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Human Medicines Division

# Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

## Soliris

Eculizumab

Procedure no: EMEA/H/C/000791/P46/063

## Note

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

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| Status of this report and steps taken for the assessment | | | | |
|---|---|---|---|---|
| **Current step** | **Description** | **Planned date** | **Actual Date** | **Need for discussion** |
| ☐ | Start of procedure | 26 Feb 2024 | 26 Feb 2024 | ☐ |
| ☐ | CHMP Rapporteur Assessment Report | 02 Apr 2024 | 09 Apr 2024 | ☐ |
| ☐ | CHMP members comments | 15 Apr 2024 | 15 Apr 2024 | ☐ |
| ☐ | Updated CHMP Rapporteur Assessment Report | 18 Apr 2024 | n/a | ☐ |
| ☒ | CHMP adoption of conclusions: | 25 April 2024 | 25 April 2024 | ☐ |

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# 1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory demyelinating disease of the central nervous system characterized by attacks of optic neuritis, longitudinally extensive transverse myelitis, and less frequently, postrema syndrome, acute brainstem syndrome, acute diencephalic clinical syndrome or symptomatic cerebral syndrome. NMO is a severe condition, which results in early and permanent neurological disability. The anti-aquaporin-4 (AQP4) serum autoantibody is a specific biomarker for NMOSD, although 12% percent of patients with a clinical diagnosis of NMOSD are seronegative for AQP-4-IgG.

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 seropositive NMOSD patients.

The use of eculizumab in this condition is based on the role of the complement activation in the disease pathogenesis in patients with NMOSD. 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.

Eculizumab was approved by the European Commission on 26 Aug 2019 for the 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.

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

On January 2024, the MAH submitted a paediatric study for Soliris (eculizumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. These data are submitted as part of the post-authorisation measure.

# 2. Scientific discussion

## *2.1. Information on the development program*

A Paediatric Investigation Plan (PIP) has been agreed with the Paediatric committee (PDCO) for eculizumab in the treatment of Neuromyelitis Optica Spectrum Disorder (NMOSD) including the following measures:

- Study 1: A Phase 2/3 Open-Label Safety and Efficacy Study of Eculizumab in Pediatric Patients with Relapsing Neuromyelitis Optica Spectrum Disorder (ECU-NMO-303).

- Study 4: Observational Paediatric Data Collection Study on NMOSD pediatric patients.

No quality-related or non-clinical measures were required.

The original Pediatric Investigational Plan (PIP) (EMEA-000876-PIP03-14) for eculizumab in the treatment of relapsing NMO was submitted to EMA on 12 May 2014.

On 25 Oct 2019 Alexion submitted a request seeking agreement from the Paediatric Committee (PDCO) for a modification. This modification aimed to reduce the number of participants evaluable for

the primary analysis of ECU-NMO-303 from 12 to 10. The proposal was grounded in updated estimates derived from the results of Study ECU-NMO-301. Additionally, it proposed a two-year delay in completing the study due to recruitment challenges identified during the pediatric development program. The PDCO adopted a favourable Opinion on the modification.

On 17 Nov 2022 Alexion requested a modification to reduce the number of participants in Study ECU-NMO-303 from at least 10 participants to at least 2 participants evaluable for the primary analysis (EMEA-000876-PIP03-14-M06). On 14 Apr 2023, the EMA's decision confirmed the PDCO's Opinion to refuse the requested changes to reduce the number of participants in Study ECU-NMO-303, and that it was appropriate to grant a waiver on the grounds that conducting clinical trials was deemed not feasible.

## *2.2. Information on the pharmaceutical formulation used in the study*

Eculizumab (Soliris) was administered as vials containing 300 mg concentrate for solution for infusion (10 mg/ml). After dilution, the final concentration of the solution to be infused is 5 mg/ml.

No specific paediatric formulation is available.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH has submitted a final report for Study ECU-NMO-303: A Phase 2/3 Open-Label, Single-Arm Trial to Evaluate the Safety and Activity of Eculizumab in Pediatric Patients with Relapsing Neuromyelitis Optica Spectrum Disorder.

**Table 1: Listing of Clinical Studies**

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Participants (Planned/ Treated) | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| *Uncontrolled Clinical Studies* | | | | | | | | |
| Efficacy, Safety, PK, and PD | ECU-NMO-303 | M5.3.5.2 | Evaluate safety and efficacy of eculizumab in pediatric participants; characterization of eculizumab PK and PD in pediatric participants with relapsing NMOSD | Phase 2/3, open-label, single-arm, multi-center | Eculizumab was initiated with a weekly weight-based induction regimen.<br>Weight > 40 kg: Induction Period 900 mg qw × 4 doses. Maintenance Phase 1200 mg at Week 4, then q2w<br>Weight 30 to < 40 kg: Induction Period 600 mg qw × 2 doses. Maintenance Phase 900 mg at Week 2, then q2w<br>Weight 20 to < 30 kg: Induction Period 600 mg qw × 2 doses. Maintenance Phase 600 mg at Week 2, then q2w<br>Weight 10 to < 20 kg: Induction Period 600 mg qw × 1 dose. Maintenance Phase 300 mg at Week 1, then q2w | Planned: 15 enrolled in order to achieve 12 evaluable participants<br>Treated: 5 participants | Variable duration of treatment for each participant, with an observed maximum duration of 98.1 weeks from first dose to last dose | Completed; final abbreviated CSR |

Abbreviations: CSR = clinical study report; EOS = end of study; IV = intravenous; NMOSD = neuromyelitis optica spectrum disorder; PD = pharmacodynamics; PK = pharmacokinetics; qw = once weekly; qXw = once every X week(s)

## 2.3.2. Clinical study ECU-NMO-303

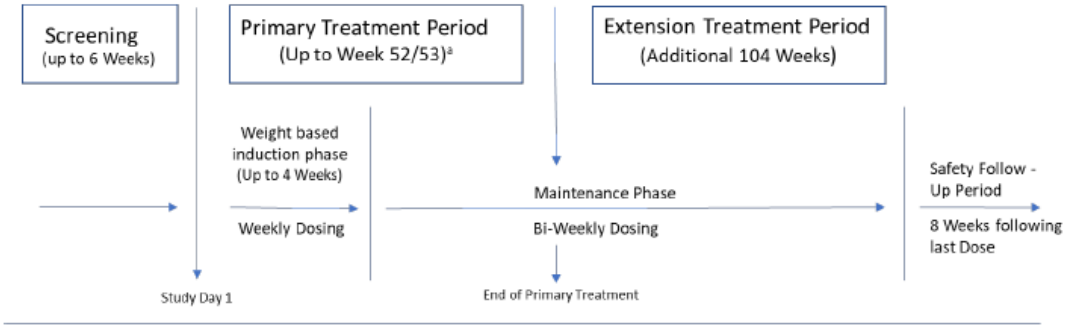
***A Phase 2/3 Open-Label, Single-Arm Trial to Evaluate the Safety and Activity of Eculizumab in Pediatric Patients with Relapsing Neuromyelitis Optica Spectrum Disorder.***

## Description

Study ECU-NMO-303 was a Phase 2/3 open-label, multicentre, single-arm study to evaluate the safety and efficacy of eculizumab in pediatric patients with relapsing NMOSD.

The study consisted of the following periods:

**Figure 1: Study Schema**




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

## Methods

***Study participants***

This study enrolled pediatric participants with NMOSD who were 2 to < 18 years of age and met the study entry criteria.

Main Inclusion Criteria:

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

• Documented vaccination against Haemophilus influenzae type b and Streptococcus pneumoniae infections 2 weeks prior to dosing as per local and country-specific immunization guidelines for the appropriate age group.

• Anti-AQP4 antibody-positive and diagnosis of NMOSD as defined by the 2015 IPND criteria.

• Historical Relapse Rate of at least 2 relapses in the last 2 years, and with at least 1 relapse in the year prior to Screening.

• EDSS score ≤ 7.

• Participants who enter the study receiving supportive IST(s) (eg, corticosteroid, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, or cyclophosphamide) for the prevention of relapse, either in combination or monotherapy, must be on a stable dosing regimen of adequate duration prior to Screening.

***Treatments***

Eculizumab was initiated with a weekly weight-based induction regimen for up to 4 weeks. Thereafter, participants were dosed every 2 weeks. The dosage regimen was based on the participant's body weight.

**Table 2: Body Weight-Based Dosage Regimen of Eculizumab**

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

a Day 1 and Maintenance Period dose regimen was based on the current visit's recorded body weight. If site/institution policies prohibited study intervention to be prepared on the day of visit, the weight from the most recent study visit was used.
b During the initial Induction Period, the dose regimen was based on the participant's weight on Day 1 (Visit 2).
c All participants remained in the same weight cohort throughout the Induction Period, regardless of change in weight.

***Objective(s)***

Primary Treatment Period

*Primary Objective*

- Evaluate the efficacy of eculizumab in relapsing pediatric patients with NMOSD.

*Secondary Objectives*

- Evaluate the safety and tolerability of eculizumab treatment in relapsing pediatric patients with NMOSD.
- Evaluate the efficacy of eculizumab by additional efficacy measures including:
  - Disease-related disability
  - Quality of life
  - Change in ophthalmologic examination findings
- Describe the PK and PD of eculizumab in relapsing pediatric patients with NMOSD
- Evaluate the efficacy of eculizumab by additional efficacy measures including Quality of life

Extension Treatment Period

- Characterize long-term safety of eculizumab treatment in pediatric patients with NMOSD.
- Characterize long-term efficacy of eculizumab treatment in pediatric patients with NMOSD

***Outcomes/endpoints***

Efficacy

- The change from Baseline in the Annualized Relapse Rate (ARR) at 52/53 Weeks.
- Time to First Relapse (TFR).
- Change from Baseline in EDSS score at 52/53 weeks in patients ≥ 5 years of age.

• Change from Baseline in the HAI score at 52/53 weeks.

• Change from Baseline in PedsQL at 52/53 weeks in patients ≥ 5 years of age.

• Change from Baseline in PedsQL Parent Proxy at 52/53 weeks in patients < 5 years of age.

• Change from Baseline in Visual Acuity (VA) as measured by the Snellen or LEA symbols Eye Chart examination at 52/53 weeks in all patients.

• Change from Baseline in Confrontational Visual Fields (VF) as measured during ophthalmologic examination at 52/53 weeks in all patients.

• Change from Baseline in color vision as measured during ophthalmologic examination at 52/53 weeks in all patients.

• Change from Baseline in the EQ-5D-Y score for patients ≥ 8 years of age and EQ-5D-Y Proxy score for patients aged between 5-7 years, at 52/53 weeks

PK/PD

• Changes in serum eculizumab concentration over time.

• Changes in serum free complement protein 5 (C5) concentrations and in vitro hemolytic activity over time.

Safety

• Incidence of TEAEs, SAEs, and AEs leading to study drug discontinuation.

• Incidence of ADA.

• Changes from Baseline in vital signs, ECG parameters, and clinical laboratory assessments.

• Change from Baseline in both weight and height.

The safety and efficacy endpoints of the Primary Treatment Period will be evaluated during the Extension Treatment Period.

***Sample size***

The study planned to enrol approximately 15 participants to include the minimum of 12 evaluable participants. Of the 12 evaluable participants, at least 3 of the participants were planned to be aged 2 to < 12 years at the time of enrolment, and at least 5 participants were planned to be aged 12 to < 18 years at the time of enrolment.

***Randomisation and blinding (masking)***

This study was an open-label single-arm study.

***Statistical Methods***

Summary statistics were computed and displayed by visit where applicable. Descriptive statistics for continuous variables included the number of participants, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies, and percentages were presented. Graphical displays were provided as appropriate. All statistical analyses were performed based on a 2-sided Type I error of 5% unless noted otherwise. Missing data were not imputed.

## Results

### *Participant flow*

Study ECU-NMO-303 was terminated by Alexion, as only 5 of 12 participants were enrolled due to difficulty in recruitment. One of the 5 participants withdrew after completing the Primary Treatment Period, and 2 participants withdrew during the Extension Treatment Period. These 3 participants discontinued from the study to enrol in another Alexion pediatric NMOSD study (Study ALXN1210-NMO-317). The other 2 participants discontinued prior to completing the Primary Treatment Period.

**Table 3: Participant Disposition – All Treated Participants**

| | **Eculizumab (N = 5) n (%)** |
|---|---|
| Treated | 5 |
| Completed the Primary Treatment Period | 3 (60.0) |
| Discontinued the Primary Treatment Period | 2 (40.0) |
| Adverse Event | 1 (20.0) |
| Withdrawal by Participant | 1 (20.0) |
| Continuing in the Extension Treatment Period | 2 (40.0) |
| Completed the Extension Treatment Period | 0 (0.0) |
| Discontinued the Extension Treatment Period | 2 (40.0) |
| Other | 2 (40.0) |
| Discontinued the Study | 5 (100.0) |
| Adverse Event | 1 (20.0) |
| Withdrawal by Participant | 1 (20.0) |
| Other | 3 (60.0) |

Notes: Percentages are based on the number of participants in the treatment group.
The Other category for discontinuation reasons includes transition to Study ALXN1210-NMO-317.

Two global protocol amendments (one of them after the original protocol was released) and 6 local amendments were implemented for this study. The main changes in the conduct of the study that were implemented by global protocol amendments were the following ones:

- Criteria on vaccination against Neisseria meningitidis, Haemophilus influenzae type b and Streptococcus pneumoniae were updated.
- The number of participants enrolled was reduced from 15 to 12, and the number of evaluable participants for the primary analysis was reduced from 12 to 10.
- ECG assessment was added to Week 26.
- Text was added to specify that supportive ISTs was to remain stable during the Screening Period.
- Clarifications on the exclusion of participants with active infection within 14 days prior to study administration and those currently treated with a biologic medication that may affect immune system functioning were added.

***Recruitment***

This study was conducted at 4 centres in 4 countries (Canada, Spain, Italy, and Japan).

First participant first visit: 14 Jan 2020

Last participant last visit: 31 Jul 2023

***Baseline data***

The median (min, max) age at first dose for the 5 participants was 13 (5, 16). Two participants were in the 2 to < 12-year age category and 3 participants were in the 12 to < 18 age category. Four of the 5 (80%) participants were female, and 3 (60%) were not Hispanic or Latino. All 5 enrolled patients were ≥40 kg with a mean weight [SD] of 52.70 [6.852] kg.

Per protocol, the study was comprised of participants with NMOSD as defined by the 2015 IPND criteria and were anti-AQP4 antibody-positive. The historical median (min, max) ARR within 24 months prior to Screening was 2.24 (1.4, 7.4).

The median (min, max) age at NMOSD diagnosis was 10 (4, 16) years. The 2 most commonly reported initial clinical presentations of NMOSD were: acute myelitis (3 [60%]) and acute brainstem syndrome (2 [40%]). The median (min, max) time between initial NMOSD clinical presentation and first dose of study intervention was 2.07 (0.29, 5.96) years. All 5 participants previously received medications for NMOSD treatment.

All 5 enrolled participants received eculizumab treatment. The median (min, max) number of infusions per participant was 29 (3, 52). All 5 participants had 100% compliance. The full intended dose was administered at all infusions. No relapses were reported during the study; therefore, no plasmapheresis/plasma exchanges were reported for On-Trial Relapses.

***Number analysed***

Full Analysis Set: 5 participants

Safety Analysis Set: 5 participants

PK/PD Analysis Set: 5 participants

Completed the Primary Treatment Period: 3 participants

***Efficacy results***

All 5 enrolled participants received eculizumab treatment. The median (min, max) number of infusions per participant was 29 (3, 52). All 5 participants had 100% compliance (Table 10). The full intended dose was administered at all infusions.

Primary Efficacy Endpoints

The co-primary efficacy endpoints were:

- Change between the Baseline ARR and the On-Trial ARR at 52/53 weeks.
- Time to first On-Trial Relapse.

No relapses were reported for any participant during the Primary and Extension Treatment Periods, with 4.89 participant-years of follow-up.

**Table 4: On-Trial Annualized Relapse Rate During the Primary Treatment Period - Full Analysis Set**

| Variable | Statistic | Eculizumab (N = 5) |
|---|---|---|
| On-trial Participant ARR[a] | n | 5 |
| | Mean (SD) | 0.00 (0.000) |
| | Median | 0.00 |
| | Q1, Q3 | 0.00, 0.00 |
| | Min, Max | 0.00, 0.00 |
| Change in ARR between historical ARR[b] and on-trial ARR | n | 5 |
| | Mean (SD) | -3.01 (2.504) |
| | Median | -2.24 |
| | Q1, Q3 | -2.53, -1.44 |
| | Min, Max | -7.41, -1.44 |
| | 95% CI for Mean | (-6.120, 0.098) |
| On-trial study-level ARR | | |
| Total number of relapses | Sum | 0 |
| Total number of participant -years | Sum | 3.34 |
| Study-level ARR | Rate[c] | 0.000 |
| | 95% CI[d] | (NA, 1.108) |

a ARR is calculated as the number of relapses for each participant divided by the number of years in the Primary Treatment Period for that participant; summary statistics across all participants are presented.
b Historical ARR was based on 24 months prior to screening.
c Calculated as the total number of relapses during the Primary Treatment Period from all participants, divided by the total number of participant-years in the Primary Treatment Period.
d Exact confidence interval based on poisson regression.

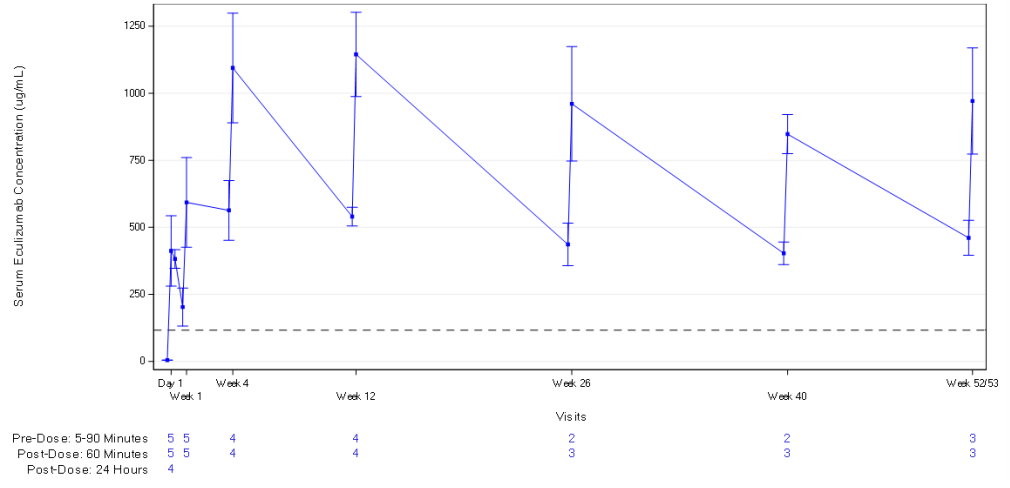
Secondary Efficacy Endpoints

- Change from Baseline in EDSS Score at 52/53 Weeks: The median (min, max) change from Baseline in EDSS score at Week 52/53 for the 3 participants completing the Primary Treatment Period was 0.0 (−3.0, 1.0), with a decrease in score representing improvement.
- Change from Baseline in the Hauser Ambulatory Index Score at 52/53 Weeks: No changes were observed among the 3 participants at Week 52/53.
- Change from Baseline in Self-Reported Pediatric Quality of Life Inventory (PedsQL) Scores at 52/53 Weeks: The median (min, max) change from Baseline in PedsQL total score at Week 52/53 in participants ≥ 5 years of age was −4.48 (−19.57, 0.00). The median (min, max) change from Baseline in PedsQL Psychosocial Health Summary Score and Physical Health Score at Week 52/53 was −5.38 (−25.00, 0.00) and −4.02 (−9.38, 0.00), respectively.
- Change from Baseline in Visual Acuity (VA) as Measured by the Snellen or LEA Symbols Eye Chart Examination at 52/53 Weeks in All Participants: No meaningful changes in VA were observed among the 3 participants completing Week 52/53 on trial. All 3 participants at Week 52/53 had a VA between 20/20 - 20/29.
- Change from Baseline in Confrontational Visual Fields (VF) as Measured During Ophthalmologic Examination at 52/53 Weeks in All Participants: No meaningful changes in VF were observed among the 3 participants completing Week 52/53 on study.
- Change from Baseline in Color Vision as Measured During Ophthalmologic Examination at 52/53 Weeks in All Participants: All assessments of color vision were normal throughout the study.

PK

• Median (min, max) serum eculizumab concentration was 420.0 (200.0, 537.0) µg/mL at 60 minutes after dosing on Day 1. For all participants with available data, serum eculizumab concentrations were maintained above the therapeutic threshold of 116 µg/mL for complete terminal complement inhibition of free C5 through Week 52/53 (Figure 2).

**Figure 2: Mean (+/- SD) Serum Eculizumab Concentration (µg/mL) during the Primary Treatment Period, Linear Scale - PK/PD Analysis Set (Study ECU-NMO-303)**

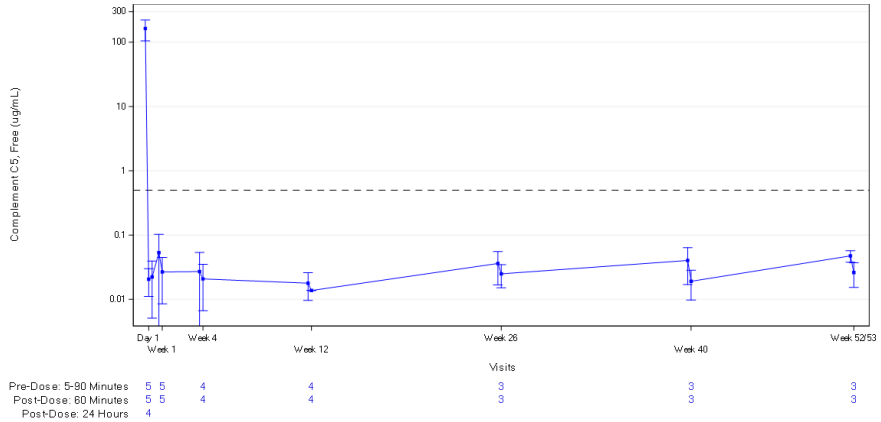



Baseline is defined as the last available assessment prior to the first study intervention infusion.
Eculizumab below the lower limit of quantification (BLOQ) values were imputed as lower limit of quantification (LLOQ)/2 = 4.69 ug/mL; all baseline values were BLOQ.
Abbreviations: PD = pharmacodynamic(s); PK = pharmacokinetic(s); SD = standard deviation

PD

• The median (min, max) Baseline serum free C5 concentrations for the 5 participants was 157.0 (93.40, 224.00) µg/mL, and 60 minutes following administration of eculizumab on Day 1, the median serum free C5 concentration was 0.0137 (0.014, 0.032) µg/mL. Serum free C5 levels were suppressed below 0.5 µg/mL, the concentration necessary for complete terminal complement inhibition post dose on Day 1 through Week 52/53 (Figure 3).

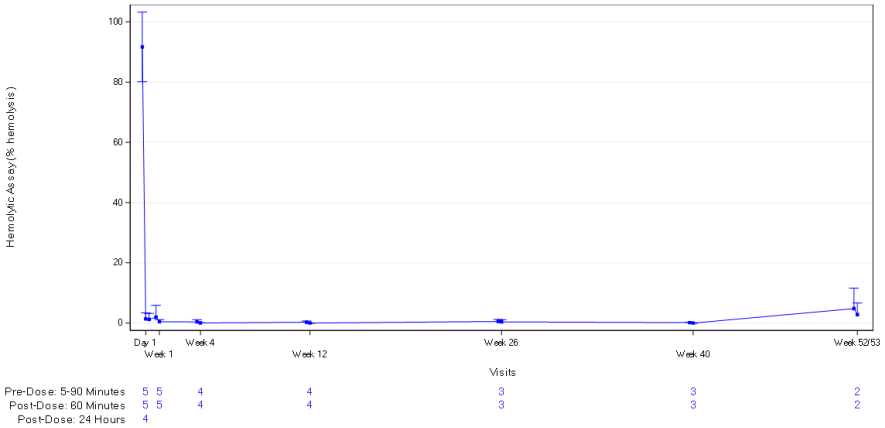
**Figure 3: Mean (+/- SD) Serum Free C5 (µg/mL) during the Primary Treatment Period, Semi-Log Scale - PK/PD Analysis Set (Study ECU-NMO-303)**




Baseline is defined as the last available assessment prior to the first study intervention infusion.
Free C5 level below lower limit of quantitation (0.0274 µg/mL) was analyzed as 0.0137 µg/mL.
Abbreviations: C5 = complement component 5; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SD = standard deviation

• Median serum hemolytic complement activity was reduced by 99.7% at 60 minutes postdose on the Day 1 Visit, and was sustained through Week 52/53.

**Figure 4: Mean (+/- SD) Hemolysis (%) during the Primary Treatment Period, Linear Scale - PK/PD Analysis Set (Study ECU-NMO-303)**




Baseline is defined as the last available assessment prior to the first study intervention infusion.
Abbreviations: PD = pharmacodynamic(s); PK = pharmacokinetic(s); SD = standard deviation

***Safety results***

The Safety Analysis Set included all 5 participants who received at least 1 dose of eculizumab.

A total of 46 TEAEs were reported among all 5 enrolled participants. The majority of events (35/46 [76.1%]) were classified as not related to eculizumab treatment by the Investigator.

There were 11 TEAEs reported in 3 participants that were assessed as related to eculizumab by the Investigator:

- liver function test increased (5 events in 1 participant)
- encephalitis meningococcal
- nausea
- vomiting
- pyrexia
- pain in extremity
- amenorrhea

The majority of events (42/46 [91.3%]) were classified as Grade 1 or 2 in severity. Each of the 3 events classified as Grade 3 were liver function test increased, and were reported for 1 participant. One Grade 4 event of encephalitis meningococcal was reported. The participant was monitored and promptly evaluated in a manner consistent with established risk mitigation procedures in the protocol.

During the entire study period, 2 TESAEs were reported in 2 participants: liver function test increased and encephalitis meningococcal. Both TESAEs were assessed as related to eculizumab by the Investigator, and the 2 events subsequently resolved.

No deaths were reported.

Discontinuations and/or Dose Modifications due to Adverse Events

The participant who reported the TESAE of liver function test increased also reported 4 nonserious liver function test increased events. One of the 4 nonserious liver function test increased events resulted in the only study intervention withdrawal due to an AE during the study.

The participant was a 5-year-old who was diagnosed with NMOSD at 4 years of age. The participant weighed 47.1 kg and was 114.9 cm tall at Baseline. The participant received the first dose of eculizumab 900 mg on Day 1 (14 Jan 2021). The participant received 4 induction phase infusions and 5 maintenance phase infusions.

The last infusion was received on. The participant experienced a Grade 1 liver function test increased event that was classified as related to treatment. On (Day 111) the LFT levels were elevated and considered a Grade 3 event with the following laboratory values: ALT 291 U/L, AST 268 U/L, and total bilirubin 2.0 µmol/L. On (Day 133) LFTs remained elevated with ALT 254 U/L and AST 252 U/L. An abdominal ultrasound was normal. On (Day 135), the participant was hospitalized for elevated LFTs that was considered an SAE, and a liver biopsy was performed. The pathology demonstrated the evidence of mild inflammation with some fibrosis and no steatosis. The participant was diagnosed with transaminitis. On (Day 136) the participant was discharged from the hospital in stable condition. The Grade 3 nonserious LFT increased event resolved on with the following laboratory values: ALT 67 U/L and AST 63 U/L.

Adverse Events of Special Interest

One participant reported an event of encephalitis meningococcal.

The participant was a 15-year-old  who was diagnosed with NMOSD at 10 years of age. The participant weighed 63 kg and was 173 cm tall at Baseline. The participant received the first dose of eculizumab 900 mg on Day 1 . The participant received a total of 3 induction phase infusions.

On (Day 22) the participant presented with nausea, vomit, and fever (all categorized as moderate intensity) that worsened rapidly and the participant subsequently developed a state of confusion. That same day, the participant was hospitalized and placed in the intensive care unit first and subsequently in infectious diseases for suspected meningitis. On (Day 23), a Grade 4 SAE of encephalitis meningococcal meningoencephalitis was reported due to Neisseria meningitis (infection serotype unknown). A CT of the brain showed no ongoing supratentorial or sub tentorial blood loss, the normal amplitude of the ventricular system which laid on the axis, midline axes, flattened convexity grooves with suspected minimal subcortical white matter hypodensity bilateral frontally suspected edematous changes.

The participant had a prompt clinical recovery with the resolution of fever and presenting symptoms. On (Day 38), the event was considered resolved, and the participant was discharged from the hospital. After the occurrence of this life-threatening SAE, the participant discontinued from the study during the PTP.

Evaluation of Clinical Laboratory Tests and Other Safety Evaluations

Most laboratory findings were not clinically significant. One participant had clinically significant increases in liver function tests starting on Day 69.

No clinically meaningful findings were observed in the vital signs assessments (body temperature, heart rate, respiratory rate, diastolic blood pressure, systolic blood pressure, weight and height), ECG assessments (PR duration, QRS duration, QT duration, RR duration, QTcF, ventricular rate) or physical examination assessments (weight, height and BMI).

Immunogenicity

No treatment-emergent antidrug antibody (ADA) positive responses were observed following eculizumab treatment at any timepoint.

## 2.3.3. Discussion on clinical aspects

The efficacy and safety profile of eculizumab in anti-AQP4 antibody-positive NMOSD patients was established in adults. Two studies were conducted in this population: a pivotal study (Study ECU-NMO-301) and its long-term extension (Study ECU-NMO-302).

A pediatric study is now submitted as part of the post-authorisation measure. The use of eculizumab (an anti-C5 mAb) in this population is based on the approved use in adult patients and the claimed similarity of the condition in both populations.

## Design and conduct of clinical studies

Study ECU-NMO-303, is a Phase 2/3 open-label study to evaluate the efficacy and safety of eculizumab in pediatric patients aged 2 to < 18 years with relapsing NMOSD. The study was conducted in Canada, Italy, Japan and Spain. Due to difficulty in recruitment the study was prematurely terminated by the MAH as only 5 of 12 participants were enrolled due to difficulty in recruitment.

Patient population

This study enrolled male and female pediatric participants aged 2 to < 18 years with relapsing NMOSD. Eligible participants were anti-AQP4 antibody-positive with a diagnosis of NMOSD as defined by the 2015 IPND criteria. Participants were also required to have experienced at least 2 relapses in the last 2 years, and with at least 1 relapse in the year prior to Screening.

During the study patients could be treated with ISTs (eg, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, or cyclophosphamide) either in combination or monotherapy, at stable doses.

A total of 5 patients were enrolled in the study. Only 3 out 5 enrolled patients completing the Primary Treatment Period and none of them completing the Extension Treatment Period. These three patients were enrolled in another study (ALXN1210-NMO-317)[1].

Most of the patients included in the study were female (80%). Mean age was 13 years (2 patients in the <12 year group and 3 in the 12 to <18 year group). All 5 enrolled patients were ≥40 kg.

Patients included in the study presented acute myelitis in 3 cases and acute brainstem syndrome in 2 cases, with a median duration of the condition of 10 years from diagnosis. All of them had previously received medications for NMOSD treatment. Corticosteroids, azathioprine and tacrolimus were reported to be concomitantly used during the study.

Treatment regimen

No specific dose-response studies have been conducted for this indication. Patients received a weekly weight-based induction regimen. The selected dosing regimens were those previously approved for paediatric patients with aHUS and gMG based on the patient's body weight. Since all patients were in the body weight range > 40 kg, subjects received the dosing regimen for adult patients.

According to the PK and PD data obtained in the 5 participants, serum eculizumab concentrations achieved with the treatment were above the therapeutic threshold. Similarly, the complete inhibition of free C5 and haemolysis was shown in these patients.

[1] A Phase 2/3, Open-label, Historical-controlled, Single-arm, Multicenter Study to Evaluate the Efficacy, Pharmacokinetics, Pharmacodynamics, and Safety of Ravulizumab in Children and Adolescents With Aquaporin-4 antibody Positive (AQP4-Ab [+]) Neuromyelitis Optica Spectrum Disorder (NMOSD)

### Efficacy data

Efficacy was based on the effect of eculizumab on the occurrence of relapses (on-trial relapse rate and time to first on-trial relapse). Since disability in NMOSD is strongly associated with relapses it appears to be relevant measures.

Secondary endpoints were based on clinical assessments (focusing on changes in EDSS score, Hauser Ambulatory Index, visual function) and quality of life variables (EQ-5D).

The selected efficacy variables are validated scales used in the clinical development of medicinal products for the treatment of NMOSD in adults. They are also used in clinical investigation in paediatric patients although with a limited experience.

No relapses were reported during the study. No relevant changes in clinical endpoints were measured. Considering the small number of patients included in the study and the lack of control arm the evidence of the effect based on differences with respect to baseline values is difficult to interpret.

### Safety data

Although the safety data from paediatric patients with NMOSD are consistent with the known safety profile of eculizumab in adult patients with NMOSD and paediatric patients with other conditions and no new adverse events have been reported in this new population, the limited number of patients included in the study ECU-NMO-303 prevents from characterising the safety profile of eculizumab in this population.

## 3. Rapporteur's overall conclusion and recommendation

Eculizumab has shown an effect on the control of relapses in adult NMOSD patients. The MAH has submitted the results from Study ECU-NMO-303 in pediatric NMODS patients aged 2 to 18 years treated with eculizumab. The small number of subjects (only 5 patients were included) and the lack of a control arm, prevents from concluding on the results measured. In this limited context the absence of reported relapses and the reported clinical stability cannot be considered as a proof of efficacy.

The safety data are consistent with the known safety profile of eculizumab in adult NMOSD patients, and paediatric patients with other conditions. However, the reduced safety database is the main limitation.

The MAH is planning to submit a Type II variation for Final Clinical Study Report for Study ECU-MG-303 (Submission due date 06 May 2024). In this procedure the MAH is expected to update the Product Information accordingly. The MAH has expressed the intention of not pursuing an indication in pediatric NMOSD.

### ☒ Fulfilled:

No regulatory action required.