (91.4%) in study ALXN1210-NMO-307 reported AEs. COVID-19 (24.1%), headache (24.1%), back pain (12.1%), arthralgia (10.3%), and urinary tract infection (10.3%) were the most frequently reported AEs (≥ 10% of patients).

The majority of the events were of mild or moderate severity. Severe events were reported by 9 patients (15.5%) treated with ravulizumab. Severe TEAEs were most common in the SOC of Infections and infestations (1 [1.7%] patient each with encephalitis meningococcal, intervertebral discitis, meningococcal sepsis, pneumonia, and upper respiratory tract infection), which is consistent with the mechanism of action of ravulizumab.

Out of the 328 events that were reported, 38 (11.6%) in 44.8% of the patients were considered related to treatment. Related TEAEs were most common in the SOCs of Infections and infestations (15.5% of the patients) and Injury, poisoning and procedural complications (6.9%). Related TEAEs in the Infections and infestations SOC included cystitis, urinary tract infection, and upper respiratory tract infection (2 [3.4%] patients each) and nasopharyngitis, sinusitis, encephalitis meningococcal, meningococcal sepsis, and pneumonia (1 [1.7%] patient each). Related TEAEs in the Injury, poisoning and procedural complications SOC included 7 events of infusion related reaction in 4 (6.9%) patients. Related TEAEs in the Injury, poisoning and procedural complications SOC included 7 events of infusion related reaction in 4 (6.9%) patients. The following adverse events were considered related to study drug in study ALXN-1210-NMO-307 but have not been included as adverse drug reactions in the SmPC: cystitis, urinary tract infection (which was also one of the most common adverse events), sinusitis and pneumonia. The MAH provided an analysis of these adverse events during the procedure, showing that in the cases of pneumonia, cystitis and sinusitis, the patients had underlying medical conditions that may have contributed to the events. However, no relevant medical history was reported for the two patients with urinary tract infections that were assessed as related to treatment. Considering the high frequency of

urinary tract infections and the lack of justification for the two events related to ravulizumab, a causal possibility between ravulizumab and urinary tract infections has not been ruled out by the Applicant. Urinary tract infections have been included as an adverse drug reaction in section 4.8 of the SmPC.

No additional safety issues were identified with prolonged and repeated administration of ravulizumab. Incidence of AEs decreased with repeated administration: 70.7% of patients reported AEs in the first 6month treatment period compared to 50.0% of the patients in the > 24 to 30 months period.

Overall, the AE profile of ravulizumab in NMOSD is consistent with that known for ravulizumab in other indications.

There were no deaths in Study ALXN1210-NMO-307. Eight (13.8%) patients each reported a single TESAE during the study. The most frequently reported SAEs were those related to infections. Three (5.2%) patients reported TESAEs that were considered related to study drug, including encephalitis meningococcal, meningococcal sepsis, and pneumonia (1 [1.7%] patient each). The overall rate of TESAEs did not increase with increased exposure to ravulizumab, and no TESAEs were reported in the ravulizumab group in the 21 patients treated beyond 18 months.

The main risk associated to ravulizumab and C5 inhibitors in general is an increased susceptibility to infections caused by Neisseria sp., especially *Neisseria meningitidis*. Patients are required to be vaccinated against meningococcal infections (as described in section 4.4 of the SmPC). In study ALXN1210-NMO-307, meningococcal infection was considered an adverse event of special interest. Two (3.4%) patients experienced one AE of special interest each (meningococcal sepsis and encephalitis meningococcal), which were considered serious. The two patients had received vaccines against serogroups A, C, Y, W 135 and B. Both patients were treated promptly with antibiotics and recovered with no sequelae. One patient discontinued the study drug and study as a result of this event, and the other patient was continuing to receive ravulizumab in the study as of the data cut-off date.

Twenty (34.5%) patients had 1 or more TEAEs identified as potential infusion reactions, which is similar to the rate reported in patients with Myasthenia Gravis in Study ALXN1210-MG-306. None of these events were serious, and none resulted in withdrawal of ravulizumab, although 4 (6.9%) patients had infusion reactions that lead to study drug interruption during 5 infusions. The total infusion volume was subsequently administered in each case. No patients experienced an anaphylactic reaction.

A total of 15 (25.9%) patients with 16 adverse events indicating COVID-19 infection, positive test for SARS-CoV-2, and/or complications of COVID-19 infection were identified. No patients died of COVID-19 during the study, and none of the TEAEs related to COVID-19 were serious or considered related to the study drug. All cases of COVID-19 resolved, including the 1 case of post-acute COVID-19 syndrome.

No clinically significant changes in the laboratory results, vital signs, physical examinations, and electrocardiograms were detected.

Five (8.6%) patients were classified as having pre-existing immunoreactivity. As of 15 Jun 2022, no treatment-emergent ADA response or treatment-boosted ADA response was observed following ravulizumab treatment in patients with NMOSD and no NAb positive results were observed for any of the ravulizumab-treated patients. The observed pre-existing immunoreactivity in the 5 patients was associated with very low titers which were not boosted during the treatment or the extension period. This finding is consistent with the few treatment-emergent ADA responses in patients with PNH, aHUS, or gMG treated with ravulizumab. Upon request, the Applicant provided an analysis of the safety profile of patients with pre-existing ADAs compared to the rest of the patients during the Primary Treatment Period of study ALXN1210-NMO-307, which did not suggest a different safety profile between patients with and without pre-existing ADA. Therefore, no impact of immunogenicity on ravulizumab safety was

observed in any of the patients with NMOSD treated with ravulizumab during the Primary Treatment Period of study ALXN1210-NMO-307.

Since only 7 elderly patients were enrolled in NMOSD program it is not possible to obtain any reliable conclusions on safety in this population.

Regarding the safety of ravulizumab in children and adolescents, a phase 2/3, open-label, historical-controlled, single-arm trial of ravulizumab in children and adolescents from 2 to less than 18 years of age with aquaporin-4 antibody positive NMOSD (study ALXN1210-NMO-317) was initiated on 23 Jun 2022.

Overall, one (1.7%) patient experienced 3 TEAEs (bronchitis, encephalitis meningococcal, and stenotrophomonas infection) that resulted in withdrawal from the study drug.

The postmarketing data do not seem to show any new safety concern.

2.5.2. Conclusions on clinical safety

The safety database of ravulizumab in the applied indication is considered limited both in terms of the number of exposed patients and the duration of the exposure. The small size of the safety database is not unexpected considering the rarity of the condition.

Overall, the reported safety profile of ravulizumab in NMOSD patients appears comparable to that observed in other indications. The most commonly reported adverse events with ravulizumab in study ALXN1210-NMO-307 were COVID-19, headache, back pain, arthralgia and urinary tract infection.

Meningococcal infection is an important risk of ravulizumab related to its mechanism of action. Two cases of meningococcal infection were reported in Study ALXN1210-NMO-307.

The Long-Term Extension Period of Study ALXN1210-NMO-307 is ongoing. The MAH should submit the results when available in order to complete the long-term safety assessment.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The Applicant submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.0 is acceptable. The CHMP endorsed the Risk Management Plan version 7.0 with the following content.

During the evaluation of this procedure, changes in the RMP were requested within another parallel procedure. In line with guidance on post-authorisation procedures, if the parallel applications reach the finalisation stage at the same time, the consolidated RMP version will be adopted by the relevant Committee and will become the approved version of the RMP. Hence, the Applicant did submit a consolidated RMP version 7.0.

Safety concerns

Table 42: Summary of safety concerns

Summary of Safety Concerns	
Important identified risks	Meningococcal infection
Important potential risks	Serious haemolysis after drug discontinuation in PNH patients Severe TMA complications in aHUS patients after ravulizumab discontinuation Immunogenicity Serious infections Malignancies and haematologic abnormalities in PNH patients
Missing information	Use in pregnant and breast-feeding women

aHUS = atypical haemolytic uraemic syndrome; PNH = paroxysmal nocturnal haemoglobinuria; TMA = thrombotic microangiopathy

Pharmacovigilance plan

Table 43: Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 – required additional pharmacovigilance activities				
"A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)" (ALXN1210-PNH-301) Ongoing	To evaluate the safety and efficacy of ALXN1210 administered by intravenous infusion to adult patients with PNH who are naïve to complement inhibitor treatment To collect and evaluate safety data specific to the use of ULTOMIRIS and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in treated PNH patients	Meningococcal infection Serious haemolysis after drug discontinuation in PNH patients Immunogenicity Serious infections Malignancies and haematologic abnormalities in PNH patients Use in pregnant and breast-feeding women	Final CSR	Oct 2023
"A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated with Eculizumab" (ALXN1210-PNH-302) Ongoing	To collect and evaluate efficacy and safety data specific to the use of ULTOMIRIS and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in treated PNH patients	Meningococcal infection Serious haemolysis after drug discontinuation in PNH patients Immunogenicity Serious infections Malignancies and haematologic abnormalities in PNH patients Use in pregnant and breast-feeding women	Final CSR	Dec 2022

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
"Paroxysmal Nocturnal Hemoglobinuria (PNH) Registry" M07-001 Ongoing	To collect and evaluate safety data specific to the use of SOLIRIS / ULTOMIRIS and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in SOLIRIS / ULTOMIRIS and non-SOLIRIS / ULTOMIRIS treated patients.	Meningococcal infection Serious haemolysis after drug discontinuation in PNH patients Serious infections Malignancies and haematologic abnormalities in PNH patients Use in pregnant and breast-feeding women	Interim data analysis	Every 2 years interim data analysis report
"Atypical Hemolytic Uremic Syndrome (aHUS) Registry" (M11-001) Ongoing	To collect and evaluate safety and effectiveness data specific to the use of eculizumab / ravulizumab in aHUS patients To assess the long-term manifestations of TMA complications of aHUS as well as other clinical outcomes, including mortality and morbidity in aHUS patients receiving eculizumab / ravulizumab treatment or other disease management.	Meningococcal infection Severe TMA complications in aHUS patients after ravulizumab discontinuation Immunogenicity Serious infections Use in pregnant and breast-feeding women	Interim data analysis	Every 2 years interim data analysis report
"Single Arm Study of ALXN1210 in Complement Inhibitor Treatment-Naïve Adult and Adolescent Patients with Atypical Hemolytic Uremic Syndrome (aHUS)" (ALXN1210-aHUS-311) Ongoing	To assess the efficacy and long-term safety of ravulizumab in complement inhibitor treatment-naïve adolescent and adult patients with aHUS to inhibit complement-mediated TMA as characterised by thrombocytopenia, haemolysis, and renal impairment	Meningococcal infection Severe TMA complications in aHUS patients after ravulizumab discontinuation Immunogenicity Serious infections Use in pregnant and breast-feeding women	Final CSR	Dec 2023

Risk minimisation measures

Table 44: Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Meningococcal infection	**Routine risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	– SmPC sections 4.3, 4.4, and 4.8 – PL sections 2 and 4 Recommendations for vaccination/antibiotic prophylaxis in SmPC section 4.4 and PL section 2 Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL section 2 Restricted medical prescription **Additional risk minimisation measures:** Educational materials – PNH/aHUS/gMG/NMOSD Physician's Guide – PNH/aHUS/gMG/NMOSD Patient's Information Brochure – PNH/aHUS Parent's Information Brochure – Patient card Controlled distribution Revaccination reminder	**reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – PNH registry (M07-001) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 (final study report date: Dec 2023)
Serious haemolysis after drug discontinuation in PNH patients	**Routine risk minimisation measures:** – SmPC section 4.4 – PL section 3 Monitoring of patients who discontinued ULTOMIRIS recommended in SmPC section 4.4 and PL section 3 **Additional risk minimisation measures:** Educational materials – PNH Physician's Guide – PNH Patient's Information Brochure	**Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – PNH registry (M07-001)
Severe TMA complications in aHUS patients after ravulizumab discontinuation	**Routine risk minimisation measures:** – SmPC section 4.4 **Additional risk minimisation measures:** Educational materials – aHUS Physician's Guide – aHUS Patient's Information Brochure	**Additional pharmacovigilance activities:** – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 (final study report date: Dec 2023)
Immunogenicity	**Routine risk minimisation measures:** – SmPC sections 4.4 and 4.8 **Additional risk minimisation measures:** Educational materials – PNH/aHUS/gMG/NMOSD Physician's Guide – PNH/aHUS/gMG/NMOSD Patient's Information Brochure	**Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 (final study report date: Dec 2023)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious infections	**Routine risk minimisation measures:** – SmPC sections 4.3, 4.4 and 4.8 – PL sections 2, 3 and 4 Recommendations for vaccination of paediatric patients against *Haemophilusinfluenzae* and pneumococcal infections in SmPC section 4.4 and PL section 2. **Additional risk minimisation measures:** Educational materials – PNH/aHUS/gMG/NMOSD Physician's Guide – PNH/aHUS/gMG/NMOSD Patient's Information Brochure – PNH/aHUS Parent's Information Brochure	**Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – PNH registry (M07-001) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 (final study report date: Dec 2023)
Malignancies and haematologic abnormalities in PNH patients	**Routine risk minimisation measures:** – None proposed **Additional risk minimisation measures:** Educational materials – PNH Physician's Guide – PNH Patient's Information Brochure	**Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – PNH registry (M07-001)
Use in pregnant and breast-feeding women	**Routine risk minimisation measures:** – SmPC sections 4.6 and 5.3 – PL section 2 Recommendations on contraception in SmPC section 4.8 and PL section 2 **Additional risk minimisation measures:** Educational materials – PNH/aHUS/gMG/NMOSD Physician's Guide – PNH/aHUS/gMG/NMOSD Patient's Information Brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** – Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – PNH registry (M07-001) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 (final study report date: Dec 2023)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ultomiris 300 mg/30 mL concentrate for solution for infusion. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The new proposed indication for Ultomiris (ravulizumab) is for the treatment of adult patients with NMOSD who are AQP4 antibody-positive.

NMOSD is an inflammatory demyelinating disease of the central nervous system characterized by attacks of optic neuritis, longitudinally extensive transverse myelitis, and less frequently, postrema syndrome, acute brainstem syndrome, acute diencephalic clinical syndrome or symptomatic cerebral syndrome.

NMOSD is a severe condition, which results in early and permanent neurological disability. Within 5 years, more than 50% of patients are functionally blind or have lost the ability to ambulate without assistance. Mortality rates are high, most frequently secondary to neurogenic respiratory failure, which occurs with extension of cervical lesions into the brainstem or from primary brainstem lesions[20,21].

The AQP4 serum autoantibody is a specific biomarker for NMOSD, although 10-27% of patients with a clinical diagnosis of NMOSD are seronegative for AQP-4-IgG[22].

In NMOSD patients, any relapse can result in the accumulation of neurological disability, including blindness and paralysis, which highlights the immediate need for immunotherapies that effectively prevent NMOSD relapses.

3.1.2. Available therapies and unmet medical need

Disability is attack related and the early treatment of the relapses together with prevention of further episodes is essential for reducing progressive accumulation of neurologic disability. Acute episodes are generally treated with high-dose intravenous glucocorticoids and therapeutic plasma exchange in patients with severe symptoms, unresponsive to glucocorticoids. Regarding the prevention of relapses, patients with NMOSD have been treated with off-label immunosuppressive therapies, such as azathioprine, mycophenolate mofetil, prednisolone or rituximab. Three monoclonal antibodies have been approved by the EMA since 2019 for the treatment of NMOSD in adult patients who are anti-AQP4 antibody-positive: eculizumab, inebilizumab, and satralizumab, targeting different components of the immune system, with the aim of preventing NMOSD relapses. No direct comparison has been made between these three monoclonal antibodies.

Ravulizumab was structurally derived from eculizumab and they share the same mechanism of action. As a result of the differences in molecular features, the serum elimination half-life of ravulizumab is longer than that of eculizumab, enabling an extended dosing interval of every 8 weeks as compared to a dosing interval of every 2 weeks with eculizumab.

[20]Sellner J et al. Eur J Neurol. 2010;17(8):1019-32.
[21] EMA/CHMP/SAWP/712652/2014
[22]Hamid SH et al. J Neurol 2017; 264(10):2088-2094.

3.1.3. Main clinical studies

The submission of ravulizumab for the treatment of NMOSD is based on one single pivotal trial: Study ALXN1210-NMO-307: A phase 3 randomized, external placebo-controlled, open-label, multicenter study (still ongoing).

3.2. Favourable effects

No patients in the ravulizumab group had an adjudicated On-trial Relapse during the 73.5 mean weeks of duration. In the external placebo control a total of 20 relapses were adjudicated by the external adjudication committee during 36 weeks. The primary endpoint was met. The hazard ratio (95% CI) for ravulizumab compared with placebo was 0.014 (0.000, 0.103), representing a 98.6% reduction in the risk of relapse. All patients on ravulizumab were relapse-free at the end of the Primary Treatment Period (versus 63.2% in placebo-treated patients).

The adjudicated ARR (95% CI) was 0.0 (NA, 0.044) in the ravulizumab group.

As for the neurological functioning, clinically important worsening from baseline measured by HAI score was reported for 2 (3.4%) patients in the ravulizumab group compared to 11 (23.4%) patients in the placebo group.

3.3. Uncertainties and limitations about favourable effects

The main concerns with the submitted data package relate to the uncontrolled open label nature of the pivotal study, the (lack of/limited) comparability of the two non-contemporary groups used for the primary estimation of ravulizumab efficacy (i.e. study ALXN1210-NMO-307 was conducted between December 2019 and March 2022 while study ECU-NMO-301 was conducted between 2014 and 2018) and the intrinsic differences between a group of patients prospectively studied (ravulizumab group) and a retrospectively selected placebo group, without the protection from bias of randomisation.

Indeed, differences with respect to baseline disease status and in exposure were shown between patients treated in the external placebo arm and those included in the ravulizumab group. Overall, patients in study ECU-NMO-301 showed more disability, higher disease activity, more had been previously treated, and the percentage of patients who were on treatment during the study was also higher. In terms of exposure the external placebo group was followed for a shorter period of time.

From a methodological point of view, the use of the placebo group from study ECU-NMO-301 as an external control for study ALXN1210-NMO-307, for the primary estimation of ravulizumab efficacy is of concern.

A total of 55 patients were enrolled, which is a limited number of patients integrating an efficacy database.

The clinical (secondary) endpoints are mainly related with disability. In NMOSD, disability is driven by uncomplete recovery from relapses. As no relapses were observed in the ravulizumab arm no relevant improvement was observed in visual and motor function secondary endpoints. This is also the case for QoL where no relevant changes are expected with respect to baseline except for the safety profile of ravulizumab. In any case, the interpretation of any change is challenging in these circumstances, given the absence of a concomitant comparator, the limited number of patients treated and the differences in exposure between the active treatment and the external placebo.

3.4. Unfavourable effects

AEs considered related to the study drug were reported in 44.8% of the patients. Related TEAEs were most common in the SOCs of Infections and infestations (including cystitis, urinary tract infection, upper respiratory tract infection, nasopharyngitis, sinusitis, encephalitis meningococcal, meningococcal sepsis, and pneumonia) and Injury, poisoning and procedural complications (7 events of infusion related reaction).

There were no deaths in study ALXN1210-NMO-307. SAEs were reported in 13.8% of the patients during the study. The most frequently reported SAEs were those related to infections. Three (5.2%) patients reported TESAEs that were considered related to study drug, including encephalitis meningococcal, meningococcal sepsis, and pneumonia. Two (3.4%) patients experienced one AE of special interest each (meningococcal sepsis and encephalitis meningococcal), which were considered serious. Both patients were treated promptly with antibiotics and recovered with no sequelae.

Overall, the safety profile of ravulizumab in this indication is related to its mechanism of action (inhibition of terminal complement activity) and is consistent with that known for ravulizumab in other indications

3.5. Uncertainties and limitations about unfavourable effects

Since only 7 elderly patients were enrolled in study ALXN1210-NMO-307 it is not possible to obtain any reliable safety conclusion in this population.

Given the low prevalence of NMOSD, drug exposure can be considered acceptable for the short-term safety assessment of ravulizumab. As for the long-term safety profile, the safety database is too limited (n=58) to allow to draw any conclusion, but no additional safety issues were identified as of the cut-off date of 15 Jul 2022 and the extension study is ongoing.

With regard to immunogenicity, no treatment-emergent ADA responses were observed in NMOSD patients treated with ravulizumab and no impact on ravulizumab PK, PD, safety or efficacy was observed in any of the patients with NMOSD treated with ravulizumab.

3.6. Effects Table

Table 45: Effects Table for ravulizumab in NMOSD (data cut-off: 15 Feb 2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
			Ravulizumab	External placebo(study ECU-NMO-301)		
			n=58	n=47		
Primary analysis Patients with an adjudicated On-trial Relapse		n (%)	0 (0.0)	20 (42.6)	long-rank p<0.0001 HR 0.014 (95% CI: 0.000, 0.103); Limitations: Indirect external comparison. Risk of bias.	Study ALXN1210-NMO-307 Study ECU-NMO-301
Secondary analysis Adjudicated On-trial annualized Relapse Rate	Tested against the null hypothesis of 0.25 (1 relapse in 4 patient-	Total number of patient-years in study	84.01	N/A	Ravulizumab was compared versus a rate of 0.25 (1 relapse per 4 patient-years)	Study ALXN1210-NMO-307

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
(ARR)	years)	period			Rate: 0.000 (95% CI: NA, 0.044). P-value based on a Poisson distribution< 0.0001. Limitations: Risk of bias	
Unfavourable Effects						
Related AEs	Proportion	n (%)	26 (44.8)	N/A		Study ALXN1210-NMO-307
SAEs	Incidence of serious adverse events regardless of causality	n (%)	8 (13.8)	N/A		Study ALXN1210-NMO-307
Related SAEs	Proportion	n (%)	3 (5.2)	N/A		Study ALXN1210-NMO-307
Deaths	Proportion	n (%)	0	N/A		Study ALXN1210-NMO-307
COVID-19	Common TEAE	n (%)	14 (24.1)	N/A		Study ALXN1210-NMO-307
Headache	Common TEAE	n (%)	14 (24.1)	N/A		Study ALXN1210-NMO-307
Back pain	Common TEAE	n (%)	7 (12.1)	N/A		Study ALXN1210-NMO-307
Urinary Tract Infection	Common TEAE	n (%)	6 (10.3)	N/A		Study ALXN1210-NMO-307

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

No patients in the ravulizumab group had an adjudicated On-trial Relapse. The main concern was that the results come from a single arm trial. In order to reduce the potential bias derived from the non-randomised design of study ALXN1210-NMO-307, the Applicant implemented a number of measures. These include the comparison with an external placebo arm (where a total of 20 relapses were adjudicated), the evaluation of the primary event by an external adjudication committee, the similar design, outcomes and procedures to those followed in study ECU-NMO-301, the detection of potential cases of relapses and the additional statistical measures including sensitivity analyses. Overall, it is felt that these measures provide certain reassurance even if they do not fully address the uncertainties/concerns inherent to the uncontrolled design of the study.

The safety database of ravulizumab in the proposed indication is considered limited both in terms of the number of exposed patients and the duration of the exposure. Given the low prevalence of NMOSD, drug exposure can be considered acceptable for the short-term safety assessment of ravulizumab in this indication. In addition, the available safety information of ravulizumab in the already authorised indications (PNH, aHUS, gMG) can be taken as supportive, considering that the dosing regimen is the same regardless of the indication. Overall, the reported AE profile is consistent with that known for

ravulizumab in other indications, with no unexpected findings. The updated analysis of study ALXN1210-NMO-307 (data cut-off date 15 Jul 2022) includes data from 56 ravulizumab-treated patients with a median study duration of 90.93 weeks.

3.7.2. Balance of benefits and risks

Results from a single pivotal open label study (ALXN1210-NMO-307) have been provided to support this application. An external placebo control (instead of a concurrent control arm) has therefore been used for interpretation of the data, that diminishes the strength of the efficacy results presented. Even if the particularities of both the disease and the drug are acknowledged, the risk of overestimation of the treatment effect cannot be ruled out in an uncontrolled open label study. The Applicant explained the measures implemented during the study to reduce the potential bias and provided additional sensitivity analyses. These efforts are acknowledged and although the uncertainties are not fully addressed there is sufficient evidence to confirm the effect of ravulizumab in the intended indication.

The observed safety profile of ravulizumab in this indication does not raise any unexpected concerns and it is consistent with that known for ravulizumab in other indications. However, conclusions are based on a very limited safety database, both in terms of number of exposed patients and long-term exposure.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Ultomiris is positive

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends , by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody-positive, based on interim results from study ALXN1210-NMO-307; this is a phase 3, external placebo-controlled, open-label, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with NMOSD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ultomiris is not similar to Enspryng and similar to Eculizumab within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Derogation from market exclusivity

The CHMP by consensus is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000 the following derogation laid down in Article 8.3 of the same Regulation apply:

the holder of the marketing authorisation for Soliris has given his consent to the Applicant.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0032