25 July 2019
EMA/CHMP/400124/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Soliris

International non-proprietary name: eculizumab

Procedure No. EMEA/H/C/000791/II/0105

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

Abbreviation	Explanation
ADA	antidrug antibodies
ADR	adverse drug reaction
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
AQP4	aquaporin-4
ARR	annualized relapse rate
AUC_{ss}	area under the concentration-time curve within 1 dosing interval at steady state
C5	complement component 5
CL	clearance
cRBC	chicken red blood cell
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
Ctrough	trough concentration
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
EOS	end of study
EQ-5D	European Quality of Life Health 5-item questionnaire
EUPI	European Union Product Information
FAS	Full Analysis Set
gMG	generalized myasthenia gravis
HAI	Hauser Ambulation Index
IST	immunosuppressive therapy
IV	Intravenous
JPI	Japanese Package Insert
KFS	Kurtzke functional system
Max	maximum
Min	minimum
mRS	Modified Rankin Scale
NA	not applicable
NAb(s)	neutralizing antidrug antibody(ies)
Neuro-QoL Fatigue	Quality of Life in Neurological Disorders Fatigue scale
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorder
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PT	preferred term
PY	patient years
RAC	Relapse Adjudication Committee
REMS	Risk Evaluation and Mitigation Strategies
RMP	Risk Management Plan
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
USPI	United States Package Insert
V1	volume of distribution in the central compartment
VA	visual acuity
VAS	visual analogue scale

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 9 January 2019 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, II and IIIB

Extension of Indication to include Neuromyelitis Optica Spectrum Disorder (NMOSD) Anti-aquaporin-4 (AQP4) antibody (Ab) positive for Soliris; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and Annex II of the SmPC are updated. The Package Leaflet is updated in accordance. The updated RMP version 19 has also been submitted.

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

Soliris was designated as an orphan medicinal product EU/3/13/1185 on 05 August 2013 in the following indication: treatment of neuromyelitis optica (NMO). During the development of eculizumab, there has been a change in classification of the designated orphan condition. On 21 Dec 2018, Alexion Europe SAS submitted an ODD amendment to align the designated orphan indication to the current classification, i.e. "Treatment of Neuromyelitis Optica Spectrum Disorder".

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0364/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0364/2018 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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH received Protocol assistance at the SAWP (EMEA/H/SA/515/2/2012/II) for the development of this submission and in 2015 for pediatric development (EMEA/H/SA/515/5/2015/PA/PED/II CORRIGENDUM).

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	9 January 2019
Start of procedure:	27 January 2019
CHMP Rapporteur Assessment Report	30 March 2019
PRAC Rapporteur Assessment Report	1 April 2019
PRAC members comments	3 April 2019
Updated PRAC Rapporteur Assessment Report	4 April 2019
PRAC Outcome	11 April 2019
CHMP members comments	15 April 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 April 2019
Request for supplementary information (RSI)	26 April 2019
CHMP Rapporteur Assessment Report	1 July 2019
PRAC Rapporteur Assessment Report	2 July 2019
PRAC members comments	3 July 2019
Updated PRAC Rapporteur Assessment Report	9 July 2019
PRAC Outcome	11 July 2019
CHMP members comments	N/A
Updated CHMP Rapporteur Assessment Report	N/A
CHMP Opinion	25 July 2019

2. Scientific discussion

2.1. Introduction

Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory disorder of the central nervous system characterized by severe immune-mediated neuro-axonal injury predominantly targeting optic nerves and spinal cord (*Stellmann JP, et al. JNNP 2017;0:1–9*).

The incidence of NMOSD ranges from 0.053 to 0.4 per 100,000 individuals with prevalence rates from 0.52 to 4.4 per 100,000. NMOSD is more prevalent among non-Caucasians and 5 to 10 times more often in women than men int recurrent form of this condition (*Stellmann JP, et al. JNNP 2017;0:1–9*).

In 2015, The International Panel for NMO Diagnosis revised diagnostic criteria based on autoantibodies against aquaporin-4 (AQP4-IgG) status (*Wingerchuk DM et al. Neurology 2015;85(2):177-189*). Approximately 80% of the patients with NMOSD have pathogenic serum autoantibodies AQP4-IgG (*Jarius S, Clin Exp Immunol 2014 176:149–64*) and around 20–30% of NMOSD patients have a co-existing immune-mediated disease and autoantibodies other than anti-AQP4 can be detected in up to 40% (*Kitley J et al. Brain 2012: 135; 1834-1849).* In patients with positive AQP4-IgG status, a diagnosis of NMOSD can be made if at least one of the three core clinical characteristic of NMOSD is present and after excluding alternative diagnosis. The three-core characteristic includes the classical syndromes of optic neuritis and longitudinally extensive transverse myelitis (LETM) and a more recently described area postrema syndrome core syndrome characterized by intractable episodes of hiccups or nausea and vomiting. When AQP4 antibodies are absent or where serologic testing is unavailable, the presence of two core characteristics and additional neuroimaging findings are required for diagnosis of NMOSD (*Wingerchuk DM et al. Neurology 2015;85(2):177-189*).

AQP4 is a water channel that is predominantly expressed on the cell membrane of astrocytic end-feet, forming part of the blood–brain barrier. In NMOSD, antibodies binding AQP4 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 (*Broadley S, et al L, ACNR 2017;17(1):11-14).*

Nearly 90% of the patients had a relapsing course of NMOSD with a clinical pattern characterized by recurrent attacks preferentially in the brainsteam, optic nerves and spinal cords. On average, relapses tend to occur within the first year following an initial event in 60% of patients and within three years in 90%. In NMOSD, relapses are typically severe with incomplete recovery leading to rapid development of disability (*Kitley J et al. Brain 2012: 135; 1834-1849).*

Initial or recurrent episodes are usually treated with high-dose intravenous methylprednisolone. Therapeutic plasmapheresis is effective in patients with severe symptoms that fail to improve or progress despite treatment with corticosteroids (*Sellner J et al. EJN 2010, 17: 1019–1032).*

In order to prevent subsequent relapses, patients with NMOSD require immunosuppression. In this light, there is evidence that immunomodulatory therapies used for MS appear to aggravate NMO (*Mealy MA, et al. JAMA Neurol. 2014;71(3):324–330*). The current standard of care in NMOSD includes the use of azathioprine, mycophenolate mofetil, and rituximab for which there is evidence supporting effectivity coming from observational studies. However, no controlled randomized trials of immunosuppressive therapies have been conducted for NMOSD. Consequently, there is an unmet need for this orphan condition.

Eculizumab (Soliris®) is a humanized monoclonal antibody directed against the human complement component 5 (C5), inhibiting C5 enzymatic cleavage and thereby preventing the generation of the proinflammatory/prothrombotic complement activation products C5a and the cytolytic and proinflammatory/prothrombotic membrane attack complex C5b-9 that are responsible for the inflammatory consequences of terminal complement activation (*Rother RP et al Nat Biotechnol. 2007 Nov;25(11):1256-64.*). Eculizumab (Soliris®) is approved for use in 3 complement-mediated diseases, namely paroxysmal nocturnal haemoglobinuria (PNH), atypical haemolytic uremic syndrome (aHUS), and generalized myasthenia gravis (gMG) in many regions including the European Union, the United States, Japan, and Canada.

The following additional indication is proposed:

Soliris® (eculizumab) is indicated for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.

The dosing regimen is identical for patients with NMOSD to that approved for the treatment of adult patients (≥ 18 years of age) with aHUS and gMG. The dosing regimen consists of a 4-week initial phase followed by a maintenance phase:

• Initial phase: 900 mg of Soliris® administered via a 25–45-minute intravenous (IV) infusion every week for the first 4 weeks.

• Maintenance phase: 1,200 mg of Soliris® administered via a 25–45-minute IV infusion for the fifth week, followed by 1,200 mg of Soliris® administered via a 25 - 45-minute IV infusion every 14 ± 2 days.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application.

2.2.1. Ecotoxicity / environmental risk assessment

The scope and legal basis of the 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.

2.2.2. Conclusion on the non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP. As Eculizumab is a protein, no Environmental Risk Assessment is needed for this type II variation.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The applicant 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.

Table 1 Completed and Ongoing Clinical Studies with Eculizumab in NMOSD

Descriptor	Study Number	
	ECU-NMO-301	ECU-NMO-302
Study design	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter, time-to-event study; Randomization 2:1 (eculizumab:placebo); Endpoints: efficacy, safety, and PK/PD	Phase 3, open-label, extension study of Study ECU-NMO-301; All patients treated with eculizumab; Endpoints: long-term efficacy, safety, and PK/PD
Countries where patients were enrolled	70 sites in 18 countries (Argentina, Australia, Croatia, Czech Republic, Denmark, Germany, Hong Kong, Italy, Japan, Malaysia, Republic of Korea, Russia, Spain, Taiwan, Thailand, Turkey, United Kingdom, and United States)	As of database cutoff date: 33 sites in 15 countries (Argentina, Croatia, Czech Republic, Denmark, Germany, Hong Kong, Italy, Japan, Republic of Korea, Russia, Spain, Thailand, Turkey, United Kingdom, and United States)
Study status	Completed	Ongoing
Patient status	Randomized and treated: 143 (96 eculizumab, 47 placebo) Completed: 124 (80 eculizumab, 44 placebo) Discontinued early: 19 (16 eculizumab, 3 placebo)	As of database cutoff date: Treated: 39 (14 eculizumab/eculizumab; 25 placebo/eculizumab) Completed: 0 Ongoing: 33 (12 eculizumab/eculizumab; 21 placebo/eculizumab) Discontinued early: 6 (2 eculizumab/eculizumab; 4 placebo/eculizumab)
Dosing regimen	Eculizumab group: 900-mg dose of eculizumab once weekly for 4 weeks followed by a 1200-mg dose of eculizumab 1 week later and then once every 2 weeks thereafter. Placebo group: matched treatment without eculizumab All treatments administered IV.	To maintain the blinded nature of Study ECU-NMO-301, all patients who entered Study ECU-NMO-302 had a Blind Induction Phase prior to entering the Open-label Maintenance Phase of the study. During the Blind Induction Phase, all patients receive 4 vials of blinded study drug weekly (± 2 days) for 4 doses: • Patients who received placebo during Study ECU-NMO-301: eculizumab/placebo (3 vials/900 mg, plus 1 vial/0 mg, respectively) on Study Day 1 and Weeks 1 through 3 (Visits 1 through 4). • Patients who received eculizumab during Study ECU-NMO-301: eculizumab (4 vials/1200 mg) on Study Day 1 and Week 2 (Visits 1 and 3), and placebo (4 vials/0 mg) at Weeks 1 and 3 (Visits 2 and 4). Open-label Maintenance Phase: All patients received 1200-mg dose of eculizumab once every 2 weeks starting at Week 4. All treatments administered IV.
Analysis cutoff date for CSR	Completed (Last patient visit: 17 Jul 2018)	First interim data cut: 31 May 2018

Abbreviations: CSR = clinical study report; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics.

2.3.2. Pharmacokinetics

2.3.2.1. Analytical methods

2.3.2.2.

Pre-study validation

Analytical methods used in the clinical development of eculizumab for NMOSD were validated by MPI Research (Mattawan MI, USA), and used in the analysis of samples for Study ECU-NMO-301.

In study-validation

1. Eculizumab in human serum

The total eculizumab concentration (bound plus free) in human serum samples from Clinical Protocol Number ECU-NM0-301 was measured using a validated ELISA method utilizing human complement protein C5 as the capture reagent and horseradish peroxidase (HRP) conjugated anti-human immunoglobulin G4 (IgG4) for detection with tetramethylbenzidine (TMB) substrate (please refer to the validation report 1727-112). The quantitation range for the assay was 9.38 to 600µg/mL of eculizumab in serum. A summary of the bioanalytical results is displayed in Table 2.

Table 2 Summary of the bioanalytical results for Eculizumab in human serum

Analytical site	MPI Research 54943 North Main Street Mattawan, Michigan 49071
Immunology Method Number	IM-1727-112: Enzyme Linked Immunosorbent Ligand Binding Method for the Detection of Eculizumab in Human Serum
Capture Reagent	C5 Purified Human Complement Protein
Detection Antibody	Monoclonal Anti-Human IgG4 (Peroxidase Conjugate)
Analysis Period	April 7th, 2016 to July 20th, 2018
Regression Type	4PL with 1/y weighting
Calibration Curve Range	9.38 (LLOQ) to 600 (ULOQ) µg/mL Anchor points of 4.69 and 1,200 µg/mL On Runs 91, 95, 105. 127, 158 and 160 the calibration curve was truncated and LLOQ adjusted 18.8 µg/mL (all BLQ results on truncated plates were re-analysed).
Storage Stability	Samples were analysed within 1240 days of collection. Additional stability testing is ongoing to cover the duration of sample storage. Stability testing is ongoing under MPI Research Study Number 1727-112 to cover the duration of sample storage. At the time of this report, 15 of 3,037 total samples require validation of storage duration.
Samples	A total of 3,037 study samples were analysed for eculizumab. Reportable results were not obtained for two samples due to insufficient sample quantity.
ISR	Reproducibility of incurred samples was performed, and the results met acceptance criteria (≤ 30%) with a pass rate of 81.4%.

A total of 3,037 study samples were analysed for eculizumab in 197 runs. Out of these, sixty-three (63) runs were rejected due to QCs and/or calibrations standards did not meet the acceptance criteria, due to exceeding incubation time or contamination or plating error.

Calibration Curve Standards

For eculizumab, with each calibration curve, samples were analysed in each batch with seven calibrators in duplicate (plus to anchor point 4.69 and 1200 µg/mL).

In all valid runs, eighteen (18) calibration standards were rejected. No more than two was rejected at the same run, although for runs 91, 95, 105. 127, 158 and 160, both LLOQ replicates were rejected and the calibration curve was truncated and the LLOQ adjusted 18.8 µg/mL.

Correlation coefficients (r^2) were ≥ 0.9972.

The between-run precision (%RSD) and accuracy (%RE) ranged from 2.6% to 8.7% and from -3.2% to 3.3%, respectively.

Quality Control Sample

For eculizumab, with each calibration curve, samples were analysed in each batch with three QCs (i.e., 25, 100 and 480 µg/mL) in quadruplicate.

In all valid runs, there were one hundred and ten (110) QCs out of the acceptance range. No more than four was rejected at the same run and at least 50% at each concentration level met de acceptance criteria.

The between-run precision (%RSD) and accuracy (%RE) ranged from 7.6% to 18.9% and from -8.8% to 10.0%, respectively.

A total of 512 samples were re-analysed due to the following reasons

- Above Limit of Quantitation ALQ (422 samples)
- Below truncated LLQ (26 samples)
- HCV, ALQ (3 samples)
- PK/TK Request (24 samples). Out of these, 10 samples had a greater than 30% difference between the original and final reported values, and 3 samples had BLQ values. The reported values are presented in the Table 3.

Table 3 PK/TK sample re-assays for Eculizumab in human serum

Subjects	Time	Original values	Reported values
0038-001A	Peak	32.0 µg/mL	953 µg/mL
0041-006A	Trough	1550 µg/mL	1280 µg/mL
0041-006A	Peak	1550 µg/mL	1330 µg/mL
0050-005A	Peak	553 µg/mL	443 µg/mL
0055-004A	Peak	570 µg/mL	813 µg/mL
0069-001A	Trough	16.6 µg/mL	BLQ
0084-001A	Post PE/Prior IP	BLQ	280 µg/mL
0085-002A	Peak	251 µg/mL	289 µg/mL
0085-002A	Trough	127 µg/mL	564 µg/mL
0141-003A	Peak	372 µg/mL	304 µg/mL
0141-003A	Peak	319 µg/mL	330 µg/mL
0145-001A	Trough	27.1 µg/mL	22.7 µg/mL
0145-001A	Peak	25.6 µg/mL	22.0 µg/mL
0176-004A	Peak	449 µg/mL	391 µg/mL
0177-001A	Peak	448 µg/mL	407 µg/mL
0177-001A	Peak	418 µg/mL	966 µg/mL
0177-002A	Trough	482 µg/mL	374 µg/mL
0177-002A	Peak	142 µg/mL	132 µg/mL
0177-002A	Peak	16.9 µg/mL	16.5 µg/mL
0177-003A	Peak	397 µg/mL	388 µg/mL
0310-001A	Peak	405 µg/mL	329 µg/mL
0320-002A	Trough	17.1 µg/mL	BLQ
0320-002A	Trough	566 µg/mL	265 µg/mL
0320-002A	Peak	426 µg/mL	353 µg/mL

- High within sample %RSD (3 samples)
- Above Limit of Quantitation, PK/TK Request, Inadvertent Reanalysis (1 sample)
- ALQ, Inadvertent Reanalysis (5 samples)
- Above Limit of Quantitation, PK/TK Request, HCV Treatment Descriptions (1 sample)
- ALQ, Inadvertent Reanalysis A (1 sample)

- Inadvertent Reanalysis (1 sample)
- Above Limit of Quantitation, PK/TK Request (9 samples)
- Quantity Not Sufficient QNS (3 samples)
- Below truncated LLOQ, Sample processing error (1 sample)
- PK/TK Request, ALQ (1 sample)
- Diluted Sample, BLQ result (1 sample)
- ALQ, HCV (1 sample)

The original values, repeat values and accepted values have been submitted for each repeated sample.

Reproducibility of Incurred Samples

A total of 204 samples out of 3,037 samples were selected, re-assayed and evaluated for the ISR assay. The ISR assay complied with the acceptance criteria as 166 samples out of 204 samples (81.4%) were within the acceptance criteria (±30%).

2. Eculizumab in human Cerebral Spinal Fluid (CSF)

The total eculizumab concentration (bound plus free) in human CSF samples from Clinical Protocol Number ECU-NM0-301 was measured using an ECL assay on the Meso Scale Discovery (MSD®) platform (please refer to the validation report 1727-113). Human complement protein C5 was utilized as the capture reagent and SULFO-TAG labelled anti-human IgG4 for detection. The quantitation range for the assay was 0.00309 to 0.400µg/mL of eculizumab in CSF. A summary of the bioanalytical results is displayed in Table 4.

Table 4 Summary of the bioanalytical results for Eculizumab in human CSF

Analytical site	MPI Research 54943 North Main Street Mattawan, Michigan 49071
Validation Report Reference:	IM-1727-113: Electrochemiluminescence Ligand Binding Method for the Detection of Eculizumab in Human Cerebrospinal Fluid
Antibody	C5 Purified Human Complement Protein
Analysis Period	June 28th, 2017 to July 19th, 2018
Regression Type	4PL with $1/y^2$ weighting
Calibration range	3.08 (LLOQ) to 400.00 (ULOQ) ng/mL Anchor point of 2.06 ng/mL
Storage Stability	Samples were analysed within 891 days of collection. At the time of this report, 11 of 28 total samples require validation of storage duration.
Samples	A total of 28 study samples were analysed for eculizumab.

A total of 28 study samples were analysed for eculizumab in 7 runs. None of them were rejected.

Calibration Curve Standards

For eculizumab, with each calibration curve, samples were analysed in each batch with thirteen calibrators in singlet (plus to anchor point 2.06 ng/mL).

In all valid runs, no calibration standard was rejected.

Correlation coefficients (r^2) were ≥ 0.9982.

The between-run precision (%RSD) and accuracy (%RE) ranged from 1.4% to 4.4% and from -2.9% to 2.0%, respectively.

Quality Control Sample

For eculizumab, with each calibration curve, samples were analysed in each batch with three QCs (i.e., 9.0, 50.0 and 300 ng/mL) in duplicate.

In all valid runs, no QC was out of the acceptance range.

The between-run precision (%RSD) and accuracy (%RE) ranged from 6.4% to 7.9% and from 2.0% to 5.7%, respectively.

A total of 17 samples were re-analysed due to samples above ULOQ.

The original values, repeat values and accepted values have been submitted for each repeated sample.

Reproducibility of Incurred Samples

No ISR was performed.

3. Haemolytic Activity Analysis

The method assesses the complement activity in human serum via activation of the classical pathway. This assay measures the haemoglobin release from sensitized chicken red blood cells (cRBCs) due to lysis by the human terminal complement complex (C5b-9) deposited on the surface of these cells. The haemolysis of QC and test samples were normalized to the positive control standard and reported as percent haemolysis using the following formula: ([ODsample-ODSample EDTA control] ÷ [ODPC-ODNC])*100). A summary of the bioanalytical results is displayed in Table 5.

Table 5 Summary of the bioanalytical results for haemolytic activity

Analytical site	MPI Research 54943 North Main Street Mattawan, Michigan 49071
Validation Report Reference:	IM-1727-097: A Method for the Detection of Haemolytic Activity in Normal Human Serum
Antibody	Anti-Chicken Red Blood Cell (RBC) (Rabbit) Antibody
Analysis Period	March 08th, 2016 to July 19th, 2018
Regression Type	4PL with 1/y weighting
Control Samples	HHS: % Haemolysis above 86.9% threshold MHS: Results below the plate HHS %Haemolysis and above the plate LHS % Haemolysis LHS: % Haemolysis below 12.1% threshold Precision must be less than or equal to 20% based on OD.
Storage Stability	Samples were analysed within 1,323 days of collection. At the time of this report, 34 of 3,033 total samples required validation of storage duration. 168 haemolysis samples were reanalysed “due to a PK reason” and 74 samples had divergent results upon reanalysis.
Samples	A total of 3,033 human serum samples were collected in both eculizumab and placebo treated patients. In the eculizumab treatment group, the number of haemolytic samples analysed and included in the dataset was 2,114 (out of total 2,128). There were 14 samples analysed but not included in the dataset due to non-reportable results for analytical reasons (e.g. insufficient sample volume).

These samples were analyzed for hemolytic activity in 229 runs. Out of these runs, 34 runs were rejected due to PC, NC, HHS, MHS, and/or LHS control did not meet the acceptance criteria. Quality control samples performed within the acceptance criteria established in method validation (Table 6).

Table 6 Precision of the quality control samples for the analytical methods during sample analysis.

	NC	PC	LHS	MHS	HHS
Inter-assay OD Mean:	0.116	1.075	0.124	0.664	1.072
Inter-assay OD SD:	0.015	0.134	0.075	0.307	0.130
Inter-assay OD %CV:	13.170	12.428	60.247	46.171	12.106
Inter-assay Mean %Hemolysis:	NA	NA	0.4	56.8	99.7
Inter-assay SD %Hemolysis:	NA	NA	0.5	30.1	3.2

3. Free C5 in human serum

The concentration of free (unbound) C5 in serum samples was measured using an ECL assay. Eculizumab was used as the capture reagent and the non-competitive anti-human C5 antibody N19/8, conjugated with MSD SULFO-TAG, was used for detection (please refer to the validation report 1727-114). The quantitation range for the assay was 0.00274 to 20.00 µg/mL of C5 in serum. A summary of the bioanalytical results is displayed in Table 7.

Table 7 Summary of the bioanalytical results for Free-C5 in serum

Analytical site	MPI Research 54943 North Main Street Mattawan, Michigan 49071
Validation Report Reference	IM-1727-114:Electrochemiluminescent Method for the Detection of Free C5 in C5-Depleted Human Serum
Capture Reagent	Eculizumab
Detection Reagent	N19/8-Sulfo-TAG
Analysis Period	April 08th, 2016 to July 19th, 2018
Regression Type	5PL with 1/y weighting
Calibration Curve Range:	0.0274 (LLOQ) to 20.0 (ULOQ) µg/mL Anchor point of 0.00914 µg/mL
Minimum Required Dilution:	1:2 (v:v) in assay buffer (1% BSA in 1X PBS). As needed, additional dilutions were prepared in C5-depleted human serum prior to further diluting the sample to the 1:2 (v:v) MRD in assay buffer
Storage Stability	Samples were analysed within 1,189 days of collection. Stability testing is ongoing under MPI Research Study Number 1727-114(1) to cover the duration of sample storage. At the time of this report, 12 of 3,033 total samples required validation of storage duration.
Samples	A total of 3,033 samples collected in both eculizumab and placebo treated patients. In the eculizumab treatment group, the number of free-C5 samples analysed and included in the dataset was 2126 (out of total 2128). There were 2 samples analysed but not included in the dataset (<0.1% of total samples analysed) due to non-reportable results for analytical reasons (e.g. insufficient sample volume).

These samples were performed in 131 runs. Out of these runs, sixteen runs were rejected due to QCs and/or CS did not meet the acceptance criteria.

Calibration Curve Standards

For Free C5, with each calibration curve, samples were analysed in each batch with seven calibrators in duplicate (anchor point 0.00914 µg/mL).

In all valid runs, both replicates of intermediate concentration (0.0823 µg/mL) were rejected in run 95.

Correlation coefficients (r^2) were ≥ 0.9969.

The between-run precision (%RSD) and accuracy (%RE) ranged from 2.5% to 8.4% and from -1.1% to 3.5%, respectively.

Quality Control Sample

For Free C5, with each calibration curve, samples were analysed in each batch with three QCs (i.e., 0.060, 0.200 and 15.000 µg/mL) in quadruplicate.

In all valid runs, there were sixty-three (63) QCs out of the acceptance range. No more than four were rejected at the same run, although in run 95 and run 98, there were five QCs out of the acceptance range and three of them correspond to the LQC. In addition, run 121 did not meet the acceptance criteria (at least 50% at each concentration level must have accuracy within ±20%) since only one LQC meet the acceptance criteria.

The between-run precision (%RSD) and accuracy (%RE) ranged from 8.0% to 37.6% (including outlier) and from-6.0% to 10.0%, respectively.

A total of 250 samples were re-analysed due to the following reasons:

- High within sample %RSD
- Diluted Sample, BLQ result
- Above Limit of Quantitation ALQ
- Quantity Not Sufficient QNS
- Inadvertent Reanalysis
- Reconciliation Repeat
- PK/TK Request. Although, the re-analysis of samples for PK reasons is not acceptable, only one sample resulted in a change in categorization from complete terminal complement inhibition (ie, originally reported as BLQ) to partial or no terminal complement inhibition (ie, reported serum free C5 concentration of 80.8µg/mL) (Table 8).

Table 8 PK/TK sample re-assays for Free-C5 in serum

Subjects	Time	Original values	Reported values
0071-001A	Trough	42.5 µg/mL	68.9 µg/mL
0177-002A	Trough	0.0298 µg/mL	0.0357 µg/mL
0293-001A	Trough	63 µg/mL	159 µg/mL
0349-001A	Peak	BLQ	80.8 µg/mL
0370-003A	Trough	BLQ	0.0487 µg/mL

- ALQ, Anomalous Result, Per Event-17-15507

Reproducibility of Incurred Samples

No ISR was performed.

4. Free C5 in human cerebrospinal fluid (CSF)

The concentration of free (unbound) C5 in CSF was measured using an ECL assay derived from the serum assay. Eculizumab was used as the capture reagent and the non-competitive anti-human C5 antibody N19/8, conjugated with MSD SULFO-TAG, was used for detection (please refer to method validation report 1727-116). The quantitation range for the assay was 3.00 to 400 ng/mL of C5 in CSF. A summary of the bioanalytical results is displayed in Table 9.

Table 9 Summary of the bioanalytical results for Free C5 in human CSF

Analytical site	MPI Research 54943 North Main Street Mattawan, Michigan 49071
Validation Report Reference	IM-1727-116: Electrochemiluminescent Method for the Detection of Free C5 in Human cerebrospinal fluid (CSF)
Capture Reagent	Eculizumab
Detection Reagent	N19/8-Sulfo-TAG
Analysis Period	December 08th, 2017 to July 16th, 2018
Regression Type	4PL with 1/y weighting
Calibration Curve Range:	3.00 (LLOQ) to 400.0 (ULOQ) ng/mL Anchor points of 1.51 and 826 ng/mL
Minimum Required Dilution	1/2 (v/v) in assay buffer (1% BSA in 1X PBS). As needed, additional dilutions were performed using 1% BSA in artificial CSF prior to diluting to MRD in assay buffer.
Storage Stability	Samples were analysed within 891 days of collection. Stability testing is ongoing under MPI Research Study Number 1727-116 to cover the duration of sample storage. At the time of this report, 2 of 28 total samples require validation of storage duration.
Samples	A total of 28 human CSF samples were analysed for free C5

A total of 28 samples were performed in 3 runs. None of them were rejected.

Calibration Curve Standards

For Free C5, with each calibration curve, samples were analysed in each batch with seven calibrators in singlet (Anchor points of 1.51 and 826 ng/mL).

In all valid runs, no calibration standard was rejected.

Correlation coefficients (r^2) were ≥ 0.9994.

The between-run precision (%RSD) and accuracy (%RE) ranged from 1.5% to 4.7% and from -1.1% to 1.7%, respectively.

Quality Control Sample

For Free C5, with each calibration curve, samples were analysed in each batch with five QCs (i.e., 9.00, 74.5, and 320.00 ng/mL) in duplicate.

In all valid runs, no QC was out of the acceptance range.

The between-run precision (%RSD) and accuracy (%RE) ranged from 4.0% to 7.9% and from--10.0% to -5.2%, respectively.

A total of 3 samples were re-analysed due to samples above ULOQ.

Reproducibility of Incurred Samples

No ISR was performed.

5. Immunogenicity Assay Analysis Summary

Antidrug antibodies (ADA) to eculizumab were measured using a solution phase bridging assay with ECL detection. This method was performed with 2 eculizumab-derived reagents, biotin conjugated eculizumab (Ec-Bio) for capture and SULFO-TAG-conjugated eculizumab (Ec-STAG) for detection. The method utilized a tiered approach, with a screening assay designed to produce a 5% false positive rate and a confirmatory step designed to produce a 1% false positive rate, to identify samples as positive or negative for the presence of ADA to eculizumab. The assay was validated by MPI Research (Mattawan MI, USA) as described in the validation report 1727-118. A summary of the bioanalytical results is displayed in Table 10.

Table 10 Summary of the bioanalytical results for Immunogenicity Assay

Analytical site	MPI Research 54943 North Main Street Mattawan, Michigan 49071
Immunology Method	IM-1727-118: Electrochemiluminescence Ligand Binding Method for the Detection of Anti-Eculizumab Antibodies in Human Serum
Capture Antibody	Biotinylated Eculizumab
Positive Control Antibody	Anti-eculizumab [also known as E11 (hG1)
Detection Antibody:	SULFO-TAG™-Eculizumab
Analysis Period	April 07th, 2016 to July 19th, 2018
Samples	A total of 1,312 human serum samples were screened for anti-eculizumab antibodies. Of the 1,312 samples, 161 screened positive, 20 confirmed positive, and 2 had titer results greater than the minimum dilution, resulting in a false positive rate of 10.7%. Subject 0009-003A at pre-dose on Day 1 and subject 0536-002A at pre-dose on Day 1 both confirmed positive for anti-eculizumab antibodies, but a titer result of <4.00 was obtained. One sample had insufficient volume for analysis. The results from control samples demonstrated acceptable performance of the method for all reported levels.
Storage Stability	All samples were analysed within the established storage stability determined under MPI Research Study Number 1727-118

6. Neutralizing Antibody Analysis Summary

A summary of the bioanalytical results is displayed in Table 11.

Table 11 Summary of the bioanalytical results for Neutralizing Antibody (NAbs) Analysis

Analytical site	MPI Research 54943 North Main Street Mattawan, Michigan 49071
Immunology Method	IM-1727-117: Electrochemiluminescence Ligand Binding Method for the Detection of Neutralizing Anti-Eculizumab Antibodies in Human Serum
Capture Antibody	Biotinylated Eculizumab
Positive Control Antibody	Anti-Eculizumab E11
Analysis Period	July 20th, 2018
Matrix Testing	Results above the neutralizing antibody cut point were considered negative for neutralizing anti-eculizumab antibodies. Results at or below the neutralizing antibody cut point were considered positive for neutralizing anti-eculizumab antibodies.
Samples	A total of 20 human serum samples were analysed for neutralizing anti-eculizumab antibodies. Subject 0179-001A Week 144 had an indeterminate result; the other 19 samples were negative. The results from control samples demonstrated acceptable performance of the method for all reported levels.
Storage Stability	All samples were analysed within the established storage stability determined under MPI Research Study Number 1727-117

7. Deviations and investigation occurred during the study

The following deviations occurred from the study plan.

7.1 Sample Deviations

Per the study plan, study samples should be stored in a freezer set to -70°C. Several days a freezer containing study samples rose above the study plan-specified maximum temperature with a peak between -39.9 °C and -58.2 °C.

7.2 PK investigations and deviations

The following PK investigation occurred during the study.

- Event-17-20065 and Event-18-04462: due to consecutive run failures in the serum assay, investigations were conducted under MPI Research Study Number 1727-112. While no root cause could be identified for the failures, automation was implemented for the preparation of standard curves to confer additional accuracy and reproducibility.
- Event-17-15418: plate maps should reflect the actual plating location of samples. In runs 113 of the serum assay, the plate map was not updated prior to the upload of data. The run was rejected and repeated.

7.3 Haemolytic Activity Deviations:

The following unplanned deviation occurred as the result of an unintended deviation from the study plan.

Per the study plan, samples should have been analysed per their arrival demarcation. Samples labelled for PK or free C5 were analysed for haemolytic activity in run 45. All sample aliquots for a specific time point are generated from a single blood draw and processing, so there is no impact to the data produced.

7.4 Free Complement Factor 5 investigation and deviations

The following deviation occurred during the study.

- Event-17-15507: a single result on run 40 of the free C5 in serum assay was anomalous. The sample was analysed in duplicate using a backup aliquot, and the result on run 40 was confirmed to be anomalous.

- Event-17-15510: multiple samples on run 46 of the free C5 in serum assay had results that were inconsistent with the subject profile. A plating error was suspected, and all results from run 46 were rejected and the samples repeated.
- Event-17-1546: per the method for free C5 in serum, the assay plate should be incubated for 60 minutes after the addition of the detection reagent. In run 50, the plate was incubated for 4 minutes. Run 50 was aborted, and samples were analysed in a subsequent run.

7.5 ADA Deviations

The following deviation occurred during the study.

- Event-17-14120: analytical runs 7 and 9 were built in Watson IRM without appropriate controls. The error was noted after upload of data. Due to limitations within Watson IRM, data for runs 7 and 9 were uploaded as runs 41 and 42.
- Event-17-16967: for immunodepletion assessments, the unfortified sample typically has a higher signal than the fortified sample. In runs 44 and 45, most samples had signals opposite the standard pattern. Runs 44 and 45 were rejected, and all samples were repeated on later runs. Upon repeat, all samples showed the typical decrease in signal when test article was present.
- Event-18-11925: due to insufficient sample volume, a sample on run 78 was replaced after issue of the dataset. The change in sample container number was made on the paper dataset but not Watson. After data was uploaded, the error was noted. Run 78 was rejected and recreated as run 79 in Watson, with the correct sample containers
- Event-17-1087: in run 31, confirmatory controls were documented as being prepared incorrectly. The run was rejected, and samples were repeated in a subsequent run.

7.6 NAb Deviations

An insignificant method deviation was acknowledged by the Bioanalytical Monitor and documented in the raw data.

2.3.2.3. Population-PK analysis

A population-PK analysis was performed using all eculizumab-treated patients included in Study ECU-NMO-301 for which at least 1 quantifiable eculizumab concentration was available.

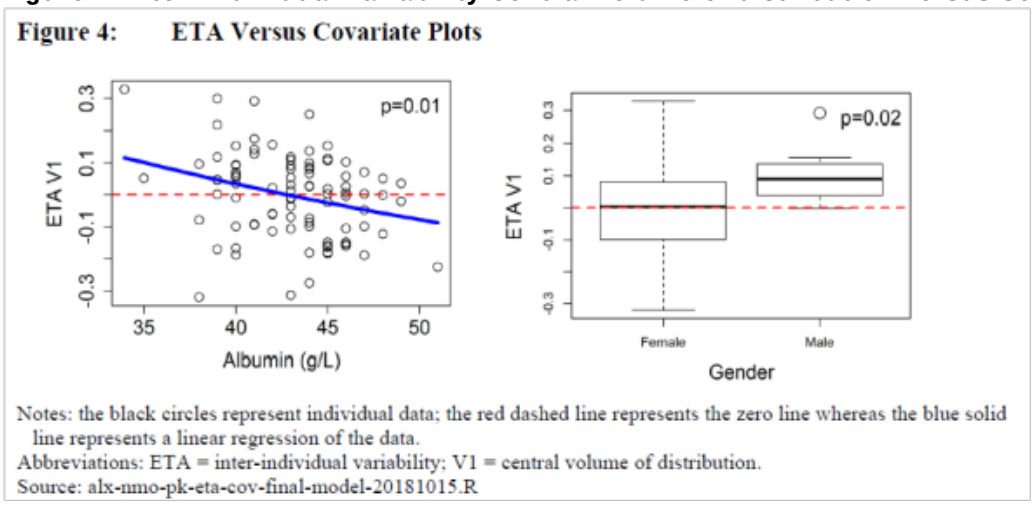
Total serum (bound plus free) concentrations of eculizumab were quantified using a validated assay (IM-1727-112). Total CSF (bound plus free) concentrations of eculizumab were quantified using a validated assay (IM-1727-113).

Model development was carried out using first-order, conditional estimation with interaction. The 2-compartment model with first-order elimination, including time-variant body weight effects and plasmapheresis/plasma exchange effects, was defined as the base model and was the starting point for the covariate assessment. A full covariate search was performed on the base model to evaluate the impact of covariates on PK. Visual predictive check (VPC) and non-parametric bootstrap analyses were performed to evaluate model performance and robustness.

A total of 96 patients treated with eculizumab from Study ECU-NMO-301 were available, with a total of 2130 PK observations and 4660 dosing records. In addition, 15 plasmapheresis/plasma exchange events were recorded for 4 eculizumab-treated patients in Study ECU-NMO-301. One eculizumab-treated patient (0294-002) was excluded from the population-PK because no PK assessments were available. Another patient (all 6 PK samples) was excluded due to an unusual PK profile (0177-002). There was 1 pre-first

dose sample with eculizumab concentration above LLOQ (for Patient 0370-003), which was excluded from the population-PK analysis. Furthermore, there were 101 samples below the limit of quantitation (BLQ), mostly from pre-first dose samples that were excluded. The previously developed 2-compartment model with clearances and volumes of distribution allometrically scaled by body weight (gMG patient population, ECU-MG-Adult PK-PD Modelling Report Addendum ECU-MG-302) was fitted to the Study ECU-NMO-301 data as a starting model. To account for the extended treatment duration in Study ECU-NMO-301 (up to 204 weeks), body weight was included as a time-variant covariate. The model included a plasmapheresis/plasma exchange effect on eculizumab CL (additive effect) to account for changes in CL due to plasmapheresis/plasma exchange procedures. The exploration of potential covariate effects showed no trends between covariates of interest and CL or central volume of distribution (V1), except for albumin and gender on V1 (Figure 1) that were the only 2 covariates showing a p-value close to 0.01. No other available covariates were found to influence eculizumab exposure.

Figure 1 Inter-Individual variability Central volume of distribution versus Covariate Plots



To determine the contribution of these covariates, a search was performed within NONMEM using stepwise forward addition (threshold p=0.01) followed by backward elimination (threshold p=0.001) for these 2 potential covariates. Neither of them met the criteria to be retained in the model.

Other explored covariates included: age, race, Japanese origin, height, body mass index (BMI), estimated glomerular filtration rate (eGFR), serum creatinine (SCr), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), bilirubin, lymphocytes, anti-aquaporin-4 antibody (anti-AQP4 Ab) at baseline, historical ARR in the prior 24 months, EDSS at baseline, immunosuppressive therapy (IST) status at baseline, primary IST medication at baseline, region, anti-anaemic medication, systemic antibacterial medication, antihypertensive medication, and anti-infective medication.

The Final population-PK model parameter estimates are presented in Table 12.

Table 12 Parameter Estimates of Final Population-PK Model (Run011)

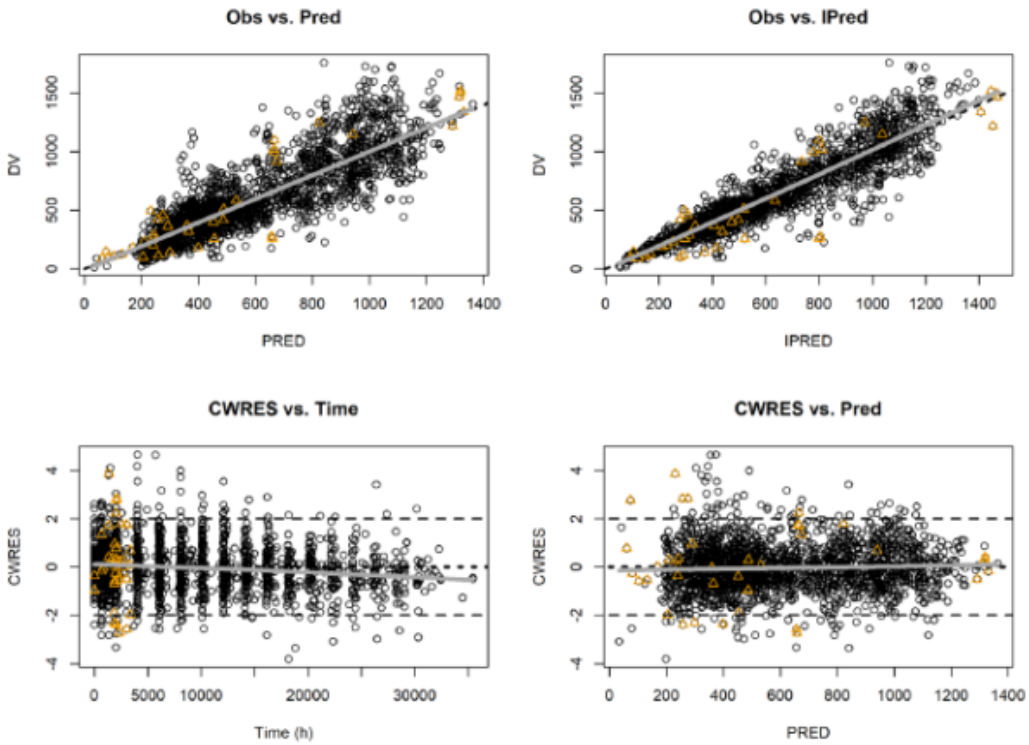
Parameter	Final Model			Bootstrap	
	Estimate	95% CI	RSE (%)	Median	95% CI
CL (L/h)	0.00749	0.00712-0.00788	0.5	0.00746	0.00703-0.0079
V_1 (L)	2.37	2.13-2.64	6.4	2.4	2.02-2.66
V_2 (L)	2.16	1.82-2.56	11.3	2.13	1.61-2.62
Q (L/h)	0.243	0.118-0.5	26.0	0.225	0.0371-0.491
Weight effect on CL/Q	0.908	0.780-1.04	7.2	0.897	0.686-1.07
Weight effect on V_1/V_2	0.594	0.421-0.767	14.9	0.6	0.472-0.716
PP/PE effect on CL (L/h)	1.79	1.21-2.37	16.6	1.79	1.26-3.91
Interindividual Variability					
CL (%CV)	24.5	20.4-28.2	15.6	24.4	20.6-28.0
V_1 (%CV)	16.3	10.7-20.5	28.7	15.7	11.7-21.1
Proportional error (%CV)	21.0	20.3-21.7	1.7	20.9	19.2-22.9

Note: 1000 replicates were run for the bootstrap analysis. Shrinkage for CL and V1 were 2.8% and 19.9%, respectively.

Abbreviations: CI = confidence interval; CL = clearance; PE = plasma exchange; PP = plasmapheresis; Q = intercompartmental clearance; RSE = relative standard error; V_1=volume of distribution in the central compartment; V_2 = volume of distribution in the peripheral compartment.

According to Figure 2, there was an appropriate goodness-of-fit of the final model.

Figure 2 Goodness-of-fit plots of the Final Model (Run011)

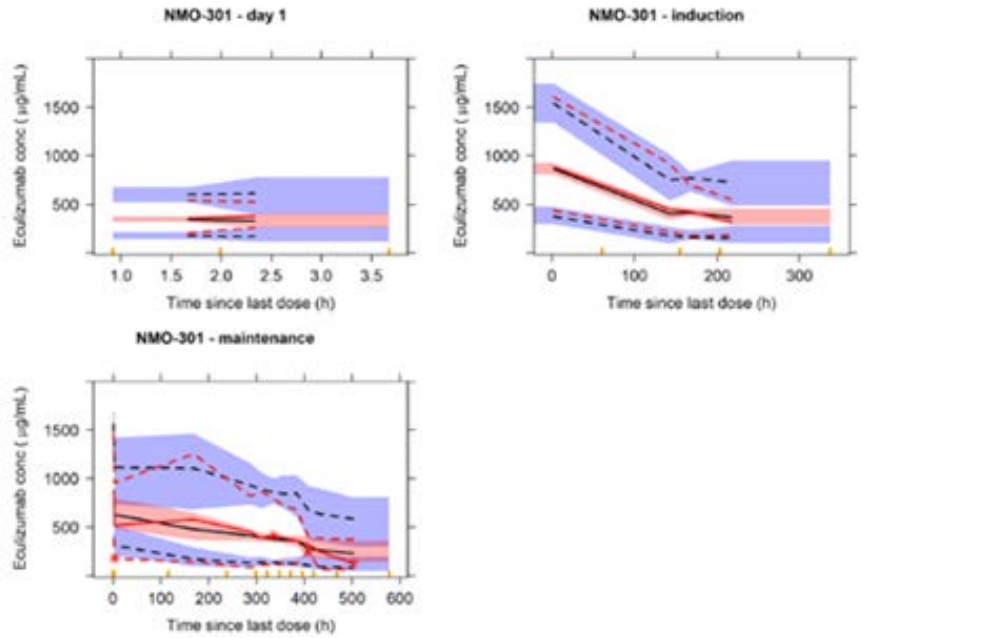


Note: The black circles represent individual observations; the orange triangles represent individual observations in patients with plasma exchange events; the grey solid line a LOESS line of the presented data and the black dotted lines represent the identity line for DV/PRED-IPRED plots and the zero line for CWRES plots. The black dashed lines represent the -2 to 2 boundary for the CWRES plots.

Abbreviations: CWRES = conditional weighted residuals; DV = dependent variable; IPRED = individual predictions; Obs = observations; PRED = population predictions.

The final model was evaluated by a prediction corrected VPC as implemented in PsN (Figure 3).

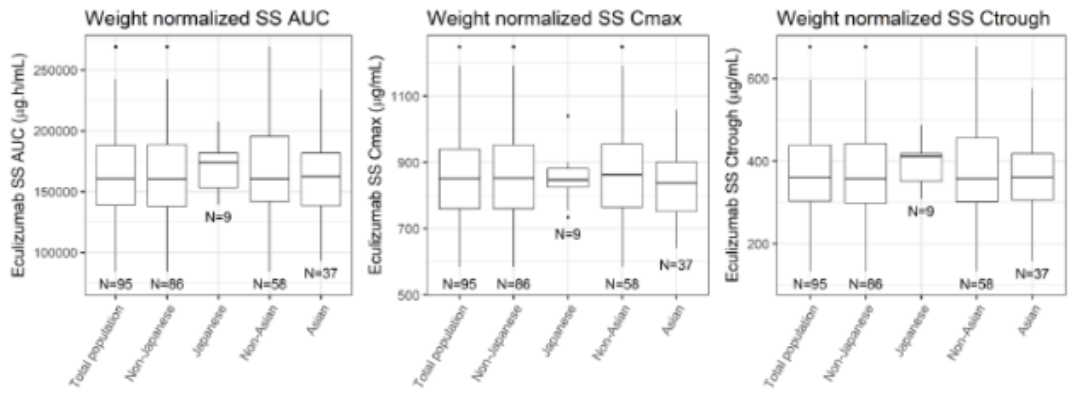
Figure 3 Prediction Corrected Visual Predictive Check (VPC) of Final Model (Run 011) stratified by phase (induction versus maintenance) and plotted versus time since last dose



Note: Top left and right and bottom left panels show VPCs stratified by day1, induction phase, and maintenance phase. The red solid and dashed lines represent median and 5th to 95th percentiles of the observed data. The black solid and dashed lines represent median and 5th to 95th percentiles of the simulated data. Shaded areas represent the 90% CIs of the simulated medians (red) and 5th to 95th percentiles (blue).
Abbreviations: CI = confidence interval; conc = concentration; NMO-301 = Study ECU-NMO-301; VPC = visual predictive check.

According to Figure 4, the exposure distributions are largely overlapping between the various subgroups, confirming that there is no difference in exposure between the subgroups of interest.

Figure 4 Estimated weight-normalized steady state exposure parameters for overall, Asian, Non-Asian, Japanese and Non-Japanese patients based on the final population-PK Model in Study ECU-NMO-301



Notes: Top left, top right, and bottom left panels show, respectively, results for steady state AUC, C_{max}, and C_{trough}. Exposures were normalized by body weight using the exponent estimated in the final model.
Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum concentration; C_{trough} = concentration at the end of the dosage interval; SS = steady state.

2.3.3. PK/PD modelling

2.3.3.1. Methods

A population pharmacokinetic modelling and exposure-response analysis for eculizumab in patients with NMOSD has been developed. The clinical data for analyses described in this report were from Phase 3 Study ECU-NMO-301.

The primary objective of this modelling analysis was to demonstrate that the dosing regimen used in Study ECU-NMO-301 (i.e., 900 mg intravenous [IV] once per week for the first 4 weeks followed by 1200 mg IV 1 week later and then once every 2 weeks thereafter) achieves immediate, complete, and sustained terminal complement inhibition in the NMOSD patient population.

Other objectives included:

- To explore the PK/PD relationships for the primary efficacy endpoint (time to first adjudicated On-trial Relapse) and sensitivity analysis (time to first On-trial Relapse as determined by the Treating Physician).
- To explore the PK/PD relationships for selected secondary efficacy endpoints (adjudicated On-trial ARR and the sensitivity analysis of On-trial ARR [as determined by the Treating Physician] as well as change from Baseline to EOS for EDSS, mRS, and HAI).
- To explore exposure-response relationships across the treatment population for safety endpoints (treatment-emergent adverse events of special interest (TEAESIs) defined as infections [meningococcal infections, Aspergillus infections, other serious infection, or sepsis], infusion reactions, serious cutaneous adverse reactions, cardiac disorders, and angioedema) as well as treatment-emergent adverse events (TEAEs) that occurred in ≥ 5% of the eculizumab-treated patients). This analysis was also aimed to investigate if any dose adjustments were required for special populations based on intrinsic and extrinsic factors identified to be influential with respect to PK, PK/PD, or exposure-response relationship.

The analysis populations included the following datasets:

- Population-PK/PD analysis dataset for free C5 and hemolysis: All eculizumab-treated patients dosed in Study ECU-NMO-301 with at least 1 time-matched PK and free C5 assessment or hemolysis, respectively
- Population-PK-Efficacy analysis dataset: All eculizumab-treated patients from the FAS for whom posthoc PK parameters were available as well as all placebo-treated patients from the FAS. Here, FAS refers to all patients who were randomized to treatment and who have received at least 1 dose of study drug, as defined in protocol.
- Population-PK-Safety analysis dataset: This dataset contained all eculizumab-treated patients from the FAS for whom posthoc PK parameters were available as well as all placebo-treated patients from the FAS. Here, FAS refers to all patients who were randomized to treatment and who received at least 1 dose of study drug, as defined in protocol.

Serum free C5 concentration was quantified using a validated enzyme-linked immunosorbent assay. Cerebrospinal fluid free C5 concentration was quantified using a validated assay. Measurement of haemolytic activity as % cRBC hemolysis was performed using a validated qualitative method.

A. **PK/PD Analysis for Free C5 and Haemolytic Activity**: Exploratory plots were generated and summary statistics were calculated for free C5 and haemolytic activity by visit. Because complete inhibition was achieved in almost all eculizumab-treated patients, the data are insufficient for

development of PK/PD models for either free C5 or haemolytic activity. Therefore, PK/PD modelling for free C5 and haemolytic activity was not performed. The eculizumab threshold concentration to achieve complete terminal complement inhibition established previously using population-PK/PD data from the generalized myasthenia gravis (gMG) Phase 3 registration trial was used as a benchmark to assess the relationship between eculizumab exposures and PD endpoints.

B. **Exposure-Response Analysis for Efficacy Endpoints**: For the primary endpoint, Kaplan-Meier relapse free survival plots were generated and the incidence was tabulated by exposure quartiles to explore exposure effects. In addition, exploratory exposure-response plots were generated for the secondary endpoints. Linear regression analysis was applied to explore exposure-response trends for efficacy endpoints.

C. **Exposure-Response Analysis for Safety Endpoints**: Occurrence of TEAEIS and TEAEs was tabulated by treatment and by exposure quartiles.

D. **Analysis of Cerebrospinal Fluid Eculizumab Concentrations**: In exploratory analysis, the eculizumab CSF concentration in the subset of patients who consented to CSF sampling was summarized. Line plots for individual patients were generated. Population analysis of CSF PK was not planned to be conducted because only a limited number of patients were expected to consent to collection of CSF samples through lumbar puncture.

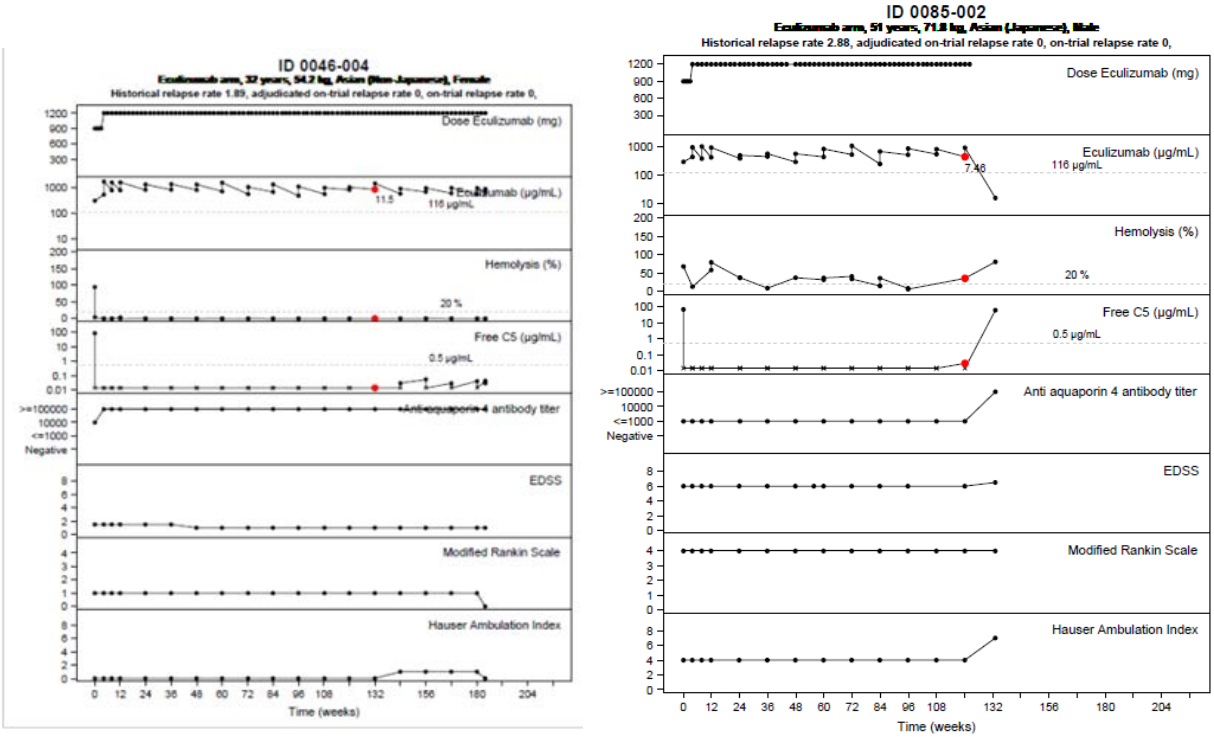
2.3.3.2. Results

A PK/PD Analysis for Free C5 and Haemolytic Activity

Anti-drug antibodies:

A total of 2 ADA positive results and 0 NAb positive result were observed in Study ECU-NMO-301. Titer values for these 2 ADA positive samples were low and transient in time; subsequent samples were negative for ADA screening and had no impact on population-PK or PK/PD analyses and on efficacy (Figure 5).

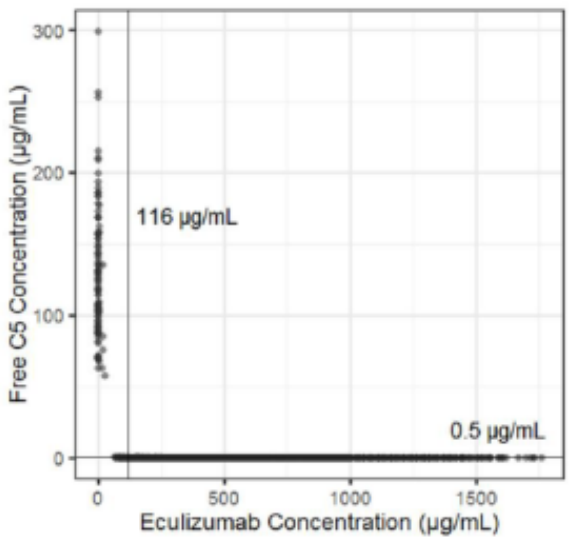
Figure 5 Composite Plot for Eculizumab Patients with a positive ADA Result and Quantitative ADA Titer



Free C5 Analysis:

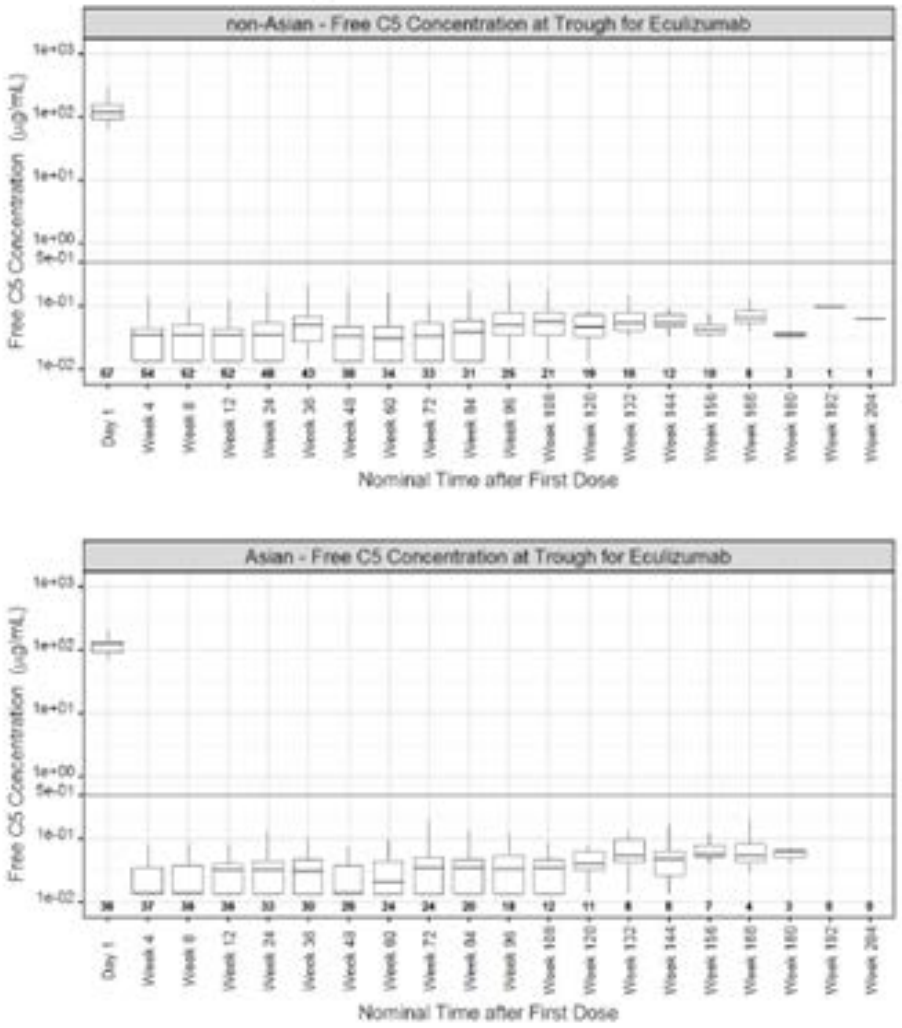
Figure 6 showing time-matched free C5 and eculizumab concentrations for eculizumab-treated patients confirmed that at the achieved exposure range in Study ECU-NMO-301, free C5 concentrations are reduced below the threshold of 0.5µg/mL. Complete, and sustained terminal complement inhibition was achieved in eculizumab-treated patients from Study ECU-NMO-301 as shown by Figure 7. A total of 13 (0.6%) out of 2031 free C5 concentrations assessed post the first eculizumab dose in the eculizumab-treated patients were above the threshold of 0.5µg/mL. Eight out of the 13 free C5 samples came from same patient.

Figure 6 Scatter Plot of Free C5 concentration versus Eculizumab concentration in Study ECU-NMO-301



Note: Vertical (at 116 µg/mL) and horizontal (at 0.5 µg/mL) lines show thresholds for eculizumab serum concentration and free C5 concentration.
Abbreviation: C5 = complement component 5.

Figure 7 Boxplots of serum free C5 concentrations over time at trough for patients administered Eculizumab in Study ECU-NMO-301 stratified by Asian and non-Asian and Asian population



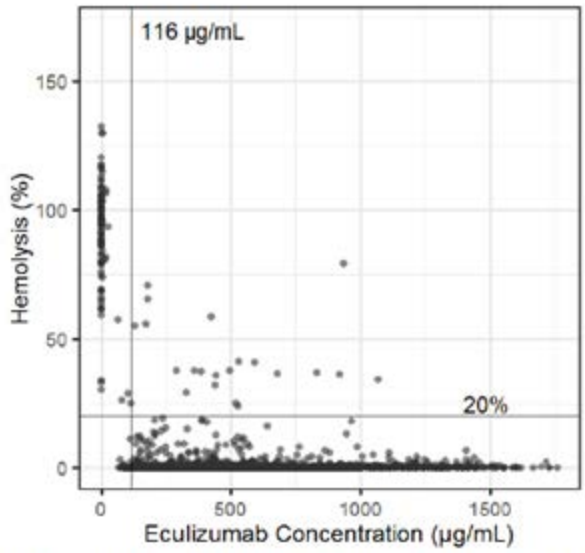
Note: The numbers reported in the box plots represent the number of free C5 samples. Only samples from scheduled visits are shown. Free C5 concentrations below the LLOQ (0.0274 µg/mL) from samples post first eculizumab dose were analyzed as 0.5 × LLOQ µg/mL Two trough (predose) Study Day 1 samples with eculizumab concentration > LLOQ were excluded (0177-002, 0370-003). No free C5 data available for one patient (0294-002).

Haemolysis Analysis:

Figure 8 showing time-matched haemolysis and eculizumab concentrations for eculizumab-treated patients confirmed that the distribution of the data did not allow further characterization of the exposure-response profile and would have had not enable estimation of an EC50 in case of fitting an Emax model.

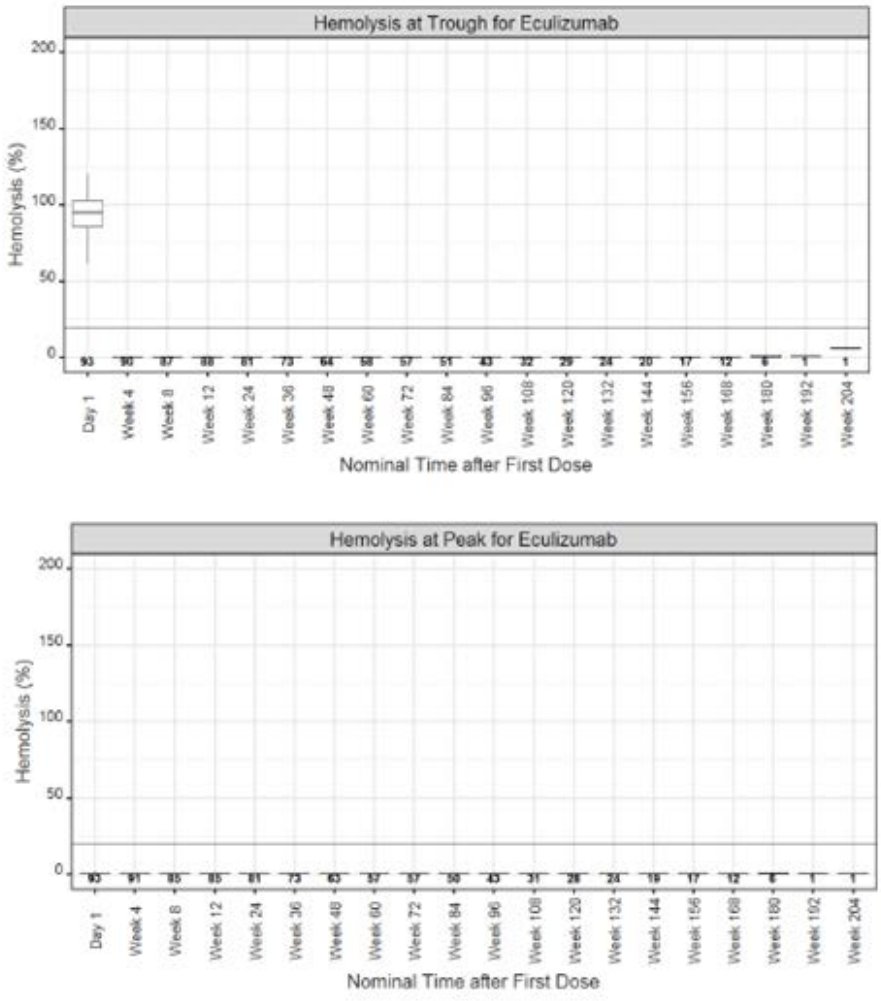
Figure 9 showed that at each visit the percentage of patients with haemolysis below the threshold of 20% at trough for eculizumab was≥ 97%, except for Weeks 72, 108, 120, and 132 at which the number (percentage) of patients with haemolysis below 20% was 55/57 (96.5%), 30/32 (93.8%), 26/29 (89.7%), and 23/24 (95.8%), respectively.

Figure 8 Scatter Plot of Percent Chicken Red Blood Cell Haemolysis versus Eculizumab Concentration in Study ECU-NMO-301



Note: Vertical (at 116 µg/mL) and horizontal (at 20% activity) lines show thresholds for eculizumab serum concentration and hemolysis activity.

Figure 9 Percentage of Chicken Red Blood Cell Haemolysis at Eculizumab Trough and Peak versus Time profiles from Study in Study ECU-NMO-301



CSF Free C5 Concentrations:

The subset of patients for which CSF samples were available consisted of 8 eculizumab- (one patient did not have study day 1 CSF sample) and 2 placebo-treated patients. However, post first dose CSF samples at scheduled visits were only available for 4 eculizumab-treated patients (Table 13).

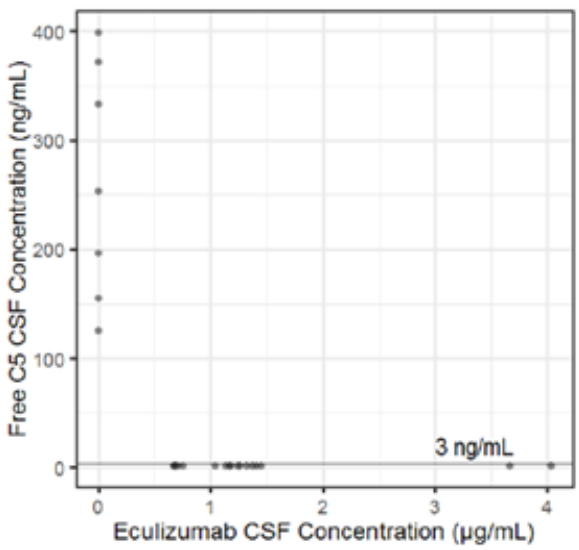
Table 13 Summary of CSF Free C5 Concentrations at Trough for Eculizumab for treated group (N=8) by visit in Study ECU-NMO-301

Visit	n	n <LLOQ	Free C5 Concentrations (ng/mL)			
			Median	Mean	SD	%CV
Observed CSF Free C5 Concentration at Trough for Eculizumab (ng/mL)						
Study Day 1	7	0	253	262	108	41.4
Week 12	4	4	1.5	1.5	0	0
Week 24	3	3	1.5	1.5	0	0
Week 48	2	2	1.5	1.5	0	0
Week 72	2	2	1.5	1.5	0	0
Week 96	2	2	1.5	1.5	0	0
Week 120	1	1	1.5	1.5	NC	NC
Observed Serum / CSF Free C5 Ratio at Trough for Eculizumab						
Study Day 1	7	0	362	396	221	55.9
Week 12	4	4	NC	NC	NC	NC
Week 24	3	3	NC	NC	NC	NC
Week 48	2	2	NC	NC	NC	NC
Week 72	2	2	NC	NC	NC	NC
Week 96	2	2	NC	NC	NC	NC
Week 120	1	1	NC	NC	NC	NC

Note: CSF free C5 concentrations below the LLOQ (3.00 ng/mL) were analyzed as 0.5 × LLOQ ng/mL. Only samples that were taken at scheduled visits are included. CSF samples were collected in 8 eculizumab-treated patients with 4 patients having post first dose CSF assessments at scheduled visits. Ratio was only calculated when both the serum and time-matched CSF samples were above LLOQ.
Abbreviations: C5 = complement component 5; CSF = cerebrospinal fluid; CV = coefficient of variation; LLOQ = lower limit of quantitation; n = number of patients at the given visit; NC = not calculated; SD = standard deviation.

Figure 10 showing time-matched CSF free C5 and CSF eculizumab concentrations for eculizumab-treated patients shows that at the achieved CSF exposure range in Study ECU-NMO-301 (0.7–4 µg/mL), free C5 concentrations were below the threshold of 3 ng/mL.

Figure 10 Scatter plot of CSF Free C5 concentration versus CSF Eculizumab concentration in Study ECU-NMO-301

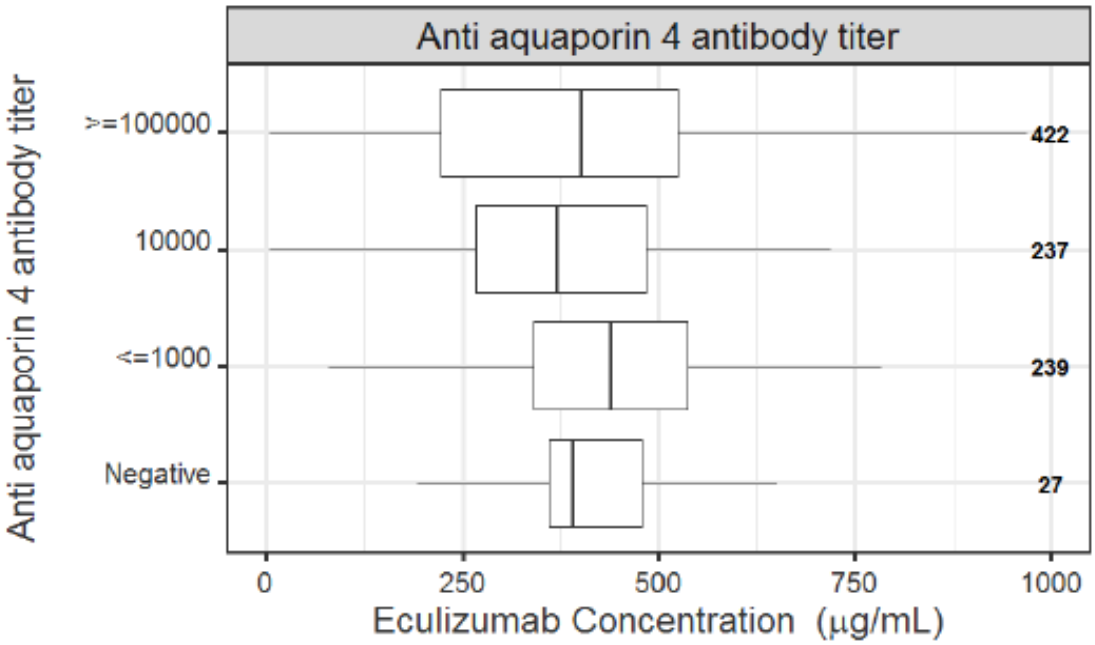


Note: Horizontal line at 3 ng/mL reflects LLOQ for CSF free C5.
Abbreviations: C5 = complement component 5; CSF = cerebrospinal fluid; LLOQ = lower limit of quantitation.

Data Exploration – Anti-Aquaporin 4 Antibody

Eculizumab serum concentrations were similar across the 4 anti-AQP4 Ab titer levels (Figure 11)

Figure 11 Time-matching Anti-aquaporin-4 antibody titer versus serum eculizumab concentrations in Study ECU-NMO-301



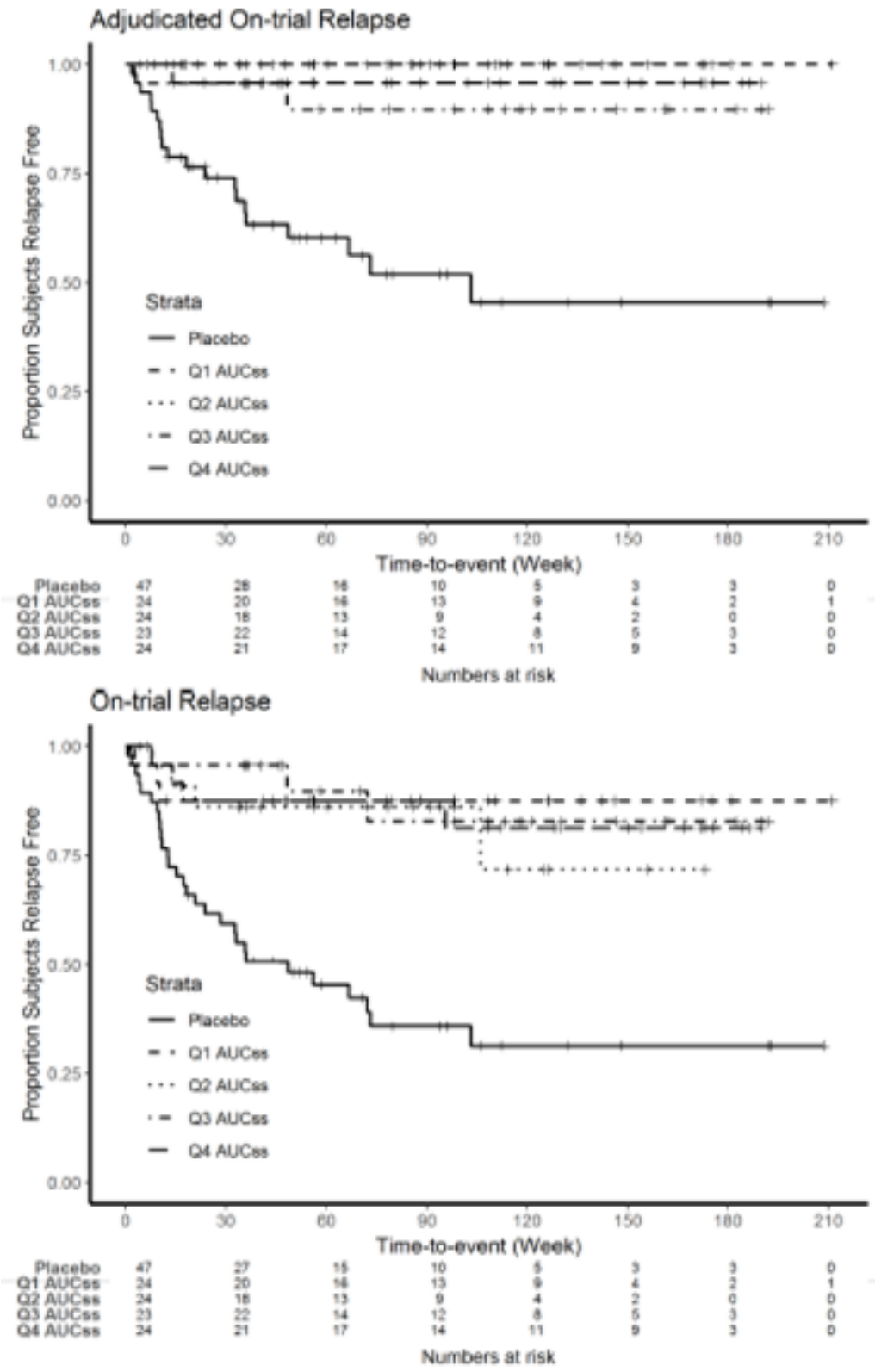
Note: A total of 925 anti-aquaporin 4 antibody titer observations time-matched with eculizumab concentrations obtained from 94 eculizumab-treated patients were available. No post first eculizumab dose observations were available for Patients 0006-002 and 0294-002. The lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). Numbers of observations shown on right side of plot.
The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Outlying points are not shown.
Abbreviation: IQR = interquartile range.

B Exposure-Response Analysis

1.- Primary Efficacy Endpoint (Time to First Adjudicated On-trial Relapse) and Sensitivity Analysis (Time to First On-trial Relapse as Determined by the Treating Physician).

To explore primary efficacy endpoint, the eculizumab-treated patients were binned into 4 quartiles (Q1 AUCss: 58714 – 143644 µg*h/mL; Q2 AUCss: 144679 –179692 µg*h/mL; Q3 AUCss: 181113 – 216888 µg*h/mL; and Q4 AUCss: 218938 – 331373 µg*h/mL) of AUC at steady state exposure bins and compared with the placebo group overall. Figure 12 showed a clear separation between the placebo relapse free survival curve and those corresponding to the eculizumab quartiles for both analyses supporting efficacy of Eculizumab. Conversely, there was no clear separation between relapse-free survival curves across the exposure quartiles suggesting no evidence of increased efficacy with increased eculizumab exposure. The low number of adjudicated On-trial Relapses (n = 3) in eculizumab-treated patients prevented a meaningful interpretation of treatment effects among exposure quartiles. The number of eculizumab-treated patients with On-trial Relapse as determined by the Treating Physician (n = 14) was equally distributed across the exposure quartiles.

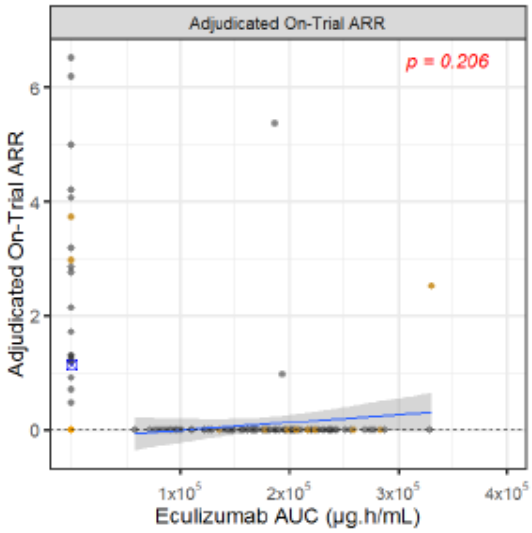
Figure 12 Kaplan-Meier Plots for Proportion of patients without relapse for Adjudicated on-trial relapse and on-trial relapse as determined by the treating physician in Study ECU-NMO-301

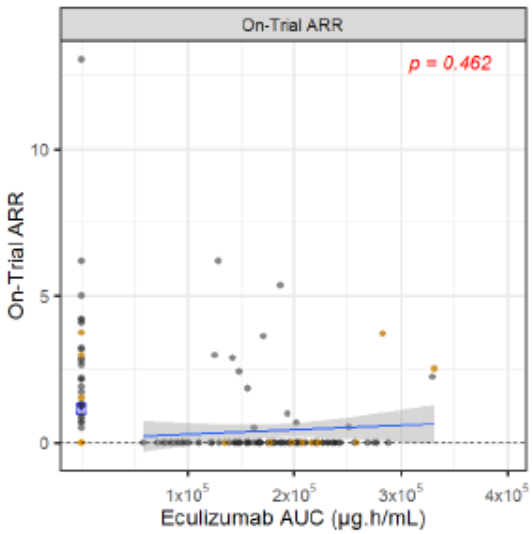


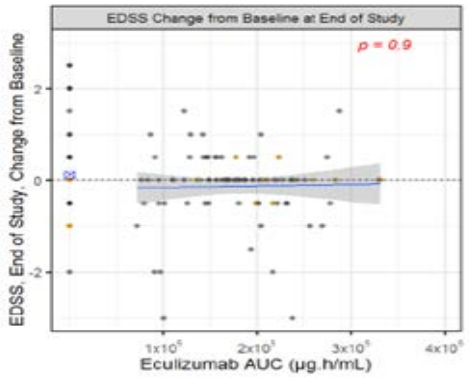
2.- Selected secondary efficacy endpoints

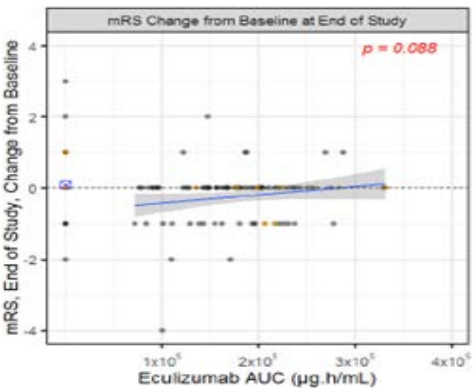
Adjudicated On-trial ARR and On-trial ARR (as determined by the Treating Physician) was lower in Eculizumab-treated group compared with placebo. A linear regression analysis did not show an exposure effect on ARR, indicating that the exposure-response profile was flat over the investigated exposure range (Figure 13). There were not significant differences between placebo- and eculizumab-treated patients for the change in EDSS, mRS and HAI from baseline to the EOS. A linear regression analysis did not show an exposure effect on any of these scores (Figure 14).

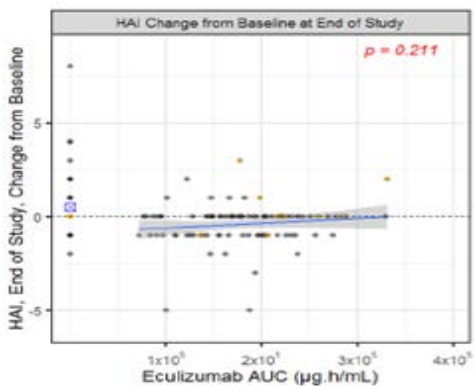
Figure 13 Exposure-Response for adjudicated on-trial ARR and on-trial ARR as determined by the Treating Physician in Study ECU-NMO-301
Figure 14 Exposure-Response for EDSS (upper) and mRS (middle) and HAI (lower) from baseline to End of Study in Study ECU-NMO-301











C. Exploratory Exposure-Safety Analysis

No relevant differences are observed between eculizumab- and placebo-treated patients, and no trends were observed at increasing eculizumab exposure.

2.3.4. Discussion on clinical pharmacology

The pharmacokinetics of eculizumab was studied in a total of 96 patients NMOSD treated with 900 mg intravenous once per week for the first 4 weeks followed by 1200 mg intravenous one week later and then once every two weeks thereafter. A population pharmacokinetic model was developed using a two compartmental model with first order elimination and time-variant body weight effects as starting model. Plasmapheresis/plasma exchange effect was successfully incorporated into the model. Apart from albumin and gender no other studied covariates showed significant correlation with the individual estimated parameters. Neither albumin nor gender could be incorporated into the model.

The model predicted the following parameters (relative standard error): CL, 0.0070 L (0.5%); V1, 2.37 L (6.4%); V2, 2.16 L (11.3%); Q, 0.243 L/h (26 %); weight effect on CL/Q, 0.908 (7.2%); body weight effect on V1/V2, 0.594 (14.9); PP/PE effect on CL, 1.79 L/h (16.6%). Interindividual was estimated for Cl (24.5% (15.6%) and V1 (16.3 % (28.7%)). Goodness of fit plots are reasonable, as well as the prediction corrected VPC plots.

CSF exposure was only evaluated in four patients, and 12 samples in total. All measured concentrations were below 5 µg/ml, although these values should be cautiously interpret due to the low number of observations.

95.8% of patients presented free C5 concentrations below the threshold of 0.5 µg/mL by the end of the infusion and it was maintained throughout the entire treatment period. Similar results were obtained for cRBC haemolysis. Values<20% were observed in 92.6% of the patients at the end of the infusion and were maintained throughout the treatment period. The distribution of data for these two variables did not enable the development of a PKPD model.

The relationship between the exposure and efficacy endpoints was graphically explored. The eculizumab-treated patients were binned into 4 quartiles of AUC at steady state exposure bins. Differences between placebo and treated patients were observed for the primary efficacy endpoints (time to first adjudicated On-trial Relapse and sensitivity analysis endpoint of On-trial Relapse), but no differences among the 4 bins of AUC were observed. There were no significant differences for any of the secondary efficacy endpoints (adjudicated On-trial ARR, the sensitivity analysis of On-trial ARR, and change from Baseline to EOS for EDSS, mRS, and HAI). Therefore no PKPD model was developed, probably due to the fact that the majority of the patients presented an almost complete inhibition of terminal complement after the treatment start. Safety endpoints included in the exposure-response analysis were treatment-emergent AESIs and TEAEs that occurred in ≥ 5% of the eculizumab-treated patients. No differences were observed between patients treated with eculizumab or placebo. No trends are observed at increasing eculizumab exposure.

2.3.5. Conclusions on clinical pharmacology

The pharmacokinetics of eculizumab in patients suffering NMOSD was evaluated by means of a population approach. Parameter estimates were similar to those estimated for other indications. Eculizumab produced an almost complete inhibition of terminal complement from the first measurement after drug intake and this fact precluded the possibility of finding exposure-effect relationships for the studied efficacy primary or secondary variables. Neither was possible to correlate drug exposure with safety endpoints.

At the time of this assessment report, there were samples requiring validation of storage duration according to the Applicant (Tables 3 5 6 8 10). At request, MAH committed to submit these long-term storage data and in case of failure, an impact analysis by the end of Dec 2020. Due to the limited number

of samples not yet covered by validated storage stability, no impact to the study was anticipated in the event of failing to provide coverage.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- The MAH commits to submit long-term storage data by the end of Dec 2020 as a PAM

2.4. Clinical efficacy

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

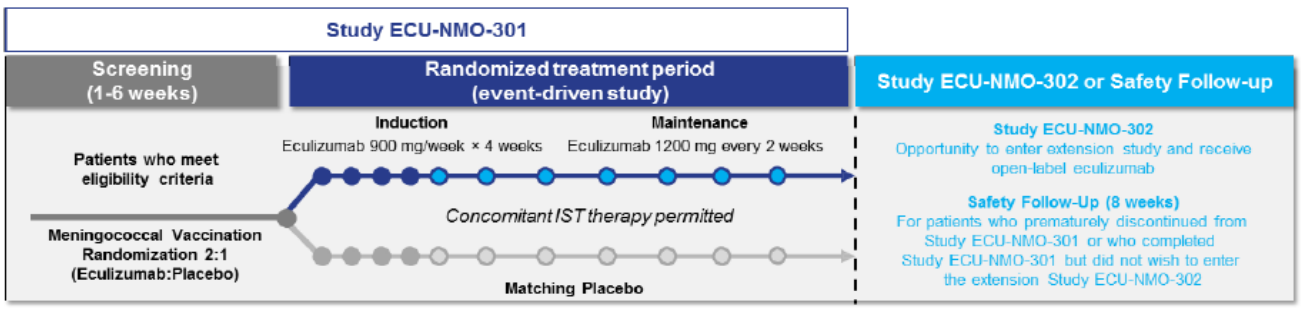
• A Phase 3 randomized, double-blind, placebo-controlled, multicenter study (Study ECU-NMO-301; completed)

• A Phase 3, open-label, multicenter extension study of Study ECU-NMO-301 (Study ECU-NMO-302; ongoing)

2.4.1. Main Study

Study ECU-NM0-301: A randomized, double-blind, placebo-controlled, multicenter trial to evaluate the safety and efficacy of Eculizumab in patients with relapsing Neuromyelitis optica (NMO)

Figure 15 Study ECU-NMO-301 Design



Patients completed the study if they experienced an On-trial Relapse per the Treating Physician or once the pre-specified number of patients had experienced a positively-adjudicated On-trial Relapse, whichever occurred first. Patients were provided the opportunity to participate in an extension study to receive eculizumab after completion of this study.

2.4.1.1. Methods

Study participants

Main Inclusion Criteria:

1. Male or female ≥ 18 years of age
2. Diagnosis of NMO as defined by 2006 criteria (Wingerchuk, 2006), or NMOSD as defined by 2007 criteria (*Wingerchuk, 2007a*)
3. Anti-aquaporin 4 antibody seropositive
4. Historical relapse (as defined by the protocol) of at least 2 relapses in last 12 months or 3 relapses in the last 24 months with at least 1 relapse in the 12 months prior to Screening

5. Expanded Disability Status Scale (EDSS) score ≤ 7
6. If a patient entered the study receiving immunosuppressive therapy (IST) for relapse prevention, the patient must have been on a stable maintenance dose of IST(s), as defined by the Treating Physician, prior to Screening and must have remained on that dose for the duration of the study, unless the patient experienced a relapse

Main Exclusion Criteria:

1. Use of rituximab 3 months prior to Screening
2. Use of mitoxantrone 3 months prior to Screening
3. Use of intravenous immunoglobulin (IVIg) within 3 weeks prior to Screening
4. If a patient entered the study receiving oral corticosteroid(s) with or without other IST(s), the daily corticosteroid dose must be no more than prednisone 20 mg/day (or equivalent) prior to the Screening, and must remain on that dose for the duration of the study or until the patient experiences a relapse
5. Pregnant, breastfeeding, or intending to conceive during the course of the study
6. Unresolved meningococcal disease
7. Any systemic bacterial or other infection that was clinically significant in the opinion of the Investigator and had not been treated with appropriate antibiotics
8. Had previously been treated with eculizumab
9. Hypersensitivity to murine proteins or to 1 of the excipients of eculizumab
10. Any medical condition that, in the opinion of the Investigator, might have interfered with the patient's participation in the study, posed any added risk for the patient, or confounded the assessment of the patient

Treatments

The proposed commercial formulation, dosage form, and route of administration are identical to that used in Studies ECU-NMO-301 and ECU-NMO-302 as well as that currently marketed (Soliris) for use in PNH, aHUS, and gMG.

- Induction Period: Patients received either eculizumab 900 mg or matching placebo via intravenous (IV) infusion once a week (every 7 ± 2 days) for 4 weeks followed by eculizumab 1200 mg or matching placebo for the fifth dose.
- Maintenance Period: Patients received either eculizumab 1200 mg or matching placebo via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose onwards.
- Supplemental Doses: If plasmapheresis or plasma exchange (PE) was administered for On-trial Relapse, supplemental study drug (600 mg of eculizumab or matching placebo) was administered within 1 to 2 hours after the end of each plasmapheresis/PE session.

Patients could continue to receive a stable dose of the ISTs they were taking at the time of Screening (with the exception of protocol-specified disallowed medications), but no new ISTs and no change in IST dosage were permitted during the study except for a known toxicity or side effect associated with the given IST. After an On-trial Relapse, there were no restrictions on IST adjustments or changes. If a patient entered the study receiving corticosteroids either as monotherapy or in combination with another

IST, the daily corticosteroid dose could not be more than prednisone 20 mg daily (or equivalent). The patient must have remained on that dose for the duration of the study unless the patient experienced a relapse.

All patients must have been vaccinated against N. meningitidis if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer.

Objectives

The primary objective was to assess the efficacy of eculizumab treatment, as compared with placebo, in patients with NMOSD based on time to first relapse.

The main secondary clinical efficacy objective was to evaluate the efficacy of eculizumab compared with placebo by additional efficacy measures including:

- Annualized relapse rate (ARR)
- Disease related disability
- Neurologic function
- Quality of life

Outcomes/endpoints

Outcomes

- *On-trial Relapse*: a relapse that occurs during the Study Period, 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*: an On-trial Relapse that was positively adjudicated by the Relapse Adjudication Committee (RAC).
- *Historical relapse*: a relapse that occurred prior to the ECU-NMO-301 Screening Visit, including the first NMO attack. For this study, historical relapse was defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination (clinical findings or magnetic resonance imaging [MRI] findings or both) that persisted for more than 24 hours and/or the new onset of neurologic symptoms or worsening of existing neurologic symptoms that required treatment. Treatment was defined as use of high-dose IV corticosteroids, PE, or IVIg. Events that occurred within a 30-day interval were considered as 1 relapse.
- *EDSS*: an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. The Kurtzke functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral) and ambulation are rated in the context of a standard neurological examination, and then these ratings (KFS scores) are used in conjunction with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign an EDSS score. EDSS steps 1.0 to 4.5 refer to people who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by impairment to ambulation.
- *Modified Rankin Scale (mRS):* a commonly administered scale by the Treating Physician for measuring the degree of disability or dependence in the daily activities of people suffering from a neurological disability. The scale ranges from 0 (no disability) to 6 (death).
- *Hauser Ambulation Index (HAI)*: a sale to assess the time and effort used by the patient to walk 25 feet (8 meters). The scale ranges from 0 to 9, with 0 being the best score (asymptomatic; fully

ambulatory with no assistance) and 9 being the worst (restricted to wheel chair; unable to transfer self independently).

- *European Quality of Life Health 5-Dimension Questionnaire (EQ-5D)*: a generic, standardized patient self-administered instrument that provides a simple, descriptive profile and a index value for health status. The EQ-5D comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of 3 levels (some, moderate, extreme problems), generating a total of 243 theoretically possible health states. The response period is the day of assessment only. Assessments were also made using the EQ-5D Visual Analogue Scale (EQ-5D VAS).
- *Visual Assessment*: Assessment of the optic disc, Visual Fields (VFs), the presence or absence of a scotoma, and visual acuity measured using the Snellen chart.
- *Study 36-item Short Form (SF-36):* a patient self-administered questionnaire designed to assess generic health-related quality of life in healthy and ill adult populations. The SF-36 consists of 36 items organized into 8 scales. The SF-36 also yields 2 summary measures of physical health and mental health derived from scale aggregates. Higher global scores are associated with better quality of life.

Endpoints

Primary Endpoint: time to first adjudicated On-trial Relapse by the Relapse Adjudication Committee (RAC)

Secondary Endpoints (hierarchical)

1. Adjudicated On-trial ARR
2. Change from Baseline in EDSS score at End Of Study (EOS)
3. Change from Baseline in Modified Rankin Scale (mRS) score at EOS
4. Change from Baseline in ambulatory function as measured by Hauser Ambulation Index (HAI) at EOS
5. Change from Baseline in European Quality of Life Health 5-dimension Questionnaire (EQ-5D) at EOS. The EQ-5D has 2 endpoints, the index score and EQ-5D visual analogue scale (VAS). For the purposes of this closed testing procedure, the EQ-5D VAS score was analysed first and the EQ-5D Index score was analysed second for the EQ-5D analyses.

Tertiary Endpoints

1. Change from Baseline in ambulatory function as measured by HAI at EOS in patients with abnormal baseline ambulatory function
2. Change from Baseline in visual function as measured by visual acuity at EOS in all patients and in patients with abnormal baseline visual function
3. Change from Baseline in the Medical Outcomes Study 36-item Short Form at EOS
4. Change from Baseline in the EDSS functional system scores at EOS

Other Efficacy Endpoints

1. Severity of an individual relapse as assessed by Optic Spinal Impairment score (OSIS) and relapse recovery as assessed by changes in EDSS score.
2. Anti-AQP4 Ab titers in blood samples (from all patients) and cerebrospinal (CSF) samples (from patients who consented to CSF testing).

Sample size

The sample size and power calculation assumptions for this time to first event study were as follows:

- Log-rank test for comparison of eculizumab to placebo
- 2:1 randomization (eculizumab : placebo)
- Power 90%
- Two-sided 5% level of significance
- Drop-out rate 10%
- Accrual period of approximately 21 months
- Relapse-free rate of 80% for the eculizumab group at 12 months
- Hazard ratio of 0.24 (-log hazard ratio = 1.41), which corresponds to a relapse-free rate of 40% for the placebo group at 12 months

The total number of relapses anticipated to be observed for this study was 24 relapses (adjudicated On-trial Relapses) in 24 distinct patients. With these assumptions, a sample size of approximately 132 patients (88 eculizumab and 44 placebo) was expected to provide 90% power to detect a treatment difference in time to first relapse.

Randomisation

Patients were randomized on a 2:1 basis to the eculizumab group or the placebo group. Randomization was performed across sites and stratified according to the following two variables:

1) Patients' EDSS score at randomization (≤ 2.0; ≥ 2.5 and ≤ 7.0).

2) Patients' prior IST and IST status at randomization:

a. Treatment-naïve patients (ie, patients with no prior or current ISTs, except corticosteroids alone)
b. Patients continuing on the same IST(s) since the last relapse (ie, including patients with dose adjustments since the last relapse)
c. Patients with changes in IST(s) since the last relapse (ie, switched IST(s), added IST(s), or withdrew any IST).

Blinding (masking)

All study patients, investigational site personnel; Alexion staff, Alexion designees, and all staff directly associated with the conduct of the study were blinded to the patient treatment assignments.

Statistical Analyses

Analysis Populations

- *Full Analysis Set (FAS)*: The population on which primary, secondary, tertiary, and other efficacy analyses was performed consisted of all patients who were randomized to treatment and who received at least 1 dose of study drug (*modified* Intention to Treat). Patients were compared for efficacy according to the treatment they were randomized to receive, irrespective of the treatment they received.

- *Per Protocol (PP) Set*: The PP Set is a subset of the FAS includes all patients who have no major protocol deviations or key inclusion/exclusion criteria deviations that might potentially affect efficacy and took at least 80% of the required treatment doses while they were in the

double-blind Study Period (for patients who had relapses, any dosing after the relapse was not included in this calculation).

- *Safety Set*: all patients who received at least 1 dose of study drug. Patients were compared for safety according to the treatment they received.
- *Pharmacokinetic/Pharmacodynamic Set*: PK/PD analyses were performed on the PK/PD Set. The PK/PD Set includes patients with at least one PK or PD observation.

Efficacy analyses were performed on the FAS. The primary efficacy analysis of time to first adjudicated On-trial Relapse was also performed on the PP Set. Baseline was defined as the last available assessment prior to treatment for all patients regardless of treatment group.

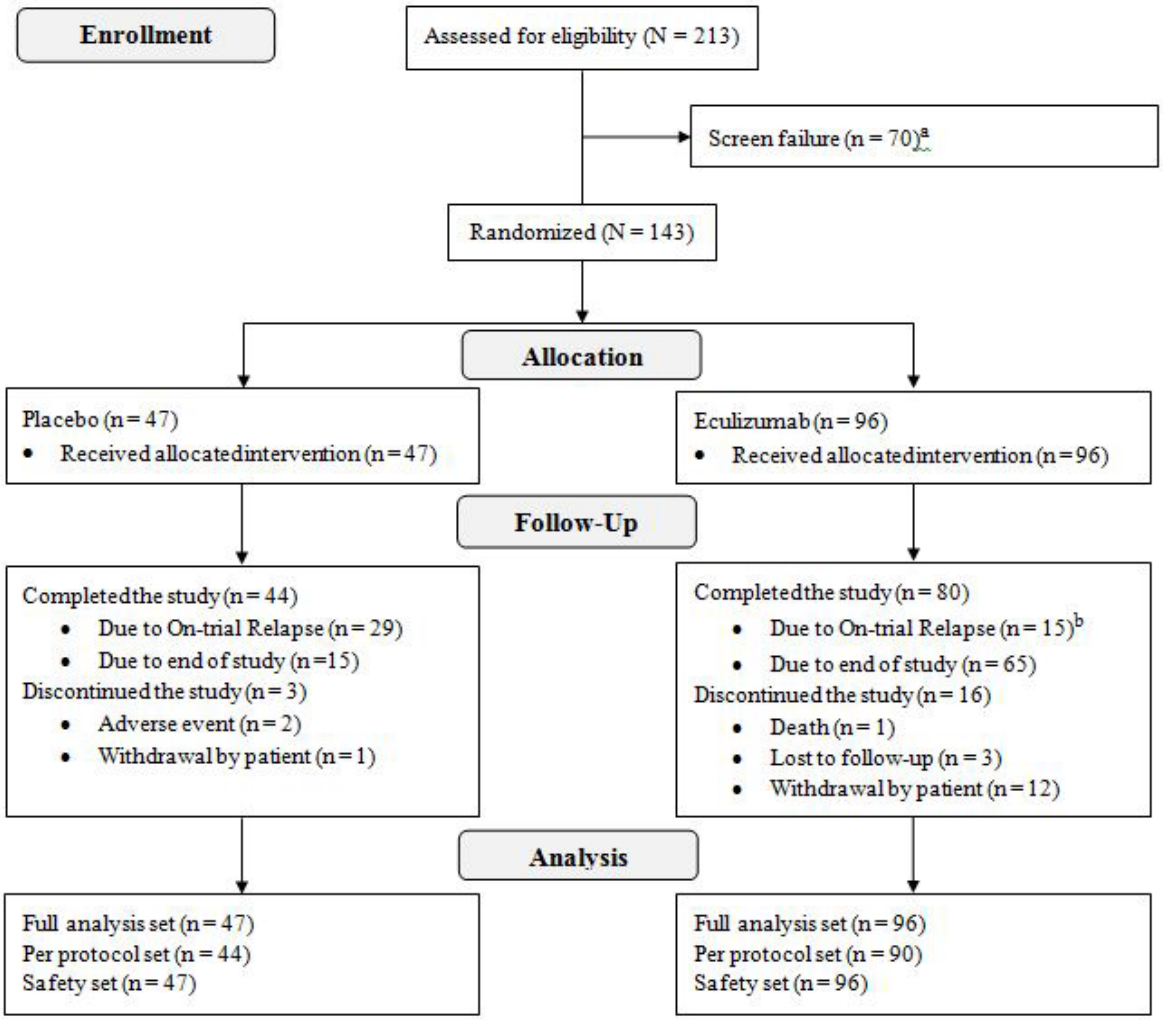
The trial was considered to have met its primary efficacy objective if a statistically significant difference was observed between the eculizumab and placebo groups for time to first adjudicated On-trial Relapse. The primary comparison of the treatment groups for time to first adjudicated On-trial Relapse and the sensitivity analysis of time to first On-trial Relapse as determined by the Treating Physician used a stratified log-rank test including strata for the randomization stratification variable. Confidence intervals (CIs) and p-values were presented. Hazard ratio and risk reduction from a stratified Cox proportional hazards model were summarized. Additional sensitivity analyses of the time to first adjudicated On-trial Relapse included an unstratified log-rank test and a multivariate Cox proportional hazards model. An additional sensitivity analysis was performed on the time to first adjudicated On-trial Relapse as determined by the Relapse Adjudication Committee. Summaries of subgroups are provided for adjudicated On-trial Relapses and On-trial Relapses as determined by the Treating Physician based on region, age, sex, race, and IST subgroups.

Hypothesis testing comparing eculizumab and placebo for the secondary efficacy analyses was performed using a closed testing procedure with the rank order as pre-specified in the statistical analysis plan : (1) Adjudicated ARR; (2) Change from Baseline in EDSS score at EOS; (3) Change from Baseline in mRS score at EOS; (4) Change from Baseline in ambulatory function as measured by HAI at EOS; (5) Change from Baseline in EQ-5D at EOS.. The hypothesis testing proceeded from highest rank (#1) to the lowest rank (#5).. If statistical significance was not achieved at an endpoint ($p \leq 0.05$), then endpoints of lower rank were considered not to be statistically significant. Confidence intervals and p-values were presented for all secondary efficacy endpoints for descriptive purposes, regardless of the outcome of the closed testing procedure.

The adjudicated On-trial ARR and On-trial ARR (as determined by the Treating Physician) were analysed using a Poisson regression analysis, with treatment group, historical ARR, and randomization strata as covariates. The change from Baseline in EDSS score, mRS score, HAI score, EQ-5D VAS score, and EQ-5D Index score at EOS were analysed using a randomization-based nonparametric analysis of covariance (ANCOVA) adjusted for baseline score (on that particular scale) and stratified by randomization strata. Sensitivity analyses included: (1) change from Baseline at EOS using an ANCOVA adjusted for baseline score (on that particular scale) and randomization strata; (2) change from Baseline at all scheduled visits using a mixed model for repeated measures, with baseline score (on that particular scale), observed strata, treatment group, and study visit as covariates; and (3) change from Baseline at all scheduled visits over Year 1 using a mixed model for repeated measures with baseline score (on that particular scale), observed strata, treatment group, study visit, and study visit by treatment interaction as covariates.

2.4.1.2. Results

Figure 16 Participant flow



[a] Reasons for screen failure include AQP4-Ab seronegative (n = 42); not having ⩾ 2 relapses in the last 12 months or 3 relapses in the last 24 months with at least 1 in the 12 months prior (n = 11); EDSS score > 7 (n = 5); Investigator decision (n = 5); daily corticosteroid dose more than prednisone 20 mg/day (or equivalent) after Screening (n = 3); patient not willing or able to comply with the protocol requirements (n = 3); and patient did not give written informed consent (n = 2). If a patient was screened more than once, the last screen failure reason is presented. A patient may have more than one reason for screen failure.

b This includes 1 patient who experienced a relapse that was outside of the analysis window defined for an "On-trial Relapse"; thus, this relapse is not considered an On-trial Relapse in the efficacy analyses

Abbreviations: AQP4-Ab = aquaporin 4 antibody; EDSS = Expanded Disability Status Scale.

Table 14: Patient Disposition – All Randomized Patients

Status	Placebo (N = 47) n (%)	Eculizumab (N = 96) n (%)	Total (N = 143) n (%)
Randomized	47 (100.0)	96 (100.0)	143 (100.0)
Treated	47 (100.0)	96 (100.0)	143 (100.0)
Completed the study	44 (93.6)	80 (83.3)	124 (86.7)
Completed due to On-trial Relapse	29 (61.7)	15 (15.6)[a]	44 (30.8)
Completed due to end of study	15 (31.9)	65 (67.7)	80 (55.9)
Discontinued	3 (6.4)	16 (16.7)	19 (13.3)
Adverse event	2 (4.3)	0	2 (1.4)
Death	0	1 (1.0)	1 (0.7)
Lost to follow-up	0	3 (3.1)	3 (2.1)
Withdrawal by patient	1 (2.1)	12 (12.5)	13 (9.1)
PY on study	53.1	172.8	226.0
Rate of discontinuation	5.6 per 100 PY	9.3 per 100 PY	8.4 per 100 PY
Enrolled in open-label extension study (Study ECU-NMO-302)	41 (87.2)	78 (81.3)	119 (83.2)

Note: Percentages are based on the number of randomized patients in each treatment column.
[a] This includes 1 patient who experienced a relapse that was outside of the analysis window defined for an "On-trial Relapse"; thus, this relapse is not considered an On-trial Relapse in the efficacy analyses
Abbreviations: PY = patient years

During the first request for supplementary information, the applicant provided further information about the differential withdrawal rates between patients from eculizumab arm (16/96; 16.7%) and placebo arm (3/47; 6.4%). When adjusted for study duration, study discontinuation in the eculizumab group occurred at a rate of 9.3/100 patient years (PY) compared with 5.6/100 PY for the placebo group. This difference was primarily driven by a greater number of patients who elected to withdraw in the eculizumab group (12 [12.5%] patients) compared with the placebo group (1 [2.1%] patient). For the eculizumab patient withdrawals, time on study ranged from 106 to 835 days and the majority of withdrawals (8/12) were attributed to changes in life circumstances including change of employment and relocation. Since only three cases were due to unknown reasons, difference in the withdrawals could not be related with the treatment (non-informative censoring).

Recruitment

The study was conducted at 130 centres in North America, South America, Europe, Australia, and Asia, of which only 70 centres enrolled patients.

- Date first patient enrolled: 11 Apr 2014
- Date last patient completed: 17 Jul 2018
- Date locking database: 17 Sept 2018

Conduct of the study

The 24th adjudicated On-trial Relapse was planned to trigger end of study activities. In May 2018, Alexion ended the study at 23th adjudicated On-trial Relapses.

Protocol amendment

The protocol was globally amended 5 times during the study, with the first patient enrolled under Amendment 3 (ie, Protocol Version 4.0). The following significant changes from the original protocol were included:

1. *Protocol Version 2.0 (Global), 15 Mar 2013 (No patients enrolled)*

- Included the option to perform an interim analysis when a minimum of 70% of expected events had occurred in order to stop the trial for efficacy
- Increased the screening window from 1-2 weeks to 1-3 weeks
- Allowed the use of methotrexate and tacrolimus as supportive therapies
- Updated the EDSS randomization strata from 3 strata to 2 strata (≤ 2.0 vs. ≥ 2.5 to ≤ 7)
- Updated the IST status randomization strata from 2 strata to 3 strata
- Provided a Patient Education Card that details the signs and symptoms of a potential relapse, with instructions to contact the Investigator at the first sign or symptom of a potential relapse
- Provided clarification on the visit interval between this study and the extension study
- Added change from Baseline in mRS score at EOS as a secondary endpoint
- Deleted the secondary endpoint of change from Baseline visual function as measured by visual acuity at EOS
- Updated definition of treatment naïve
- Deleted the restriction that relapses occurring within the first 14 days of study drug administration would not count as events
- Added the C-SSRS as a safety outcome measure
- Incorporated new sensitivity analyses for the primary efficacy endpoint
- Added PK/PD sampling at Relapse Evaluation Visits

2. *Protocol Version 3.0 (Global), 15 May 2013 (No patients enrolled)*

- Updated the IST status randomization strata from patients who are treatment naïve vs. patients who have failed ISTs and are receiving IST at randomization vs. patients who have failed ISTs and are not receiving IST at randomization to treatment naïve patients vs. prior IST and are receiving IST at randomization patients vs. prior IST and are not receiving IST at randomization patients
- Deleted Inclusion Criteria #6 around prior ISTs: updated to reflect that the DMC will receive reports concerning patients who have dropped out and any patients who have missing primary and secondary efficacy data; the DMC will also review summaries of all patient-reported relapses to assure no bias has occurred in relapse assessments by the Treating Physician

3. *Protocol Version 4.0 (Global), 16 Oct 2013*

- Assumptions for sample size and event-driven power calculations were updated
- Increased the number of study centers from 100 to 100-120 to enhance recruitment
- Updated the anticipated sample size based on power calculations requiring 24 relapses in 24 distinct patients
- Updated the IST status randomization strata from treatment naïve patients vs. prior IST and are receiving IST at randomization patients vs. prior IST and are not receiving IST at randomization patients to treatment naïve patients vs. patients continuing on the same IST(s) since last relapse vs. patients with changes in IST(s) since last relapse
- Expanded on the clinical information to be collected for historical relapses
- Safety follow-up was extended from 4 weeks to 8 weeks
- Updated the inclusion criterion around historical relapses to be less restrictive
- Updated the inclusion criterion around concomitant IST use during the study to be less restrictive and better aligned with current clinical practice
- Added exclusion criterion #4, as high corticosteroid doses may decrease the relapse rate in some patients, confounding the interpretation of study results

4. *Protocol Version 5.0 (Global), 25 Feb 2015*

- Changed the inclusion criterion “NMO-IgG seropositive at screening visit” to “NMO-IgG seropositive” to allow historically seropositive patients
- Allowed qualified non-physician healthcare professionals (eg, nurses) to conduct the EDSS rating with the Sponsor’s approval

- Expanded the number of sites from 100-120 to 120-150 to meet recruitment challenges
- Removed an interim analysis, in alignment with recommendations from regulatory agencies
- Removed text emphasizing reporting the IST use "within 24 months prior to the Screening Visit" to encourage obtaining all available history on IST use for relapse prevention
- Clarified that supportive ISTs are for relapse prevention, so as not to be confused with ISTs administered for relapse treatment or other medical reasons
- Extended the Screening Period from 1-3 weeks to 1-6 weeks
- Provided some flexibility for the supplemental study drug dose administration time from "within 60 minutes" to "preferably within 1-2 hours" after each PE cycle to address operational challenges
- Changed the definition of the PP Set from patients who have "no major protocol deviations or inclusion/exclusion criteria deviations" to "no major protocol deviations or key inclusion/exclusion criteria deviations that might potentially affect efficacy" to prevent the exclusion of patients from the PP Set with deviations not relevant for assessing the efficacy and safety of eculizumab

5. *Protocol Version 6.0 (Global), 01 Jul 2016*

- Established the RAC for adjudication of all On-trial Relapses
- Updated the primary endpoint of the study from "time to first Relapse" to "time to first adjudicated On-trial Relapse"
- Added a sensitivity analysis of time to first On-trial Relapse using a log-rank test including strata for the randomization stratification variables
- The secondary efficacy endpoint was changed from ARR to adjudicated ARR
- Added a sensitivity analysis for ARR using all On-trial Relapses in a Poisson regression analysis with treatment group, stratification variables, and baseline ARR as covariates in the model, and the log of time in the study was used as the offset variable

Protocol Deviations

There were a total of 138 major protocol deviations in 57 (39.9%) patients. Major deviations that occurred in more than 10% of patients overall included those related to informed consent, randomization strata errors, and visit schedule. Three patients had major protocol deviations related to inclusion and exclusion criteria and were excluded from the PP Set: 1 patient in each treatment group had a daily corticosteroid dose greater than prednisone 20 mg/day (or equivalent) after Screening and 1 patient in the eculizumab group used rituximab within 3 months prior to Screening. Eleven (7.7%) patients overall had an SAE that was not reported within 24 hours, which was considered a major protocol deviation (Table 15).

Table 15 Major Protocol Deviations – Full Analysis Set

Type of Deviation Category	Placebo (N = 47) n (%)	Eculizumab (N = 96) n (%)	Total (N = 143) n (%)
Any major deviation	20 (42.6)	37 (38.5)	57 (39.9)
Informed consent	9 (19.1)	13 (13.5)	22 (15.4)
Randomization	6 (12.8)	9 (9.4)	15 (10.5)
Visit schedule	8 (17.0)	7 (7.3)	15 (10.5)
Study procedures/tests	3 (6.4)	11 (11.5)	14 (9.8)
Safety reporting	4 (8.5)	7 (7.3)	11 (7.7)
Investigational product	1 (2.1)	9 (9.4)	10 (7.0)
Concomitant medication	1 (2.1)	5 (5.2)	6 (4.2)
Source document	1 (2.1)	5 (5.2)	6 (4.2)
Eligibility and entry criteria	1 (2.1)	2 (2.1)	3 (2.1)

Baseline data

The majority of the patients were females with an average age of 45 years old. Nearly 50% of the participants were White-Caucasian and nearly a third came from a European Country (Table 16). On average, age at initial clinical presentation was 36 years and age at first dose was 45 years. The most commonly reported onset syndromes were optic neuritis and transverse myelitis (Table 17) On average, patients entering this study had a median EDSS of 4 steps (Table 18) and were experiencing approximately 2 relapses per year for the 2 years prior to study start and most of them were under IST or immunomodulation at the time of the historical relapses (Table 19). Indeed, the majority of patients had received prior supportive ISTs for NMOSD. Of the total patients, 98 (68.5%), 87 (60.8%), 46 (32.2%), and 42 (29.4%) had received prior supportive corticosteroids, azathioprine, rituximab, and mycophenolate mofetil, respectively (Table 20). Thirty-four patients were not under any IST, the majority of them (24/34) had received supportive ISTs prior to study enrolment. In accordance with the study protocol, information was not collected at screening regarding reasons for IST discontinuation prior to study entry. In the position of the MAH, this situation would be consistent with inadequate disease control despite prior IST use since these patients met relapse entry criteria for the study. Of the 10 patients who had not received treatment with supportive ISTs prior to study entry, the majority (6 of 10 patients) were from a single country (Russia). The remaining 4 patients were from Germany, Italy, Turkey, and the USA. These 10 patients were also diagnosed more recently prior to study entry than patients who had received prior ISTs, with a median (minimum, maximum) time between diagnosis and first dose of study drug of 0.73 (0.23, 3.76) years and 3.29 (0.15, 15.65) years, respectively.

Overall, treatment compliance was high during the study in both treatment groups. The mean (SD) treatment compliance in the Safety Set was 96.8% (5.08%) in the eculizumab group and 97.7% (4.76%) in the placebo group. The majority of patients (86 [89.6%] patients in the eculizumab group and 43 [91.5%] patients in the placebo group) had treatment compliance of ≥ 90%. Only 1 patient overall (eculizumab group) had compliance of ≥ 70% to < 80%, with all other patients having compliance of ≥ 80%.

Table 16 Demographics and Baseline Characteristics – Full Analysis Set

Variable	Statistic	Placebo (N = 47)	Eculizumab (N = 96)	Total (N = 143)
Age at first dose (years)	n	47	96	143
	Mean (SD)	45.0 (13.29)	43.9 (13.32)	44.3 (13.27)
	Median	44.0	45.0	45.0
	Min, max	21, 75	19, 70	19, 75
Sex				
Male	n (%)	5 (10.6)	8 (8.3)	13 (9.1)
Female	n (%)	42 (89.4)	88 (91.7)	130 (90.9)
Ethnicity				
Hispanic or Latino	n (%)	3 (6.4)	13 (13.5)	16 (11.2)
Not Hispanic or Latino	n (%)	41 (87.2)	78 (81.3)	119 (83.2)
Not reported	n (%)	1 (2.1)	4 (4.2)	5 (3.5)
Unknown	n (%)	2 (4.3)	1 (1.0)	3 (2.1)
Race				
Asian	n (%)	15 (31.9)	37 (38.5)	52 (36.4)
Black or African American	n (%)	8 (17.0)	9 (9.4)	17 (11.9)
White	n (%)	24 (51.1)	46 (47.9)	70 (49.0)
Other or unknown	n (%)	0	4 (4.2)	4 (2.8)
Japanese Patient				
Yes	n (%)	5 (10.6)	9 (9.4)	14 (9.8)
No	n (%)	42 (89.4)	87 (90.6)	129 (90.2)
Region[a]				
Americas	n (%)	15 (31.9)	29 (30.2)	44 (30.8)
Europe	n (%)	19 (40.4)	32 (33.3)	51 (35.7)
Asia-Pacific	n (%)	13 (27.7)	35 (36.5)	48 (33.6)
Weight (kg)	n	47	96	143
	Mean (SD)	69.65 (16.441)	68.39 (20.249)	68.80 (19.032)
	Median	67.00	64.50	64.80
	Min, max	46.1, 116.0	37.4, 127.9	37.4, 127.9
BMI (kg/m^2)	n	47	96	143
	Mean (SD)	25.65 (5.240)	25.79 (7.008)	25.74 (6.462)
	Median	24.73	24.68	24.73
	Min, max	17.7, 38.5	15.4, 49.0	15.4, 49.0

[a] Americas: Argentina and United States of America; Europe: Czech Republic, Germany, Denmark, Spain, United Kingdom, Croatia, Italy, Russia, and Turkey; Asia-Pacific: Australia, Hong Kong, Japan, Korea, Malaysia, Thailand, and Taiwan.

Abbreviations: BMI = body mass index; max = maximum; min = minimum.

Table 17 NMOSD History – Full Analysis Set

Variable	Statistic	Placebo (N = 47)	Eculizumab (N = 96)	Total (N = 143)
Age at NMOSD initial clinical presentation (years)	n	47	96	143
	Mean (SD)	38.5 (14.98)	35.8 (14.03)	36.6 (14.35)
	Median	38.0	35.5	36.0
	Min, max	12, 73	5, 66	5, 73
Age at NMOSD diagnosis (years)	N	47	96	143
	Mean (SD)	41.1 (14.36)	40.6 (14.00)	40.8 (14.07)
	Median	42.0	40.0	41.0
	Min, max	14, 73	15, 67	14, 73
NMOSD grouped initial clinical presentation				
Optic neuritis[a]	n (%)	17 (36.2)	41 (42.7)	58 (40.6)
Transverse myelitis[b]	n (%)	21 (44.7)	36 (37.5)	57 (39.9)
Optic neuritis and transverse myelitis[c]	n (%)	2 (4.3)	12 (12.5)	14 (9.8)
Area postrema syndrome[d]	n (%)	8 (17.0)	13 (13.5)	21 (14.7)
Other[e]	n (%)	1 (2.1)	5 (5.2)	6 (4.2)
NMOSD diagnosis				
Definitive neuromyelitis optica	n (%)	38 (80.9)	69 (71.9)	107 (74.8)
NMO spectrum disorder[f]	n (%)	9 (19.1)	27 (28.1)	36 (25.2)
Longitudinally extensive transverse myelitis	n (%)	5 (10.6)	14 (14.6)	19 (13.3)
Optic neuritis	n (%)	2 (4.3)	8 (8.3)	10 (7.0)
Optic neuritis or longitudinally extensive transverse myelitis coexisting with systemic autoimmune disease	n (%)	1 (2.1)	3 (3.1)	4 (2.8)
Optic neuritis or transverse myelitis associated with brain lesions typical of NMO	n (%)	1 (2.1)	1 (1.0)	2 (1.4)
Other	n (%)	0	1 (1.0)	1 (0.7)
Time from initial clinical presentation to first dose of study drug (years)	n	47	96	143
	Mean (SD)	6.601 (6.5863)	8.156 (8.5792)	7.645 (7.9894)
	Median	3.760	5.030	4.800
	Min, max	0.51, 29.10	0.41, 44.85	0.41, 44.85

Note: Patients can have more than 1 initial clinical presentation.
a Patients with optic neuritis but no transverse myelitis.
b Patients with transverse myelitis (ataxia, dysaesthesia, paresthesia, transverse myelitis or longitudinally extensive transverse myelitis) but no optic neuritis.
c Patients with both optic neuritis and transverse myelitis.
d Patients with area postrema syndrome (hiccoughs or intractable nausea/vomiting).
e Patients with any other presentations.
f NMOSD, as defined by Wingerchuk (Wingerchuk, 2007a), per the study protocol.
Abbreviations: Max = maximum; Min = minimum; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder.

Table 18 Baseline NMOSD Neurological Status – Full Analysis Set

Variable	Statistic	Placebo (N = 47)	Eculizumab (N = 96)	Total (N = 143)
Baseline EDSS score	n	47	96	143
	Mean (SD)	4.26 (1.510)	4.15 (1.646)	4.18 (1.598)
	Median	4.00	4.00	4.00
	Min, max	1.0, 6.5	1.0, 7.0	1.0, 7.0
Baseline HAI score	N	47	96	143
	Mean (SD)	2.1 (1.40)	2.4 (2.17)	2.3 (1.95)
	Median	2.0	2.0	2.0
	Min, max	0, 6	0, 8	0, 8
Baseline mRS score	N	47	96	143
	Mean (SD)	2.1 (0.98)	2.1 (1.14)	2.1 (1.09)
	Median	2.0	2.0	2.0
	Min, max	0, 4	0, 4	0, 4
Overall stratification group (4 strata)				
Low EDSS at randomization (≤ 2.0)	n (%)	5 (10.6)	11 (11.5)	16 (11.2)
High EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomization	n (%)	5 (10.6)	12 (12.5)	17 (11.9)
High EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization	n (%)	22 (46.8)	44 (45.8)	66 (46.2)
High EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization	n (%)	15 (31.9)	29 (30.2)	44 (30.8)
OSIS visual acuity	N	46	96	142
	Mean (SD)	2.5 (2.50)	2.9 (2.67)	2.8 (2.62)
	Median	2.0	2.0	2.0
	Min, max	0, 8	0, 8	0, 8
OSIS motor function	N	46	96	142
	Mean (SD)	2.1 (1.18)	2.1 (1.70)	2.1 (1.55)
	Median	2.0	2.0	2.0
	Min, max	0, 5	0, 6	0, 6
OSIS sensory function	N	46	96	142
	Mean (SD)	1.5 (1.13)	1.7 (1.04)	1.6 (1.07)
	Median	2.0	2.0	2.0
	Min, max	0, 3	0, 3	0, 3
OSIS sphincter function	N	46	96	142
	Mean (SD)	1.0 (1.05)	1.1 (1.23)	1.1 (1.17)
	Median	1.0	1.0	1.0
	Min, max	0, 4	0, 4	0, 4

Abbreviations: EDSS = Expanded Disability Status Scale; HAI = Hauser Ambulation Index; ISTs = immunosuppressive therapies; max = maximum; min = minimum; mRS = Modified Rankin Scale; NMOSD = neuromyelitis optica spectrum disorder; OSIS = Optic Spinal Impairment Score.

Table 19 History of Prior NMOSD Relapse – Full Analysis Set

Variable	Statistic	Placebo (N = 47)	Eculizumab (N = 96)	Total (N = 143)
Historical ARR (within the 24 months prior to Screening)	Mean (SD)	2.07 (1.037)	1.94 (0.896)	1.99 (0.943)
	Median	1.92	1.85	1.92
	Min, max	1.0, 6.4	1.0, 5.7	1.0, 6.4
Type of historical relapses 24 months prior to Screening				
Optic neuritis	n (%)	22 (46.8)	58 (60.4)	80 (55.9)
Unilateral left	n (%)	10 (21.3)	33 (34.4)	43 (30.1)
Unilateral right	n (%)	11 (23.4)	29 (30.2)	40 (28.0)
Bilateral	n (%)	5 (10.6)	16 (16.7)	21 (14.7)
Transverse myelitis	n (%)	42 (89.4)	74 (77.1)	116 (81.1)
Partial	n (%)	24 (51.1)	45 (46.9)	69 (48.3)
Complete	n (%)	4 (8.5)	11 (11.5)	15 (10.5)
Partial longitudinally extensive	n (%)	19 (40.4)	31 (32.3)	50 (35.0)
Complete longitudinally extensive	n (%)	10 (21.3)	19 (19.8)	29 (20.3)
Brain stem symptoms	n (%)	15 (31.9)	18 (18.8)	33 (23.1)
Cerebral symptoms	n (%)	5 (10.6)	10 (10.4)	15 (10.5)
Other symptoms	n (%)	10 (21.3)	23 (24.0)	33 (23.1)
Patient on ISTs or immunomodulators at the time of any of the historical relapses				
Yes	n (%)	32 (68.1)	78 (81.3)	110 (76.9)
No	n (%)	15 (31.9)	18 (18.8)	33 (23.1)
Acute treatments of relapses within 24 months prior to Screening				
Treatment with corticosteroids[a]	n (%)	44 (93.6)	95 (99.0)	139 (97.2)
High dose oral corticosteroids	n (%)	25 (53.2)	50 (52.1)	75 (52.4)
IV methylprednisolone	n (%)	40 (85.1)	91 (94.8)	131 (91.6)
Plasma exchange	n (%)	17 (36.2)	50 (52.1)	67 (46.9)
IVIg	n (%)	3 (6.4)	6 (6.3)	9 (6.3)
Other	n (%)	14 (29.8)	23 (24.0)	37 (25.9)
Other therapy[b]	n (%)	19 (40.4)	27 (28.1)	46 (32.2)

a Some patients might be treated with both high dose oral corticosteroids and IV methylprednisolone.
b Other therapy includes physical therapy, occupational therapy, speech therapy, and other.
Abbreviations: ARR = annualized relapse rate; ISTs = immunosuppressive therapies; IV = intravenous; IVIg = intravenous immunoglobulin; max = maximum; min = minimum; NMOSD = neuromyelitis optica spectrum disorder.

Table 20 Supportive IST for NMOSD Used Prior to Study Treatment by Treatment Group – Full Analysis Set

IST Subgroup	Placebo (N = 47)	Eculizumab (N = 96)	Total (N = 143)
Corticosteroids alone	11 (23.4)	16 (16.7)	27 (18.9)
AZA subgroup	13 (27.7)	37 (38.5)	50 (35.0)
AZA alone	6 (12.8)	8 (8.3)	14 (9.8)
AZA + corticosteroids	7 (14.9)	29 (30.2)	36 (25.2)
MMF subgroup	8 (17.0)	17 (17.7)	25 (17.5)
MMF alone	5 (10.6)	10 (10.4)	15 (10.5)
MMF + corticosteroids	3 (6.4)	7 (7.3)	10 (7.0)
Other IST(s)	2 (4.3)	5 (5.2)	7 (4.9)
Other IST(s) alone	0	1 (1.0)	1 (0.7)
Other IST(s) + corticosteroids	2 (4.3)	4 (4.2)	6 (4.2)
No IST usage	13 (27.7)	21 (21.9)	34 (23.8)

IST Categorization Generic Name	Placebo (N = 47) n (%)	Eculizumab (N = 96) n (%)	Total (N = 143) n (%)
Patients with any prior medications	45 (95.7)	88 (91.7)	133 (93.0)
Corticosteroids	30 (63.8)	68 (70.8)	98 (68.5)
AZA	26 (55.3)	61 (63.5)	87 (60.8)
Rituximab	20 (42.6)	26 (27.1)	46 (32.2)
MMF	15 (31.9)	27 (28.1)	42 (29.4)
Cyclophosphamide	5 (10.6)	8 (8.3)	13 (9.1)
Methotrexate	5 (10.6)	4 (4.2)	9 (6.3)
Cyclosporine and tacrolimus	3 (6.4)	3 (3.1)	6 (4.2)
Mitoxantrone and 2-CDA	3 (6.4)	3 (3.1)	6 (4.2)
IVIg	2 (4.3)	2 (2.1)	4 (2.8)
Mizoribine	2 (4.3)	1 (1.0)	3 (2.1)
Tocilizumab	0	2 (2.1)	2 (1.4)

Notes: Supportive ISTs are defined as those therapies used for relapse prevention. Prior medication is defined as any medication taken by a patient prior to the first dose of study drug. Medications are coded to generic name using WHO-Drug Dictionary Version March 2018. Multiple records of the same generic name used by a patient are counted once within the generic name; the generic names are sorted by decreasing overall frequency.
Abbreviations: AZA = azathioprine; IST = immunosuppressive therapy; MMF = mycophenolate mofetil.

Numbers analysed

All 143 patients who were randomized (96 in the eculizumab group and 47 in the placebo group) were treated and are included in both the FAS and the Safety Set. Of the patients included in the FAS and Safety Set, 90 (93.8%) patients in the eculizumab group and 44 (93.6%) patients in the placebo group are included in the PP Set. Reasons for exclusion from the PP Set were as follows: changes in IST(s), key eligibility criteria violations, emergency unblinding, and treatment compliance < 80%.

Outcomes and estimation

Primary Efficacy Endpoint

In the FAS, 3 (3.1%) patients in the eculizumab group and 20 (42.6%) patients in the placebo group had an adjudicated On-trial Relapse, with a median follow-up time of 89.43 weeks and 36.00 weeks in the eculizumab group and the placebo group, respectively (Table 21). A significant effect on the time to first adjudicated On-trial Relapse was observed for eculizumab compared with placebo ($p<0.0001$), confirming that the primary endpoint of the study was met. The hazard ratio (95% CI) for eculizumab compared with placebo was 0.058 (0.017, 0.197), representing a 94.2% reduction in the rate of relapse. The estimated proportion of patients (95% CI) relapse-free at 48 weeks was 0.979 (0.918, 0.995) in the eculizumab group and 0.632 (0.468, 0.758) in the placebo group. At 144 weeks, the estimated proportion

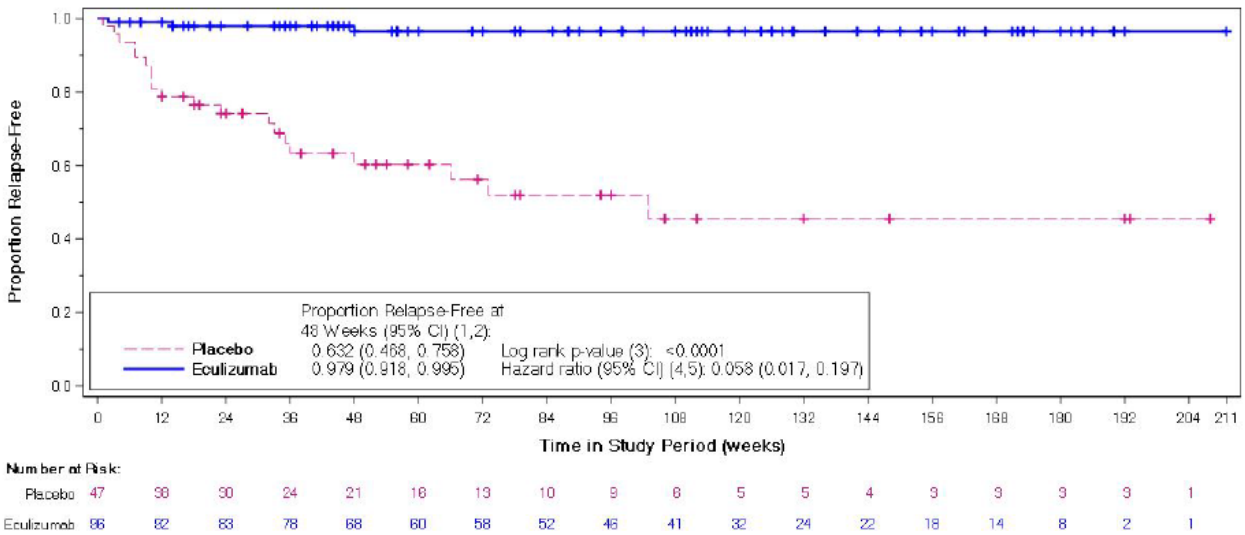
of patients (95% CI) relapse-free was 0.964 (0.891, 0.988) in the eculizumab group and 0.454 (0.262, 0.628) in the placebo group (Table 21 and Figure 17).

Table 21: Time to First Adjudicated On-trial Relapse – Full Analysis Set

Variable	Statistic	Placebo (N = 47)	Eculizumab (N = 96)
Patients with a relapse	n (%)	20 (42.6)	3 (3.1)
Follow-up time (weeks)	Median (min, max)	36.00 (1.86, 208.57)	89.43 (2.57, 211.14)
Estimated proportion of patients relapse-free at:			
48 weeks	Cumulative probability[a] (95% CI[b])	0.632 (0.468, 0.758)	0.979 (0.918, 0.995)
96 weeks		0.519 (0.341, 0.670)	0.964 (0.891, 0.988)
144 weeks		0.454 (0.262, 0.628)	0.964 (0.891, 0.988)
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] (eculizumab/placebo)	…	0.058
	95% CI[e]	…	0.017, 0.197
	% reduction[d] (eculizumab/placebo)	…	94.2
	95% CI[e]	…	80.3, 98.3

Note: Patients who did not experience an adjudicated On-trial Relapse were censored at the end of the Study Period. Stratified analyses are based on 4 randomization strata: (1) low EDSS at randomization (≤ 2.0); (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomization; (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization; (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.
a Based on the Kaplan-Meier product limit method.
b Based on the complementary log-log transformation.
c Based on a stratified log-rank test.
d Based on a stratified Cox proportional hazards model.
e Wald confidence interval.
Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; IST = immunosuppressive therapy; max = maximum; min = minimum; NA = not applicable.

Figure 17 Kaplan-Meier Survival Estimates for Time to First Adjudicated On-trial Relapse – Full Analysis Set



Note: Patients who did not experience an adjudicated On-trial Relapse were censored at the end of the Study Period. Stratified analyses are based on 4 randomization strata: (1) low EDSS at randomization (≤ 2.0), (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomization, (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization, (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.
1 Based on the Kaplan-Meier product limit method.
2 Based on the complementary log-log transformation.
3 Based on a stratified log-rank test.
4 Based on a stratified Cox proportional hazards model.

5 Wald confidence intervals.
Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; IST = immunosuppressive therapy.

Sensitivity Analyses

In the FAS, 14 (14.6%) patients in the eculizumab group and 29 (61.7%) patients in the placebo group had an On-trial Relapse as determined by the Treating Physician, with a median follow-up time of 89.43 weeks and 36.00 weeks in the eculizumab group and the placebo group, respectively (Table 22).

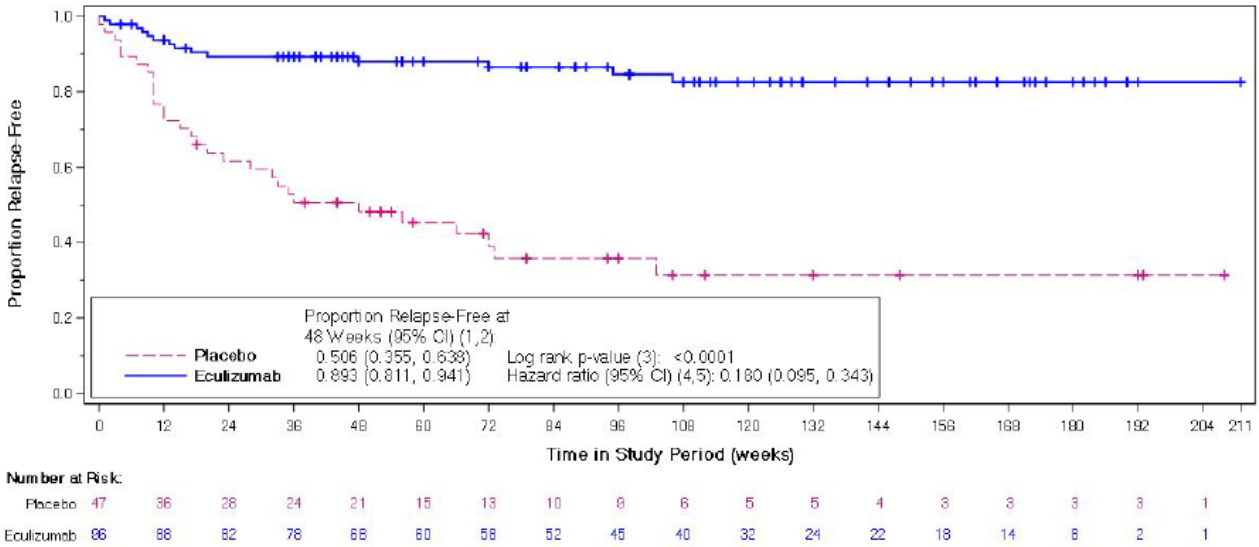
A significant effect on the time to first On-trial Relapse as determined by the Treating Physician was observed for eculizumab compared with placebo ($p<0.0001$). The hazard ratio (95% CI) for eculizumab compared with placebo was 0.180 (0.095, 0.343), representing an 82.0% reduction in the risk of relapse (Table 22 Figure 18).

Table 22 Time to First On-trial Relapse (as Determined by the Treating Physician) – Full Analysis Set

Variable	Statistic	Placebo (N = 47)	Eculizumab (N = 96)
Patients with a relapse	n (%)	29 (61.7)	14 (14.6)
Follow-up time (weeks)	Median (min, max)	36.00 (0.57, 208.57)	89.43 (1.29, 211.14)
Estimated proportion of patients relapse-free at:			
48 weeks	Cumulative probability[a] (95% CI[b])	0.506 (0.355, 0.638)	0.893 (0.811, 0.941)
96 weeks		0.358 (0.213, 0.505)	0.846 (0.746, 0.909)
144 weeks		0.313 (0.169, 0.469)	0.825 (0.717, 0.895)
Relapse-free time (weeks)	Percentile[a]		
	10th	4.43	20.86
	25th	12.57	NA
	50th	48.57	NA
Treatment effect	p-value[c]	…	<0.0001
	Hazard ratio[d] (eculizumab/placebo)	…	0.180
	95% CI[e]	…	0.095, 0.343
	% reduction[d] (eculizumab/placebo)	…	82.0
	95% CI[e]	…	65.7, 90.5

Note: Patients who did not experience an On-trial Relapse were censored at the end of the Study Period. Stratified analyses are based on 4 randomization strata: (1) low EDSS at randomization (≤ 2.0); (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomization; (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization; (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.
a Based on the Kaplan-Meier product limit method.
b Based on the complementary log-log transformation.
c Based on a stratified log-rank test.
d Based on a stratified Cox proportional hazards model.
e Wald confidence interval.
Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; IST = immunosuppressive therapy; max = maximum; min = minimum.

Figure 18 Kaplan-Meier Survival Estimates for Time to First On-trial Relapse (as Determined by the Treating Physician) – Full Analysis Set



Note: Patients who did not experience an On-trial Relapse as determined by the Treating Physician were censored at the end of the Study Period. Stratified analyses are based on 4 randomization strata: (1) low EDSS at randomization (≥ 2.0), (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomization, (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization, (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.
1 Based on the Kaplan-Meier product limit method.
2 Based on the complementary log-log transformation.
3 Based on a stratified log-rank test.
4 Based on a stratified Cox proportional hazards model.
5 Wald confidence interval.
Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; IST = immunosuppressive therapy.

During the first request for supplementary information, the MAH provided further information about:

- The potential impact of the inclusion of the independent RAC once the recruitment had started in the primary endpoint.
- Clarification for difference between adjudicated On-trial Relapse On-trial relapse determined by the treating physician and the reasons for negative qualification.

According to the positon of the applicant, all relapses were adjudicated on a retrospective basis, using all data as collected per protocol, and only after the Treating Physician had made a determination of whether a relapse had occurred and had treated the patient based on their presenting signs and symptoms.

Of the 43 patients with an On-trial Relapse as determined by the Treating Physician and that were subsequently referred to the RAC for adjudication, 23 patients had a relapse that occurred prior to 14 Jul 2016 (date of implementation of the RAC) and 20 patients had a relapse that occurred after the RAC was implemented. There was no statistically significant difference in the proportion of the relapses adjudicated by RAC before and after RAC implementation (Table 23).

Table 23 Evaluation of RAC Adjudication Relative to RAC Implementation – Full Analysis Set with an On-trial Relapse

Variable	Statistic	RAC Adjudication		p-value
		Negative (N=20)	Positive (N=23)	
Relapse identified relative to implementation of the RAC[a]				
Before	n (%)	11 (47.8)	12 (52.2)	1.0000
After	n (%)	9 (45.0)	11 (55.0)	

Note: Fisher's exact test was used to test the association between variables.
a The relapse adjudication committee was implemented on 14 Jul 2016.
Abbreviations: RAC = Relapse Adjudication Committee.

During the study ECU-NMO-301, 14 patients on eculizumab and 29 patients on placebo had an On-trial Relapse determined by the treating physician. However, 2 of the placebo patients had 2 On-trial Relapses each. In one of those patients, both relapses were adjudicated positively by the RAC. When analysed by the total number of On-trial Relapses as opposed to the total number of patients with an On-trial Relapse, this results in 31 relapses referred to the RAC in the placebo group, with 21 of these 31 positively adjudicated (Table 24).

In reviewing the reasons reported by the RAC for the negative adjudications in eculizumab-treated patients, for 8 relapses there was insufficient documented evidence for objective neurologic change on their examinations, for 1 relapse there was an alternative explanation for the new symptoms other than neuromyelitis optica spectrum disorder (NMOSD), and for 2 relapses both reasons were applicable (Table 25)

The RAC negatively adjudicated 10 On-trial Relapses reported for placebo-treated patients. In reviewing the reasons reported by the RAC for the negative adjudications, for 8 relapses there was insufficient documented evidence for objective neurologic change on their examinations, for 1 relapse there was an alternative explanation for the new symptoms other than NMOSD, and for 1 relapse the symptoms were not preceded by 30 days of stability (Table 25).

Table 24 Adjudicated On-Trial Relapses versus on-trial relapses as Determined by the Treating Physician in Study ECU-NMO-301

	Placebo	Eculizumab	Total
Total number of Physician-reported On-trial Relapses, n (%)	31 (68.9%)	14 (31.1%)	45 (100%)
Physician-reported On-trial Relapses adjudicated negatively, n (%)	10 (47.6%)	11 (52.4%)	21 (46.7%)
Physician-reported On-trial Relapses adjudicated positively, n (%)	21 (87.5%)	3 (12.5%)	24 (53.3%)
Proportion of Physician-reported On-trial Relapses adjudicated positively/Total number of Physician-reported On-trial Relapses, n (%)	21/31 (67.7%)	3/14 (21.4%)	24/45 (53.3%)

Table 25 Reasons for Negative Adjudication by RAC in in Study ECU-NMO-301

	Placebo (N = 31)	Eculizumab (N = 14)	Total (N = 45)
Relapses adjudicated negatively, n (%)	10 (32.3)	11 (78.6)	21 (46.7)
Reasons for negative adjudication[a], n (%)			
Insufficient evidence of objective change in the neurologic examination, n (%)	8 (80.0)	10 (90.9)	18 (85.7)
Signs and symptoms not attributed to NMOSD relapse, n (%)	1 (10.0)	3 (27.3)	4 (19.0)
Not preceded by at least 30 days of clinical stability, n (%)	1 (10.0)	0	1 (4.8)

Note: N is the total number of On-trial Relapses as determined by the Treating Physician during the study period.
aA patient may have more than 1 relapse and a relapse may have had more than 1 reason for negative adjudication.
Abbreviations: NMOSD = neuromyelitis optica spectrum disorder

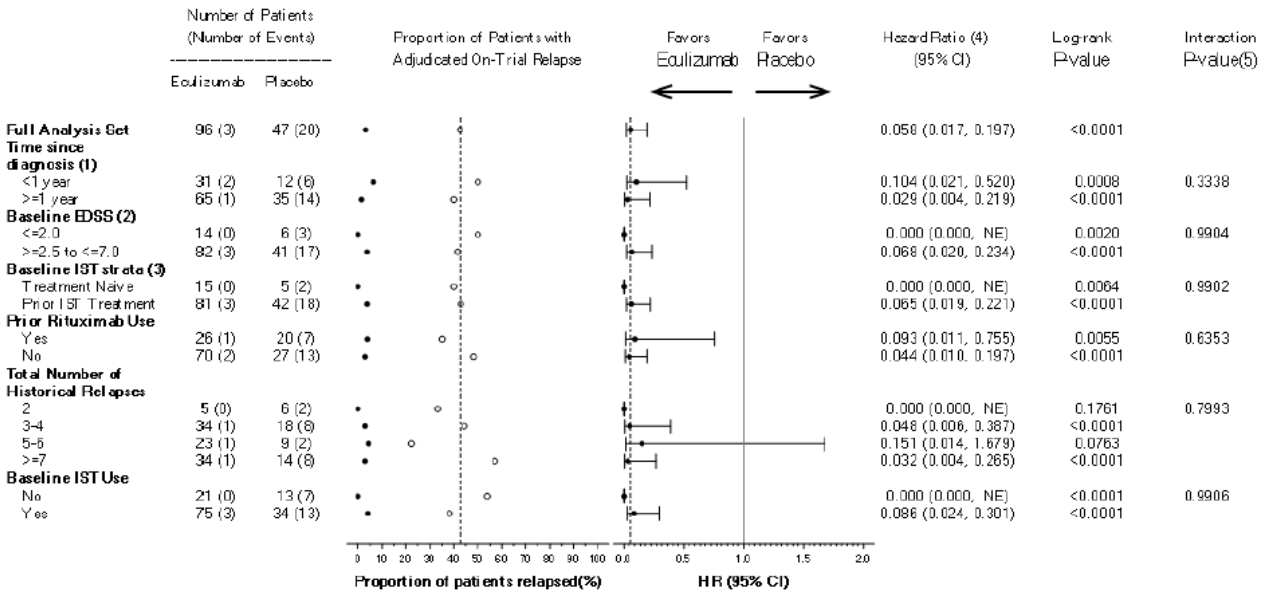
The over-reporting of relapses by the treating physician was acknowledged considering the severity of the condition and the negative consequences of leaving a relapse untreated. Also, a lower rate of relapses (whether on-trial or adjudicated relapses) in eculizumab treated patients was expected. However, there was unbalanced rate of positive adjudications between placebo treated patients (21/31; 67.7%) and eculizumab treated patients (3/14; 21.4%). Whether it was the result of the small numbers or the modification of the course of the condition or the relapses; or whether it could be a question of bias was not totally clarified.

Subgroup analyses

- A treatment effect of eculizumab was observed in patients across all randomization strata, age group, sex, and race subgroups on the time to first adjudicated On-trial Relapse and time to first On-trial Relapse as determined by the Treating Physician.
- A treatment effect of eculizumab was observed in patients across all regions on the time to first adjudicated On-trial Relapse.
- A treatment effect of eculizumab was observed in patients across all IST subgroups (baseline corticosteroids alone, baseline azathioprine, baseline mycophenolate mofetil, no IST use, and prior rituximab) including the subgroup with no ISTs at Baseline ($p<0.0001$), on the time to first adjudicated On-trial Relapse.

During the first request for supplementary information, the MAH submitted further subgroup analyses in order to document the efficacy of eculizumab in some subpopulations less represented such as patients with early diagnosis, low inflammatory activity and baseline disability status as well as different levels of immunosuppression use (Figure 19). Overall, the efficacy is comparable between groups (eculizumab vs placebo) regardless the selected criteria (time since diagnosis, disability burden, relapse history, prior IST use, concomitant IST use). However, these analyses included a limited number of patients in some subgroups and some of them were no pre-specified in the statistical plan analysis.

Figure 19 Subgroup analyses based on time since diagnosis, baseline EDSS, total number of historical relapses, baseline IST strata/use and rituximab use in FAS.



Notes: dotted vertical lines show the overall placebo proportion with a relapse and the overall hazard ratio for the Full Analysis Set; open circles = placebo, closed circles = eculizumab. Primary results for the Full Analysis Set are from a stratified analysis; subgroup analyses are from an unstratified analysis.
(1) Time since diagnosis to first dose of study drug.
(2) Observed baseline EDSS.
(3) Observed baseline IST stratification (treatment naïve: patients with no prior or current ISTs, except corticosteroids alone).
(4) Based on a Cox proportional hazards model with treatment covariate.
(5) Based on a Cox proportional hazards model with interaction term.
Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; IST= immunosuppressive therapy; NE = not estimable.

Secondary Efficacy Endpoints

Annualized Relapse Rate

The total number of adjudicated On-trial Relapses in the eculizumab group and placebo group was 3 and 21, respectively, and the adjusted adjudicated On-trial ARR (95% CI) in the eculizumab group and placebo group was 0.016 (0.005, 0.050) and 0.350 (0.199, 0.616), respectively. The adjudicated On-trial ARR ratio (95% CI) for eculizumab compared to placebo patients was 0.045 (0.013, 0.151; p<0.0001), representing a 95.5% reduction in adjudicated On-trial ARR for patients treated with eculizumab compared with placebo (Table 26).

Table 26 Adjudicated On-trial Annualized Relapse Rate – Full Analysis Set

Variable	Statistic	Placebo (N = 47)	Eculizumab (N = 96)
Number of patients with a total relapse count of			
0	n (%)	27 (57.4)	93 (96.9)
1	n (%)	19 (40.4)	3 (3.1)
2	n (%)	1 (2.1)	0
Patient relapse rate[a]	N	47	96
	Mean (SD)	1.14 (1.770)	0.09 (0.610)
	Median	0	0
	25th, 75th percentile	0, 1.71	0, 0.00
	Min, max	0, 6.52	0, 5.37
Total number of relapses	Sum	21	3
Total number of PY in study period	Sum	52.41	171.32
Adjusted adjudicated ARR[b]	Rate	0.350	0.016
	95% CI	0.199, 0.616	0.005, 0.050
Treatment effect[b]	Rate ratio (eculizumab/placebo)	...	0.045
	95% CI	...	0.013, 0.151
	p-value	...	<0.0001

a The number of relapses for each patient divided by the number of years in the study for that patient; summary statistics across all patients are presented.
b Based on a Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to Screening.
Abbreviations: ARR = annualized relapse rate; CI = confidence interval; max = maximum; min = minimum; PY = patient years.

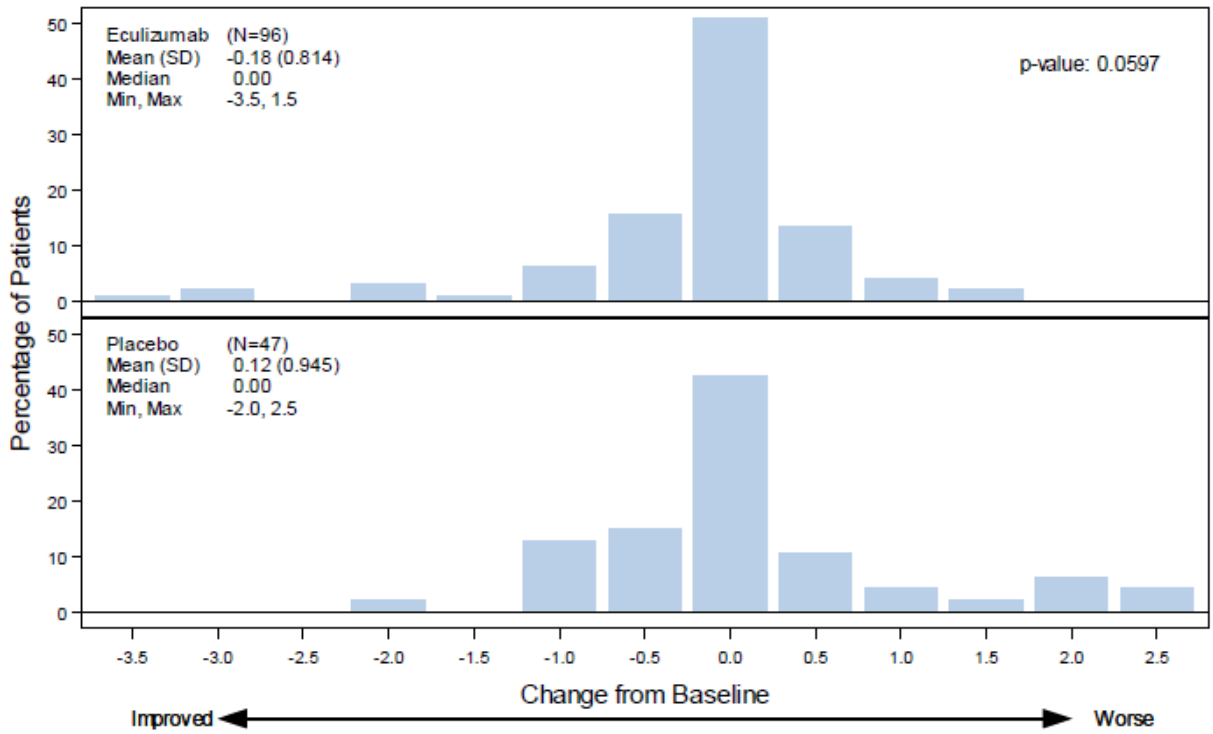
The total number of On-trial Relapses in the eculizumab group and placebo group was 14 and 31, respectively, and the adjusted On-trial ARR (95% CI) in the eculizumab group and placebo group was 0.066 (0.036, 0.120) and 0.446 (0.272, 0.732), respectively. The On-trial ARR ratio (95% CI) for eculizumab compared to placebo patients was 0.147 (0.078, 0.278; p<0.0001), representing an 85.3% reduction in On-trial ARR for patients treated with eculizumab compared with placebo.

Change from Baseline in Kurtzke Expanded Disability Status Scale Score at End of Study

Patients reported at entry a baseline mean EDSS score of 4.18 (4.26 in placebo group and 4.15 in eculizumab group). At the end of the study, patients on eculizumab reported a mean improvement in the mean EDSS score of -0.18 and patients on placebo reported a mean deterioration in the mean EDSS score of 0.12. It is difficult to give value to these figures, when they are mainly driven by the number of relapses and the lack of progression out of relapses.

The median (min, max) change from Baseline in EDSS score at End of Study was 0.00 (-3.5, 1.5) in the Eculizumab group and 0.00 (-2.0, 2.5) in the placebo group (p=0.0597), with a decrease in score representing improvement. A histogram of the overall distribution showing the change from Baseline in EDSS score to End of Study is provided by treatment group in (Figure 19). The distribution for the change from Baseline to End of Study in EDSS score showed 51.0% of the eculizumab-treated patients and 42.6% of the placebo-treated patients had no change, 29.2% of the eculizumab-treated patients and 29.8% of the placebo-treated patients had a ≥ 0.5-point improvement in EDSS score, while 19.8% of the eculizumab-treated patients and 27.7% of the placebo-treated patients had a ≥ 0.5-point worsening in EDSS score.

Figure 20 Change from Baseline to End of Study in EDSS Score by Treatment Group – Full Analysis Set



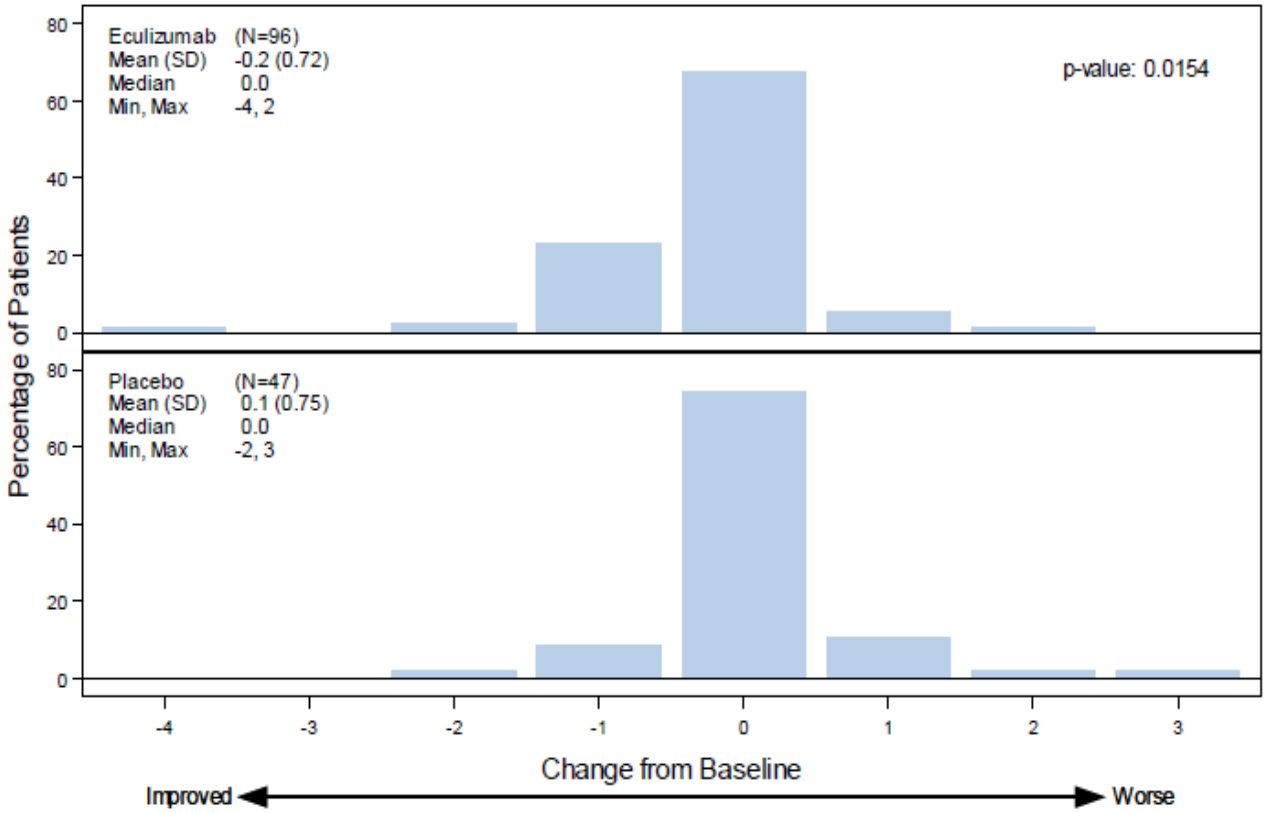
Notes: p-value from randomization-based nonparametric ANCOVA adjusted for baseline score and stratified by randomized IST strata:
(1) Treatment naïve at randomization.
(2) Continuing on the same IST(s) since last relapse at randomization.
(3) Changes in IST(s) since last relapse at randomization.
Abbreviations: ANCOVA = analysis of covariance; EDSS = Expanded Disability Status Scale; IST(s) = immunosuppressive therapies, max = maximum, min = minimum.

Change From Baseline in Modified Rankin Scale Score at End of Study

The median (min, max) change from Baseline in mRS at End of Study was 0.00 (-4, 2) in the eculizumab group and 0.00 (-2, 3) in the placebo group (nominal p=0.0154), with a decrease in score representing improvement. A histogram of the change from Baseline in mRS to End of Study is provided by treatment group in Figure 21 The distribution for the change from Baseline to End of Study in mRS score showed

67.7% of the eculizumab-treated patients and 74.5% of the placebo-treated patients had no change, 26.0% of the eculizumab-treated patients and 10.6% of the placebo-treated patients had a ≥ 1-point improvement in mRS score, while 6.3% of the eculizumab-treated patients and 14.9% of the placebo-treated patients had a ≥ 1-point worsening in mRS score.

Figure 21 Change from Baseline to End of Study in mRS Score by Treatment Group - Full Analysis Set

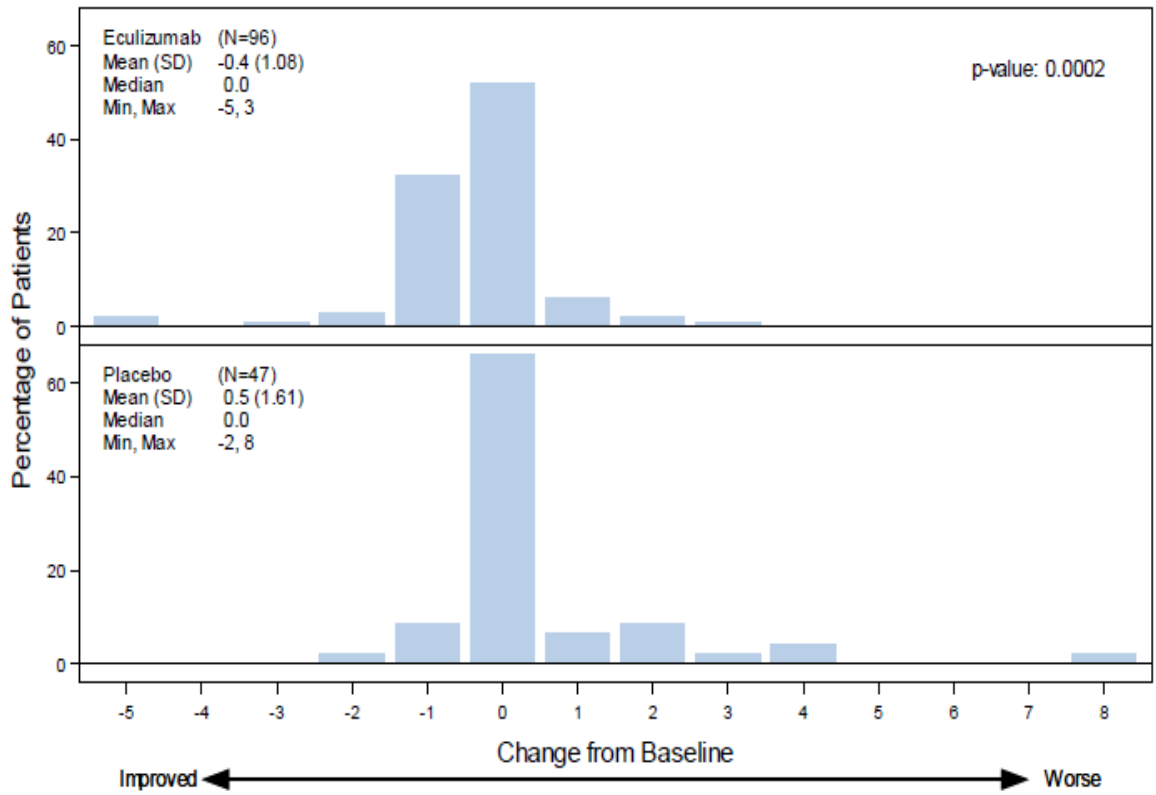


Notes: p-value from randomization-based nonparametric ANCOVA adjusted for baseline score and stratified by 4 randomization strata:
(1) Low EDSS at randomization (≤ 2.0).
(2) High EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomization.
(3) High EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization.
(4) High EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.
Abbreviations: ANCOVA = analysis of covariance; EDSS = Expanded Disability Status Scale; IST(s) = immunosuppressive therapies; max = maximum; min = minimum; mRS = Modified Rankin Scale.

Change From Baseline in Hauser Ambulation Index Score at End of Study

The median (min, max) change from Baseline in HAI score at End of Study was 0.0 (-5, 3) in the eculizumab group and 0.0 (-2, 8) in the placebo group (nominal p=0.0002), with a decrease in score representing improvement. A histogram of the change from Baseline in HAI score to End of Study is provided by treatment group in Figure 22. The distribution for the change from Baseline to End of Study in HAI score showed 52.1% of the eculizumab-treated patients and 66.0% of the placebo-treated patients had no change, 38.5% of the eculizumab-treated patients and 10.6% of the placebo-treated patients had a ≥ 1-point improvement in HAI score, while 9.4% of the eculizumab-treated patients and 23.4% of the placebo-treated patients had a ≥ 1-point worsening in HAI score.

Figure 22 Change From Baseline to End of Study in HAI Score by Treatment Group - Full Analysis Set

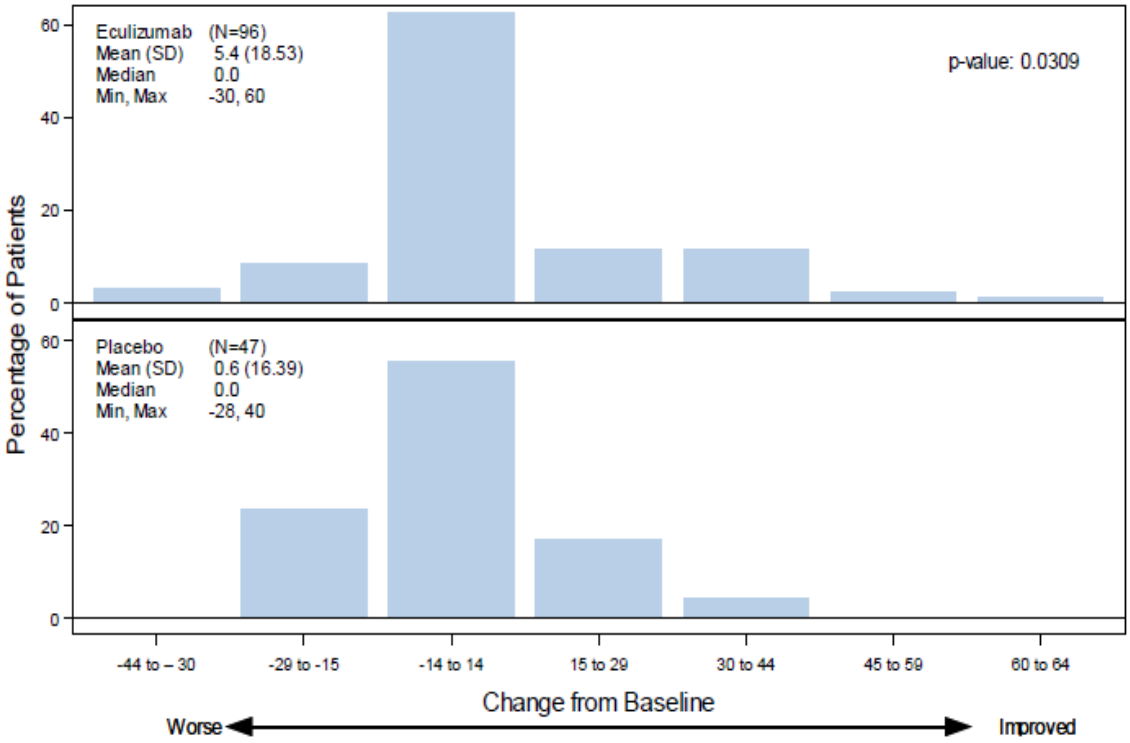


Notes: p-value from randomization-based nonparametric ANCOVA adjusted for baseline score and stratified by 4 randomization strata:
(1) Low EDSS at randomization (≤ 2.0).
(2) High EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomization.
(3) High EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization.
(4) High EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.
Abbreviations: ANCOVA = analysis of covariance; EDSS = Expanded Disability Status Scale; HAI = Hauser Ambulation Index; IST(s) = immunosuppressive therapies; max = maximum; min = minimum.

European Quality of Life Health 5-Dimension Questionnaire

The median (min, max) change from Baseline in EQ-5D VAS score at End of Study was 0.0 (-30, 60) in the eculizumab group and 0.0 (-28, 40) in the placebo group (nominal p=0.0309), with an increase in score representing improvement. A histogram of the change from Baseline in EQ-5D VAS score to End of Study is provided by treatment group in Figure 23. The distribution for the change from Baseline to End of Study in EQ-5D VAS score showed 62.5% of the eculizumab-treated patients and 55.3% of the placebo-treated patients had changes that ranged from ≥ -14 to ≤ 14, 26.0% of the eculizumab-treated patients and 21.3% of the placebo-treated patients had a > 14-point improvement in EQ-5D VAS score, while 11.5% of the eculizumab-treated patients and 23.4% of the placebo-treated patients had a > 14-point worsening in EQ-5D VAS score.

Figure 23 Change From Baseline to End of Study in EQ-5D VAS Score by Treatment Group – Full Analysis Set



Notes: p-value from randomization-based nonparametric ANCOVA adjusted for baseline score and stratified by 4 randomization strata:
(1) Low EDSS at randomization (≤ 2.0).
(2) High EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomization.
(3) High EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization.
(4) High EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.
Abbreviations: ANCOVA = analysis of covariance; EDSS = Expanded Disability Status Scale; EQ-5D VAS = European Quality of Life Health 5-dimension questionnaire visual analogue scale; IST(s) = immunosuppressive therapies; max = maximum; min = minimum.

Other Efficacy Endpoints

Relapse Severity and Type of Relapse

Most of the relapses in the placebo-group were classified as major while minor relapses were more frequent in the Eculizumab group (Table 27). A total of 6 (6.3%) patients in the eculizumab group and 15 (31.9%) patients in the placebo group experienced an On-trial Relapse as determined by the Treating Physician that required hospitalization.

Table 27 Summary of Severity of Relapse by Patient – Full Analysis Set with an On-trial Relapse

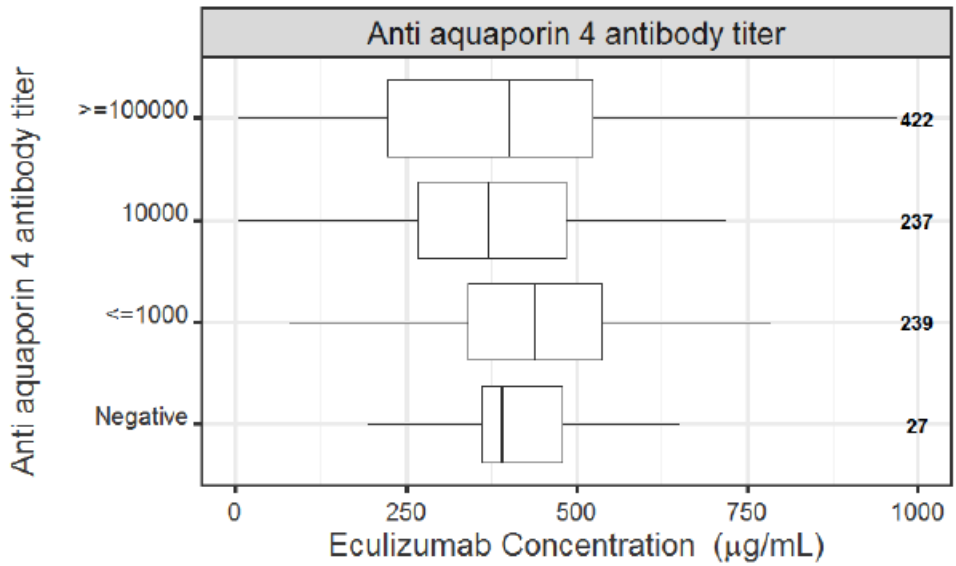
Variable	Placebo, n (%)	Eculizumab, n (%)
Patients with an adjudicated On-trial Relapse	20	3
Major	13 (65.0)	1 (33.3)
Minor	6 (30.0)	2 (66.7)
Unknown	1 (5.0)	0
Patients with an On-trial Relapse as determined by the Treating Physician	29	14
Major	16 (55.2)	3 (21.4)
Minor	12 (41.4)	10 (71.4)
Unknown	1 (3.4)	1 (7.1)

Note: If a patient had more than 1 relapse, the relapse used for time to first relapse analysis is presented in the table. If the relapse includes more than 1 type of relapse, the worst severity is presented in the table. Severity of a relapse as measured by OSIS was only classified for optic neuritis and transverse myelitis relapses; patients with other types of relapses are reported as unknown. Abbreviations: OSIS = Optic Spinal Impairment Score.

Biomarker

Figure 24 displays 925 anti-AQP4 Ab titer observations with time-matched serum eculizumab concentrations from 94 eculizumab-treated patients. Anti-AQP4 Ab titers were binned in 4 groups (negative, ≤ 1000, 10000, and ≥ 100000). For 2 eculizumab-treated patients no post-first eculizumab dose anti-AQP4 Ab titer observations were obtained. Eculizumab serum concentrations were similar across the 4 anti-AQP4 Ab titer level bins. Therefore, eculizumab exposure was not directly impacted by anti-AQP4 Ab titer.

Figure 24 Time-Matched Anti-Aquaporin-4 Antibody Titer Versus Serum Eculizumab Concentration in Study ECU-NMO-301

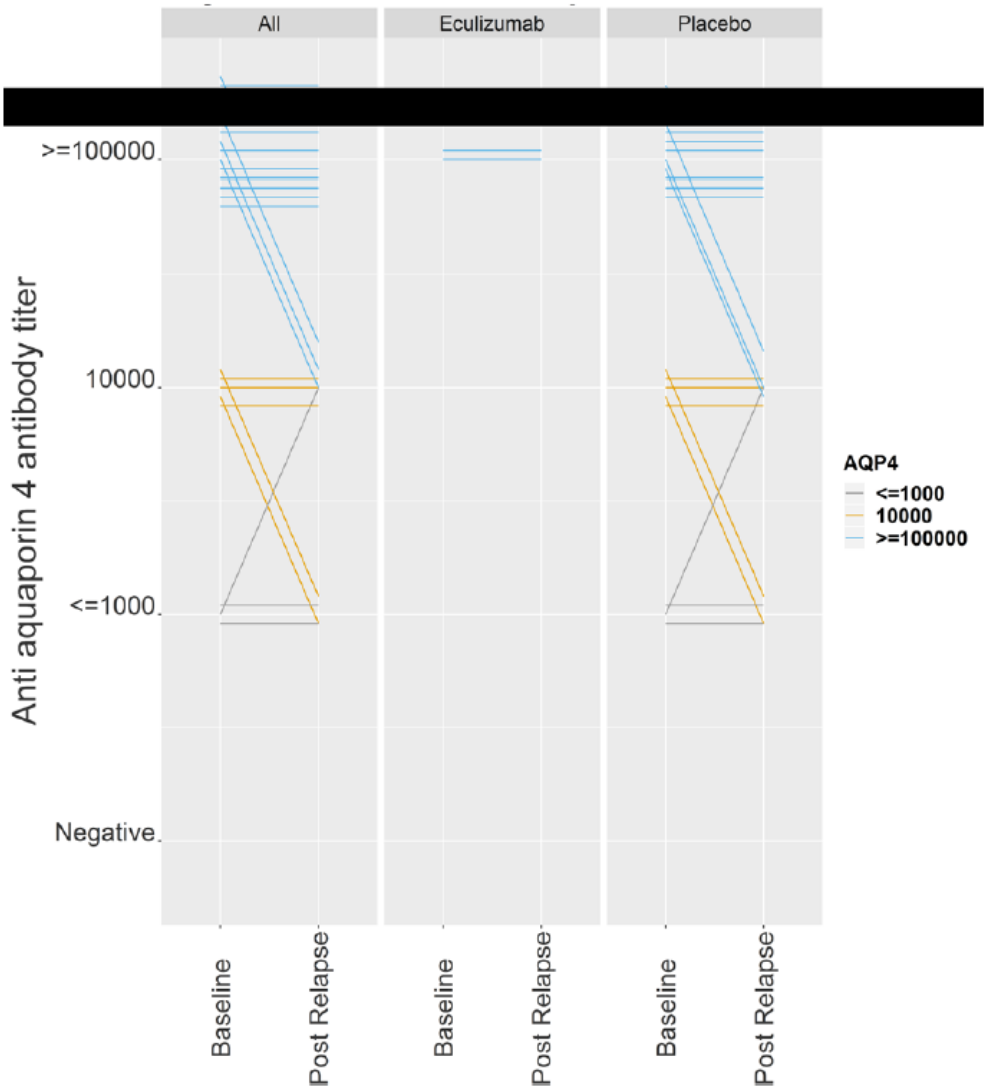


Numbers of observations are shown on the right side of plot. The lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5 × IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 × IQR of the hinge. Outlying points are not shown.
Abbreviation: IQR = interquartile range.

In Study ECU-NMO-301, 3 eculizumab-treated patients had an adjudicated On-trial Relapse and anti-AQP4 Ab titer data were not available for one patient per local protocol requirement prohibiting the collection of samples). In addition, 20 placebo-treated patients had an adjudicated On-trial Relapse (Baseline and/or post-relapse anti-AQP4 Ab titer data were not available for 3 placebo-treated patients.

Figure 25 presents the anti-AQP4 Ab titers at Baseline and post-relapse for all patients regardless of treatment group who had an adjudicated On-trial Relapse in Study ECU-NMO-301, and for whom antiAQP4 Ab titer data were available at Baseline and post relapse (eculizumab-treated patients, n=2; and placebo-treated- patients, n = 17). Anti-AQP4 Ab titers did not change from Baseline to post relapse for the 2 eculizumab-treated patients. In the placebo treatment group, 11 of the 17 patients did not have a change in anti-AQP4 Ab titer category, 5 of the patients had a decrease in category, and 1 had an increase in category. Therefore, there was no consistent trend between change in anti-AQP4 Ab titer and adjudicated On-trial Relapse.

Figure 25 Anti-Aquaporin-4 Antibody Titers at Baseline and Post Relapse for Patients with an Adjudicated On-trial Relapse in Study ECU-NMO-301



Abbreviations: Ab = antibody; Adj. = adjudicated; AQP4 = aquaporin 4

Summary of main study

Table 28 summarises efficacy results from the main study supporting the present application which should be read in conjunction with the discussion on clinical efficacy and the BR assessment (see later sections).

Table 28 Summary of the main study

Title: a randomized, double-blind, placebo-controlled, multi-center trial to evaluate the safety and efficacy of eculizumab in patients with relapsing neuromyelitis optica (NMO)				
Study identifier	ECU-NM0-301			
Design	randomized, double-blind, placebo-controlled, multicenter study			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Time to event study 1-6 weeks not applicable	
Hypothesis	Superiority			
Treatments groups	Eculizumab		Eculizumab 900 mg IV once a week for 4 weeks followed by 1200 mg every 2 weeks. N = 96 patients	
	Placebo		Matching treatment N= 47 patients	
Endpoints and definitions	Primary endpoint	Time to first Adjudicated On-Trial relapse		
	Secondary endpoint	Adjudicated On-trial ARR		
	Secondary endpoint	Change in EDSS score at EOS	Change from Baseline in Expanded Disability Status Scale at End Of Study	
Database lock	17 Sept 2018			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group		Eculizumab	Placebo
	Number of subject		96	47
	Patients with an on trial adjudicated relapse (%)		3 (3.1%)	20 (42.6%)
	Follow-up time (weeks) Median (min, max)		89.43 (2.57, 211.14)	36.00 (1.86, 208.57)
Effect estimate per comparison	Primary endpoint		Comparison groups	
			Hazard ratio	0.058
			95%CI	0.017, 0.197
			P-value	<0.0001
Analysis description	**Sensitivity analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group		Eculizumab	Placebo
	Number of subject		96	47
	Patients with an on trial adjudicated relapse (%)		14 (14.6%)	29 (61.7%)
	Follow-up time (weeks) Median (min, max)		89.43 (1.29, 211.14)	36.00 (0.57, 208.57)
Effect estimate per comparison	Primary endpoint		Comparison groups	
			Hazard ratio	0.180
			95%CI	0.095, 0.343
			P-value	<0.0001
Analysis description	**Secondary analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate	Treatment group		Eculizumab	Placebo
	Number of subject (n)		96	47

variability	Patient relapse rate (mean)	0.09	1.14
	Variability (SD)	0.610	1.770
Effect estimate per comparison	Adjusted adjudicated ARR	Eculizumab	
		Rate	0.016
		95%CI	0.055, 0.050
	Adjusted adjudicated ARR	Placebo	
		Rate	0.350
		95%CI	0.199, 0.616
	Treatment effect	Comparison groups	
		Rate ratio (Ecu/PCB)	0.045
		95%CI	0.013, 0.151
		P-value	<0.0001
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Eculizumab	Placebo
	Number of subject	96	47
	Change from Baseline in EDSS score at EOS Median	0.00	0.00
	(min, max)	(-3.5, 1.5)	(-2.0, 2.5)
Effect estimate per comparison	Treatment effect	Comparison groups	
		P-value	0.0597
Notes	Considering second-rank secondary endpoint was p>0.05, other secondary end-points were considered to be non-significant.		

2.4.2. Supportive study

2.4.2.1. Methods

Study ECU-NMO-302

Study ECU-NMO-302 is an ongoing, Phase 3, open-label, extension study of Study ECU-NMO-301 to evaluate the long-term safety and efficacy of eculizumab in the treatment of patients with NMOSD. All patients in Study ECU-NMO-302 were treated with open-label eculizumab after a 4-week blind induction Phase.

Patients who completed Study ECU-NMO-301 were to have their first Study ECU-NMO-302 visit no later than 2 weeks (14 ± 2 days) after the last dose of study drug in Study ECU-NMO-301. Patients who prematurely discontinued or whose treatment assignment was unblinded in Study ECU-NMO-301 were not eligible to enrol in Study ECU-NMO-302.

In the Day 90, only data for patients who completed Study ECU-NMO-301 due to an On-trial Relapse were included in the analyses (cut-off date 31 May 2018). At the day 120, the MAH provided updated results (cut-off date 31 October 2018).

The SAP for Study ECU-NMO-302 was originally finalized in Dec 2015. The SAP was amended on 01 Jun 2018 for this interim analysis, prior to locking and unblinding of the Study ECU-NMO-301 clinical database. As a consequence of this amendment, 2 separate SAP documents were created: 1 for this interim analysis of Study ECU-NMO-302, and 1 for the Combined Safety Set for presentation of safety from Studies ECU-NMO-301 and ECU-NMO-302.

Efficacy endpoint analyses were performed on the Extension FAS, which consists of all patients who received at least 1 dose of eculizumab in Study ECU-NMO-302.

The primary efficacy endpoint is the ARR based on all On-trial Relapses as determined by the Treating Physician. The primary analysis is the analysis of the change from historical patient-level ARR (which is comprised of the 24 months prior to Study ECU-NMO-301) to Study ECU-NMO-302 patient-level On-trial ARR for all patients in Study ECU-NMO-302; the change in ARR was evaluated using the Wilcoxon signed-rank test. A sensitivity analysis of the change in ARR from historical patient-level ARR to adjudicated On-trial ARR was also presented.

The secondary efficacy endpoints were the change from Baseline in EDSS score, mRS score, EQ-5D VAS and Index scores, and HAI score and Visual KFS score in patients with abnormal Study ECU-NMO-301 baseline ambulatory or visual function. Note: updated (31 October 2019) results from second interim analyses are included for the primary endpoints. No updated (19 May 2019) results were provided for secondary endpoints).

2.4.2.2. Results

Baseline data

By 31 October 2018, a total of 119 patients had enrolled and were treated in Study ECU-NMO-302 (41 patients in the placebo/eculizumab group who received placebo in Study ECU-NMO-301 and 78 patients in the eculizumab/eculizumab group who received eculizumab in Study ECU-NMO-301).

Demographic characteristics of participants were similar to the ones reported for Study ECU-NMO-301. Patients enrolled in Study ECU-NMO-302 experienced a median of 1.92 relapses per year in the 2 years prior to the start of Study ECU-NMO-301. Almost 80% of patients were receiving ISTs or immunomodulators at the time of the historical relapses. Approximately half (47.9%) of patients had received PE during the 2 years prior to entering the Study ECU-NMO-301. Almost all (111 [93.3%]) patients were reported to have received supportive ISTs prior to treatment in Study ECU-NMO-301, with the most frequently reported IST being corticosteroids (85 [71.4%] patients). The median (min, max) Expanded Disability Status Scale (EDSS) score at ECU-NMO-302 Baseline was 4.00 (0.0, 7.5).

A total of 87 (73.1%) patients used supportive IST treatment during Study ECU-NMO-302. The most frequently used ISTs were corticosteroids (63 [52.9%] patients), azathioprine (34 [28.6%] patients), and mycophenolate mofetil (24 [20.2%] patients). Thirty-four (28.6%) patients had changes in concomitant supportive IST use during the study. The most frequent change was a decrease in IST dose or stopping an IST, which occurred in 30 (25.2%) patients overall.

A total of 9 (7.6%) patients discontinued from the study (7 [17.1%] patients in the placebo/eculizumab group and 2 [2.6%] patients in the eculizumab/eculizumab group). Four patients withdrew consent, 2 patients discontinued due to physician decision, and 2 patients discontinued due to “other.” One patient discontinued the study due to treatment-emergent adverse events

Patients had been on treatment during Study ECU-NMO-302 for a median (min, max) of 20.00 (0.1, 198.4) weeks.

Outcomes and estimation

Primary Efficacy Endpoint

Primary Efficacy Endpoint: On-trial Annualized Relapse Rate (as Determined by the Treating Physician)

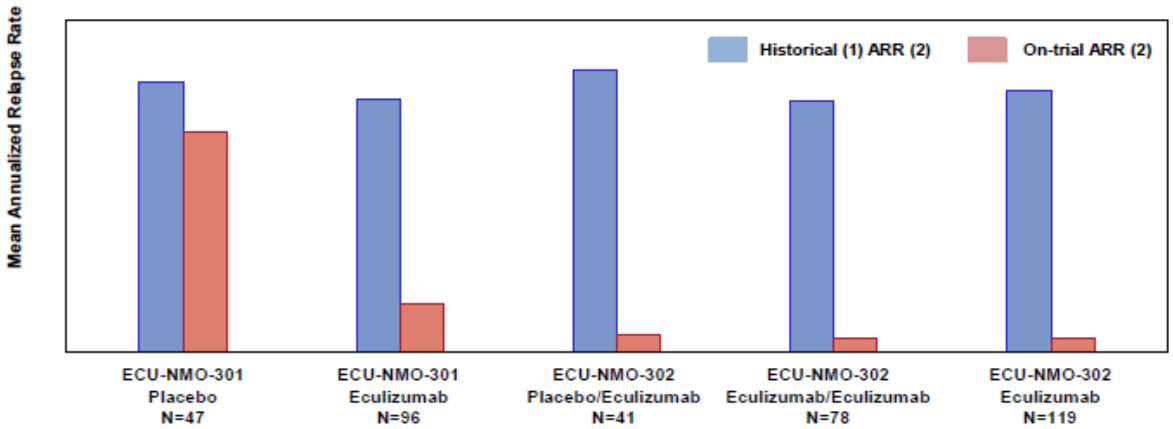
The median (min, max) reduction in the On-trial ARR as determined by the Treating Physician in Study ECU-NMO-302 (-1.829 [-6.38, 1.63]) represents a significant treatment effect of eculizumab compared with the historical ARR (p<0.0001) (Table 29 and Figure 26).

Table 29: Change from Historical Annualized Relapse Rate to On-trial Annualized Relapse Rate (as Determined by the Treating Physician) in Study ECU-NMO-302 – Extension Full Analysis Set

Variable	Statistic	Placebo/Eculizumab (N = 41)	Eculizumab/Eculizumab (N = 78)	Total (N = 119)
Historical[a] patient ARR[b]	Mean (SD)	2.164 (1.0642)	1.934 (0.9513)	2.013 (0.9932)
	Median	1.923	1.442	1.923
	25th, 75th percentile	1.442, 2.404	1.442, 2.404	1.442, 2.404
	Min, max	0.96, 6.38	0.96, 5.71	0.96, 6.38
Patient On-trial ARR[b] in ECU-NMO-302	Mean (SD)	0.134 (0.4674)	0.101 (0.4490)	0.112 (0.4537)
	Median	0.000	0.000	0.000
	25th, 75th percentile	0.000, 0.000	0.000, 0.000	0.000, 0.000
	Min, max	0.00, 2.46	0.00, 2.61	0.00, 2.61
Change in ARR between historical ARR and ECU-NMO-302 On-trial ARR	Mean (SD)	-2.030 (1.2028)	-1.833 (1.0217)	-1.901 (1.0865)
	Median	-1.923	-1.442	-1.829
	25th, 75th percentile	-2.404, -1.442	-2.256, -1.442	-2.404, -1.442
	Min, max	-6.38, 1.02	-5.71, 1.63	-6.38, 1.63
	95% CI for mean	(-2.410, -1.651)	(-2.063, -1.602)	(-2.098, -1.703)
	p-value[c]	<0.0001	<0.0001	<0.0001

a Based on the 24 months prior to screening in Study ECU-NMO-301.
b The number of relapses for each patient divided by the number of years in the Study Period for that patient; summary statistics across all patients are presented.
c From Wilcoxon signed-rank test.
Abbreviations: ARR = annualized relapse rate; CI = confidence interval; max = maximum; min = minimum.

Figure 26 Mean On-Trial Annualized Relapse Rates as Determined by the Treating Physician - Full Analysis Set (Cut-off Date of 31 Oct 2018)



(1) Based on 24 months prior to screening in Study ECU-NMO-301
(2) The number of relapses for each patient divided by the number of years in the study period for that patient; the mean across all patients is presented. Abbreviations: ARR = annualized relapse rate.

Among the 119 patients reported in this interim analysis, only 3 patients have experienced a worsening of On-trial ARR from their historical ARR. One patient in the placebo/eculizumab group had experienced a worsening of ARR from 1.44 historically to 2.46, and 2 patients in the eculizumab/eculizumab group experienced a worsening of ARR from 0.96 to 2.59 and from 2.40 to 2.61, respectively, as of the clinical database cut-off date for the interim analysis.

The majority of patients (109 [91.6%]) in the Extension FAS did not experience an On-trial Relapse during the study. Of the 10 patients who experienced an On-trial Relapse as determined by the Treating

Physician, 7 patients had 1 relapse, 1 patient had 2 relapses, and 2 patients had 3 relapses (Table 30). The total number of PY in the Study Period was 105.76, for a study-level On-trial ARR of 0.142 (95% CI: 0.086, 0.235).

Table 30 Summary of On-trial Annualized Relapse Rate (as Determined by the Treating Physician) in Study ECU-NMO-302 – Extension Full Analysis Set

Variable Category	Statistic	Placebo/Eculizumab (N = 41)	Eculizumab/Eculizumab (N = 78)	Total (N = 119)
Number of patients with a total On-trial Relapse count during Study ECU-NMO-302 of the following:				
0	n (%)	37 (90.2)	72 (92.3)	109 (91.6)
1	n (%)	1 (2.4)	6 (7.7)	7 (5.9)
2	n (%)	1 (2.4)	0	1 (0.8)
3	n (%)	2 (4.9)	0	2 (1.7)
Total number of On-trial Relapses	Sum	9	6	15
Total number of PY in the Study Period	Sum	51.64	54.12	105.76
Study level On-trial ARR	Rate[a]	0.174	0.111	0.142
	95% CI[b]	(0.091, 0.335)	(0.050, 0.247)	(0.086, 0.235)

a Calculated as the total number of On-trial Relapses during the Study Period for all patients, divided by the total number of PY in the Study Period.
b Wald confidence interval from Poisson regression.
Abbreviations: ARR = annualized relapse rate; CI = confidence interval; PY = patient-years.

Adjudicated On-trial Annualized Relapse Rate (Sensitivity Analysis)

An adjudicated On-trial ARR was computed for a sensitivity analysis based on all adjudicated On-trial Relapses for each patient in the Extension FAS. The median (min, max) reduction in the adjudicated ARR (-1.829 [-6.38, 1.63]) in Study ECU-NMO-302 represents a significant treatment effect of eculizumab compared with the historical ARR ($p<0.0001$) (Table 31). When patients who received placebo in the Study ECU-NMO-301 were treated with eculizumab in Study ECU-MG-302 a median reduction (improvement) of -1.923 was reported. In patients previously treated with eculizumab the response was consistently maintained through Study ECU-NMO-302 with a median reduction -1.442.

Table 31 Change from Historical Annualized Relapse Rate to Adjudicated On-trial Annualized Relapse Rate in Study ECU-NMO-302 – Extension Full Analysis Set

Variable	Statistic	Placebo/Eculizumab (N = 41)	Eculizumab/Eculizumab (N = 78)	Total (N = 119)
Historical[a] patient ARR[b]	Mean (SD)	2.164 (1.0642)	1.934 (0.9513)	2.013 (0.9932)
	Median	1.923	1.442	1.923
	25th, 75th percentile	1.442, 2.404	1.442, 2.404	1.442, 2.404
	Min, max	0.96, 6.38	0.96, 5.71	0.96, 6.38
Patient adjudicated ARR[b] in ECU-NMO-302	Mean (SD)	0.044 (0.1995)	0.075 (0.4184)	0.064 (0.3577)
	Median	0.000	0.000	0.000
	25th, 75th percentile	0.000, 0.000	0.000, 0.000	0.000, 0.000
	Min, max	0.00, 1.00	0.00, 2.61	0.00, 2.61
Change in ARR between historical ARR and ECU-NMO-302 adjudicated ARR	Mean (SD)	-2.120 (1.1018)	-1.859 (1.0449)	-1.949 (1.0674)
	Median	-1.923	-1.442	-1.829
	25th, 75th percentile	-2.404, -1.442	-2.404, -1.442	-2.404, -1.442
	Min, max	-6.38, -0.62	-5.71, 1.63	-6.38, 1.63
	95% CI for mean	(-2.467, -1.772)	(-2.095, -1.623)	(-2.143, -1.755)
	p-value[c]	<0.0001	<0.0001	<0.0001

a Based on the 24 months prior to screening in Study ECU-NMO-301.
b The number of relapses for each patient divided by the number of years in the Study Period for that patient; summary statistics across all patients are presented.
c From Wilcoxon signed-rank test.
Abbreviations: ARR = annualized relapse rate; CI = confidence interval; max = maximum; min = minimum.

There were a total of 6 adjudicated On-trial Relapses in 5 patients (2 patients in the placebo/ eculizumab group, 1 of whom experienced 2 adjudicated On-trial Relapses, and 3 patients in the eculizumab/eculizumab group who each experienced 1 adjudicated On-trial Relapse), with a study-level adjudicated On-trial ARR of 0.057 (95% confidence interval [CI]: 0.025, 0.126) (Table 32).

Table 32 Summary of Adjudicated On-trial Annualized Relapse Rate in Study ECU-NMO-302 – Extension Full Analysis Set

Variable Category	Statistic	Placebo/Eculizumab (N = 41)	Eculizumab/Eculizumab (N = 78)	Total (N = 119)
Number of patients with a total adjudicated On-trial Relapse count during Study ECU-NMO-302 of the following:				
0	n (%)	39 (95.1)	75 (96.2)	114 (95.8)
1	n (%)	1 (2.4)	3 (3.8)	4 (3.4)
2	n (%)	1 (2.4)	0	1 (0.8)
3	n (%)	0	0	0
Total number of adjudicated On-trial Relapses	Sum	3	3	6
Total number of PY in the Study Period	Sum	51.64	54.12	105.76
Adjudicated On-trial ARR	Rate[a]	0.058	0.055	0.057
	95% CI[b]	(0.019, 0.180)	(0.018, 0.172)	(0.025, 0.126)

a Calculated as the total number of relapses during the Study Period for all patients, divided by the total number of PY in the Study Period.
b Wald confidence interval from Poisson regression.
Abbreviations: ARR = annualized relapse rate; CI = confidence interval; PY = patient-years.

Time to First On-trial Relapse in Study ECU-NMO-302 (as Determined by the Treating Physician)

The estimated proportion (95% CI) of patients who were relapse-free in Study ECU-NMO-302 as determined by the Treating Physician was 0.918 (0.812, 0.965) at Week 48, with similar results observed in each treatment group (Table 33).

Table 33 Time to First On-trial Relapse (as Determined by the Treating Physician) in Study ECU-NMO-302 – Extension Full Analysis Set

Variable	Statistic	Placebo/Eculizumab (N = 41)	Eculizumab/Eculizumab (N = 78)	Total (N = 119)
Patients with a relapse	n (%)	4 (9.8)	6 (7.7)	10 (8.4)
Follow-up time (weeks)	Median (Min, max)	21.860 (1.43, 179.29)	20.140 (13.43, 164.29)	20.290 (1.43, 179.29)
Estimated proportion of patients relapse-free at the following:				
48 weeks	Cumulative probability[a] (95% CI[b])	0.924 (0.782, 0.975)	0.886 (0.626, 0.969)	0.918 (0.812, 0.965)
96 weeks		0.866 (0.655, 0.952)	0.787 (0.458, 0.929)	0.846 (0.685, 0.928)
144 weeks		0.866 (0.655, 0.952)	0.787 (0.458, 0.929)	0.846 (0.685, 0.928)
Relapse-free time (weeks)	Percentile[a]			
	10th	53.00	26.71	53.00
	25th	NA	162.14	162.14
	50th	NA	162.14	NA

Note: Patients who did not experience an On-trial Relapse were censored at the last visit prior to the date of database cut-off, or at their end of the Study Period.
a Based on the Kaplan-Meier product limit method.
b Based on the complementary log-log transformation.
Abbreviations: CI = confidence interval; max = maximum; min = minimum; NA = not applicable.

Time to First Adjudicated On-trial Relapse in Study ECU-NMO-302

The estimated proportion (95% CI) of patients with no adjudicated On-trial Relapse in Study ECU-NMO-302 was 0.946 (0.838, 0.983) at Week 48, with similar results observed in each treatment group (Table 34).

Table 34 Time to First Adjudicated On-trial Relapse in Study ECU-NMO-302 –Extension Full Analysis Set

Variable	Statistic	Placebo/Eculizumab (N = 41)	Eculizumab/Eculizumab (N = 78)	Total (N = 119)
Patients with a relapse	n (%)	2 (4.9)	3 (3.8)	5 (4.2)
Follow-up time (weeks)	Median (Min, max)	28.290 (1.43, 179.29)	20.140 (13.43, 198.43)	20.290 (1.43, 198.43)
Estimated proportion of patients relapse-free at the following:				
48 weeks	Cumulative probability[a] (95% CI[b])	0.975 (0.835, 0.996)	0.904 (0.640, 0.977)	0.946 (0.838, 0.983)
96 weeks		0.921 (0.695, 0.982)	0.904 (0.640, 0.977)	0.911 (0.766, 0.968)
144 weeks		0.921 (0.695, 0.982)	0.904 (0.640, 0.977)	0.911 (0.766, 0.968)
Relapse-free time (weeks)	Percentile[a]			
	10th	NA	NA	NA
	25th	NA	NA	NA
	50th	NA	NA	NA

Note: Patients who did not experience an adjudicated On-trial Relapse were censored at the last visit prior to the date of database cut-off, or at their end of the Study Period.
a Based on the Kaplan-Meier product limit method.
b Based on the complementary log-log transformation.
Abbreviations: CI = confidence interval; max = maximum; min = minimum; NA = not applicable.

Relapse Concordance and Treatment

Of the 15 total On-trial Relapses as determined by the Treating Physician, the majority (9 [60.0%]) were adjudicated negatively. A total of 8 cases of interest (a potential relapse event that was not determined to be an on-trial relapse by the treating physician) were identified, all of which were negatively adjudicated.

Secondary endpoints (as of 31 May 2018)

Overall, results for secondary endpoints (change from both the Baseline of Study ECU-NMO-301 and Baseline of Study ECU-NMO-302 in EDSS, mRS, HAI, EQ-5D Visual Analogue Scale, EQ-5D Index, and visual KFS) showed no apparent changes in disability and QoL.

2.4.3. Discussion on clinical efficacy

The evidence of the efficacy of Soliris (eculizumab) in the treatment of neuromyelitis optica spectrum disorder (NMOSD) patients with anti-aquaporin-4 (AQP4) antibody-positive consisted of one Phase III clinical trial, i.e. Study ECU-NMO-301 and one open-label extension study currently ongoing, i.e. Study ECU-NMO-302.

In general one pivotal study could be acceptable for the target population and pursued indication if its results are compelling. This approach as well the clinical design, selected endpoints and population were discussed in both the Scientific Advice given in 2013 (EMA/CHMP/SAWP/3657/2013) and in the EMA Workshop on NMO held in 2014 (EMA/CHMP/SAWP/712652/2014).

Design and conduct of clinical studies

Patient population

Adult patients diagnosed as having NMO (based on the 2006 NMO criteria) or NMOSD (based on the 2007 diagnostic criteria) and were positive for AQP4-Abs were eligible for the study.

The NMOSD diagnostic criteria were updated in 2015, including the serum AQP4-IgG as one of the requisites. It could be that differences in diagnostic criteria may result in dissimilar selected populations, and could limit the assumption of the results. In this case, given that Study 301 included only AQP4-IgG seropositive patients no differences were expected, as also suggested by literature.

The Study ECU-NMO-301 enrolled relapsing patients with at least 2 documented relapses in the 12 months preceding randomization (or 3 in the last 24 months) so that the study could be feasible in a reasonable timeframe and patients with more “benign” forms of the condition were excluded. Qualification of previous relapses was based on clinical (and MRI, if appropriate) criteria were judged by the Treating Physician.

A total of 213 patients were screened for this study, of which 143 patients were randomized (96 patients randomized to the eculizumab group, and 47 patients randomized to the placebo group). Most of them (n= 124; 86.7%) completed the study: 44 patients due to the occurrence of a relapse and 80 patients due to the end of the study. The rate of withdrawal from the study were12.5% and 2.1% for eculizumab and placebo groups, respectively.

Most of baseline demographics and disease characteristics were well balanced over treatment arms. Females represented 91% of the population. Relapsing NMO is reported to be more prevalent in females whereas a more equal female/male distribution (48%) is reported in monophasic disease. Mean age of patients was approximately 44 years (ranging from 19 to 75 years). Only 9 patients were equal or older than 65 years of age. Half of subjects were White (49%) but African American subjects were more represented in the placebo group than in the eculizumab group (17.0% vs 9.4%). Ethnic differences have been reported in relation to age of onset (younger onset age in Asian and 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-descendent patients compared to Caucasian patients). This may impact the extrapolability of the results to European patients, who represent around one third (36%) of patients recruited even though White race is 50% of the ITT population.

Patients reported a mean of 7.6 years (from 0.4 to 44.8 years) of course of the condition. Most of the included patients presented optic neuritis (40%) and transverse myelitis (40%), with mild to moderate optic-spinal impairment (according to OSIS scale), still ambulatory but mean EDSS was 4. Patients have had a mean of 2 annual relapses (between 1 and 6.4) in the past 2 years, most of them (76.9%) while they were being treated. About 31% of patients needed to change their treatment after the last relapse. Azathioprine, mycophenolate mofetil and (or) corticosteroids were the most widely used treatments, which is in line with current recommendations. While the standard of care is the treatment of patients after the first episode in seropositive patients for prevention of further attacks, 34 subjects (23.8% of recruited patients) were not being treated with any supportive IST at baseline note, and 10 patients had not received any prior supportive IST for NMOSD. At request, the MAH has explained that this finding could be attributed to the lack of efficacy of previous treatments (in the group of 24 patients who had received prior IST treatment but stopped it before entering Study ECU-NMO-301), recent diagnosis of the disease or the fact that a number of them were enrolled in Russia (6 patients with no prior IST use).

The trial was planned to end for a patient when the patient experienced an on-trial relapse or when 24 adjudicated on-trial relapse events were reached in the study (whichever came first).

Treatment regimen

No specific dose-response studies have been conducted for this indication. The selected dose regimen (eculizumab 900 mg weekly for 4 weeks followed by 1200 mg for the 5th dose and then every two weeks) is the one that has been approved for the treatment of patients with aHUS and gMG. It is based on the inhibition of terminal complement activation achieved by >90% of patients.

Both naïve and previously treated patients were allowed (except for rituximab), provided that immunosuppressive agents were administered at stable doses at entry.

Endpoints

The evaluation of efficacy mainly relies on the occurrence of relapses as the main source of disability. The selected endpoints were discussed with the SAWP in the Scientific Advice procedure (EMA/CHMP/SAWP/3657/2013) and also endorsed in the EMA workshop on clinical trials design in NMOSD held on October 2014 (EMA/CHMP/SAWP/712652/2014) .

The primary efficacy endpoint was the time to first adjudicated On-trial relapse. The relapse was 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. There is no a general agreement in the definition of relapse and MRI parameters have also been considered in some operative definitions. The adjudication was made by an independent committee (Relapse Adjudication Committee) based on the relapses assessed and treated by the Investigator occurred during the treatment period.

The inclusion of external committed of adjudication of events is welcome taking into account the potential variability in diagnostic procedures and management of patients related to the number of centres included (70 centres) and the wide geographical distribution. However, this committee was implemented once the recruitment had started and only those events previously selected by investigators were submitted to the committee for revision. At request, MAH explained that all the relapses were retrospectively adjudicated by the RAC during the trial once the decision on the episode was made by the treating physician. With respect to the potential impact on the previous episodes on the adjudication of the subsequent episodes, no differences were shown in the adjudication process between the episodes identified before the implementation of the RAC and those identified after that point.

Secondary endpoints were based on the total number of relapses (ARR), clinical assessments (focusing on changes in EDSS score, Modified Rankin Scale score and Hauser Ambulatory Index) and quality of life variables (EQ-5D).

AQP4-Abs (but not MRI) were included among the measured biomarkers. In case of relapse, additional tests (MRI, CT scan, laboratory tests) could be performed at the discretion of the Investigator.

Randomization of subjects was stratified on the basis of EDSS scores and background therapy (IST). Four strata resulted from combination of two stratification factors: 1) low EDSS at randomization ($\leq$ 2.0); 2) high EDSS ($\geq$ 2.5 and $\leq$ 7.0) and treatment naïve at randomization; 3) high EDSS and continuing on the same IST(s) since last relapse at randomization; and 4) high EDSS and changes in IST(s) since last relapse at randomization.

Statistical analysis

Efficacy analyses were performed on the FAS. The total number of relapses anticipated to be observed for this study was 24 relapses (adjudicated On-trial Relapses) in 24 distinct patients. A sample size of approximately 132 patients (88 eculizumab and 44 placebo) was expected to provide 90% power to detect a treatment difference in time to first relapse.

The primary analysis was based on the time to first relapse occurred during the trial adjudicated by the RAC and among those determined by the Treating Physician using a stratified log-rank test including strata for the randomization stratification variable. Additional sensitivity analyses of the time to first adjudicated On-trial Relapse included an unstratified log-rank test and a multivariate Cox proportional hazards model.

For the relevant secondary endpoints, baseline was defined as the last available assessment prior to treatment for all patients regardless of their treatment group. Hypothesis testing comparing eculizumab treatment with placebo treatment for the secondary efficacy analyses was performed using a closed testing procedure with the following rank order: 1) Adjudicated On-trial ARR; 2) Change from Baseline in EDSS score at the EOS; 3) Change from Baseline in mRS score at the EOS; 4) Change from Baseline in ambulatory function as measured by HAI at the EOS; 5) Change from Baseline in EQ-5D at the EOS. The adjudicated on-Trial ARR and On-trial ARR as determined by treating physician used a Poisson regression analysis with treatment group, historical ARR and randomization strata as covariates. Other secondary endpoints used a randomization-based ANCOVA adjusted by baseline score and stratified by randomization strata.

Efficacy data and additional analyses

Primary endpoint

During the study relapses were assessed by the treating physician and treated, if they were confirmed based on clinical criteria. The treatment for relapse was at the discretion of the treating physician. According to the study protocol, the recommended treatment included one gram IV methylprednisolone (IVMP) administered daily for 3-5 days followed by an oral prednisone tapering. Plasma exchange was recommended in case of insufficient response to methylprednisolone. During the relapse treatment the investigational product was administered as scheduled. If plasma exchange was performed additional doses of the investigational product was provided. Once the relapse was over the patient was withdrawn from the study and included in the Study ECU-302 (open label extension).

A total of 23 relapses (20 in the placebo group [42.6%] and 3 in eculizumab group [3.1%]) were adjudicated by the RAC. The primary endpoint of the study was met. The analysis shows a significantly lower relapse rate after treatment with a hazard ratio of 0.058 95% CI (0.017- 0.197); $p < 0.0001$) for eculizumab versus placebo.

Pre-specified sensitivity analysis of the primary endpoint showed a statistically significant difference between eculizumab and placebo. A total of 14 (14.6%) patients [14 relapses] on eculizumab and 29 (61.7%) [31 relapses] on placebo had an on-trial relapse ($p < 0.0001$). In both treatment groups, there were more On-trial Relapses as determined by the Treating Physician than adjudicated On-trial Relapses. The over-reporting of relapses by the treating physician was acknowledged given the severity of the condition and the negative consequences of leaving a relapse untreated. It was also expected a lower rate of relapses (whether on-trial or adjudicated relapses) in eculizumab treated patients. The unbalanced rate of positive adjudications between placebo treated patients (21/31; 67.7%) and eculizumab treated patients (3/14; 21.4%) was not totally explained by the MAH. Whether it was the result of the small numbers or the modification of the course of the condition or the relapses; or whether it could be even a question of bias was not totally clarified. This is also relevant because the study ended for these patients and relapsing patients were not followed up in Study 301. Since the extension Study 302 was not controlled (all patients were treated with eculizumab) the effect of Eculizumab versus Placebo on time to further relapses is unknown. Finally, when the 23 relapses were achieved and the study formally ended, a total of 81 patients (66 on eculizumab, 15 on placebo) were censored without having experienced a relapse and included in Study 302.

As for the concomitant treatment, relapses occurred in 1/17 patients treated with mycophenolate mofetil and 2/37 patients on azathioprine in eculizumab group. Among patients on placebo those treated with steroids, azathioprine and mycophenolate showed a lower number of relapses compared to those with other IST or without IST. The small size of some subgroups, the low number of relapses and the lack of controlled follow-up of the patients after the first relapse prevents from reaching any solid conclusion on the benefit of one combination over the others (or even the effect of monotherapy vs combination therapy). At request, the MAH provided the results of a subgroup analysis in order to document the efficacy of eculizumab in some subpopulations less represented in the study and support a broad indication. Some of these results should be considered as exploratory because they were not pre-specified in the statistical plan and results were based on a limited number of patients. Despite of these limitations, the efficacy was comparable between groups (eculizumab vs placebo) regardless the selected criteria (time since diagnosis, disability burden, relapse history, prior IST use, concomitant IST use).

Secondary endpoints

The adjusted (adjudicated) ARR (95% CI) was 0.016 (0.005, 0.050) in the eculizumab group versus 0.350 (0.199, 0.616) in the placebo group, representing a 95% reduction over placebo ($p < 0.0001$). When using the analysis based on relapses as determined by the treating physician, the reduction over placebo in the ARR was 85.3%, for eculizumab compared to placebo ($p < 0.0001$). However, as relapsing patients finalised the study, there were differences in exposure between both arms (median treatment duration in eculizumab group 89.43 weeks vs 41.29 weeks in placebo group). In addition, most of the patients across the treatment groups experienced no relapse (eculizumab n= 93 [96.9%], placebo n=27 [57.4%]) with a relatively high number of censored patients in eculizumab group.

With respect to the level of disability patients reported at entry a baseline mean EDSS score of 4.18 (4.26 in placebo group and 4.15 in eculizumab group). At the end of the study, patients on eculizumab reported a mean improvement in the mean EDSS score of -0.18 and patients on placebo reported a mean deterioration in the mean EDSS score of 0.12 ($p=0.0597$). Considering the relatively low number of relapses and the lack of progression out of relapses, these results should be interpreted with caution.

One of the relevant prognostic factors for disability is the severity of the relapses. Some clues point out a better outcome for eculizumab: more placebo patients than patients treated with eculizumab had major relapses and need of hospitalization due to relapses. However, the disability scales measured during the acute episodes (differences between baseline relapse evaluation and 6 weeks evaluation) did not show differences between arms. Globally, there results did not allow concluding on the effect of eculizumab on the severity of the relapses.

Given the pathogenic role of AQP-4 Ab in NMOSD, examining the titers course during the study appears of interest. AQP4-ab has been identified as risk factor for attacks under therapy and it is not clear whether the antibodies by themselves are sufficient to cause pathology, or whether ongoing inflammation is required. Monitoring of Abs is not currently recommended in routine clinical practice.

No relationship could be established between AQP-4 Ab titers and eculizumab concentrations or relapses so that a specific recommendations could be given for treatment or monitoring of the response. Further graphical comparisons provided by the MAH showed no evidence of increased efficacy with increased eculizumab exposure, compatible with the use of a therapeutic dose that achieves maximal benefit.

The maintenance of the effect of eculizumab for the treatment of patients with NMOSD was assessed in the open label treatment Study ECU-NMO-302. The study is still ongoing. Results from an interim analysis from the subset of patients who relapsed in Study 301 were provided at the time of submission (cut-off date of 31 May 2018 n=39). At request, further updated with cut-off date of 31 October 2018 (n=119) was provided given the uncertainties of the sustainability of the effect in the first cut-off. A total of 119

patients were treated (41 patients in the placebo/eculizumab group and 78 patients in eculizumab/eculizumab group). Eculizumab (or placebo) was added on top of patient background therapy and no changes were allowed during the Study ECU-NMO-301. In Study ECU-NMO-302, the majority of patients were receiving concomitant treatment at entry (87 patients [73%]). During this extension study the concomitant treatment could be adapted. A total of 30 patients reduced the dose or stopped immunosuppressive medication.

In total 10 patients had experienced 15 on-trial relapses as determined by the treating physician (9 in placebo/eculizumab group and 6 in eculizumab/eculizumab group. A total of 6 of these episodes were adjudicated by the RAC in 5 patients (2 in placebo/eculizumab group and 3 in the eculizumab/eculizumab group). Results from the second interim analysis indicated a positive effect on the maintenance of the response to eculizumab. The On-trial ARR were 0.174 for the placebo/eculizumab group and 0.111 for the eculizumab/eculizumab group during study ECU-NMO-302. Both groups experienced a reduction of On-trial ARR with respect to the historical ARR (median 1.923). When patients who received placebo in the Study ECU-NMO-301 were treated with eculizumab in Study ECU-MG-302 a median reduction (improvement) of -1.923 was reported. In patients previously treated with eculizumab the response was consistently maintained through Study ECU-NMO-302 with a median reduction -1.442.

Updated results from Study 302 gave support to the eculizumab effect seen during the placebo-controlled phase. The improvement observed in the prevention of relapses was maintained during the reported period. The long-term efficacy of eculizumab in this population still limited, needs to be further documented. Therefore the results from the currently ongoing Study ECU-NMO-302 will have to be submitted.

2.4.4. Conclusions on the clinical efficacy

The efficacy of eculizumab over placebo on disease activity (time to first relapse) can be considered reasonably demonstrated, even though it seems difficult to precisely quantify the exact benefit of adding eculizumab to immunosupressors.

The heterogeneity of the patients by the condition itself, the concomitant ISTs, and the number of strata may prevent from providing any useful information when the results are analysed considering the rather limited size of the study. In any case, the labelling of the product should reflect the population included in the Study.

With respect to the main drawback of the dossier related to the low number of patients and the follow-up period which is still limited for a global picture of the maintenance of the effect the final results from the currently ongoing Study ECU-NMO-302 will have to be submitted.

The CHMP considers the following measures necessary to address issues related to efficacy:

- Final results from ongoing Study ECU-NMO-302

2.5. Clinical safety

Introduction

The safety of eculizumab (Soliris®) has been evaluated in two Phase 3 clinical studies in patients with neuromyelitis optica spectrum disorder (NMOSD).

- Phase 3 Pivotal: Study ECU-NMO-301; a randomized, double-blind, placebo-controlled, multicenter Phase 3 study in 143 patients with relapsing NMOSD. The study was completed on 17 Jul 2018.
- Phase 3 Supportive: Study ECU-NMO-302; an open-label, multicenter Phase 3 extension study of Study ECU-NMO-301 with a 4-week Blind Induction Phase followed by an Open-label Maintenance Phase (ongoing, with 119 patients continued from Study ECU-NMO-301 as of the clinical database cut-off date for this analysis of 31 October 2018).

Safety analyses were performed on the Combined Safety Set (ie, all patients who received at least 1 dose of study drug [either eculizumab or placebo] in Study ECU-NMO-301) with cut-off date of 31 October 2018 using the 4 treatment group designations described as follows:

- ECU-NMO-301 placebo (n = 47)
- ECU-NMO-301 eculizumab (n = 96)
- ECU-NMO-302 eculizumab: All patients treated with eculizumab in that study (n = 119)
- All Eculizumab: All patients ever treated with eculizumab in either Studies ECU-NMO-301 or ECU-NMO-302 based on their eculizumab exposure (n = 137)

NOTE: In the first submission, the applicant provided data for the ECU-NMO-302 eculizumab for n=39 (31 May 2018). This information was thereafter updated and estimates in this assessment report were updated accordingly to reflect this updated safety information.

Patient exposure

A total of 143 adult patients with relapsing NMOSD were randomized and treated in Study ECU-NMO-301 (96 in the eculizumab group and 47 in the placebo group). As of the clinical database cut-off date of 31 October 2018, 119 of these patients had continued into the extension study, Study ECU-NMO-302, of whom 41 were in the placebo/eculizumab group and 78 were in the eculizumab/eculizumab.

In Study ECU-NMO-301, the median (min, max) treatment duration was twice as long for the eculizumab group (89.43 weeks [3.1, 211.1 weeks]) as compared with the placebo group (41.29 weeks [6.1, 208.1 weeks]). Overall treatment exposure was 170.0 PY for eculizumab and 51.5 PY for placebo.

In Study ECU-NMO-302, as of 31 October 2018, the median (min, max) treatment duration was 20.00 weeks (0.1, 198.4 weeks). Overall eculizumab exposure was 103.8 PY.

At the time of the clinical database cut-off, the total median (min, max) treatment duration for eculizumab across Studies ECU-NMO-301 and ECU-NMO-302 combined (All Eculizumab group) was 99.00 weeks (0.1, 237.9 weeks). Overall eculizumab exposure was 276.6 PY.

The total median eculizumab treatment compliance rate in both studies was high (99.0% in the eculizumab group of Study ECU-NMO-301 and 100% in Study ECU-NMO-302).

In Study ECU-NMO-301, the demographics of patients were similar in the 2 treatment groups. The majority (130 [90.9%]) of patients overall were female, White (70 [49.0%]) or Asian (52 [36.4%]); 14 (9.8%) patients were of Japanese descent.

In Study ECU-NMO-302, the majority (110 [92.4%]) of these 119 patients were female, White (61/119 [51.3%]) or Asian (45/39 [37.8%]); 12 (10.1%) patients were of Japanese descent.

Table 35 Demographic and Baseline Characteristics in Studies ECU-NMO-301 and ECU-NMO-302

Variable	Statistic	ECU-NMO-301 Placebo (N = 47)	ECU-NMO-301 Eculizumab (N = 96)	ECU-NMO-302 Eculizumab (N = 119)	All Eculizumab (N = 137)
Age at first study drug dose (years)[a]	Mean (SD)	45.0 (13.29)	43.9 (13.32)	46.4 (13.73)	44.5 (13.45)
	Median	44.0	45.0	47.0	45.0
	Min, max	21, 75	19, 70	21, 76	19, 76
Sex					
Male	n (%)	5 (10.6)	8 (8.3)	9 (7.6)	13 (9.5)
Female	n (%)	42 (89.4)	88 (91.7)	110 (92.4)	124 (90.5)
Ethnicity					
Hispanic or Latino	n (%)	3 (6.4)	13 (13.5)	13 (10.9)	15 (10.9)
Not Hispanic or Latino	n (%)	41 (87.2)	78 (81.3)	100 (84.0)	115 (83.9)
Not reported	n (%)	1 (2.1)	4 (4.2)	5 (4.2)	5 (3.6)
Unknown	n (%)	2 (4.3)	1 (1.0)	1 (0.8)	2 (1.5)
Race					
American Indian or Alaskan Native	n (%)	0	1 (1.0)	1 (0.8)	1 (0.7)
Asian	n (%)	15 (31.9)	37 (38.5)	45 (37.8)	50 (36.5)
Black or African American	n (%)	8 (17.0)	9 (9.4)	10 (8.4)	16 (11.7)
White	n (%)	24 (51.1)	46 (47.9)	61 (51.3)	67 (48.9)
Unknown	n (%)	0	2 (2.1)	1 (0.8)	2 (1.5)
Other	n (%)	0	1 (1.0)	1 (0.8)	1 (0.7)
Japanese descent					
Yes	n (%)	5 (10.6)	9 (9.4)	12 (10.1)	13 (9.5)
No	n (%)	42 (89.4)	87 (90.6)	107 (89.9)	124 (90.5)
Region[b]					
Americas	n (%)	15 (31.9)	29 (30.2)	34 (28.6)	42 (30.7)
Europe	n (%)	19 (40.4)	32 (33.3)	44 (37.0)	49 (35.8)
Asia-Pacific	n (%)	13 (27.7)	35 (36.5)	41 (34.5)	46 (33.6)

a Age = (Date of First Study Drug Dose in that Particular Study – Date of Birth) / 365.25
b Other or Unknown also includes American Indian or Alaskan Native.
c Americas: Argentina and USA; Europe: Croatia, Czech Republic, Denmark, Germany, Great Britain, Italy, Russia, Spain, Turkey; Asia-Pacific: Australia, Hong Kong, Japan, Korea, Malaysia, Taiwan, and Thailand.
Abbreviations: max = maximum; min = minimum.

Adverse events

Of the 143 patients in the Safety Set of Study ECU-NMO-301, 133 patients (93.0%) experienced TEAEs. The incidence of TEAEs was similar between the eculizumab (91.7%) and placebo groups (95.7%); the rate of TEAEs was lower in the eculizumab group (749.3 per 100 PY) than in the placebo group (1160.9 per 100 PY). The majority of TEAEs were mild or moderate in intensity and unrelated to the study drug (as determined by the Investigator).

Of the 119 patients in the Extension Safety Set of Study ECU-NMO-302, 92 patients (77.3%) experienced TEAEs. The rate of TEAEs was 793.5 per 100 PY. The majority of TEAEs were mild or moderate in intensity and unrelated to the study drug (as determined by the Investigator).

A total 125 patients (91.2 %) in the Combined Safety Set (All Eculizumab group) experienced TEAEs at a rate of 763.1 PY. An overview of TEAEs for the Combined Safety Set is provided in Table 36.

Table 36 Overview of All Treatment-emergent Adverse Events by Treatment Group – Combined Safety Set

	ECU-NMO-301 Placebo (N = 47) PY = 53.1		ECU-NMO-301 Eculizumab (N = 96) PY = 172.8		ECU-NMO-302 Eculizumab (N = 119) PY = 107.2		All Eculizumab (N = 137) PY = 282.3	
	Events, n (Rate)	Patients, n (%)	Events, n (Rate)	Patients, n (%)	Events, n (Rate)	Patients, n (%)	Events, n (Rate)	Patients, n (%)
Events and patients with events	**618 (1162.8)**	**45 (95.7)**	**1303 (754.0)**	**88 (91.7)**	**851 (793.5)**	**92 (77.3)**	**2154 (763.1)**	**125 (91.2)**
Deaths	-	**0**	-	**1 (1.0)**	-	**0**	-	**1 (0.7)**
Adverse events	**618 (1162.8)**	**45 (95.7)**	**1303 (754.0)**	**88 (91.7)**	**851 (793.5)**	**92 (77.3)**	**2154 (763.1)**	**125 (91.2)**
Related	88 (165.6)	27 (57.4)	367 (212.4)	49 (51.0)	181 (168.8)	40 (33.6)	548 (194.1)	78 (56.9)
Not related	530 (997.2)	45 (95.7)	936 (541.6)	87 (90.6)	670 (624.7)	87 (73.1)	1606 (569.0)	122 (89.1)
Mild	443 (833.5)	41 (87.2)	1079 (624.4)	86 (89.6)	630 (587.4)	87 (73.1)	1709 (605.4)	120 (87.6)
Moderate	153 (287.9)	30 (63.8)	191 (110.5)	60 (62.5)	188 (175.3)	42 (35.3)	379 (134.3)	86 (62.8)
Severe	22 (41.4)	12 (25.5)	30 (17.4)	18 (18.8)	33 (30.8)	17 (14.3)	63 (22.3)	34 (24.8)
Unknown severity[a]	0	0	3 (1.7)	3 (3.1)	0	0	3 (1.1)	3 (2.2)
Adverse events leading to withdrawal from study drug	**3 (5.6)**	**2 (4.3)**	**0**	**0**	**4 (3.7)**	**1 (0.8)**	**4 (1.4)**	**1 (0.7)**
Serious adverse events	**47 (88.4)**	**26 (55.3)**	**53 (30.7)**	**30 (31.3)**	**53 (49.4)**	**26 (21.8)**	**106 (37.6)**	**50 (36.5)**
Related	13 (24.5)	9 (19.1)	13 (7.5)	9 (9.4)	14 (13.1)	8 (6.7)	27 (9.6)	17 (12.4)
Not related	34 (64.0)	24 (51.1)	40 (23.1)	26 (27.1)	39 (36.4)	22 (18.5)	79 (28.0)	42 (30.7)
SAEs leading to withdrawal from study drug	2 (3.8)	2 (4.3)	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)

Rates are reported as per 100 PY. The TEAEs in Study ECU-NMO-301 are AEs with a start date on or after the date of the first dose of study drug in Study ECU-NMO-301 up to the day prior to the first dose date in Study ECU-NMO-302 or for patients who withdrew, up to the day of last contact. The TEAEs in Study ECU-NMO-302 are AEs with a start date on or after the date of the first dose of study drug in Study ECU-NMO-302. The TEAEs in the All Eculizumab group are AEs with a start date on or after the date of the patient's first dose of eculizumab.
Percentages are based on the total number of patients in the Combined Safety Set in the particular treatment group.
Related AEs are defined as possibly, probably, or definitely related, and Not Related AEs are defined as unrelated or unlikely.
If a patient had multiple events for a particular relationship or severity, he/she is counted only once for that relationship or severity. a Unknown severity was queried and could not be resolved. Abbreviations: AE = adverse event; PY = patient years; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Common Adverse Events

In Study ECU-NMO-301, the rate of TEAEs was lower in the eculizumab group (754.0 events per 100 PY) than in the placebo group (1162.8 events per 100 PY), although the incidence of TEAEs was generally similar between the placebo and eculizumab groups.

- The most frequently reported TEAEs in the eculizumab group were upper respiratory tract infection (29.2% of patients with a rate of 31.2 events per 100 PY), headache (22.9% of patients with a rate of 55.0 events per 100 PY), and nasopharyngitis (20.8% of patients with a rate of 28.9 events per 100 PY).
- The most frequently reported TEAEs in the placebo group were NMOSD (34.0% of patients with a rate of 33.9 events per 100 PY), nausea (25.5% of patients with a rate of 35.7 events per 100 PY), headache (23.4% of patients with a rate of 37.6 events per 100 PY), urinary tract infection (21.3% of patients with a rate of 24.5 events per 100PY and pain in extremity (21.3% of patients with a rate of 20.7 events per 100 PY).

In Study ECU-NMO-302, the most frequently reported TEAEs were headache (16.0% of patients with a rate of 55.0 events per 100 PY), nasopharyngitis (12.6% of patients with a rate of 28.0 events per 100 PY), urinary tract infection (8.4% of patients with a rate of 29.8 events per 100 PY) and upper respiratory tract infection (8.4% of patients with a rate of 17.7 events per 100 PY).

In the All Eculizumab group, the most frequently reported TEAEs were headache (27.0% of patients with a rate of 54.9 events per 100 PY), upper respiratory tract infection (25.5% of patients, with a rate of 25.9 events per 100 PY), and nasopharyngitis (22.6% of patients with a rate of 28.3 events per 100 PY).

AE that occurred in ≥ 5% of patients are shown for the Combined Safety Set in Table 37. The most frequently experienced TEAEs (≥ 20% of patients) in the All Eculizumab group by PT were headache (37 [27.0%], upper respiratory tract infection (35 [25.5%] patients), and nasopharyngitis (31 [22.2%] patients. These TEAEs are consistent with those of existing eculizumab indications.

Table 37 Treatment-emergent Adverse Events That Occurred in at Least 5% of Patients in Any Group by Preferred Term and Treatment Group – Combined Safety Set

Preferred Term	ECU-NMO-301 Placebo (N = 47) PY = 53.1		ECU-NMO-301 Eculizumab (N = 96) PY = 172.8		ECU-NMO-302 Eculizumab (N = 119) PY = 107.2		All Eculizumab (N = 137) PY = 282.3	
	Events, n (Rate)	Patients, n (%)	Events, n (Rate)	Patients, n (%)	Events, n (Rate)	Patients, n (%)	Events, n (Rate)	Patients, n (%)
Events and patients with events	**618 (1162.8)**	**45 (95.7)**	**1303 (754.0)**	**88 (91.7)**	**851 (793.5)**	**92 (77.3)**	**2154 (763.1)**	**125 (91.2)**
Headache	20 (37.6)	11 (23.4)	96 (55.5)	22 (22.9)	59 (55.0)	19 (16.0)	155 (54.9)	37 (27.0)
Upper respiratory tract infection	10 (18.8)	6 (12.8)	54 (31.2)	28 (29.2)	19 (17.7)	10 (8.4)	73 (25.9)	35 (25.5)
Nasopharyngitis	15 (28.2)	9 (19.1)	50 (28.9)	20 (20.8)	30 (28.0)	15 (12.6)	80 (28.3)	31 (22.6)
Urinary tract infection	13 (24.5)	10 (21.3)	45 (26.0)	13 (13.5)	32 (29.8)	10 (8.4)	77 (27.3)	23 (16.8)
Nausea	19 (35.7)	12 (25.5)	30 (17.4)	16 (16.7)	16 (14.9)	6 (5.0)	46 (16.3)	22 (16.1)
Back pain	9 (16.9)	6 (12.8)	17 (9.8)	14 (14.6)	16 (14.9)	8 (6.7)	33 (11.7)	21 (15.3)
Diarrhoea	19 (35.7)	7 (14.9)	23 (13.3)	15 (15.6)	11 (10.3)	7 (5.9)	34 (12.0)	21 (15.3)
Arthralgia	10 (18.8)	5 (10.6)	12 (6.9)	11 (11.5)	10 (9.3)	8 (6.7)	22 (7.8)	19 (13.9)
Pain in extremity	11 (20.7)	10 (21.3)	13 (7.5)	11 (11.5)	17 (15.9)	7 (5.9)	30 (10.6)	17 (12.4)
Constipation	3 (5.6)	3 (6.4)	9 (5.2)	9 (9.4)	7 (6.5)	7 (5.9)	16 (5.7)	16 (11.7)
Contusion	8 (15.1)	2 (4.3)	11 (6.4)	10 (10.4)	8 (7.5)	7 (5.9)	19 (6.7)	16 (11.7)
Cough	9 (16.9)	7 (14.9)	13 (7.5)	11 (11.5)	10 (9.3)	7 (5.9)	23 (8.1)	16 (11.7)
Dizziness	6 (11.3)	6 (12.8)	19 (11.0)	14 (14.6)	2 (1.9)	2 (1.7)	21 (7.4)	16 (11.7)
Influenza	2 (3.8)	2 (4.3)	19 (11.0)	11 (11.5)	11 (10.3)	7 (5.9)	30 (10.6)	16 (11.7)
Bronchitis	3 (5.6)	3 (6.4)	12 (6.9)	9 (9.4)	5 (4.7)	4 (3.4)	17 (6.0)	13 (9.5)
Fatigue	5 (9.4)	5 (10.6)	16 (9.3)	7 (7.3)	14 (13.1)	7 (5.9)	30 (10.6)	13 (9.5)
Pyrexia	5 (9.4)	4 (8.5)	10 (5.8)	7 (7.3)	8 (7.5)	6 (5.0)	18 (6.4)	13 (9.5)
Conjunctivitis	8 (15.1)	4 (8.5)	10 (5.8)	9 (9.4)	3 (2.8)	3 (2.5)	13 (4.6)	12 (8.8)
Cystitis	1 (1.9)	1 (2.1)	8 (4.6)	8 (8.3)	7 (6.5)	5 (4.2)	15 (5.3)	12 (8.8)
Paraesthesia	5 (9.4)	3 (6.4)	9 (5.2)	8 (8.3)	4 (3.7)	4 (3.4)	13 (4.6)	12 (8.8)
Pharyngitis	3 (5.6)	3 (6.4)	13 (7.5)	10 (10.4)	2 (1.9)	2 (1.7)	15 (5.3)	12 (8.8)
Vomiting	10 (18.8)	8 (17.0)	10 (5.8)	10 (10.4)	3 (2.8)	2 (1.7)	13 (4.6)	12 (8.8)
Muscle spasms	2 (3.8)	2 (4.3)	5 (2.9)	5 (5.2)	8 (7.5)	5 (4.2)	13 (4.6)	10 (7.3)
Musculoskeletal pain	0	0	7 (4.1)	6 (6.3)	4 (3.7)	4 (3.4)	11 (3.9)	10 (7.3)
Neuromyelitis optica spectrum disorder	18 (33.9)	16 (34.0)	7 (4.1)	7 (7.3)	6 (5.6)	4 (3.4)	13 (4.6)	10 (7.3)
Oropharyngeal pain	3 (5.6)	2 (4.3)	11 (6.4)	7 (7.3)	9 (8.4)	7 (5.9)	20 (7.1)	10 (7.3)
Anaemia	1 (1.9)	1 (2.1)	2 (1.2)	2 (2.1)	8 (7.5)	7 (5.9)	10 (3.5)	9 (6.6)
Dyspepsia	4 (7.5)	4 (8.5)	31 (17.9)	6 (6.3)	5 (4.7)	4 (3.4)	36 (12.8)	9 (6.6)
Insomnia	4 (7.5)	4 (8.5)	6 (3.5)	6 (6.3)	4 (3.7)	3 (2.5)	10 (3.5)	9 (6.6)
Iron deficiency anaemia	1 (1.9)	1 (2.1)	3 (1.7)	3 (3.1)	6 (5.6)	6 (5.0)	9 (3.2)	9 (6.6)
Oral herpes	2 (3.8)	2 (4.3)	7 (4.1)	4 (4.2)	14 (13.1)	5 (4.2)	21 (7.4)	9 (6.6)
Asthenia	1 (1.9)	1 (2.1)	6 (3.5)	5 (5.2)	3 (2.8)	3 (2.5)	9 (3.2)	8 (5.8)
Sinusitis	0	0	8 (4.6)	6 (6.3)	6 (5.6)	3 (2.5)	14 (5.0)	8 (5.8)
Abdominal pain upper	3 (5.6)	3 (6.4)	6 (3.5)	6 (6.3)	1 (0.9)	1 (0.8)	7 (2.5)	7 (5.1)
Fall	9 (16.9)	4 (8.5)	5 (2.9)	4 (4.2)	10 (9.3)	3 (2.5)	15 (5.3)	7 (5.1)
Haematuria	1 (1.9)	1 (2.1)	12 (6.9)	4 (4.2)	3 (2.8)	3 (2.5)	15 (5.3)	7 (5.1)
Hordeolum	0	0	8 (4.6)	7 (7.3)	0	0	8 (2.8)	7 (5.1)
Leukopenia	1 (1.9)	1 (2.1)	8 (4.6)	5 (5.2)	6 (5.6)	4 (3.4)	14 (5.0)	7 (5.1)
Lymphopenia	0	0	7 (4.1)	5 (5.2)	4 (3.7)	3 (2.5)	11 (3.9)	7 (5.1)
Myalgia	3 (5.6)	3 (6.4)	8 (4.6)	6 (6.3)	1 (0.9)	1 (0.8)	9 (3.2)	7 (5.1)
Pain	7 (13.2)	4 (8.5)	5 (2.9)	5 (5.2)	4 (3.7)	2 (1.7)	9 (3.2)	7 (5.1)
Toothache	2 (3.8)	2 (4.3)	6 (3.5)	3 (3.1)	5 (4.7)	4 (3.4)	11 (3.9)	7 (5.1)
Abdominal pain	4 (7.5)	3 (6.4)	5 (2.9)	3 (3.1)	5 (4.7)	3 (2.5)	10 (3.5)	6 (4.4)
Alopecia	2 (3.8)	2 (4.3)	6 (3.5)	5 (5.2)	1 (0.9)	1 (0.8)	7 (2.5)	6 (4.4)
Cataract	2 (3.8)	2 (4.3)	9 (5.2)	6 (6.3)	0	0	9 (3.2)	6 (4.4)
Cellulitis	1 (1.9)	1 (2.1)	5 (2.9)	5 (5.2)	2 (1.9)	1 (0.8)	7 (2.5)	6 (4.4)
Oedema peripheral	3 (5.6)	3 (6.4)	4 (2.3)	4 (4.2)	2 (1.9)	2 (1.7)	6 (2.1)	6 (4.4)
Decreased appetite	1 (1.9)	1 (2.1)	5 (2.9)	5 (5.2)	0	0	5 (1.8)	5 (3.6)
Gastrooesophageal reflux disease	5 (9.4)	3 (6.4)	5 (2.9)	5 (5.2)	0	0	5 (1.8)	5 (3.6)
Hypoaesthesia	5 (9.4)	4 (8.5)	2 (1.2)	2 (2.1)	4 (3.7)	3 (2.5)	6 (2.1)	5 (3.6)
Pneumonia	5 (9.4)	4 (8.5)	3 (1.7)	3 (3.1)	2 (1.9)	2 (1.7)	5 (1.8)	5 (3.6)
Pruritus	8 (15.1)	4 (8.5)	3 (1.7)	3 (3.1)	2 (1.9)	2 (1.7)	5 (1.8)	5 (3.6)
Rash	4 (7.5)	4 (8.5)	4 (2.3)	4 (4.2)	1 (0.9)	1 (0.8)	5 (1.8)	5 (3.6)
Muscular weakness	3 (5.6)	3 (6.4)	1 (0.6)	1 (1.0)	3 (2.8)	3 (2.5)	4 (1.4)	4 (2.9)
Nasal congestion	3 (5.6)	3 (6.4)	6 (3.5)	2 (2.1)	2 (1.9)	2 (1.7)	8 (2.8)	4 (2.9)
Rhinitis allergic	3 (5.6)	3 (6.4)	3 (1.7)	3 (3.1)	1 (0.9)	1 (0.8)	4 (1.4)	4 (2.9)
Chest discomfort	3 (5.6)	3 (6.4)	2 (1.2)	2 (2.1)	1 (0.9)	1 (0.8)	3 (1.1)	3 (2.2)
Weight decreased	4 (7.5)	3 (6.4)	1 (0.6)	1 (1.0)	2 (1.9)	2 (1.7)	3 (1.1)	3 (2.2)
Depression	5 (9.4)	4 (8.5)	1 (0.6)	1 (1.0)	1 (0.9)	1 (0.8)	2 (0.7)	2 (1.5)

Rates are reported as per 100 PY. The TEAEs in Study ECU-NMO-301 are AEs with a start date on or after the date of the first dose of study drug in Study ECU-NMO-301 up to the day prior to the first dose date in Study ECU-NMO-302 or for patients who withdrew, up to the day of last contact. The TEAEs in Study ECU-NMO-302 are AEs with a start date on or after the date of the first dose of study drug in Study ECU-NMO-302. The TEAEs in the All Eculizumab group are AEs with a start date on or after the date of the patient's first dose of eculizumab. Percentages are based on the total number of patients in the Combined Safety Set in the treatment group. If a patient had multiple events for a Preferred Term, he/she is counted only once for that Preferred

Term. Preferred Terms are in the order of descending frequency in the All Eculizumab group. Abbreviations: AE = adverse event; NMOSD = neuromyelitis optica spectrum disorder; PY = patient-years; TEAE = treatment-emergent adverse event.

Related TEAEs that occurred in ≥ 5% of patients in either treatment group in Study ECU-NMO-301, Study ECU-NMO-302, or in patients treated with eculizumab across both studies combined are shown by Preferred Term, and treatment group for the Combined Safety Set in Table 38.

Table 38 Related Treatment-Emergent Adverse Events That Occurred in At least 5% of Patients in any Group by MedDRA Preferred Term, Grouped Relationship and Treatment Group - Combined Safety Set

Preferred Term	ECU-NMO-301 Placebo (N = 47) PY = 53.1		ECU-NMO-301 Eculizumab (N = 96) PY = 172.8		ECU-NMO-302 Eculizumab (N = 119) PY = 107.2		All Eculizumab (N = 137) PY = 282.3	
	Events n (Rate)	Patients n (%)	Events n (Rate)	Patients n (%)	Events n (Rate)	Patients n (%)	Events n (Rate)	Patients n (%)
Events and patients with events	**618 (1162.8)**	**45 (95.7)**	**1303 (754.0)**	**88 (91.7)**	**851 (793.5)**	**92 (77.3)**	**2154 (763.1)**	**125 (91.2)**
Related	88 (165.6)	27 (57.4)	367 (212.4)	49 (51.0)	181 (168.8)	40 (33.6)	548 (194.1)	78 (56.9)
Not Related	530 (997.2)	45 (95.7)	936 (541.6)	87 (90.6)	670 (624.7)	87 (73.1)	1606 (569.0)	122 (89.1)
Headache	2 (3.8)	2 (4.3)	56 (32.4)	6 (6.3)	22 (20.5)	4 (3.4)	78 (27.6)	9 (6.6)
Nausea	4 (7.5)	3 (6.4)	16 (9.3)	7 (7.3)	10 (9.3)	1 (0.8)	26 (9.2)	8 (5.8)
Upper respiratory tract infection	3 (5.6)	1 (2.1)	12 (6.9)	6 (6.3)	3 (2.8)	2 (1.7)	15 (5.3)	7 (5.1)
Urinary tract infection	5 (9.4)	5 (10.6)	4 (2.3)	3 (3.1)	11 (10.3)	3 (2.5)	15 (5.3)	6 (4.4)
Pneumonia	4 (7.5)	3 (6.4)	2 (1.2)	2 (2.1)	1 (0.9)	1 (0.8)	3 (1.1)	3 (2.2)
Vomiting	4 (7.5)	3 (6.4)	2 (1.2)	2 (1.2)	0	0	2 (0.7)	2 (1.5)
Pruritus	5 (9.4)	3 (6.4)	0	0	0	0	0	0

TEAEs in Study ECU-NMO-301 are AEs with a start date on or after the date of the first dose of study drug in Study ECU-NMO-301 up to the day prior to the first dose date in Study ECU-NMO-302 or for patients who withdrew, up to the day of last contact. TEAEs in Study ECU-NMO-302 are AEs with a start date on or after the date of the first dose of study drug in Study ECU-NMO-302. TEAEs in the All Eculizumab group are AEs with a start date on or after the date of the patient's first dose of eculizumab. Related AEs are defined as possibly, probably, or definitely related, and include any AE with an unknown relationship; and Not Related AEs are defined as unrelated or unlikely. Percentages are based on the total number of patients in the Combined Safety Set in the particular treatment group. If a patient had multiple events for a particular System Organ Class, Preferred Term or relationship, he/she is counted only once for that System Organ Class, Preferred Term, or relationship.
System Organ Classes are presented in alphabetic order. Preferred Terms are in the order of descending frequency in the All Eculizumab group. Adverse events are coded using MedDRA Dictionary Version 21.0. Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event.

Most AEs were mild or moderate in severity (Table 36). In Study ECU-NMO-301, TEAEs that were designated as severe occurred at a rate of 17.4 events per 100 PY in the eculizumab group and 30.8 events per 100 PY in the placebo group. The most frequently reported severe TEAEs in the eculizumab group were back pain, pain in extremity, pneumonia, and NMOSD (experienced by 2 [2.1%] patients each). The most frequently reported severe TEAE in the placebo group was NMOSD (6 [12.8%] patients), which was the only severe TEAE experienced by more than 1 patient in this group.

In Study ECU-NMO-302, the rate of severe TEAEs was 30.8 events per 100 PY. The most frequently reported severe TEAEs were NMOSD (4 [3.4%] patients), and optic neuritis (2 [1.7%] patients) (optic neuritis reposted separately due to a MAH decision). In the All Eculizumab group, severe events were experienced by 24.8% of patients with a rate of 21.9 events per 100 PY. In the All Eculizumab group, severe TEAEs were reported with a rate of 21.9 events per 100 PY. The most frequently reported severe TEAE was NMOSD, which was experienced by 6 (4.4%) patients.

Serious adverse event / deaths / other significant events

Deaths

One patient who was treated with eculizumab as part of this clinical program died. This patient was enrolled in Study ECU-NMO-301 and was randomized to eculizumab treatment: a 30-year-old Black or African American male tobacco user with relevant medical history of tracheal stenosis, chronic obstructive pulmonary disease, bronchiectasis, sleep apnoea, organizing pneumonia, pulmonary fibrosis, and

asthma. The first dose of eculizumab was administered on 12 May 2015. On 08 Jun 2017 (Study Day 759), he received his last infusion of study drug. On 23 Jun 2017 (Study Day 774), the patient went for his next infusion of study drug, but he had shortness of breath and could barely talk and, therefore, was not infused and instead was transported to the hospital. Upon admission, the patient was diagnosed with pneumonia and infectious pleural effusion. The patient then developed sepsis, respiratory failure, and congestive heart failure. He was intubated and was transferred to the intensive care unit. On 24 Jun 2017 (Study Day 775), a left thoracotomy with total pulmonary decortication was performed and cultures were obtained. Cultures yielded Streptococcus intermedius and Peptostreptococcus. On 26 Jun 2017 (Study Day 777), while the patient was still intubated, he developed progressive hypotension requiring vasopressor support and subsequently died. The Investigator reported that the cause of death was infectious pleural effusion.

The Investigator considered the TESAEs of congestive cardiac failure, pneumonia, respiratory failure, and sepsis to be unlikely related to the study drug, while the event of infectious pleural effusion was considered probably related to the study drug. The organisms identified in culture, however, were suggestive of aspiration pneumonia. This, together with the patient's risk factors for aspiration pneumonia, history of trachea stenosis and bronchiectasis, and use of azathioprine, all suggest factors (i.e., an aspiration event with secondary pneumonia) other than therapeutic intervention may have contributed to his clinical presentation and evolution of this outcome.

Other Serious Adverse Events

Of the 143 patients in the Safety Set of Study ECU-NMO-301, 56 patients (39.2%) experienced TESAEs. The incidence and rate of TESAEs was lower in the eculizumab group (31.3%, with 30.7 events per 100 PY) than that reported in the placebo group (55.3%, with 88.4 events per 100 PY). Of the 119 patients in the Extension Safety Set of Study ECU-NMO-302, 26 patients (21.8.%) experienced TESAEs, with a rate of 49.4 events per 100 PY. In the All Eculizumab group the incidence of TESAEs was 36.5%, with a rate of 37.6 events per 100 PY (Table 39).

The most frequently reported TESAE overall was NMOSD. Other TESAEs that were experienced by > 1 patient in any safety net are displayed in Table 39.

Table 39 Treatment-Emergent Serious Adverse Events Reported by More Than 1 Patient in Any Treatment Group by Preferred Term and Treatment Group – Combined Safety Set

Preferred Term	ECU-NMO-301 Placebo (N = 47) PY = 53.1		ECU-NMO-301 Eculizumab (N = 96) PY = 172.8		ECU-NMO-302 Eculizumab (N = 119) PY = 107.2		All Eculizumab (N = 137) PY = 282.3	
	Events n (Rate)	Patients n (%)	Events n (Rate)	Patients n (%)	Events n (Rate)	Patients n (%)	Events n (Rate)	Patients n (%)
Events and patients with events	**47 (88.4)**	**26 (55.3)**	**53 (30.7)**	**30 (31.3)**	**53 (49.4)**	**26 (21.8)**	**106 (37.6)**	**50 (36.5)**
NMOSD	18 (33.9)	16 (34.0)	7 (4.1)	7 (7.3)	6 (5.6)	4 (3.4)	13 (4.6)	10 (7.3)
Pneumonia	2 (3.8)	1 (2.1)	3 (1.7)	3 (3.1)	1 (0.9)	1 (0.8)	4 (1.4)	4 (2.9)
Urinary tract infection	0	0	2 (1.2)	2 (2.1)	3 (2.8)	2 (1.7)	5 (1.8)	4 (2.9)
Optic neuritis	0	0	0	0	3 (2.8)	3 (2.5)	3 (1.1)	3 (2.2)
Cellulitis	0	0	2 (1.2)	2 (2.1)	0	0	2 (0.7)	2 (1.5)
Cholecystitis acute	1 (1.9)	1 (2.1)	1 (0.6)	1 (1.0)	1 (0.9)	1 (0.8)	2 (0.7)	2 (1.5)
Femoral neck fracture	0	0	0	0	2 (1.9)	2 (1.7)	2 (0.7)	2 (1.5)
Osteonecrosis	0	0	0	0	2 (1.9)	2 (1.7)	2 (0.7)	2 (1.5)
Sepsis	0	0	2 (1.2)	2 (2.1)	0	0	2 (0.7)	2 (1.5)

Rates are reported as per 100 PY. The TESAEs in Study ECU-NMO-301 are SAEs with a start date on or after the date of the first dose of study drug in Study ECU-NM-301 up to the day prior to the first dose date in Study ECU-NMO-302 or for patients who withdrew, up to the day of last contact. The TESAEs in Study ECU-NMO-302 are AEs with a start date on or after the date of the first dose of study drug in Study ECU-NMO-302. The TESAEs in the All Eculizumab group are SAEs with a start date on or after the date of the patient's first dose of eculizumab.
Percentages are based on the total number of patients in the Combined Safety Set in the particular treatment group. If a patient had multiple events for a particular Preferred Term, he/she is counted only once for that Preferred Term. Preferred Terms are in the order of descending frequency in the All Eculizumab group.
Abbreviations: NMOSD = neuromyelitis optica spectrum disorder; PY = patient-years; SAE = serious adverse event; TESAE = treatment-emergent serious adverse event.

Adverse Events of Special Interest

Adverse events of special interest (AESIs) were defined according to the important risks in the Risk Management Plan (RMP) Version 12.2 and based on events monitored as part of the post marketing signal detection activities. Adverse events of special interest include the following:

a) Important identified risks
    - Infections (meningococcal infections, *Aspergillus* infections, and other serious infections)
    - Sepsis
    - Infusion reactions

b) Events monitored as part of post marketing signal detection activities
    - Serious cutaneous adverse reactions
    - Cardiac disorders
    - Angioedema

In Study ECU-NMO-301, treatment-emergent AESIs were experienced by 21.9% of patients in the eculizumab group and 21.3% of patients in the placebo group, with rates of 16.8 and 24.5 events per 100 PY, respectively. Other serious infections were experienced by 11.5% of patients in the eculizumab group and 12.8% of patients in the placebo group, with rates of 8.1 and 15.1 events per 100 PY, respectively (Table 40).

In Study ECU-NMO-302, treatment-emergent AESIs were experienced by 16.0% of patients, with a rate of 23.3 events per 100 PY. Other serious infections were experienced by 8.4% of patients, with a rate of 13.1 events per 100 PY (Table 40).

Treatment-emergent AESIs were experienced by 29.2% of patients in the All Eculizumab group, with a rate of 19.1 events per 100 PY. Other serious infections were experienced by 15.3% of patients, with a rate of 9.9 events per 100 PY (Table 40).

There were no meningococcal infections reported in the NMOSD program (Table 40). However, a case with Neisseria gonorrhoeae infection was reported in the updated safety reported submitted in the first request for supplementary information. The patient, a 29-year-old female randomized to placebo in Study ECU-NMO-301, received the first induction dose of eculizumab on Study ECU-NMO-302 on 22 Jun 2018; 4 days later (26 Jun 2018), the patient was hospitalized with fever, headache, body aches and neck tightness. The patient was diagnosed with a N. gonorrhoeae infection, and treated with empiric IV antibiotics. Six days later (02 Jul 2018), she was discharged with a peripherally inserted central catheter (PICC) line to continue ceftriaxone IV at home. The Investigator considered the events related to eculizumab. The SAEs of gonorrhoea and bacterial sepsis were considered resolved on 27 Jul 2018. The patient decided to withdraw from the study.

The most frequently reported treatment-emergent AESIs were ‘other serious infections’ (Table 40).

Table 40 Treatment-Emergent Adverse Events of Special Interest by System Organ Class, Preferred Term, and Treatment Group – Combined Safety Set

Type of Event System Organ Class Preferred Term	ECU-NMO-301 Placebo (N = 47) PY = 53.1		ECU-NMO-301 Eculizumab (N = 96) PY = 172.8		ECU-NMO-302 Eculizumab (N = 119) PY = 107.2		All Eculizumab (N = 137) PY = 282.3	
	Events n (Rate)	Patients n (%)	Events n (Rate)	Patients n (%)	Events n (Rate)	Patients n (%)	Events n (Rate)	Patients n (%)
Events and patients with events	**13 (24.5)**	**10 (21.3)**	**29 (16.8)**	**21 (21.9)**	**25 (23.3)**	**19 (16.0)**	**54 (19.1)**	**40 (29.2)**
Meningococcal infections	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Aspergillus infections	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Other serious infections	**8 (15.1)**	**6 (12.8)**	**14 (8.1)**	**11 (11.5)**	**14 (13.1)**	**10 (8.4)**	**28 (9.9)**	**21 (15.3)**
Infections and infestations	8 (15.1)	6 (12.8)	14 (8.1)	11 (11.5)	14 (13.1)	10 (8.4)	28 (9.9)	21 (15.3)
Pneumonia	2 (3.8)	1 (2.1)	3 (1.7)	3 (3.1)	1 (0.9)	1 (0.8)	4 (1.4)	4 (2.9)
Urinary tract infection	0	0	2 (1.2)	2 (2.1)	3 (2.8)	2 (1.7)	5 (1.8)	4 (2.9)
Cellulitis	0	0	2 (1.2)	2 (2.1)	0	0	2 (0.7)	2 (1.5)
Appendicitis	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Bacterial sepsis	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Bartholin's abscess	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Bronchitis	1 (1.9)	1 (2.1)	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Device related infection	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Escherichia pyelonephritis	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Gallbladder empyema	0	0	1 (0.6)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)
Gastroenteritis	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Gonorrhoea	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Infectious pleural effusion	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Infective tenosynovitis	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Influenza	1 (1.9)	1 (2.1)	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Osteomyelitis	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Pyelonephritis acute	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Renal abscess	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Staphylococcal bacteraemia	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Urinary tract infection enterococcal	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Gastroenteritis viral	1 (1.9)	1 (2.1)	0	0	0	0	0	0
Herpes zoster	1 (1.9)	1 (2.1)	0	0	0	0	0	0
Pneumococcal infection	1 (1.9)	1 (2.1)	0	0	0	0	0	0
Viral upper respiratory tract infection	1 (1.9)	1 (2.1)	0	0	0	0	0	0
Sepsis	0	0	2 (1.2)	2 (2.1)	2 (1.9)	2 (1.7)	4 (1.4)	4 (2.9)
Infections and infestations	0	0	2 (1.2)	2 (2.1)	2 (1.9)	2 (1.7)	4 (1.4)	4 (2.9)
Sepsis	0	0	2 (1.2)	2 (2.1)	0	0	2 (0.7)	2 (1.5)
Bacteraemia	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Urosepsis	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Infusion reactions	**2 (3.8)**	**2 (4.3)**	**6 (3.5)**	**6 (6.3)**	**6 (5.6)**	**6 (5.0)**	**12 (4.3)**	**12 (8.8)**
General disorders and administration site conditions	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Injection site rash	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Injury, poisoning and procedural complications	0	0	2 (1.2)	2 (2.1)	3 (2.8)	3 (2.5)	5 (1.8)	5 (3.6)
Infusion related reaction	0	0	2 (1.2)	2 (2.1)	3 (2.8)	3 (2.5)	5 (1.8)	5 (3.6)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Rhinitis allergic	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Skin and subcutaneous tissue disorders	2 (3.8)	2 (4.3)	3 (1.7)	3 (3.1)	2 (1.9)	2 (1.7)	5 (1.8)	5 (3.6)
Dermatitis	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Dermatitis allergic	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Erythema nodosum	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Rash	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Rash erythematous	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Dermatitis contact	1 (1.9)	1 (2.1)	0	0	0	0	0	0
Rash maculo-papular	1 (1.9)	1 (2.1)	0	0	0	0	0	0
Serious cutaneous adverse reactions	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Cardiac disorders	**1 (1.9)**	**1 (2.1)**	**3 (1.7)**	**3 (3.1)**	**0**	**0**	**3 (1.1)**	**3 (2.2)**
Cardiac disorders	1 (1.9)	1 (2.1)	3 (1.7)	3 (3.1)	0	0	3 (1.1)	3 (2.2)
Arrhythmia	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Atrial fibrillation	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Cardiac failure congestive	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Myocardial ischaemia	1 (1.9)	1 (2.1)	0	0	0	0	0	0
Angioedema	**2 (3.8)**	**2 (4.3)**	**4 (2.3)**	**3 (3.1)**	**3 (2.8)**	**3 (2.5)**	**7 (2.5)**	**6 (4.4)**
Eye disorders	0	0	2 (1.2)	2 (2.1)	0	0	2 (0.7)	2 (1.5)
Eyelid oedema	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Eye oedema	0	0	1 (0.6)	1 (1.0)	0	0	1 (0.4)	1 (0.7)
Gastrointestinal disorders	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Gingival swelling	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.7)
Skin and subcutaneous tissue disorders	2 (3.8)	2 (4.3)	2 (1.2)	1 (1.0)	2 (1.9)	2 (1.7)	4 (1.4)	3 (2.2)
Urticaria	2 (3.8)	2 (4.3)	2 (1.2)	1 (1.0)	2 (1.9)	2 (1.7)	4 (1.4)	3 (2.2)

Rates are reported as per 100 PY. The TEAEs in Study ECU-NMO-301 are AEs with a start date on or after the date of the first dose of study drug in Study ECU-NMO-301 up to the day prior to the first dose date in Study ECU-NMO-302 or

for patients who withdrew, up to the day of last contact. The TEAEs in Study ECU-NMO-302 are AEs with a start date on or after the date of the first dose of study drug in Study ECU-NMO-302. The TEAEs in the All Eculizumab group are AEs with a start date on or after the date of the patient's first dose of eculizumab.
Percentages are based on the total number of patients in the Combined Safety Set in the particular treatment group. If a patient had multiple events for a particular System Organ Class or Preferred Term, he/she is counted only once for that System Organ Class or Preferred Term. System Organ Classes are presented in alphabetic order. Preferred Terms are in the order of descending frequency in the All Eculizumab group.
Abbreviations: AE = adverse event; PY = patient-years; TEAE = treatment-emergent adverse event.

Laboratory findings

Overall, there were no clinically meaningful differences between the placebo group and the eculizumab group in the change from Baseline in any haematology or chemistry parameters in Study ECU-NMO-301. No difference between treatment groups was observed in vital signs, ECG parameters, or the C-SSRS.

In Study ECU-NMO-301, there was no substantial difference between treatment groups in changes related to suicidal ideation/behaviour during the study based on the C-SSRS. No patients were reported with suicidal behaviour in Study ECU-NMO-302. There was 1 shift in C-SSRS categories in a patient in the placebo/eculizumab group from no suicidal ideation at Baseline of Study ECU-NMO-301 to suicidal ideation during Study ECU-NMO-302.

No pooled analysis of immunogenicity data was performed, because immunogenicity was not analysed as part of the interim analysis for Study ECU-NMO-302. In Study ECU-NMO-301, 2 patients in the eculizumab group were positive for ADAs post baseline (one patient had an ADA titer of 11.5 at Week 132 and another had an ADA titer of 7.46 at Week 120. Both patients were negative for neutralizing antibodies. According to the applicant, these low titer positive results may reflect the actual biological variability of the test matrix.

These results were consistent with the low rate of positive ADAs and NAbs observed previously for Soliris.

Safety in special populations

Use during Pregnancy

No pregnant patients were enrolled in Study ECU-NMO-301. Two pregnancies were reported during Study ECU-NMO-301: 1 pregnancy in a patient who opted for a therapeutic abortion and continued in the study, and 1 pregnancy in the partner of a male patient. The partner of the male patient delivered a female infant by caesarean section at 35 weeks gestation; Apgar scores of 8 (max Apgar is 10) were recorded at first and second check. There were no malformations or abnormalities noted at birth. The infant was admitted to the intensive care unit for jaundice, being premature, and being at risk for congenital hip dysplasia. No further information was available regarding the infant. As of the clinical database cut-off date, no pregnancies had been reported in Study ECU-NMO-302.

Use during Lactation

No breastfeeding patients were enrolled in Study ECU-NMO-301. No breastfeeding patients were enrolled in Study ECU-NMO-302 as of the clinical database cut-off date for the interim analysis.

Geriatric Use

No apparent age-related differences were observed in the NMOSD program. The number of patients aged 65 and over (n = 9) was not sufficient to determine whether they responded differently from younger patients.

Paediatric Use

The safety and effectiveness of eculizumab therapy in paediatric patients with NMOSD below the age of 18 have not been established.

Use in Patients with Hepatic Impairment

The safety and efficacy of eculizumab has not been studied in patients with hepatic impairment.

Use in Patients with Renal Impairment

No dose adjustment is required for patients with renal impairment.

Effects on Ability to Drive or Operate Machinery

There are no data to suggest that eculizumab affects the ability to drive or operate machinery or impairs mental ability. No studies have been conducted to assess these issues, as adverse event profiles suggested no cause for concern.

Safety related to drug-drug interactions and other interactions

Drug interactions were not studied in Studies ECU-NMO-301 and ECU-NMO-302.

Discontinuation due to adverse events

In Study ECU-NMO-301, 16 (16.7%) patients in the eculizumab group and 3 (6.4%) patients in the placebo group discontinued the study. Two patients discontinued Study ECU-NMO-301 due to TEAEs; both of these patients were in the placebo group:

– A 63-year-old White female patient. Her first dose of placebo was administered on 24 Sep 2014. In Mar 2015 (exact date not provided), the patient experienced an event of pneumonia, which resulted in study drug being withdrawn. The Investigator considered the pneumonia to be probably related to study drug (placebo). The patient discontinued from the study on 12 May 2015 (Study Day 231) and was subsequently reported to have died on 29 May 2015. The final cause of death was pneumonia with a secondary diagnosis of myocardial ischemia.

– A 53-year-old Asian female patient. Her first dose of placebo was administered on 20 Aug 2015. The patient experienced an AE of prerenal failure and an SAE of pancytopenia on 22 Aug 2016 (Study Day 369). Both events resulted in study drug being withdrawn. The prerenal failure was considered resolved on 28 Aug 2016 (Study Day 375) and the pancytopenia on 13 Oct 2016 (Study Day 421). The patient was discontinued from the study due to the event of pancytopenia on 13 Oct 2016. The Investigator considered the event of prerenal failure to be unlikely related to study drug (placebo), and the event of pancytopenia to be possibly related to study drug (placebo).

In Study ECU-NMO-302, 6/39 (15.4%) patients had discontinued as of the clinical database cut-off date for the interim analysis (31 October 2018). One patient in Study ECU-NMO-302 (placebo/eculizumab) discontinued treatment due to 2 events of worsening of systemic lupus erythematosus and to newly diagnosed autoimmune thyroiditis and Sjogren's syndrome. The patient received her last dose of study drug on 10 Apr 2018 and discontinued from the study on 04 Jun 2018. The events of Sjogren's syndrome, autoimmune thyroiditis, and one event of worsening systemic lupus erythematous were ongoing at the time of study discontinuation. The Investigator considered all 4 events to be possibly related to study drug.

Overdose, Drug Abuse, Withdrawal and Rebound

There has been no known occurrence of a patient receiving an overdose of eculizumab during clinical studies in NMOSD.

The potential for drug abuse was not investigated or reported in human clinical studies of eculizumab. However, based on the pharmacological profile of eculizumab and the available post marketing data, there is no evidence of abuse or dependency.

Withdrawal or rebound effect was not specifically investigated in the clinical studies of eculizumab. Patients with NMOSD who discontinue treatment with eculizumab should be carefully monitored for signs and symptoms of disease worsening and relapse.

Long-Term Safety in Complement-Mediated Diseases

Clinical Studies of gMG and NMOSD

Since NMOSD and generalized myasthenia gravis (gMG) are autoimmune, complement-mediated inflammatory neurologic disorders in which patients are commonly treated with ISTs, NMOSD safety data from ECU-NMO-302 and All Eculizumab group were compared with the long-term safety data of gMG in Study ECU-MG-302.

The total exposure to eculizumab was similar for the populations in the final analysis of Study ECU-MG-302 (274.8 PY) and the All Eculizumab group in the NMOSD program (282.3 PY).

In study ECU-MG-302, the last patient completed the study on 15 Jan 2019. A total of 117 patients received eculizumab for a median duration of approximately 2.7 years (median [min, max] of 972 days [1, 1372]). The incidence of TEAEs and TESAEs was 97.4% and 51.3% respectively. Common TEAEs (reported in > 20% of patients) included: headache (40.2% of patients, 27.3 events per 100 PY), nasopharyngitis (35.9% of patients, 30.9 events per 100 PY), diarrhoea (24.8% of patients, 15.6 events per 100 PY), myasthenia gravis (24.8% of patients, 17.8 events per 100 PY), and upper respiratory tract infection (23.9% of patients, 23.3 events per 100 PY). The most frequently reported TESAEs were in the System Organ Class of Infections and infestations (26 patients [22.2%]) and Nervous system disorders (22 patients [18.8%]). The most common TESAEs reported within the Infections and infestations SOC were pneumonia (4 patients [3.4%]) and gastroenteritis and sepsis (3 patients each, 2.6%). MG deterioration was the most common event (16 [13.7%]) in the Nervous system disorders. Overall, the safety profile of eculizumab in gMG patients is consistent with that observed in the other approved indications.

Post marketing experience

At the time of this submission, eculizumab had been approved for the treatment of PNH in 50 countries, aHUS in 49 countries, and refractory gMG or gMG in 34 countries. From post-marketing experience, the estimated exposure to eculizumab since the international birthdate (16 Mar 2007) through 28 Feb 2019 is 48,835.8 PY. After 10 years of post-marketing experience with eculizumab, the safety profile had remained stable, with the following important identified and important potential risks being closely monitored:

- Important identified risks: meningococcal infections, serious infections (including sepsis), Aspergillus infection, severe thrombotic microangiopathy complications after discontinuation of eculizumab in aHUS patients, and infusion reactions.

- Important potential risks: serious haemolysis after discontinuation of eculizumab in PNH patients, malignancies and haematological abnormalities in PNH patients, immunogenicity, and serious infection in neonates after maternal exposure to eculizumab.

These important risks are managed by a comprehensive Risk Management Plan (RMP) with post-marketing reporting rates remaining stable over the last 10 years (Periodic Safety Update Report 16, dated 03 Dec 2018).

From the important identified risks, the most significant risk is meningococcal infection. This is a well-characterized risk known to be associated with C5 inhibition (*Lewis, 2014*). While meningococcal disease is rare, the use of eculizumab is associated with > 1000-fold increase in the incidence of meningococcal disease (*McNamara, 2017*), similar to increased risk in patients with inherited or persistent complement deficiency diseases (*Figueroa, 1991*). To mitigate this risk, routine and additional risk mitigation measures are in place in all indications in which eculizumab has been approved or is being developed. The post-marketing reporting rate of meningococcal infection over the 10 years of post-marketing experience remained stable at approximately 0.3 per 100 PY. The reporting rate for fatal outcomes has also remained stable at 0.03 per 100 PY, representing 9.2% of patients who experienced meningococcal infections, which is similar to the reporting rate from the general population (10 to 15%) (*Rosenstein, 1999; van Deuren, 2000*).

2.5.1. Discussion on clinical safety

The eculizumab clinical development programme for NMOSD consisted of one Phase 3 study (Study ECU-NMO-301) and its open label extension (Study ECU-NMO-302), involving a total of 143 patients.

Overall, 137 patients were exposed to eculizumab as of the cut-off date of 31 October 2018 (276.6.8 patient years of exposure). The extension Study ECU-NMO-302 is still ongoing and the final evaluation of efficacy is planned for a maximum duration for each patient of 5.5 years (or product registration in the country, whichever occurs first). Given the low prevalence of NMOSD, drug exposure can be considered acceptable for the short-term safety assessment of eculizumab. The available safety information of eculizumab in the already authorised indications can be taken as supportive taking into account that for several conditions (aHUS, gMG) patients have been treated with the same dosing regimen. The long-term safety profile was still based on a limited number of participants in Study ECU-NMO-302 including 119 participants (78 patients in the eculizumab/eculizumab and 41 patients in the placebo/eculizumab group) with 104 patients exposed to eculizumab for ≥ 12 months and 67 patients exposed to eculizumab for > 24 months.

In the safety net, 90% of patients were women, the mean age was 45 years (ranging from 19 to 76 years). European patients represent one third of the global population. Overall, 19 patients discontinued in Study ECU-NMO-301 the majority while being treated with Eculizumab. Two of them (on placebo) discontinued due to adverse events. Nine patients discontinued in Study ECU-NMO-302, one of them due to adverse events.

Most patients included in the placebo-controlled Phase 3 study reported AEs: in the eculizumab group (91.7%) and in the placebo group (95.7%). Of them, 51.0% of eculizumab-treated patients versus 57.4% of patients receiving placebo reported AEs considered related. In the open label extension study, 77.3% patients reported AEs and of them, 33.6% were related AEs.

In the placebo-controlled study upper respiratory infection (29.2% vs 12.8% for eculizumab and placebo, respectively), headache (22.9% vs 23.4%), nasopharyngitis (20.8% vs 19.1%), nausea (16.7% vs 25.5%), urinary tract infection (13.5% vs 21.3%), back pain (14.6% vs 12.8%), diarrhea (15.6% vs 14.9%), were the most frequently reported AEs in both eculizumab and placebo groups. During the

open-label extension headache (16%), nasopharyngitis (12.8%), urinary tract infection (8.4%) and upper respiratory infection (8.4%) were also the most frequently reported AEs.

The majority of the events were of mild or moderate severity. In ECU-NMO-301, severe events were reported by 18 of patients treated with eculizumab (18.8%) vs 12 (25.5%) of those on placebo. In ECU-NMO-302, 17 (14.3%) patients reported severe AE. Most severe AEs reported were NMOSD related. Except for those AEs related to the underlying NMOSD condition, no new adverse events have been reported for eculizumab in this new population. Overall, the AE profile is consistent with that known for eculizumab in other indications.

There was one death in Study 301. One 30-year-old male with COPD was hospitalized due to pneumonia and pleural effusion. He had been receiving eculizumab for more than 2 years. He developed sepsis, respiratory failure and congestive heart failure. *Streptococcus intermedius* and *Peptostreptococcus* were isolated. It was considered probably related to treatment.

Of the 143 patients in the Safety Set of Study ECU-NMO-301, 56 patients (39.2%) experienced TESAEs. Apart from SAEs related to the condition (NMOSD, optic neuritis) the most frequently reported SAEs were those related to infections. Similar profile was observed of ECU-NMO-302.

Adverse events of special interest included infections (meningococcal infections, aspergillus infections, and any serious infection), sepsis, infusion-related reactions, serious cutaneous reactions, cardiac disorders, and angioedema.

During the controlled study 21.3% patients on placebo and 21.9% patients on eculizumab reported an AESI. No relevant differences were observed in the incidence the events between eculizumab and placebo groups; however the number of events by group was small. No meningococcal or aspergillosis infections have been reported. In Study ECU-NMO-302, treatment-emergent AESIs were experienced by 16.0% of patients. There were no meningococcal infections reported in the NMOSD program but a case of Neisseria gonorrhoeae (sepsis) was reported.

Since only 9 elderly patients (3 on placebo, 6 on eculizumab) were enrolled in NMOSD program it was not possible to obtain any reliable safety conclusion in this population. Regarding the safety of eculizumab in children/adolescents an open-label, uncontrolled trial to evaluate safety and activity of eculizumab as add-on to background immunosuppressive therapy in children from 2 to less than 18 years of age with relapsing NMOSD is planned to be completed by October 2021.

The post marketing data do not seem to show any new safety concern. Overall, the AE profile is consistent with that known for eculizumab in other indications. As a consequence of this new application RMP is to be updated accordingly.

2.5.2. Conclusions on clinical safety

In general treatment with eculizumab was well tolerated and the safety profile is considered acceptable for the intended target population. Overall, the AE profile is consistent with that known for eculizumab in other indications, with no unexpected findings. From the data presented, it seems that the underlying condition is contributing to a high extent to the overall reporting of AEs in both treatment arms.

The extension study is still ongoing, and there is a rather limited long-term safety database. The update provided shows that no relevant safety concerns have been raised with respect to the previous assessment and also to other indications.

The CHMP considers the following measures necessary to address issues related to safety:

The final results from the current ongoing Study ECU-NMO-302 should be submitted to EMA within 6 months after conclusion.

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

The PRAC considered that the risk management plan version 19.3 is acceptable. In addition, minor revisions were recommended to be taken into account. The MAH is requested to send in a separate procedure a revised study protocol along with the relevant justifications on the changes in the sections: Section 5 'PNH registry objectives and purpose', Section 6.1 on Data collection and Section 11 on Data Analysis. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 19.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Meningococcal infections Serious infections (including sepsis) Aspergillus infection Severe TMA complications due to drug discontinuation in aHUS patients Infusion reactions
Important potential risks	Serious haemolysis after drug discontinuation in PNH patients Immunogenicity Malignancies and haematologic abnormalities in PNH patients Serious infections in neonates after maternal exposure to eculizumab
Missing information	None

Pharmacovigilance plan

Study / status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – required additional pharmacovigilance activities				
Study M07-001 "PNH Registry" Ongoing	To collect and evaluate safety data specific to the use of SOLIRIS and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in SOLIRIS and non-SOLIRIS	- Meningococcal infections - Serious infections (including sepsis) - Aspergillus infection - Infusion reactions - Serious haemolysis after drug discontinuation in PNH patients - Immunogenicity - Malignancies and hematologic abnormalities in PNH patient	Interim data analysis	Every 2 years interim data analysis report
M11-001 "aHUS REGISTRY" Ongoing	To collect and evaluate safety and effectiveness data specific to the use of eculizumab in aHUS patients To assess the long-term manifestations of TMA complications of aHUS as well as other clinical outcomes, including mortality and morbidity inaHUS patients receiving eculizumab treatment or other disease management.	- Meningococcal infections - Serious infections (including sepsis) - Aspergillus infection - Severe TMA complications due to drug discontinuation in aHUS patients - Infusion reactions - Immunogenicity	Interim data analysis	Every 2 years interim data analysis report

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Meningococcal infections	Routine risk minimisation measures: – SmPC sections 4.3 and 4.4 – PL sections 2 and 4 Recommendations for vaccination/antibiotic prophylaxis in SmPC section 4.4 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 – Physician's guides (PNH, aHUS, refractory gMG, NMOSD) – Patient's information brochure (PNH, aHUS, refractory gMG, NMOSD) – Parent's information brochure (PNH, aHUS) – Patient safety card Controlled distribution Vaccination reminder	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: PNH registry (M07-001) aHUS registry (M11-001)
Serious infections (including sepsis)	Routine risk minimisation measures: – SmPC sections 4.4 and 4.8 – PL sections 2 and 4 Restricted medical prescription Additional risk minimisation measures: Educational materials – Physician's guides (PNH, aHUS, refractory gMG, NMOSD) – Patient's information brochure (PNH, aHUS, refractory gMG, NMOSD) – Parent's information brochure	Additional pharmacovigilance activities: PNH registry (M07-001) aHUS registry (M11-001)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	(PNH, aHUS) – Patient safety card	
Aspergillus infection	Routine risk minimisation measures: – SmPC sections 4.4 and 4.8 – PL section 4 Restricted medical prescription Additional risk minimisation measures: Educational materials – Physician's guides (PNH, aHUS, refractory gMG, NMOSD)	Additional pharmacovigilance activities: PNH registry (M07-001) aHUS registry (M11-001)
Severe TMA complications due to drug discontinuation in aHUS patients	Routine risk minimisation measures: – SmPC section 4.4 – PL section 3 Monitoring of patients who discontinued SOLIRIS recommended in SmPC section 4.4 and PL section 3 Restricted medical prescription Additional risk minimisation measures: Educational materials – Physician's guide (aHUS) – Patient's/Parent's information brochure (aHUS)	Additional pharmacovigilance activities: PNH registry (M07-001) aHUS registry (M11-001)
Infusion reactions	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, and 4.8 – PL sections 2, 3, and 4 Restricted medical prescription Additional risk minimisation measures: Educational materials – Physician's guides (PNH, aHUS, refractory gMG, NMOSD) – Patient's information brochure	Additional pharmacovigilance activities: PNH registry (M07-001) aHUS registry (M11-001)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	(PNH, aHUS, refractory gMG, NMOSD) – Parent's information brochure (PNH, aHUS)	
Serious haemolysis after drug discontinuation in PNH patients	Routine risk minimisation measures: – SmPC section 4.4 – PL section 3 Monitoring of patients who discontinued SOLIRIS recommended in SmPC section 4.4 and PL section 3 Restricted medical prescription Additional risk minimisation measures: Educational materials – Physician's guide (PNH) – Patient's/Parent's information brochure (PNH) – Parent's information brochure (PNH)	Additional pharmacovigilance activities: PNH registry (M07-001) aHUS registry (M11-001)
Immunogenicity	Routine risk minimisation measures: – SmPC sections 4.4 and 4.8 – PL section 2 Restricted medical prescription Additional risk minimisation measures: Educational materials – Physician's guides (PNH, aHUS, refractory gMG, NMOSD)	Additional pharmacovigilance activities: PNH registry (M07-001) aHUS registry (M11-001)
Malignancies and haematologic abnormalities in PNH patients	Routine risk minimisation measures: – SmPC section 4.8 – PL section 4 Restricted medical prescription	Additional pharmacovigilance activities: PNH registry (M07-001) aHUS registry (M11-001)
Serious infections in neonates after maternal exposure to eculizumab	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond signal detection and adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	– SmPC section 4.6 – PL section 2 Restricted medical prescription	reactions reporting: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: PNH registry (M07-001) aHUS registry (M11-001)

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, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the address of the MAH has been updated in PI.

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 Soliris 300 mg 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

Soliris is indicated in adults for the treatment of NMOSD in patients who are AQP4 antibody-positive.

NMOSD is an inflammatory disease of the central nervous system characterized by a relapsing course of optic neuritis, longitudinally extensive transverse myelitis, and less frequently, postrema area syndrome, acute brainstem syndrome, acute diencephalic clinical syndrome or symptomatic cerebral syndrome. 10% of the patients have a monophasic course of the disease.

On average, relapses tend to occur within the first year following an initial event in 60% of patients and within three years in 90%. In NMOSD, relapses are typically severe with incomplete recovery leading to rapid development of permanent disability

The AQP4 serum autoantibody is a specific pathogenic marker for NMOSD, although 20% percent of patients with a clinical diagnosis of NMOSD are seronegative for AQP-4-IgG

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, immunosuppressive therapies are recommended at early stages in NMOSD patients. No medicinal product is approved for this indication.

3.1.3. Main clinical studies

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

- A Phase 3 randomized, double-blind, placebo-controlled, multicenter, study to evaluate the safety and efficacy of eculizumab in patients with NMOSD (Study ECU-NMO-301; completed).
- A Phase 3, open-label, multicenter extension study of Study ECU-NMO-301 to evaluate the long-term safety and efficacy of eculizumab in the treatment of patients with NMOSD (Study ECU-NMO-302; ongoing).

3.2. Favourable effects

NMOSD patients treated with eculizumab have shown a significantly lower relapse rate than patients on placebo. The primary endpoint, time to first adjudicated on-trial relapse was met with a 94.2% reduction in the risk of (first on study) relapse. A total of 23 relapses (20 in the placebo group [42.6%] and 3 in eculizumab group [3.1%]) were adjudicated by the external committee (RAC). Pre-specified sensitivity analysis of the primary endpoint (time to first On-trial relapse determined by the treating physician) showed a statistically significant difference between eculizumab y placebo. A total of 14 (14.6%) patients on eculizumab and 29 (61.7%) on placebo had an on-trial relapse ($p < 0.0001$).

The adjusted annualized (adjudicated) rate of relapses (95% CI) was 0.016 (0.005, 0.050) in the eculizumab group versus 0.350 (0.199, 0.616) in the placebo group, representing a 95% reduction over placebo ($p <0.0001$). When using the analysis based on relapses determined by the investigator, the reduction over placebo in the annualized rate of relapse was 85.3%, for eculizumab compared to placebo ($p <0.0001$).

The updated results from Study 302 give support to the eculizumab effect seen during the placebo-controlled phase. The rate of On-trial ARR was 0.174 95%CI (0.091, 0.335) for the placebo/eculizumab group and 0.111 95%CI (0.050, 0.247) for the eculizumab/eculizumab group during study ECU-NMO-302. Both groups experienced a reduction of On-trial ARR with respect to the historical ARR (median 1.923). When patients who received placebo in the Study ECU-NMO-301 were treated with eculizumab in Study ECU-NMO-302 a median reduction (improvement) of -1.923 was reported. In patients previously treated with eculizumab the response was consistently maintained through Study ECU-NMO-302 with a median reduction -1.442.

3.3. Uncertainties and limitations about favourable effects

Eculizumab (or placebo) was administered on top of the background therapy. This study approach is likely to be better accepted by patients and clinicians in a condition where the treatment for prevention of further attacks is recommended at early stages in seropositive patients. In this situation it would be expected that patients were receiving relapse prevention at recruitment. However, 34 patients (23.8% of recruited patients) were not being treated with any supportive IST at baseline note, and 10 patients had not received any prior supportive IST for NMOSD. The position of the applicant was that they may represent a group of patients with active disease (as they met inclusion criteria) with unsatisfactory

response to previous treatments (24/34 were previously treated). An alternative explanation is that they may represent a subset with better evolution/prognosis (mild relapses that no requires treatment). At request, the MAH provided the results of a subgroup analysis in order to document the efficacy of eculizumab in some subpopulations less represented in the study and support a broad indication. Overall, the efficacy was comparable between groups (eculizumab vs placebo) regardless the selected criteria (time since diagnosis, disability burden, relapse history, prior IST use, concomitant IST use). The "time-to-event" design of the study and the fact that patients ended their participation when the first relapse occurred entailed a difference in study exposure (patients at risk) between arms and it does not allow evaluating the effect of eculizumab versus placebo on time to further relapses. Additionally, when the 23 relapses were achieved and the study formally ended a total of 81 patients (66 on eculizumab, 15 on placebo) were censored without having experienced a relapse, so that the effect of eculizumab versus placebo in these participants was not determined in Study ECU-NMO-301.

Results from Study ECU-NMO-301 did not confirm a robust effect on disability. One of the relevant prognostic factors for disability is the severity of the relapses. Whereas eculizumab group showed some benefit (less major relapses or need of hospitalization than placebo group) the low number of relapses in eculizumab patients did not allow concluding on the effect of eculizumab on the severity of the relapses. Additionally no significant effect in terms of EDSS score or HAI score was observed.

Only patients with active, relapsing disease were recruited. It is under discussion whether patients with monophasic forms of NMOSD correspond to a different condition (it has been described that monophasic patients were younger, had equal sex ratios, more commonly presented with simultaneous ON and TM, and had better outcomes). In this case, Study 301 results will unlikely to be extrapolated to this monophasic subset of patients.

It is unknown whether the response observed in patients mainly suffering from classic NMO forms (optic neuritis, transverse myelitis) can be assumed by those with less represented, brain forms of NMOSD (brainstem forms, diencephalic syndrome, area postrema syndrome).

Only seropositive patients were included in the clinical programme. There are some differences apparent between seropositive and seronegative patients based on age onset, gender ratios, clinical course, which questions whether these patients represent a distinct clinical subgroup of NMO compared to patients with AQP4-mediated disease. Therefore, the extrapolation of the results to these patients may be problematic.

A number of uncertainties are referred to the effect of eculizumab on some populations:

- The limited number of elderly patients (n=9; 3 on placebo, 6 on eculizumab) does not allow concluding on the effect of eculizumab in this population.
- No children/adolescents were included in Study 301. A dedicated study is conducted and results are expected by October 2021 as part of the pediatric investigational plan.

3.4. Unfavourable effects

Upper respiratory infection, headache, nasopharyngitis, nausea, urinary tract infection, back pain, diarrhoea were the most frequently reported AEs in patients treated with eculizumab. Overall, the AE profile is consistent with that known for eculizumab in other indications, with no unexpected findings.

3.5. Uncertainties and limitations about unfavourable effects

Since only 9 elderly patients (3 on placebo, 6 on eculizumab) were enrolled in NMOSD program it is not possible to obtain any reliable safety conclusion in this population.

No data on children/adolescents are available and results from the specific study agreed in the PIP will not be available until 2021.

Given the low prevalence of NMOSD, drug exposure can be considered acceptable for the short-term safety assessment of eculizumab. As for the long-term safety profile, the safety database is still limited (n=119) and followed over a relatively short period for drawing a conclusion. The long-term efficacy of eculizumab in this population needs to be further documented. Therefore the results from the currently ongoing Study ECU-NMO-302 will have to be submitted.

3.6. Effects Table

Table 41 Effects Table for Soliris for NMOSD

Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects					
Time to first adjudicated-trial relapse rate	%	3.1	42.6	HR (95% CI)= 0.058 (0.017, 0.197)	Study ECU-NMO-301
Time to first on trial relapse by treating physician	%	14.6	61.7	HR (95% CI)= 0.180 (0.095, 0.343)	
Adjusted adjudicated On-trial ARR (95% CI)		0.016 (0.005, 0.050)	0.350 (0.199, 0.616)	Rate Ratio = 0.045 (0.013, 0.151;p<0.0001)	
Adjusted On-trial ARR by treating physician (95% CI)		0.066 (0.036, 0.120)	0.446 (0.272, 0.732)	Rate Ratio = 0.147 (0.078, 0.278;p<0.0001)	
Change in EDSS score EOS mean (SD)		-0.18 (0.814)	0.12 (0.945)	Most of patients did not relapse (p=0.0597)	
Change from historical patient level adjusted On-trial ARR by treating physician	Median	-1.442 for Ecu/Ecu	-1.923 for Control/Ecu	An improvement for those started eculizumab Response maintained for treated patients	Study ECU-NMO-302
Unfavourable Effects					
Upper respiratory infection	%	29.2	12.8	AE profile is consistent with that known for eculizumab in other indications	Study ECU-NMO-301
Headache	%	22.9	23.4		
Nasopharyngitis	%	20.8	19.1		
Nausea	%	16.7	25.5		
Urinary tract infection	%	13.5	21.3		
Back pain	%	14.6	12.8		
Diarrhoea	%	15.6	14.9		

Abbreviations: ARR (Annualized Relapse Rate); EOS (End of Study)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Relapses are the principal contributors to NMO-related disability. Thus, reducing the frequency and severity of relapses is a key therapeutic goal. Eculizumab significantly reduced the relapse rate in NMOSD patients compared to placebo. The difference was statistically significantly shown when both relapses were assessed by the treating physician and when they were confirmed by an independent adjudication

committee. This was also supported by the reduction of 95% over placebo in annualized relapse rate. There is a delay in the relapse rate in the active patients with NMOSD who received eculizumab mostly on top of the current immunosupressors. From a clinical perspective, this represents a clinically meaningful benefit.

Overall, the AE profile is consistent with that known for eculizumab in other indications, with no unexpected findings. Given the low prevalence of NMOSD, drug exposure can be considered acceptable for the short-term safety assessment of eculizumab. As for the long-term safety profile, the safety database is still limited regarding the number of patients and the length of follow-up. The available safety information of eculizumab in the already authorised indications can be taken as supportive taking into account that for several conditions (aHUS, gMG) patients have been treated with the same dosing regimen.

3.7.2. Balance of benefits and risks

No drug or treatment has been studied in NMOSD in randomized, controlled studies. Therapeutic recommendations are mainly based on results from retrospective cohort analyses and uncontrolled trials. Study ECU-NMO-301 was a prospective, randomized, study controlled with placebo, so that the evidence provided was higher than that available at present.

Results from the study are positive, and the use of eculizumab in adults with relapsing NMOSD patients with anti-aquaporin-4 (AQP4) antibody-in most of the cases on top of immnusopressor based therapy, postponed the following relapse. This benefit was observed with a known safety profile which seems tolerable enough in the current disease.

Within the submitted study, two groups of patients were unrepresented or poorly reflected. The former is the a priori a population with better prognosis (either, de novo patients or those with fewer relapses than the included in the inclusion criteria) and the latter was the group of patients without immunosupressor-based therapy. With this in mind, the MAH provided the results of a subgroup analysis in order to document the efficacy of eculizumab in some subpopulations less represented in the study and support a broad indication. However, despite the positive results from these analyses, the limitations associated to these ones hinder to reach a clear conclusion. Nevertheless, based on the mechanism of action of the drug, the CHMP was of the opinion that the final wording of the indication should not be strictly reflected the inclusion criteria of the pivotal study. On the other hand, it was also agreed that some limitations should be included in the indication taking into consideration the original intention of the study eligibility criteria to exclude patients with monophasic disease.

Therefore, and according to the available evidence, eculizumab could be indicated in adult patients for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease (see section 5.1).

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Soliris is positive

In addition, the CHMP considered that the applicant should submit the following data:

- The submission of the long-term storage data by the end of Dec 2020.

- The submission of the final results of currently ongoing Study ECU-NMO-302.

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, II and IIIB

Extension of Indication to include treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and Annex II of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP was updated to version 19.3.

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

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH shall agree the details of a controlled drug distribution system and educational material including a patient safety card with each National Competent Authority and must implement such programmes nationally to ensure that:

1. All healthcare practitioners who may prescribe eculizumab receive the appropriate educational material.

2. All patients being treated with eculizumab receive a patient safety card.

3. Drug distribution will only be possible after written confirmation that the patient received or will receive meningococcal vaccination and/or antibiotic prophylaxis.

4. Vaccination reminders are sent to the prescribers.

The educational material should be agreed with the National Competent Authority and should contain the following:

- Summary of product characteristics
- Physician's guides to prescribing
- Patient's/carer's information brochures
- Patient safety card

The physician's guides to prescribing should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection and sepsis, especially of *Neisseria meningitidis* and other *Neisseria species*, including disseminated gonorrhoeae.
- All patients must be monitored for signs of meningococcal infection.
- The need for patients to be vaccinated against Neisseria meningitidis two weeks prior to receiving eculizumab and/or to receive antibiotic prophylaxis.
- The requirement to vaccinate children against pneumococcus and Haemophilus influenzae before eculizumab treatment.
- There is an important risk of Aspergillus infection in patients treated with eculizumab. The healthcare professionals should be advised to look for risk factors and signs and symptoms of Aspergillus infection. Practical advice should be included to mitigate the risk.
- The risk of infusion reactions including anaphylaxis and advice on post-infusion monitoring.
- The risk of developing antibodies to eculizumab.

- Risk of serious haemolysis following eculizumab discontinuation and postponement of administration, its criteria, the required post-treatment monitoring and its proposed management (PNH only).
- Risk of severe thrombotic microangiopathic complications following eculizumab discontinuation and postponement of administration, its signs, symptoms, monitoring and management (aHUS only).
- Risk of substantial disease exacerbation or relapse following eculizumab discontinuation (refractory gMG only)
- The need to explain to and ensure understanding of by patients/carers:
    - the risks of treatment with eculizumab
    - the signs and symptoms of sepsis/severe infection and what action to take
    - the patient's/carer's guides and their contents
    - the need to carry the patient safety card and to tell any healthcare practitioner that he/she is receiving treatment with eculizumab
    - the requirement for vaccinations/antibiotic prophylaxis
    - the enrolment in the registries
- Details of the PNH and aHUS registries and how to enter patients.

The patient's/carer's guides should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection, especially *Neisseria meningitidis* and other *Neisseria species*, including disseminated gonorrhoeae.
- Signs and symptoms of severe infection and the need to obtain urgent medical care.
- The patient safety card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with eculizumab.
- The importance of meningococcal vaccination prior to treatment with eculizumab and/or to receive antibiotic prophylaxis.
- The need for children to be vaccinated against pneumococcus and Haemophilus influenzae before eculizumab treatment.
- The risk of infusion reactions with eculizumab, including anaphylaxis, and the need for clinical monitoring post-infusion.
- Risk of severe thrombotic microangiopathic complications (in aHUS) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations.
- Risk of serious haemolysis (in PNH) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations.

- Risk of substantial disease exacerbation or relapse (in refractory gMG) following discontinuation/postponement of eculizumab administrations and recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations.
- Enrolment in the PNH and aHUS registries.

The patient safety card should contain:

- Signs and symptoms of infection and sepsis.
- Warning to seek immediate medical care if above are present.
- Statement that the patient is receiving eculizumab.
- Contact details where a health care practitioner can receive further information.

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense eculizumab, a reminder in order that prescriber/pharmacist checks if a (re)-vaccination against Neisseria meningitidis is needed for his/her patients on eculizumab.

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

Extension of Indication to include treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and Annex II of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP was updated to version 19.3.

Summary

Please refer to the scientific discussion Soliris-H-C-791-II-0105 for further information.