22 June 2023
EMA/319068/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Soliris

International non-proprietary name: eculizumab

Procedure No. EMEA/H/C/000791/II/0126

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

AChE	acetylcholinesterase
AChR(-Ab)	acetylcholine receptor (-antibody)
ADA	Antidrug antibodies
ADRs	Adverse drug reactions
aHUS	atypical Hemolytic uremic syndrome
AUC0-τ	Area under the concentration-time curve over one dosing interval
BLOQ	Below the limit of quantification
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum serum concentration
C_{trough}	Minimum serum concentration
CV	Coefficient of variation
(m)FAS	(modified) full analysis set
EQ-5D-Y	European Quality of Life 5-Dimension Youth version
IST	Immune-suppressive therapy
IV	Intravenous
IVIg	Intravenous immunoglobulin
LLQ	Lower limit of quantification
LRP4	Lipoprotein-related protein receptor 4
LS	Least squares
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
NMOSD	Neuromyelitis optica spectrum disorder
MuSK	Muscle-specific tyrosine kinase
Neuro-QoL	Quality of Life in Neurological Disorders
(g)MG	(generalised) Myasthenia gravis
JMG	Juvenile myasthenia gravis
QMG	Quantitative Myasthenia Gravis
PD	Pharmacodynamics
PE	Plasma exchange

PIP	Paediatric investigation plan
PNH	Paroxysmal nocturnal hemoglobinuria
PK	Pharmacokinetics
Pop-PK	Population PK
QTc	QT interval
QTcB	corrected QT interval by Bazett's formula
QTcF	corrected QT interval by Fredericia's formula
SOC	System Organ Class
TE(S)AE	Treatment-Emergent (serious) adverse event
t½	Elimination half-life
V1	Central volume of distribution

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 November 2022 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of paediatric patients with refractory generalised myasthenia gravis (gMG) for Soliris, based on interim results from study ECU-MG-303; this is an open-label, multicenter, phase 3 study to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of intravenous (IV) eculizumab in paediatric patients aged 6 to less than 18 years with acetylcholine receptor-antibody (AChR-Ab) positive (+) refractory gMG. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to update section 4.8 of the SmPC in order to update the frequency of the list of adverse drug reactions (ADRs) based on cumulative safety data and to introduce minor editorial changes to the PI.

Information relating to orphan designation

Soliris, was designated as an orphan medicinal product EU/1/07/393 on 17 August 2017. Soliris was designated as an orphan medicinal product in the following indication: treatment of myasthenia gravis.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included the EMA Decision(s) P/00074/2022 on the agreement of a paediatric investigation plan (PIP) and the granting of a product-specific waiver.

At the time of submission of the application, the PIP P/00074/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/00074/2022 in October 2022.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Carolina Prieto Fernandez Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	9 November 2022
Start of procedure:	26 November 2022
CHMP Rapporteur Assessment Report	31 January 2023
PRAC Rapporteur Assessment Report	27 January 2023
PRAC members comments	1 February 2023
Updated PRAC Rapporteur Assessment Report	2 February 2023
PRAC Outcome	9 February 2023
CHMP members comments	13 February 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 February 2023
Request for supplementary information (RSI)	23 February 2023
MAH's responses to RSI	24 April 2023
CHMP Rapporteur Assessment Report	23 May 2023
PRAC Rapporteur Assessment Report	26 May 2023
PRAC members comments	31 May 2023
PRAC Outcome	08 June 2023

Timetable	Actual dates
CHMP members comments	12 June 2023
Updated CHMP Rapporteur Assessment Report	16 June 2023
Opinion	22 June 2023
The CHMP adopted a report on similarity of Soliris with Vyvgart on date	22 June 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The purpose of this application is to extend the generalized myasthenia gravis indication for eculizumab to include paediatric patients with refractory AChR-Ab+ gMG. The initially proposed indication was the following:

"Soliris is indicated in adults and children for the treatment of refractory generalized myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive."

Myasthenia gravis (MG) is an autoimmune disorder involving the neuromuscular junction (NMJ) in which there is fatigue of the skeletal musculature, which is potentially life threatening. Weakness of the muscles tends to fluctuate.[3,4]

Subtypes of childhood myasthenia gravis are neonatal MG, which is transient, owing to maternal autoantibodies transferred to foetal circulation; congenital myasthenia syndromes, which are a group of syndromes due to genetic nonimmune-mediated causes; or juvenile myasthenia gravis (JMG), which is acquired MG not related to structural disorders, occurring in childhood or adolescence (i.e. <18 years of age)[1]. JMG patients are subdivided according to the occurrence of the first symptoms as prepubertal (first symptoms before the age of 12 years) and post pubertal (first symptoms after the age of 12 years).[2]

Epidemiology

Two systematic reviews of population based epidemiological studies in MG published in 2010 reported an estimated incidence rate of 5.3 per million person-years (C.I.:4.4, 6.1), range: 1.7 to 21.33 and between 3.0 and 30.0 per million person-years4, respectively. The estimated prevalence rate was 77.7 cases per million.[6] The prevalence of MG in the European Union is estimated at 3.7 in 10,000, equivalent to a total of around 191,000 people[5] . The prevalence and incidence of MG varied substantially across geographies.

In the paediatric population the incidence is estimated to be between 1.0 and 5.0 cases per million person years.[3] A recent population based study found the incidence of juvenile myasthenia gravis to be 1.2 per

[1] Elsakka EE, Elmekky MH, Omar TE. Alex J Pediatr 2021,34:59–66
[2] Marina AD, Trippe H, Lutz S, Schara U. Neuropaediatrics 2014;45:75–83
[3] Carr AS, Carwell CR, McCarron PO, McConville J. BMC Neurology 2010; 10: 46.
[4] McGrogan A, Sneddon S, De Vries CS. Neuroepidemiology 2010; 34: 171-83.
[5] EMA 2017 Recommendation for maintenance of orphan designation at the time of addition of a new indication to the marketing authorization Soliris (eculizumab) for the treatment of myasthenia gravis. https://www.ema.europa.eu/documents/orphan-review/recommendation-maintenance-orphandesignation-time-addition-new-indication-marketing-authorisation_en.pdf

million person years.[7] It is estimated that between 10% and 15% of all cases of myasthenia occur in the paediatric population.[8] This proportion may be higher in Asian populations.[9,10]

Aetiology and pathogenesis

MG is caused by pathogenic autoantibodies that interfere with synaptic transmission at the neuromuscular junction and impair or prevent muscle contraction[6,7,8]. In approximately 85% of cases, circulating antibodies target the AChR itself. In the remaining 15%, approximately half have antibodies against muscle-specific tyrosine kinase (MuSK), while the other half may be positive for autoantibodies against lipoprotein-related protein receptor 4 (LRP4) or other antigens associated with the neuromuscular junction[9,10].

The pathogenic actions of IgG autoantibodies include functional blockade of AChR, accelerated internalization and degradation of AChR, and activation of the complement system. These pathogenic actions result in reduced density of functional AChR and simplification of the NMJ, leading to failure of neuromuscular transmission. Anti-AChR autoantibodies are of the IgG1 and IgG3 subtypes. Anti-MuSK autoantibodies are IgG4 subtype and do not activate the complement pathway[11].

AChR antibodies are less frequent in prepubertal patients than in adolescent and adult patients.

Clinical presentation, diagnosis and prognosis

Fluctuating skeletal muscle weakness with varying degrees and fatigability that worsens with exertion, and improves with rest are the main presenting symptoms of JMG. The first symptoms may develop as early as in the first year of life.

In most cases, initial symptoms are ocular and include ptosis and diplopia, but within 2 to 3 years of onset, the disease usually worsens, and other muscles become affected; this is referred to as gMG[12]. Additional symptoms typically include difficulty chewing, dysphagia, dysarthria, hypophonia, dyspnea, difficulty holding the head upright, and fatigue, marked reductions in the ability to perform activities of daily living and extreme fatigue. Children are at risk of choking or aspiration and are at increased risk of chest infection and episodes of pulmonary failure requiring mechanical ventilation[13 14].

Ocular JMG is associated with younger age at onset with higher rates seen in pre-pubertal children, regardless of race. Post-pubertal JMG more closely mirrors adult MG with a greater proportion of generalized onset and lower rates of spontaneous remission[15,16].

Hospitalizations for gMG exacerbations are common, with the need for respiratory support, including mechanical ventilation secondary to respiratory failure (e.g., myasthenic crisis).

The Myasthenia Gravis Foundation of America (MGFA) Clinical Classification categorizes patients according to clinical evaluation, which in increasing severity can be: ocular MG; mild, moderate, severe generalized symptoms of MG; MG that requires intubation[17].

[6] Gilhus NE, Verschuuren JJ. Lancet Neurology 2015; 14(10), 1023-1036.
7 Gilhus NE. N Eng J Med 2016; 375(26), 2570-2581.
8 Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Neurology 2016; 12(5), 259-268.
9 Meriggioli MN, Sanders DB. Expert Review of Clinical Immunology 2012; 8(5), 427-438.
10 Zhang B et al. Archives of Neurology 2012; 69(4), 445-451.
11 Howard JF et al. Lancet Neurol 2017;16:976-86.
12 Trouth AJ, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Autoimmune Dis. 2012; 2012: 874680.
13 Juel C et al. Orphanet J Rare Dis. 2007
14 Meriggoli MN and Sanders DB. Lancet Neurol. 2009 May; 8(5): 475–490.
15 JPeragallo JH. Paediatric Myasthenia Gravis – American Academy of Ophthalmology (aao.org)
16 O'Connell, K., Ramdas, S., & Palace, J. Frontiers in Neurology 2020, 11, 743.
17 Jaretzki A et al. Neurology 2000;55:16-23.

The diagnosis of myasthenia gravis is confirmed by the combination of relevant symptoms and signs, a positive test for specific autoantibodies and a positive neurophysiological examination, including repetitive nerve stimulation or single-fiber electromyography, and symptomatic improvement following treatment with acetylcholinesterase (AChE) inhibitors.

Children with JMG exhibit higher rates of remission than adults. This includes spontaneous remission and remission following a period of drug therapy. Remission rates also appear to be influenced by ethnic origin. Peri- or postpubertal patients presenting with JMG share more similarities with adult-onset MG. Prepubertal children have the highest rates of spontaneous remission[18].

Management

Treatment of JMG is similar to adult myasthenia gravis. Treatment commonly includes usage of symptomatic medications [anticholinesterases (mainly pyridostigmine)], immune-suppressive therapies (IST) (as azathioprine or corticosteroids with or without steroid-sparing agents), immune-modulating agents, plasma exchange (PE), intravenous immunoglobulin (IVIg), and thymectomy[3].

At the time of this application, the complement inhibitor eculizumab (Soliris) and ravulizumab (Ultomiris), efgartigimod alfa (Vyvgart) and azathioprine (Jayempi) have received regulatory approval for the treatment of gMG in adults.

Children are at particular risk of steroid side effects. Long-term treatment with corticosteroids should use the lowest effective dose to minimize side effects. Maintenance PLEX or IVIg are alternatives to IS drugs in JMG. Thymectomy should be considered in children with generalized AChR antibody–positive MG if the response to pyridostigmine and IS therapy is unsatisfactory; or in order to avoid potential complications of IS therapy.[20]

2.1.2. About the product

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[19].

Eculizumab is approved for use in 4 complement-mediated diseases, namely paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), generalized MG (gMG) and Neuromyelitis optica spectrum disorder (NMOSD).

The purpose of this application is to extend the generalized myasthenia gravis (gMG) indication for eculizumab to include paediatric patients with refractory AChR-Ab + gMG. The finally approved indication was as follows:

"Soliris is indicated in adults and children for the treatment of refractory generalized myasthenia gravis (gMG) in patients aged 6 years and above who are anti-acetylcholine receptor (AChR) antibody-positive."

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

A Paediatric Investigation Plan (PIP) has been agreed with the Paediatric committee (PDCO) for eculizumab

[18] Sanders DB, et al. Neurology 2016; 87(4):419-425.
[19] Soliris SmPC. https://www.ema.europa.eu/en/documents/product-information/soliris-epar-product-information_en.pdf

in the treatment of myasthenia gravis including the following measures:

- Study 1: open-label, multicentre study to evaluate pharmacokinetics, safety, and effect of eculizumab in paediatric patients from 6 to less than 18 years of age with refractory AChR-Ab positive generalized myasthenia gravis and to confirm the selected paediatric dosing in the modelling and simulation study (ECU-MG-303).
- Study 2: Modelling and simulation study to evaluate the use and support dosing regimen of eculizumab in paediatric patients from 6 to less than 18 years of age with refractory AChR-Ab positive generalized myasthenia gravis.
- Study 3: Extrapolation study to evaluate efficacy, pharmacokinetics(PK)/pharmacodynamics(PD), and safety of eculizumab in paediatric patients from 6 to less than 18 years of age with AChR-Ab positive generalized myasthenia gravis.

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

The first PIP was adopted by EMA on 26 Feb 2016. The latest request for modification was approved by EMA on 11 Mar 2022 (EMEA-000876-PIP05-15-M05).

The MAH did not seek protocol assistance at the CHMP.

No CHMP Guideline on the treatment of Myasthenia Gravis is currently available.

2.1.4. General comments on compliance with GCP

According to the MAH all clinical studies have been conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practices.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

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. Since eculizumab is a monoclonal antibody and thus a protein, no Environmental Risk Assessment has been provided with this Type II variation which is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

The eculizumab clinical development program in paediatric population with refractory gMG includes three studies as indicated in the above section.

GCP

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

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

- Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product; Route of Administration; Dosage Regimen	Number of Patients (Planned/ Treated)	Duration of Treatment	Study Status; Type of Report
Efficacy and safety	ECU-MG-303	M5.3.5.2	Assess efficacy, safety, PK, and PD in pediatric patients (6 to < 18 years) with refractory gMG	Phase 3, open-label, multicenter, single treatment arm study in pediatric patients with AChR-Ab + refractory gMG	Eculizumab; IV; body weight-based dosing, administered weekly during the initial Induction Phase[a] and every 2 weeks during the Maintenance Phase[b] and Extension Period.	12/11[c] (enrollment completed)	26-week Primary Evaluation Treatment Period followed by Extension Period of up to 208 weeks	Primary Evaluation Treatment Period complete[d], Extension Period ongoing; interim CSR

a Eculizumab Induction Phase: 900 mg weekly × 4 doses for patients weighing ≥ 40 kg; 600 mg weekly × 2 doses for patients weighing 30 to < 40 kg; 600 mg weekly × 2 doses for patients weighing 20 to < 30 kg; 600 mg weekly × 1 dose for patients weighing 10 to < 20 kg.
b Eculizumab Maintenance Phase: 1200 mg at Week 5, then every 2 weeks for patients weighing ≥ 40 kg; 900 mg at Week 3, then every 2 weeks for patients weighing 30 to < 40 kg; 600 mg at Week 3, then every 2 weeks for patients weighing 20 to < 30 kg; 300 mg at Week 2, then every 2 weeks for patients weighing 10 to < 20 kg.
c Among the 12 enrolled patients, 1 patient did not receive any treatment. Patient withdrew prior to receiving study drug.
d As of the data cutoff date (06 Jan 2022), 10 of the 11 patients had completed the Primary Evaluation Treatment Period and continued into the Extension Period. One patient was ongoing in the Primary Evaluation Treatment Period.
Abbreviations: AChR-Ab = acetylcholine receptor-antibody; CSR = clinical study report; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; gMG = generalized myasthenia gravis

2.3.2. Pharmacokinetics

The purpose of this analysis is to evaluate the emerging paediatric PK data from study ECU-MG-303 (Study number 1 of the PIP) and to confirm that the selected dosing regimen achieves exposures similar to the adult population, thereby addressing study 2 of the PIP.

The specific objectives of this analysis were to:

- Perform an exploratory assessment of eculizumab exposure in paediatric subjects with refractory gMG and overlay with data from adults.
- Update the previously developed eculizumab population PK (Pop-PK) model based on data from studies C08-001, ECU-MG-301 and ECU-MG-302 in adult subjects with refractory gMG, with new data from Study ECU-MG-303 in paediatric subjects with refractory MG and evaluate concordance of pharmacokinetics and eculizumab exposure between the paediatric and adult patient population.
- Perform an exploratory assessment of free C5 and haemolysis response in paediatric subjects with refractory gMG and overlay with data from adults.

Bioanalytical methods

The analysis of Eculizumab, Hemolytic Activity, Free Complement Factor 5, and Anti-Eculizumab Antibodies in Human Serum for study Number ECU-MG-303 employed different analytical methods already validated under Study Numbers 1727-097, 1727-112, 1727-114, 1727-117, and 1727-118.

Test site was Charles River Laboratories, Inc. 54943 North Main Street Mattawan, MI 49071 United States.

Total number of PK samples received: 302 (156 primary and 146 backup)

Total number of antidrug antibodies (ADA) samples received: 127 (65 primary and 62 backup)

In all analytical methods, the results from calibration standards and quality control samples demonstrated acceptable performance of the method for all reported concentrations.

In the case of the study of ADA, 61 samples were screened and all samples were negative.

Pharmacokinetics in the target population

The analysis described in this report included data from the Phase 2 Study C08-001, Phase 3 Studies ECU-MG-301 and ECU-MG-302 (interim data cut-off date September 21, 2016) and the paediatric study ECU-MG-303.

A summary of Study ECU-MG-303 and PK and PD assessments is provided in Table 1.

Table 1: Clinical Study ECU-MG-303 and PK and PD Assessments

Subject Population	Number of Subjects	Dosing schedule	PK, hemolysis, free C5 sampling
pediatric patients aged 6 to < 18 years with AChR-Ab positive refractory gMG.	N = 11	Induction Phase: weekly weight-based dosing Maintenance Phase: every two weeks weight-based dosing	Pre-dose, 60-120 min and 24 h after first dose and trough and peak on week 1, 4, 12 and 26

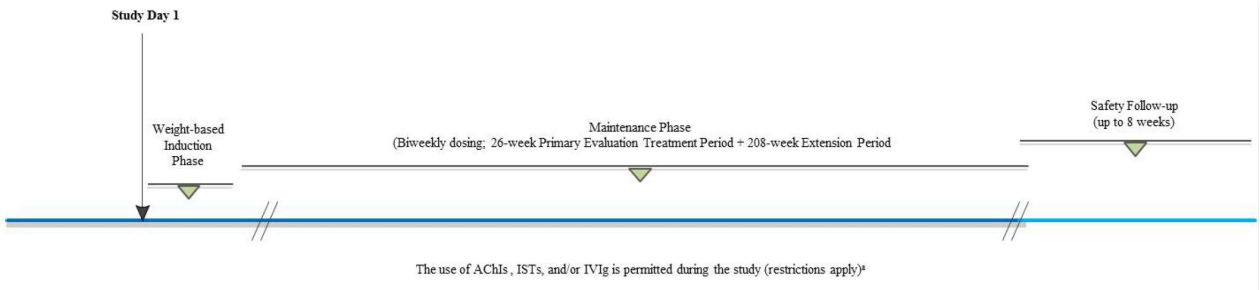
Source: Protocol ECU-MG-303, Version 4, 28-Sep-2020 Notes: Details on weight-based dosing are provided in Section 3.1.1
Abbreviations: Ab = antibody; AChR = acetylcholine receptor; gMG = generalized Myasthenia Gravis

Study ECU-MG-303

This is an open-label, multicentre study to evaluate the efficacy, safety, PK, and PD of IV eculizumab in paediatric patients 6 to < 18 years of age with AChR antibody positive refractory gMG.

The study design is shown in Figure 1. There were 4 periods in this study: screening Period (2-4 weeks), primary Evaluation treatment Period (26 weeks), extension Period (up to an additional 208 weeks), follow-up Period (8 weeks)

Figure 1: Study Design of ECU-MG-303



The noncompartmental analysis will be performed using PK data collected during the primary evaluation treatment period

Paediatric subjects were treated according to a bodyweight based dosing regimen as shown in Table 2. For subjects who enter the study on maintenance IVIg treatment, a series of supplemental doses of eculizumab were administered to account for the anticipated approximately 50% increase in eculizumab clearance according to Table 3.

Table 2: Bodyweight-based Dosing Regimen of Eculizumab in Paediatric Patients

Weight Cohort	Induction Phase	Maintenance Phase
≥ 40 kg	900 mg weekly × 4 doses	1200 mg at Week 5; then 1200 mg every 2 weeks
30 to < 40 kg	600 mg weekly × 2 doses	900 mg at Week 3; then 900 mg every 2 weeks
20 to < 30 kg	600 mg weekly × 2 doses	600 mg at Week 3; then 600 mg every 2 weeks
10 to < 20 kg	600 mg weekly × 1 dose	300 mg at Week 2; then 300 mg every 2 weeks

Note Dose regiment are equivalent to the previously approved dosing regimen for eculizumab in Atypical hemolytic uremic syndrome and Paroxysmal nocturnal hemoglobinuria.

Table 3: Bodyweight-based Supplemental Dosing Regimen of Eculizumab in Paediatric Patients

Weight Cohort	Induction Phase Supplemental Dose	Induction Phase Total Dose	Maintenance Phase Supplemental Dose	Maintenance Phase Total Dose
≥ 40 kg	600 mg	1500 mg	600 mg	1800 mg
30 to < 40 kg	300 mg	900 mg	600 mg	1500 mg
20 to < 30 kg	300 mg	900 mg	300 mg	900 mg
10 to < 20 kg	300 mg	900 mg	300 mg	600 mg

Serum collection schedules

Blood samples were collected for the measurement of serum concentrations of eculizumab. These blood samples were taken at predose and 60 to 120 minutes and 24 hours after end of infusion on Day 1, predose and 60 to 120 minutes after end of infusion on Week 1, Week 4, and Week 12, and predose on Week 26.

Pharmacokinetic Results

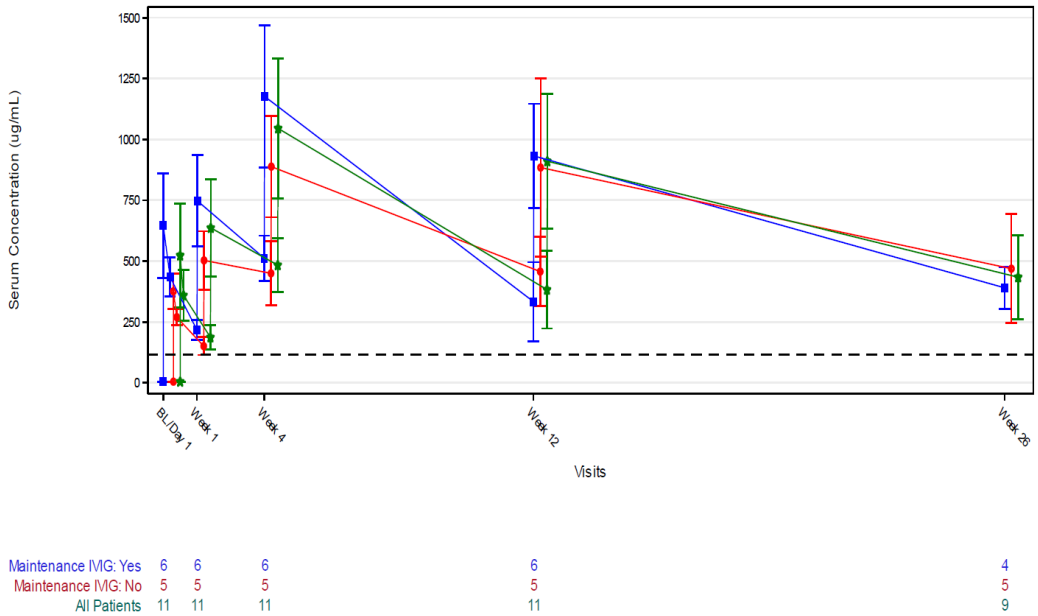
A summary of serum eculizumab concentrations following the first induction dose and at steady state is presented in Table 4 and Figure 2.

Table 4: Summary of Serum Eculizumab Concentrations (µg/mL) During the Primary Evaluation Treatment Period Following First Induction Dose and at Steady State (Pharmacokinetic Analysis Set)

Visit/Statistics	Weight Cohort: 30 to < 40 kg	Weight Cohort: ≥ 40 kg		All Patients
	Status of Maintenance IVIg (Yes)	Status of Maintenance IVIg (Yes)	Status of Maintenance IVIg (No)	
First induction dose (Day 1)				
C_{trough}				
n	1	5	5	11
Mean (SD)	BLOQ (NA)	BLOQ (BLOQ)	BLOQ (BLOQ)	BLOQ (BLOQ)
Min, max	NA	BLOQ, BLOQ	BLOQ, BLOQ	BLOQ, BLOQ
C_{max} (60 minutes postdose)				
n	1	5	5	11
Mean (SD)	510.0 (NA)	673.2 (228.59)	375.8 (73.51)	523.2 (212.59)
Min, max	510, 510	450, 1050	301, 460	301, 1050
Steady state (Week 12)				
C_{trough} (predose)				
n	0	6	4	10
Mean (SD)	NA	333.3 (162.15)	457.0 (142.60)	382.8 (159.57)
Min, max	NA	114, 560	276, 621	114, 621
C_{max}				
n	0	6	5	11
Mean (SD)	NA	932.2 (213.84)	884.4 (365.38)	910.5 (277.29)
Min, max	NA	736, 1210	379, 1270	379, 1270

Abbreviations: BLOQ = below the limit of quantification; Cmax = maximum observed serum eculizumab concentration (at 60 minutes postdose); Ctrough = serum eculizumab trough concentration (at predose); IVIg = intravenous immunoglobulin; max = maximum; min = minimum; NA = not applicable; SD = standard deviation

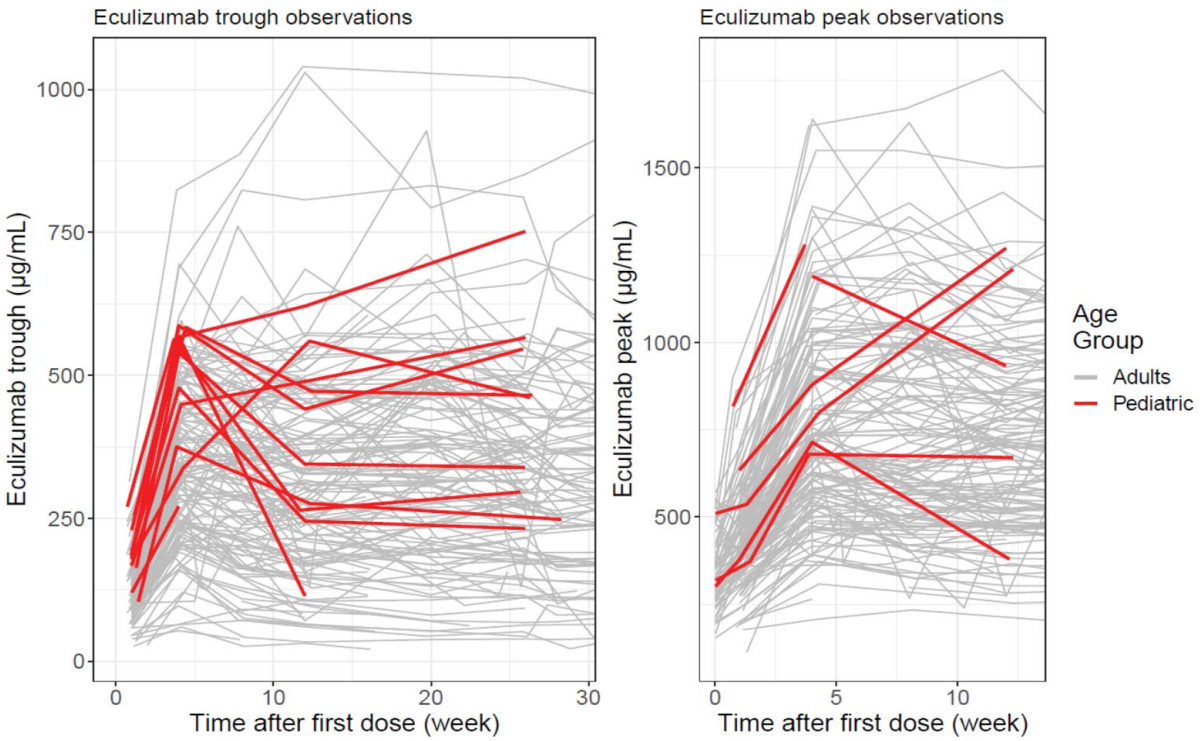
Figure 2: Mean (SD) Serum Eculizumab Concentration Over Time During the Primary Evaluation Treatment Period (Pharmacokinetic Analysis Set)



Note: Maintenance IVIg status at each timepoint is presented. Dashed horizontal lines indicate study drug serum concentration of 116 µg/mL. The sample sizes presented are the number of patients with either predose or postdose assessment at each visit. For eculizumab BLOQ values, LLOQ/2 = 4.69 µg/mL was utilized.
BL = Baseline; BLOQ = below the limit of quantification; CSR = clinical study report; IVIg = intravenous immunoglobulin; LLOQ = lower limit of quantification; SD = standard deviation

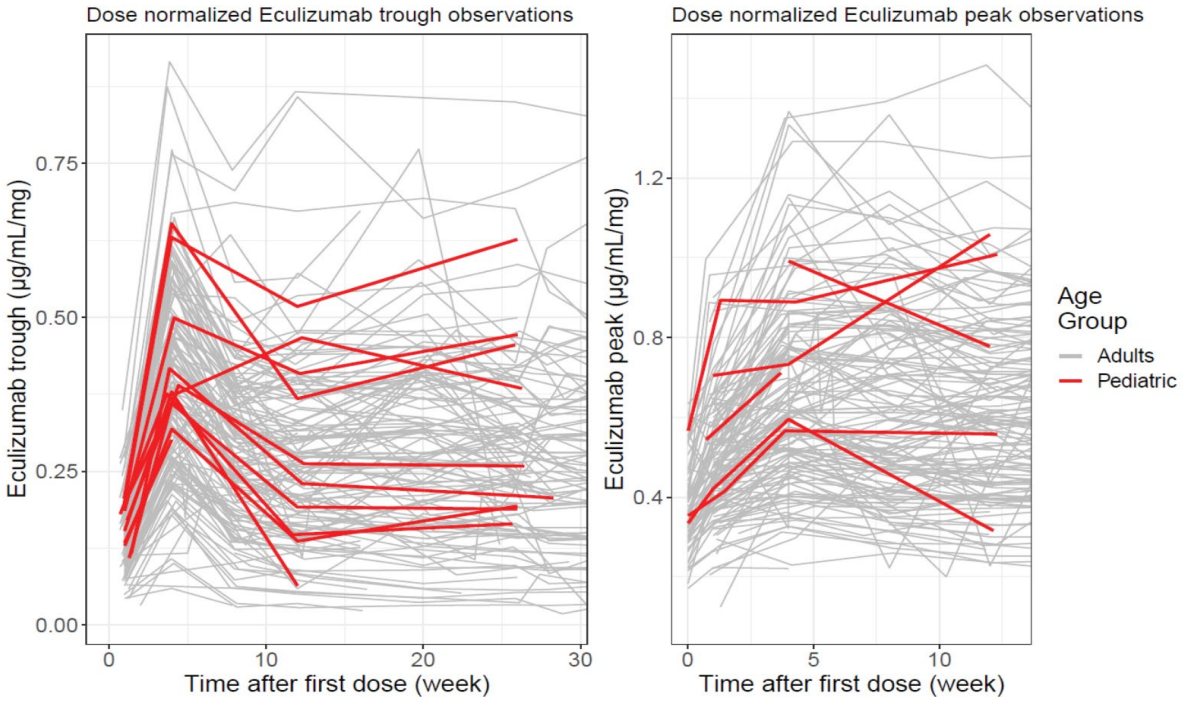
Exploratory Comparative Assessment of Exposures in Adult and Paediatric Subjects

Figure 3: Eculizumab Peak and Trough Concentration Time Profiles for Adult and Paediatric Subjects with gMG



Note: Adult data from Studies C08-001, ECU-MG-301, and ECU-MG-302. Pediatric data from Study ECU-MG-303. Pediatric samples qualified as trough concentration in case the sample was taken within 2.5 hours before dose. Pediatric samples qualified as peak concentration in case the sample was taken within 2.5 hours after dose. The plots include 41 trough and 19 peak samples. There were 36 samples that did not qualify as peak or trough sample and are not shown in the plot.
Abbreviation: gMG = generalized myasthenia gravis

Figure 4: Dose-normalized Eculizumab Peak and Trough Concentration Time Profiles for Adult and Paediatric Subjects with gMG



Note: Adult data from Studies C08-001, ECU-MG-301, and ECU-MG-302. Pediatric data from Study ECU-MG-303. Pediatric samples qualified as trough concentration in case the sample was taken within 2.5 hours before dose. Pediatric samples qualified as peak concentration in case the sample was taken within 2.5 hours after dose. The plots include 41 trough and 19 peak samples. There were 36 samples that did not qualify as peak or trough sample and are not shown in the plot.
Abbreviation: gMG = generalized myasthenia gravis

Prior Pop-PK Modelling

A pop-PK model was previously developed, using data from Phase 2 (C08-001) and Phase 3 (ECU-MG-301 and ECU-MG-302) studies for eculizumab in adults.

The eculizumab PK data were well-described by a 2-compartment model with 1st-order elimination. Random effects were included on the clearance (CL) and on the central volume of distribution (V1) and a correlation term was estimated. A combined error model (additive +proportional) adequately described residual variability of Study C08-001 data, whereas a proportional error was sufficient to describe residual variability of Study ECU-MG-301 and Study ECU-MG-302 data.

A non-linear assay conversion factor was estimated to scale Study C08-001 exposures to the levels observed in Studies ECU-MG-301 and ECU-MG-302. All PK parameters were allometrically scaled by body weight, allowing describing interindividual differences in the population of interest; in addition, PE events were modelled to account for a temporary increase in eculizumab clearance during the PE period. No other available covariates were found to influence eculizumab exposure.

The analysis dataset constituted of 135 adult eculizumab treated subjects covering a bodyweight range between 37 and 174 kg.

Table 5: Parameter Estimates of the Prior Pop-PK Model for Phase 2 (C08-001) and Phase 3 (ECU-MG-301 and ECU-MG-302) Studies

Parameter	Estimate	95% CI	RSE (%)	Shrinkage (%)
CL (L/h)	0.00752	[0.00706-0.00801]	0.7	
V1 (L)	2.64	[2.53-2.76]	2.3	
V2 (L)	1.87	[1.73-2.02]	6.4	
Q (L/h)	0.0664	[0.0466-0.0945]	6.6	
Weight effect on CL/Q	1.14	[0.982-1.30]	7.1	
Weight effect on V1/V2	0.63	[0.537-0.722]	7.5	
PE effect on CL	5.77	[4.62-6.92]	10.2	
Assay conversion factor	1.07	FIXED		
Interindividual Variability				
CL (CV%)	34.4	[29.6-38.7]	12.6	1
V1 (CV%)	20.9	[17.4-24.0]	15.4	9.1
Covariance CL-V1	0.0282	[0.0143-0.042]	25.1	0
Residual Error				
Proportional error Ph3 (%)	42.3	[41.6-43.0]	1.6	
Proportional error Ph2 (%)	23.4	[20.2-26.2]	13.0	
Additive error Ph2 (µg/mL)	12.2	[9.09-15.3]	13.0	

Abbreviations: CI=confidence interval; CL=clearance; CV=coefficient of variation; EP=proportional residual error; EPS=ε (random error); Ph2=phase 2; Ph3=phase 3; Q=inter-compartmental clearance; RSE=relative standard error; V1=central volume of distribution; V2=peripheral volume of distribution

Update of the Pop-PK Model

The prior pop-PK model was refitted to the combined adult and paediatric analysis dataset. PK parameters as well as bodyweight effects were re-estimated, and consistency of PK parameters across paediatric and adult subjects was evaluated. Differences in PK between paediatric and adult which could not be addressed by the incorporated bodyweight effects, were addressed by introducing age group specific terms in the model. No further model development or assessment of covariate effects was performed.

Data Summary

The analysis dataset for the pop-PK analysis of eculizumab comprised of 135 adult subjects from Studies 08-001, ECU-MG-301 and ECU-MG-302 (Previous Pop-PK Model Table 6) and 11 paediatric subjects from Study ECU-MG-303 for which evaluable PK observations were available (Table 7 and Table 8).

Table 6: Summary of Pop-PK Dataset

Protocol	Number of subjects	Total number of samples	BLQ samples	Eculizumab samples [1]	Number of dose records	Number of PE events
C08-001	13	144[2]	6	138	143	0
ECU-MG-301	62	827	63	764	955	11
ECU-MG-302	56[3]+60	1703	64	1639	2959	2
Total	135	2674	133	2541	4057	13

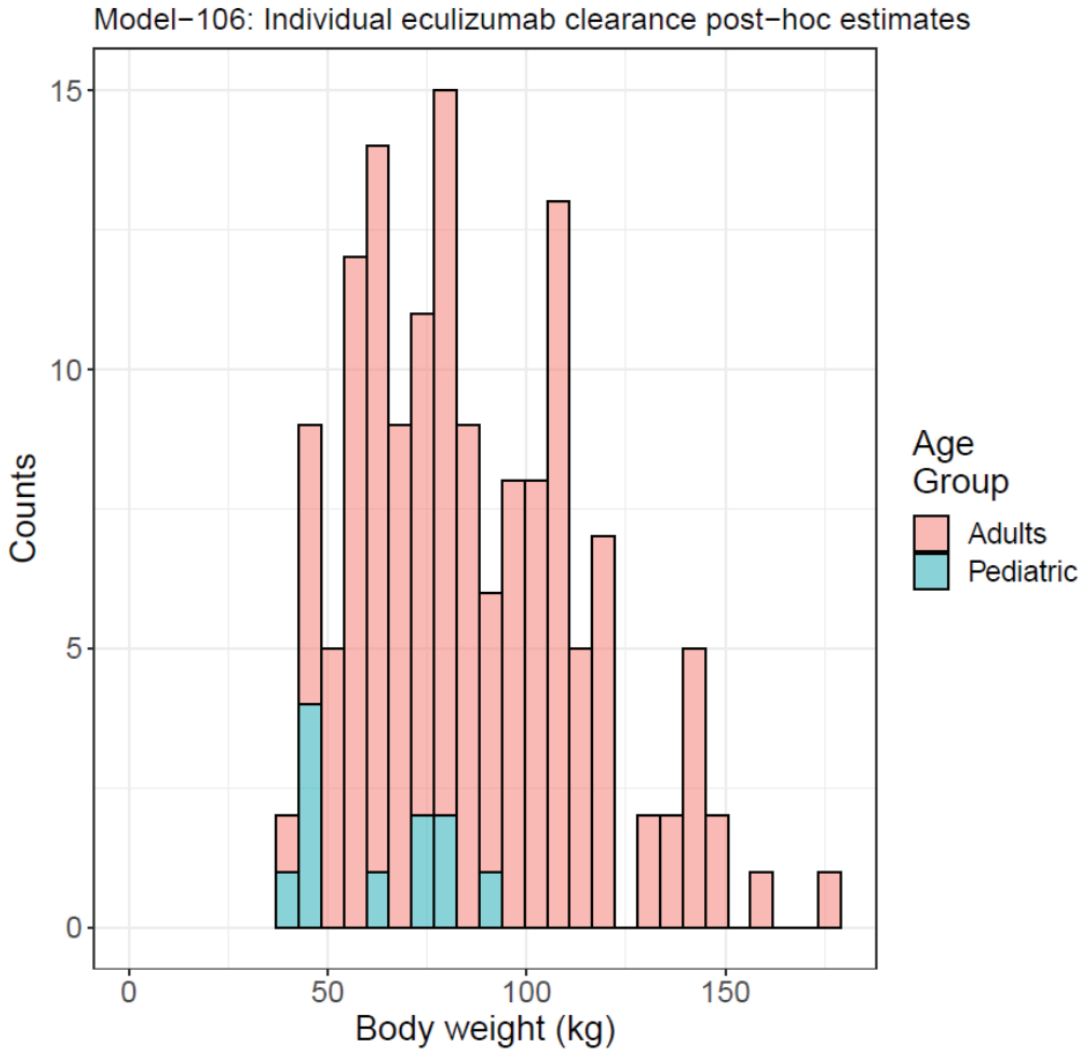
PE = plasma exchange; BLQ = below limit of quantification; [1] Samples with quantifiable eculizumab concentration [2] – All data from eculizumab treated period + 8 observations of the placebo period with concentrations above LLOQ; [3] 56 subjects coming from Study ECU-MG-301

Table 7: Summary of Newly Added Paediatric Data from Study ECU-MG-303

Protocol	Number of Subjects	Number of doses	Number of PE events	Analyte	Total number of samples	Number of BLQ samples	Number of non-BLQ samples
ECU-MG-303	11	493	20	Free C5	109	63	46
				Hemolysis	107	0	107
				Eculizumab	107	11	96

Source: explore-analysis-dataset-v5.R Notes: BLQ free C5 samples were imputed by 0.5xLLOQ and retained in the analysis.
Abbreviations. BLQ: below limit of quantification; PE: Plasma Exchange

Figure 5:Distribution of Body weight for Adult and Paediatric Subjects



The prior pop-PK model was refitted to the combined adult and paediatric PK data (run105). Parameter estimates were similar to the estimates obtained from the fit using the adult data only (Table 5) from the prior analysis. ETA plots for CL and V1 were compared between adult and paediatric subjects and indicated that ETA V1 distributions were similar and overlapping, but ETA CL values indicated that CL appeared somewhat higher for paediatric subjects compared to adults. The increased CL for paediatric subjects was included and quantified in run106, which was defined the updated pop-Pk model.

The first-order conditional estimation with interaction (FOCE INTER) method as implemented in NONMEM was used for model fitting. Key model development steps of the pop-PK model are summarized in Table 9.

Table 8: Summary of Pivotal Runs for Pop-PK Model Update

Run No.	Description	OFV (dOFV)	Comments
Run105	Prior population PK model	25482.8 (N/A)	Addition of pediatric data from ECU-MG-303
Run106	Pediatric effect on CL	25475.5 (-7.4)	Updated population PK model

Abbreviations: CL=clearance; dOFV=change in OFV; PK=pharmacokinetic; OFV=objective function value

Parameter estimates for the updated pop-PK model are reported in Table 10.

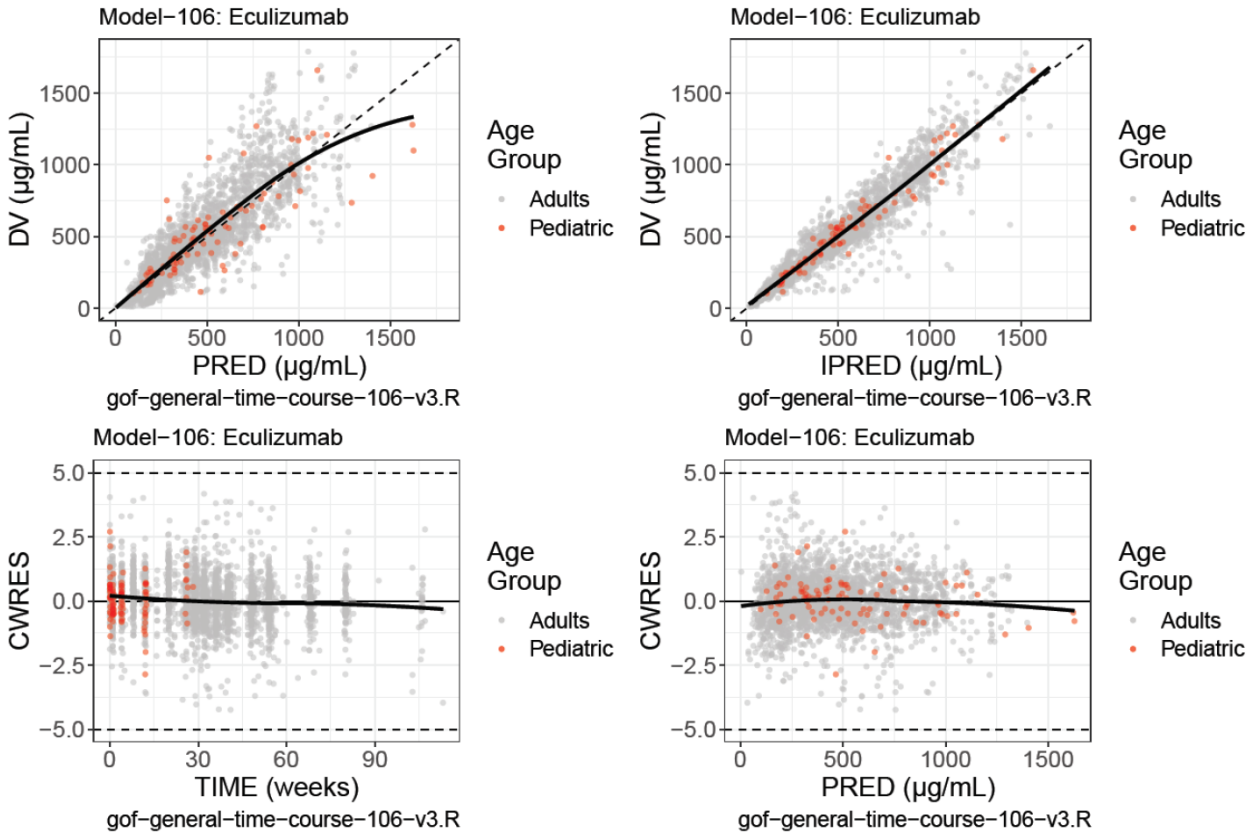
Table 9: Parameter Estimates of the Updated Pop-PK Model

Parameter	Estimate	95% CI	RSE (%)	Shrinkage (%)
CL (L/h)	0.00745	0.00695 to 0.00798	0.7	
V1 (L)	2.7	2.59 to 2.81	2.1	
V2 (L)	1.73	1.57 to 1.9	8.9	
Q (L/h)	0.0365	0.0231 to 0.0578	7.1	
Weight effect on CL/Q	1.11	0.906 to 1.31	9.4	
Weight effect on V1/V2	0.609	0.513 to 0.705	8	
PE effect on CL	5.96	4.67 to 7.25	11	
Assay conversion factor	1.07	1.07 to 1.07	0	
CL pediatric as (%) of CL adults	133	1.05 to 1.61	10.6	
Interindividual Variability				
CL (CV%)	33.5	29.2 to 37.2	12.1	1.1
V1 (CV%)	20.2	17.1 to 22.9	14.7	9.2
Covariance CL-V1	0.0286	0.0155 to 0.0417	23.4	
Residual Error				
Proportional error Ph3 (%)	0.178	0.173 to 0.183	1.5	
Proportional error Ph2 (%)	0.0544	0.0405 to 0.0683	13.1	
Additive error Ph2 (µg/mL)	12.4	9.28 to 15.5	12.8	

Abbreviations: CI=confidence interval; CL=clearance; CV=coefficient of variation; EP=proportional residual error; EPS=ε (random error); Ph2=phase 2; Ph3=phase 3; Q=inter-compartmental clearance; RSE=relative standard error; V1=central volume of distribution; V2=peripheral volume of distribution

GOF plots for the updated pop-PK model are shown in Figure 6.

Figure 6: GOF Plots for the Updated Pop-PK Model by Age Group



Note: Dots are individual data points (red: pediatric patients; gray: adult patients), and solid lines are smoothed LOESS lines. In the 2 plots in the upper row, dashed lines are lines of identity.
Abbreviations: CWRES = conditional weighted residuals; DV = dependent variable; GOF = goodness-of-fit; IPRED = individual predictions; LOESS = locally weighted scatterplot smoothing; PK = pharmacokinetic; PRED = population predictions

Model qualification

A bootstrap analysis with stratification on Study was performed to assess the robustness of the updated pop-PK model.

	Bootstrap				Model-106		
Parameter	**Median**	**Mean**	**Percentile 2.5%**	**Percentile 97.5%**	**Estimate**	**CI 95% (low)**	**CI 95% (high)**
POPCL	0.00747	0.00747	0.00708	0.00786	0.00745	0.00695	0.00798
POPV	2.7	2.7	2.59	2.82	2.7	2.59	2.81
POPV2	1.73	1.73	1.54	1.94	1.73	1.57	1.9
POPQ	0.0362	0.0376	0.0199	0.0621	0.0365	0.0231	0.0578
WTonCL	1.1	1.1	0.949	1.27	1.11	0.906	1.31
WTonV	0.603	0.603	0.507	0.693	0.609	0.513	0.705
PE.EFFECT	6.05	47700	4.59	8.17	5.96	4.67	7.25
COVPEDCL	133	134	109	160	133	105	161
BSVCL	33	33	28.3	37.3	33.5	29.2	37.2
BSVV	20.1	20.1	17.5	22.8	20.2	17.1	22.9
OMEGA.2.1.	0.0276	0.028	0.0147	0.042	0.0286	0.0155	0.0417
ERRPROP	0.177	0.177	0.164	0.194	0.178	0.173	0.183
ERRPROP.ph2	0.0525	0.052	0.0321	0.0694	0.0544	0.0405	0.0683
ERRADD.ph2	12.4	12.3	7.07	17	12.4	9.28	15.5

Abbreviations: BSVCL=interindividual variability CL; BSVV= interindividual variability V; CI=confidence interval; COVPEDCL= CL pediatric as (%) of CL adults; ERRPROP=proportional error; ERRPROP.ph2=proportional error phase 2; ERRADD.ph2= Additive error Ph2 (µg/mL); OMEGA.2.1= Covariance CL-V1;.PE.EFFECT= PE effect on CL; POPCL=clearance; POPQ=inter-compartmental clearance; POPV=central volume of distribution; POPV2=peripheral volume of distribution

Post Hoc Exposure Estimates from the Updated Pop-PK Model

Table 10: Summary Statistics of Post hoc PK parameters by Population and Body Weight

Parameter	Statistic	All pediatric subjects (n=11)	Pediatric subjects 30 to <40kg (n=1)	Pediatric subjects = 40kg (n=10)	Adult subjects (n=135)
CL (L/h)	Mean (CV)	0.00885 (36.1)	0.00516 (N/A)	0.00922 (33.7)	0.0103 (60.1)
	Median (range)	0.00956 (0.00447 to 0.0128)	0.00516 (N/A)	0.0102 (0.00447 to 0.0128)	0.00822 (0.00327 to 0.0427)
V (L)	Mean (CV)	2.47 (18.5)	1.81 (N/A)	2.53 (16.7)	3.1 (26.9)
	Median (range)	2.35 (1.81 to 3.02)	1.81 (N/A)	2.53 (1.81 to 3.02)	2.99 (1.66 to 6.17)
t1/2 (h)	Mean (CV)	365 (31)	420 (N/A)	359 (32.7)	411 (29.6)
	Median (range)	322 (252 to 619)	420 (N/A)	316 (252 to 619)	413 (139 to 880)
$AUC_{0-\tau}$ at SS (ug.hr/mL)	Mean (CV)	151000 (39.7)	174000 (N/A)	149000 (42.2)	148000 (44.3)
	Median (range)	126000 (94000 to 267000)	174000 (N/A)	118000 (94000 to 267000)	146000 (28100 to 363000)
Cmax at SS (ug/mL)	Mean (CV)	798 (26.7)	868 (N/A)	791 (28.2)	736 (35.2)
	Median (range)	696 (566 to 1150)	868 (N/A)	678 (566 to 1150)	707 (243 to 1560)
Ctrough at SS (ug/mL)	Mean (CV)	311 (51.4)	370 (N/A)	305 (54.8)	321 (51.9)
	Median (range)	258 (167 to 639)	370 (N/A)	231 (167 to 639)	315 (30.2 to 899)

Notes: AUC0-τ, Cmax and Ctrough based on the maintenance dose at steady state. Maintenance dose for adults and for pediatric subjects with body weight ≥ 40 kg 1200 mg every 2 weeks. Maintenance dose for pediatric subjects with body weight 30 - < 40 kg 900 mg every 2 weeks
Abbreviations: AUC0-τ =area under the concentration-time curve over one dosing interval at steady state; CL=clearance; Cmax=maximum concentration at steady state; Ctrough=minimum concentration at steady state; CV=coefficient of variation; t½=elimination half-life; V1=central volume of distribution.

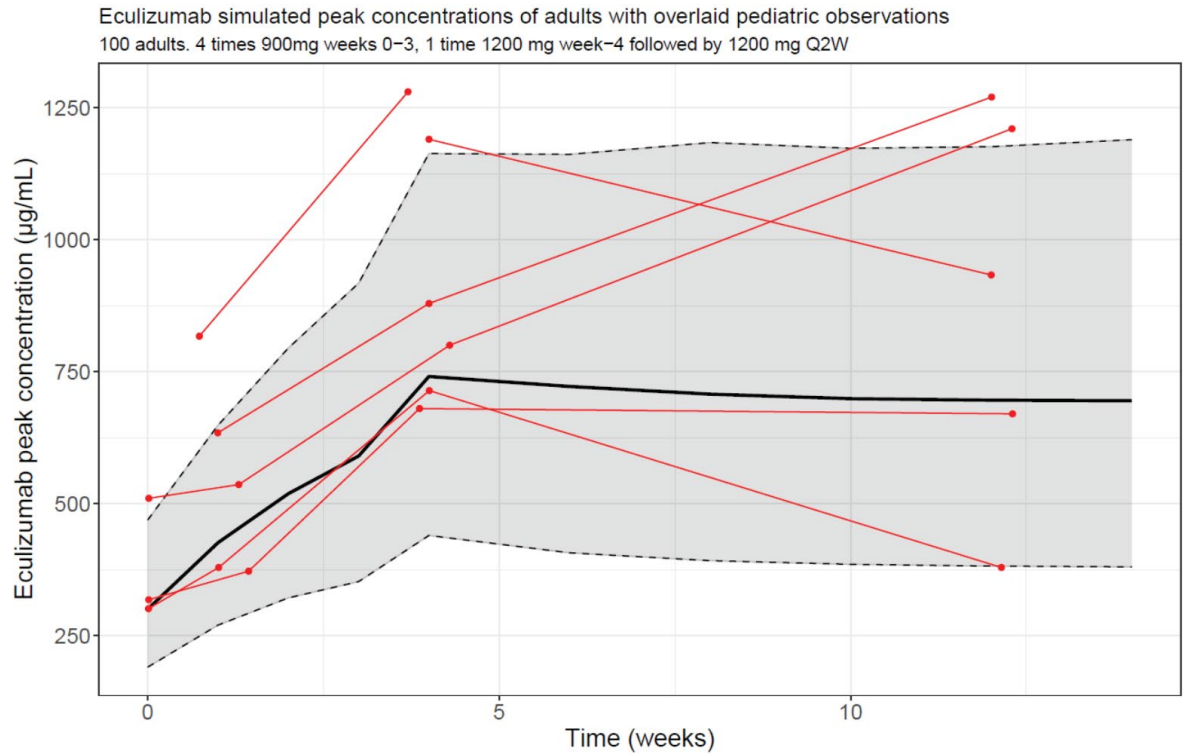
Eculizumab Pharmacokinetic Simulations

Two sets of simulations were conducted, utilizing the updated pop-PK model.

- The objective of the first simulation exercise was to illustrate the similarity between the observed paediatric and model-predicted adult exposure.
- The second simulation aimed to illustrate the adequacy of the proposed bodyweight-based dosing regimen for each of the bodyweight classes to achieve similar exposures compared to adults.

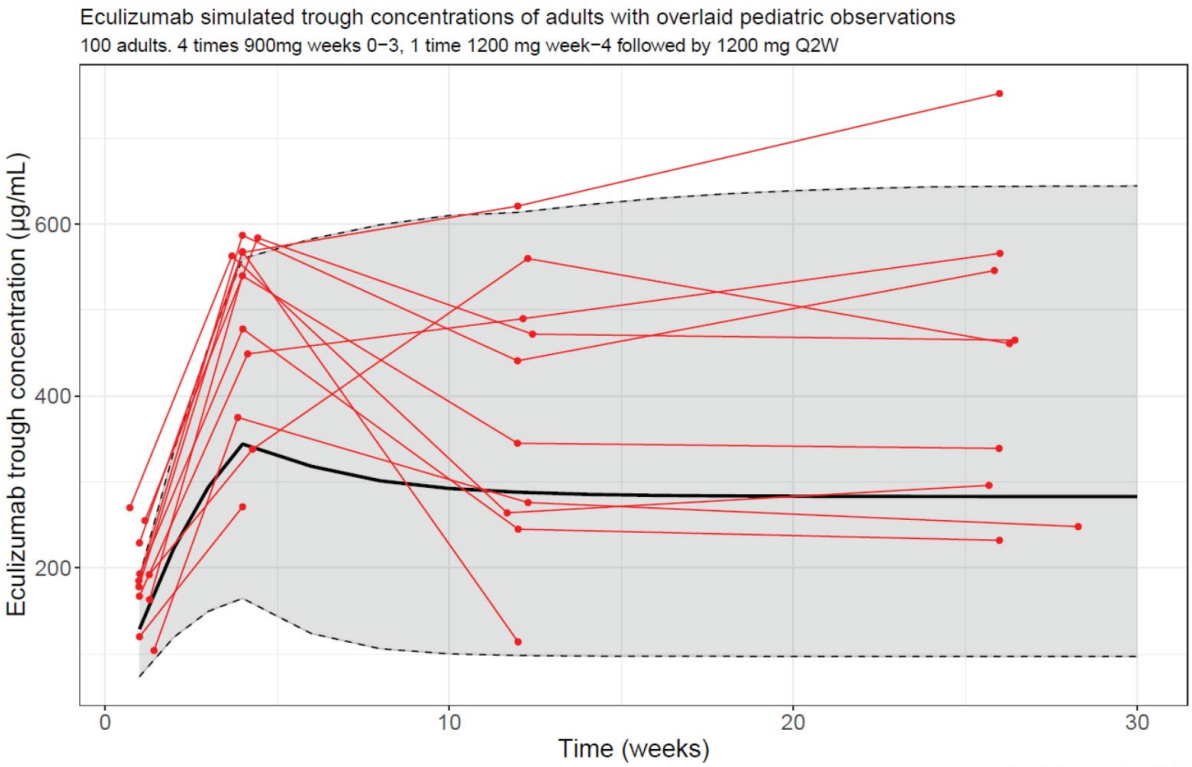
Observed eculizumab concentrations for the paediatric subjects are overlaid on the simulated concentration-time profile. The simulated dosing regimen for adults included an induction phase of four weekly 900 mg eculizumab doses followed by a dose of 1200 mg one week later. The maintenance phase then starts two weeks later using a 1200 mg every two weeks dose regimen.

Figure 7: Observed Peak Concentrations From Paediatric Subjects Overlaid on Simulations of Median Peak Eculizumab Concentration Time Profile (90% PI) for Adult Subjects Using the Updated Pop-PK Model



Abbreviations: PI=prediction interval; PK=pharmacokinetic; Q2W: every two weeks. Note: Pediatric samples qualified as trough concentration in case the sample was taken within 2.5 h before dose. Pediatric samples qualified as peak concentration in case the sample was taken within 2.5 h after dose. The plots include 41 trough (Figure 7) and 19 peak (Figure 8) samples. There were 36 samples that did not qualify as peak or trough sample and are not shown in the plots.

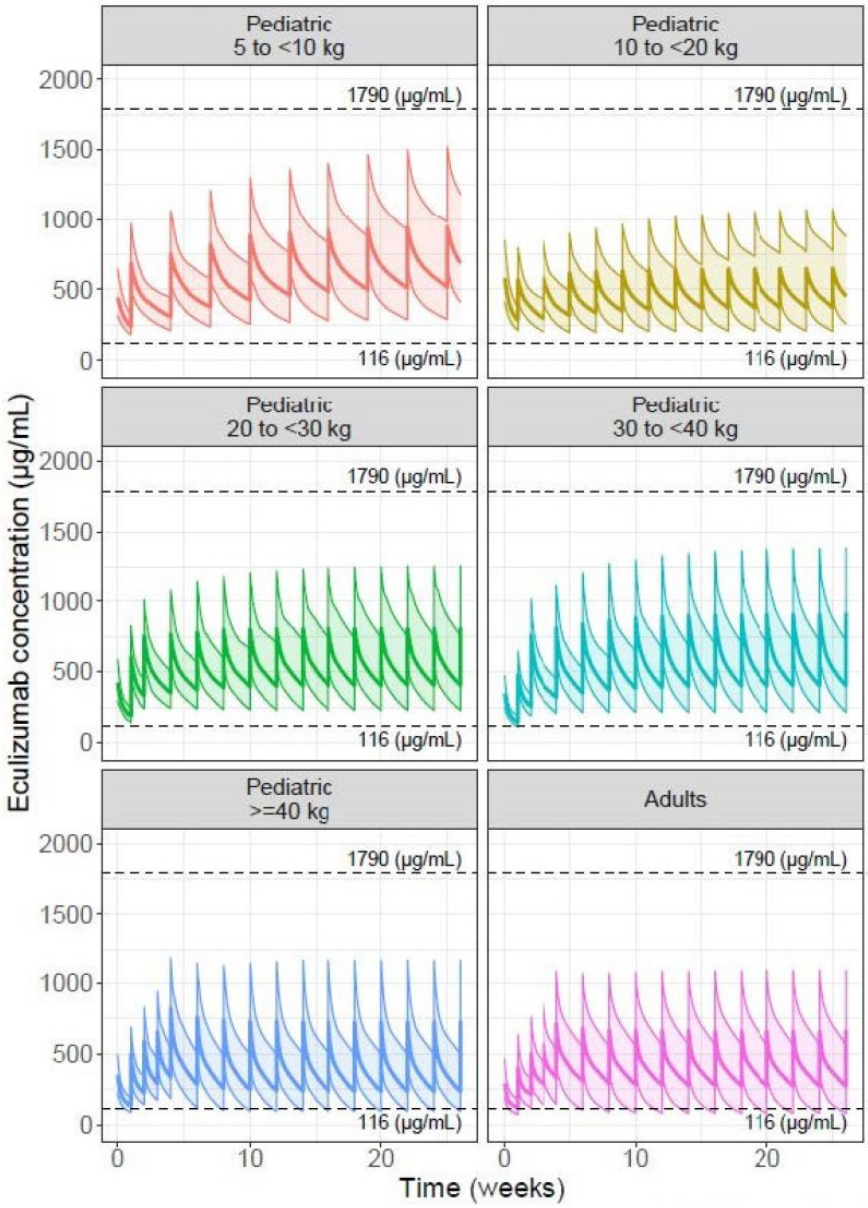
Figure 8: Observed Trough Concentrations From Paediatric Subjects Overlaid on Simulations of Median Trough Eculizumab Concentration Time Profile (90% PI) for Adult Subjects Using the Updated Pop-PK Model



Abbreviations: PI=prediction interval; PK=pharmacokinetic; Q2W: every two weeks. Note: Pediatric samples qualified as trough concentration in case the sample was taken within 2.5 h before dose. Pediatric samples qualified as peak concentration in case the sample was taken within 2.5 h after dose. The plots include 41 trough (Figure 7) and 19 peak (Figure 8) samples. There were 36 samples that did not qualify as peak or trough sample and are not shown in the plots.

Simulated PK profiles for bodyweight based dosing in paediatric subjects are provided in Figure 9, the PK profile for adult subjects treated with the approved 4 x 900 mg weekly followed by the 1200 mg every two week dosing regimen is included for reference. The exposure estimates for area under the concentration-time curve over one dosing interval at steady state ($AUC_{0-\tau}$), maximum concentration (C_{max}) at steady state and minimum concentration (C_{trough}) at steady state for the maintenance dose for paediatric subjects for each bodyweight class as well as for adults are presented in Table 12.

Figure 9: Simulated Eculizumab Concentration Time Profile (90% PI) for Paediatric Subjects by Bodyweight Class and Adult Subjects Using the Updated Pop-PK Model



Note: Central solid line represents median concentration; shaded area represents 5% to 95% prediction interval. Dashed lower line at 116 µg/mL represents the needed eculizumab concentration to achieve complete terminal complement inhibition for free C5 and upper dashed line at 1790 µg/mL represents the maximum concentration value observed in Studies ECU-MG-301 and ECU-MG-302 in adult patients with refractory gMG.
Abbreviations: C5 = complement component 5; gMG = generalized myasthenia gravis; PI = prediction interval; PK = pharmacokinetic

Table 11: Simulated Eculizumab Post hoc PK Parameters for Paediatric Subjects by Bodyweight Class and Adult Subjects Using the Updated Pop-PK Model

Parameter	Statistic	Pediatric Patients by Body Weight Class					Adult Patients
		5 to < 10 kg	10 to < 20 kg	20 to < 30 kg	30 to < 40 kg	≥ 40 kg	
$AUC_{0-\tau}$ at SS (µg·hr/mL)	Median (90% PI)	335000[a] (194000 to 592000)	156000 (90100 to 279000)	180000 (114000 to 309000)	185000 (118000 to 305000)	124000 (67800 to 217000)	130000 (53800 to 243000)
C_{max} at SS (µg/mL)	Median (90% PI)	953 (648 to 1540)	651 (443 to 1060)	810 (576 to 1250)	909 (656 to 1380)	730 (444 to 1160)	664 (391 to 1090)
C_{trough} at SS (ug/mL)	Median (90% PI)	523 (291 to 1070)	371 (206 to 760)	404 (226 to 753)	401 (212 to 719)	236 (94.4 to 502)	272 (80.4 to 564)

Note: AUC0-τ, Cmax, and Ctrough are based on the maintenance dose at steady state.
a AUC0-τ comprises a 3-week dose interval for the 5 to < 10 kg body weight class and a 2-week dose interval for other body weight classes and adult patients.
Abbreviations: AUC0-τ = area under the concentration-time curve over 1 dosing interval; Cmax = maximum observed serum eculizumab concentration; Ctrough = serum eculizumab trough concentration; hr = hour; PI = prediction interval; PK = pharmacokinetic; SS = steady state

Figure 10 shows the simulated PK profiles comparing results for pediatric and adult patients when the allometric scaling from aHUS/PNH is used. Simulations of this alternative scenario predict that patients in all weight groups will have steady state exposures within the therapeutic window.

Figure 10: Simulated Median (with 90% Prediction Interval) PK Profiles (N = 100) Stratified by Body Weight Group

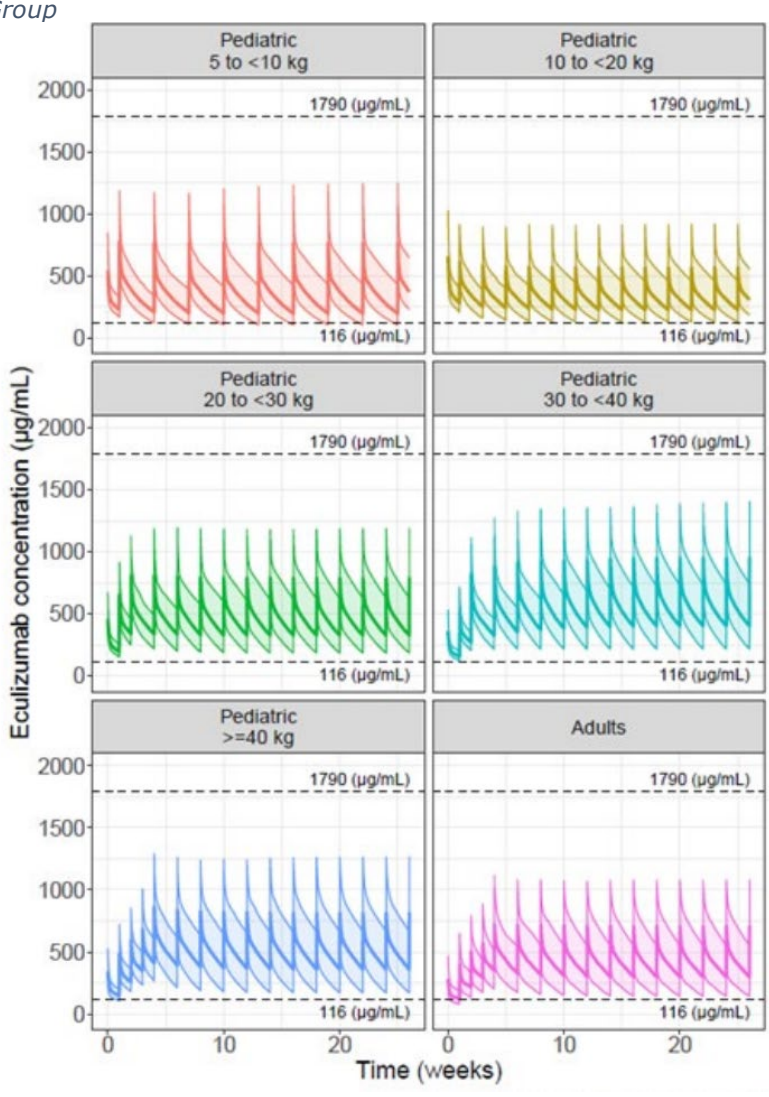


Table 13 summarizes the PK parameters and the proportion of patients with C_{trough} (at pre-dose) < 116 µg/mL and with C_{max} (at 60 minutes post-dose) > 1790 µg/mL.

Table 12: Predicted Eculizumab PK Parameter Summary in Adult and Pediatric Patients

Patient Population	Pediatric Patients					Adults
	5 to <10 kg	10 to <20 kg	20 to <30 kg	30 to <40 kg	≥40 kg	
Parameter Statistic						
$AUC_{0-\tau}$ at SS (µg.hr/mL) Median (90% PI)	170000 (103000 to 303000)	107000 (64700 to 190000)	154000 (97900 to 262000)	182000 (117000 to 303000)	165000 (93500 to 276000)	138000 (74200 to 238000)
C_{max} at SS (µg/mL) Median (90% PI)	766 (553 to 1250)	568 (405 to 916)	791 (574 to 1190)	952 (677 to 1390)	813 (527 to 1270)	707 (375 to 1080)
C_{trough} at SS (µg/mL) Median (90% PI)	196 (105 to 437)	227 (128 to 459)	327 (184 to 628)	403 (215 to 737)	359 (171 to 667)	299 (143 to 552)
Subjects with C_{trough} below 116 µg/mL at SS (%)	11	4	1	0	0	3
Subjects with C_{max} above 1790 µg/mL at SS (%)	0	0	0	0	0	0

Abbreviations: AUC0-τ = area under the concentration-time curve over the dosing interval; Cmax = maximum observed serum eculizumab concentration (at 60 minutes postdose); Ctrough = serum eculizumab trough concentration (at predose); PI = predicted interval; SS = steady state

Supplementary PK and PD Data for the Extrapolation Exercise

This section summarizes the Pop-PK and PD analyses of eculizumab in paediatric patients with a diagnosis of aHUS or PNH and in adult patients with a diagnosis of refractory gMG, for the purpose of confirming the paediatric dose regimen for the refractory gMG indication.

The objectives of the Pop-PK and PD analyses were to:

- describe the sources of variability in PK and PD parameters within a modelling framework using the available data from the adult and paediatric patients with aHUS, PNH paediatric patients, and adult refractory acetylcholine receptor antibody positive gMG (refractory gMG) patients
- conduct simulations to confirm PK and PD bridging between the aHUS and refractory gMG indications and ultimately support dose regimens for paediatric refractory gMG patients.
- conduct simulations to support the supplemental doses after PE/plasma infusion or IVIg treatment in paediatric refractory gMG patients

Table 13: Studies used for Pharmacokinetic/Pharmacodynamic Modelling

Protocol	Patient Population	Indication	Number of Patients with PK data
C08-001	Adult	Refractory gMG	13
ECU-MG-301	Adult	Refractory gMG	62
C08-002A/B	Adult and adolescent	aHUS	17
C08-003A/B	Adult and adolescent	aHUS	20
C09-001r[a]	Adult, adolescent, and paediatric (paediatric aged 2 months to 12 years)	aHUS	30
C10-003	Adolescent and paediatric (paediatric aged 1 month to 12 years)	aHUS	15
M07-005	Adolescent paediatric (paediatric aged 11 to 12 years[b])	PNH	7

a Study C09-001r was a retrospective study
b Actual age range, not the protocol range
Note: Adult patients = ≥ 18 years of age. Paediatric patients were < 18 years with subsets: adolescent patients = 13 to < 18 years of age, paediatric patients < 13 years of age Abbreviations: aHUS = atypical hemolytic uremic syndrome, gMG = generalized myasthenia gravis, PIP = Paediatric Investigation Plan, PD = pharmacodynamics, PK = pharmacokinetic, PNH = paroxysmal nocturnal hemoglobinuria

The modelling was performed using a step down approach in 3 parts as described in the bullets below.

- aHUS/PNH modelling and simulation work utilizing the data from Studies C08-002A/B, C08-003A/B, C09-001, C10-003, and M07-005
- Refractory gMG adult modelling & simulation work utilizing the data from Studies C08-001 and ECU-MG-301
- A simulation study using the models developed in the first 2 parts to identify dosing regimens for eculizumab in paediatric patients from 6 to < 18 years of age with refractory gMG

A Simulation Study using the Developed Atypical Haemolytic Uremic Syndrome and Refractory Generalized Myasthenia Gravis Population Pharmacokinetic Models to Extrapolate Atypical Haemolytic Uremic Syndrome Paediatric Dosing Regimens of Eculizumab to Refractory Generalized Myasthenia Gravis Paediatric Patients

Since this simulation study focuses on proposing paediatric dose regimens, body weight is an important covariate. For both aHUS and refractory gMG Pop-PK models, body weight is linked to predicting eculizumab exposure, and therefore categorical body-weight-based dosing is recommended in the paediatric population. The empirical body weight exponents estimated from the aHUS Pop-PK model were used, rather than the empirical body weight exponents estimated from the refractory gMG adult Pop-PK model. This is because the aHUS Pop-PK model included a wider range of body weight data spanning paediatric, adolescent, and adult patients weighing 4.4 to 127 kg (aHUS/PNH (referred to as aHUS) Pop-PK model), whereas the refractory gMG Pop-PK model used data with a much higher body weight range and an adult-only population (37 to 174 kg, ECU-MG-Adult PK-PD Modeling Report).

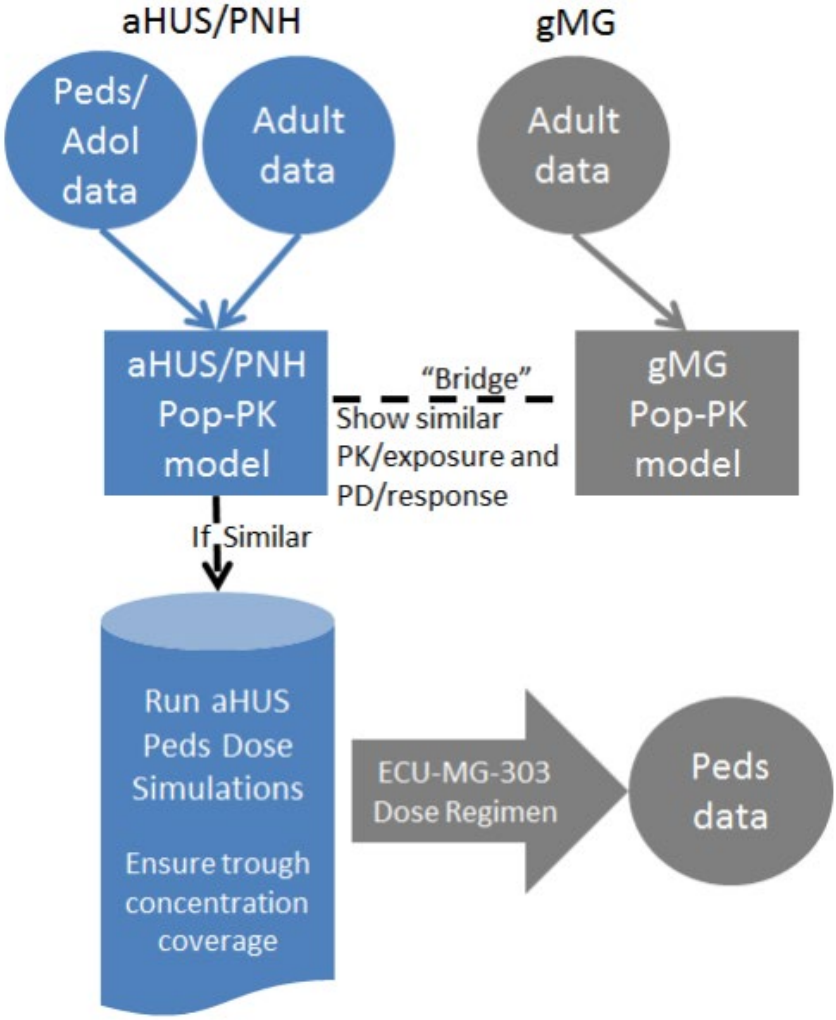
Three different simulation scenarios for the proposed dose regimens are conducted in this report:

1) Simulations to support paediatric dose regimens in refractory gMG patients

2) Simulations to support supplemental doses in the event of PE in refractory gMG patients

3) Simulations to support supplemental doses in the event of IVIg treatment in refractory gMG patients

Figure 11: Schematic of M&S Process for Assessing aHUS Paediatric Dose Regimen use for Refractory gMG Paediatric Patient Population



Abbreviations: aHUS = atypical haemolytic uremic syndrome, gMG = generalized myasthenia gravis, Peds = paediatric patients, PNH = paroxysmal nocturnal haemoglobinuria, Pop-PK = population pharmacokinetics

The PK bridging used the clinical trial simulation, as the observed eculizumab data between gMG and aHUS adult patients cannot be directly compared due to the following reasons:

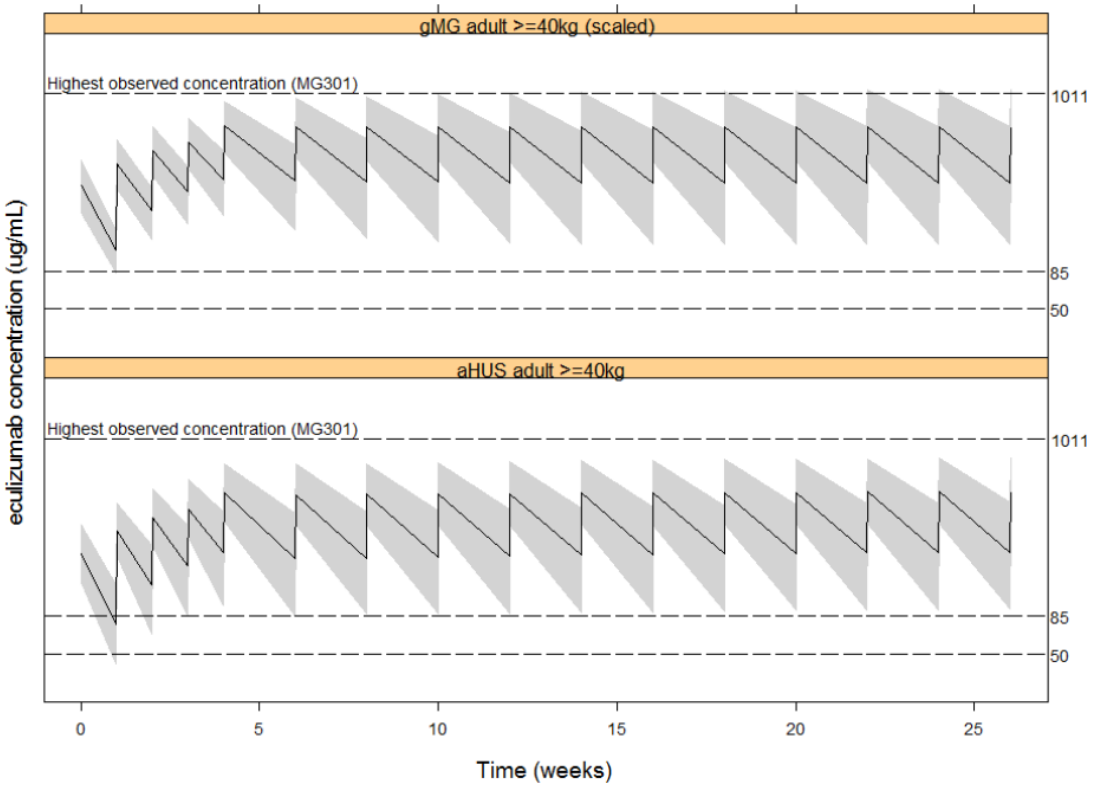
1) PK assays used for the aHUS studies were different than the PK assay used for the refractory gMG Study ECU-MG-301

2) Body weight range was different between the 2 indications; and body weight is known to significantly affect eculizumab PK.

PK/Exposure Bridging Between Adult Refractory gMG and aHUS Patients

The predicted concentration-time profiles in Figure 11 show a comparison between simulated PK levels using the aHUS Pop-PK model and the refractory gMG Pop-PK model. The refractory gMG PK levels were scaled using the inverse of the assay conversion Factor. This scaling allows a direct comparison between the aHUS and refractory gMG PK profiles.

Figure 12: Comparison of aHUS and Scaled gMG PK Profiles for Adult Patients (≥ 40 kg) – Semilog Plot



Note: Gray region represents the 90% prediction interval, i.e., 5% to 95% range; black solid line is the median of the simulated concentration-time profiles; horizontal dashed lines represent the ACF-scaled values of the highest observed concentration in Study ECU-MG-301 study (1011 µg/mL), the lower concentration boundary for complete and sustained terminal complement inhibition based on treatment of aHUS patients (50 µg/mL), and the threshold concentration of 85 µg/mL (based on Study CUMG-301), above which complete and sustained terminal complement inhibition is maintained. Abbreviations: ACF = assay conversion factor, aHUS = atypical haemolytic uremic syndrome, gMG = generalized myasthenia gravis

The scaled refractory gMG concentration-time profile agrees well with the aHUS profile. A summary of peak and trough concentrations is presented in Table 15.

Table 14: Comparison of Simulated Peak and Trough Eculizumab Concentrations from Adult Patients (≥ 40 kg)

	Induction Period (Last Dose)		Maintenance Period	
Weight Group, Conc scaling	Peak (µg/mL) Median (5%, 95%)	Trough (µg/mL) Median (5%, 95%)	Peak (µg/mL) Median (5%, 95%)	Trough (µg/mL) Median (5%, 95%)
≥ 40kg (gMG), Scaled	515 (356, 722)	308 (186, 456)	635 (393, 1071)	290 (124, 642)
≥ 40kg (aHUS), Original	373 (251, 566)	204 (99, 363)	480 (306, 767)	207 (93, 414)

Note: scaling refers to whether an ACF was applied to the concentrations, ie, Scaled=Cecu (1/1.07), where Cecu is the eculizumab concentration, and Original=no correction used (see ECU-MG-Adult PK-PD Modeling Report) Abbreviations: ACF = assay conversion factor, aHUS = atypical haemolytic syndrome, Conc = concentration, gMG = refractory myasthenia gravis

Paediatric Dose Simulations

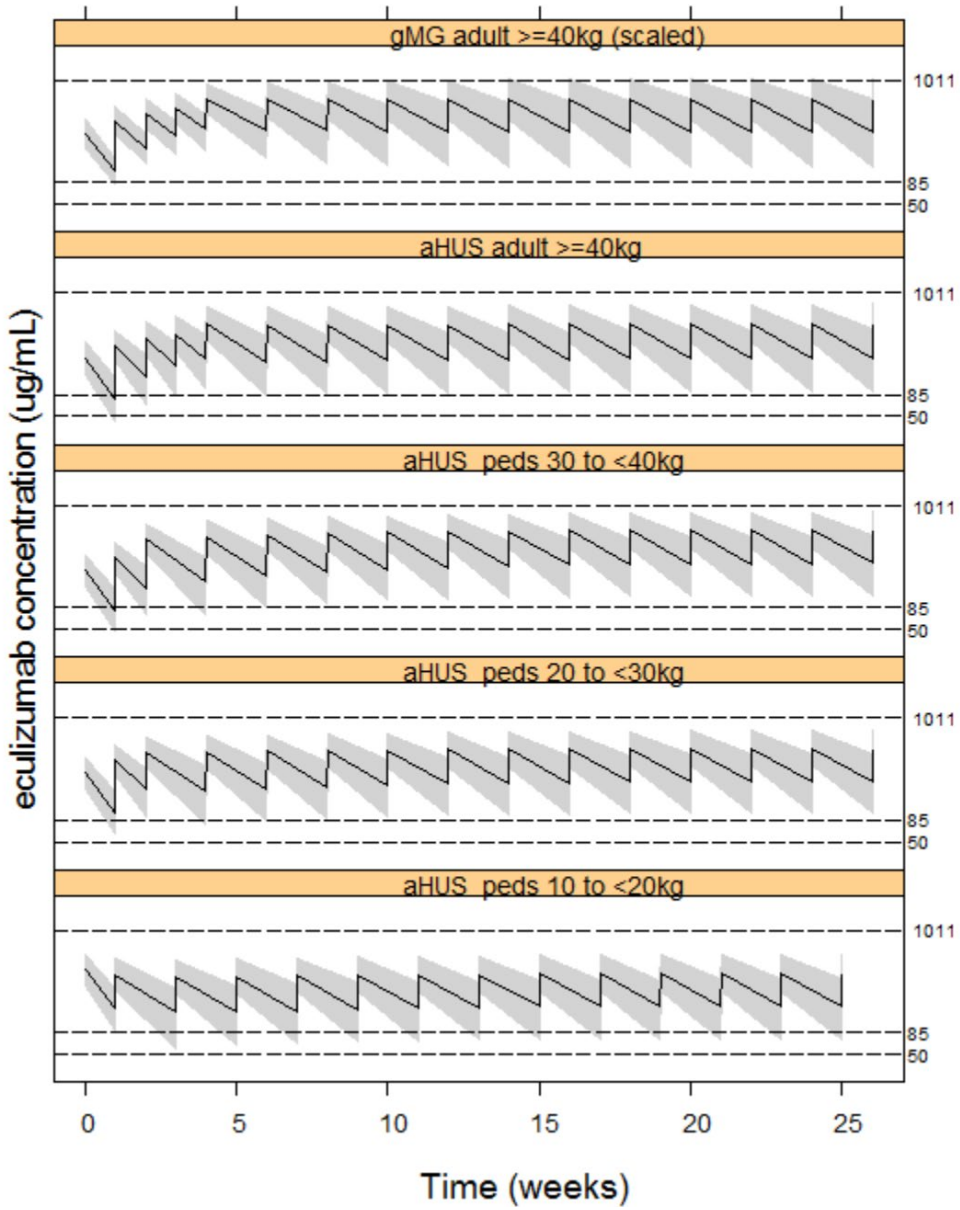
The simulation study results are summarized in Table 16 and Figure 13.

Table 15: Simulated Peak and Trough Eculizumab Concentrations for Adult and Paediatric gMG Patients

	Induction Period (Last Dose)		Maintenance Period	
Weight Group, Conc scaling[a]	Peak (µg/mL) Median (5%, 95%)	Trough (µg/mL) Median (5%, 95%)	Peak (µg/mL) Median (5%, 95%)	Trough (µg/mL) Median (5%, 95%)
≥ 40kg (gMG), Scaled	515 (356, 722)	308 (186, 456)	635 (393, 1071)	290 (124, 642)
≥ 40kg (aHUS), Original	373 (251, 566)	204 (99, 363)	480 (306, 767)	207 (93, 414)
30 to < 40kg, Original	286 (203, 403)	135 (71, 230)	559 (365, 855)	246 (114, 481)
20 to < 30kg, Original	367 (261, 520)	175 (93, 297)	484 (316, 744)	217 (100, 423)
10 to < 20kg, Original	384 (263, 561)	149 (90, 252)	356 (229, 561)	163 (73, 314)

a scaling refers to whether an assay conversion factor was applied to the concentrations, ie, Scaled=Cecu (1/1.07), where Cecu is the eculizumab concentration, and Original=no correction used (See ECU-MG-Adult PK-PD Modeling Report) Abbreviations: aHUS = atypical haemolytic syndrome, gMG = generalized myasthenia gravis

Figure 13: Simulated Pharmacokinetic Profiles for Each Weight Category with the Proposed Dosing Regimens– Semilog Plot



Note: Gray region represents the 90% prediction interval, i.e., 5% to 95% range; black solid line is the median of the simulated concentration-time profiles; horizontal dashed lines represent the ACF-scaled values of the highest observed concentration in Study ECU-MG-301 (1011 µg/mL), the lower concentration boundary for complete and sustained terminal complement inhibition based on treatment

of aHUS patients (50 µg/mL), and the threshold concentration of 85 µg/mL (based on Study ECU-MG-301), above which complete and sustained terminal complement inhibition is maintained. Abbreviations: ACF = assay conversion factor, aHUS = atypical haemolytic syndrome, gMG = generalized myasthenia gravis, peds = paediatric patients, PK = pharmacokinetic

Simulation of Supplemental Eculizumab Dose Following Plasma Exchange Intervention

When PE intervention is needed, eculizumab concentrations fall because drug is removed during the process. To maintain eculizumab concentrations within a range that provides complete and sustained complement inhibition, a supplemental dose of eculizumab is administered to compensate for the eculizumab removed from the body during PE intervention.

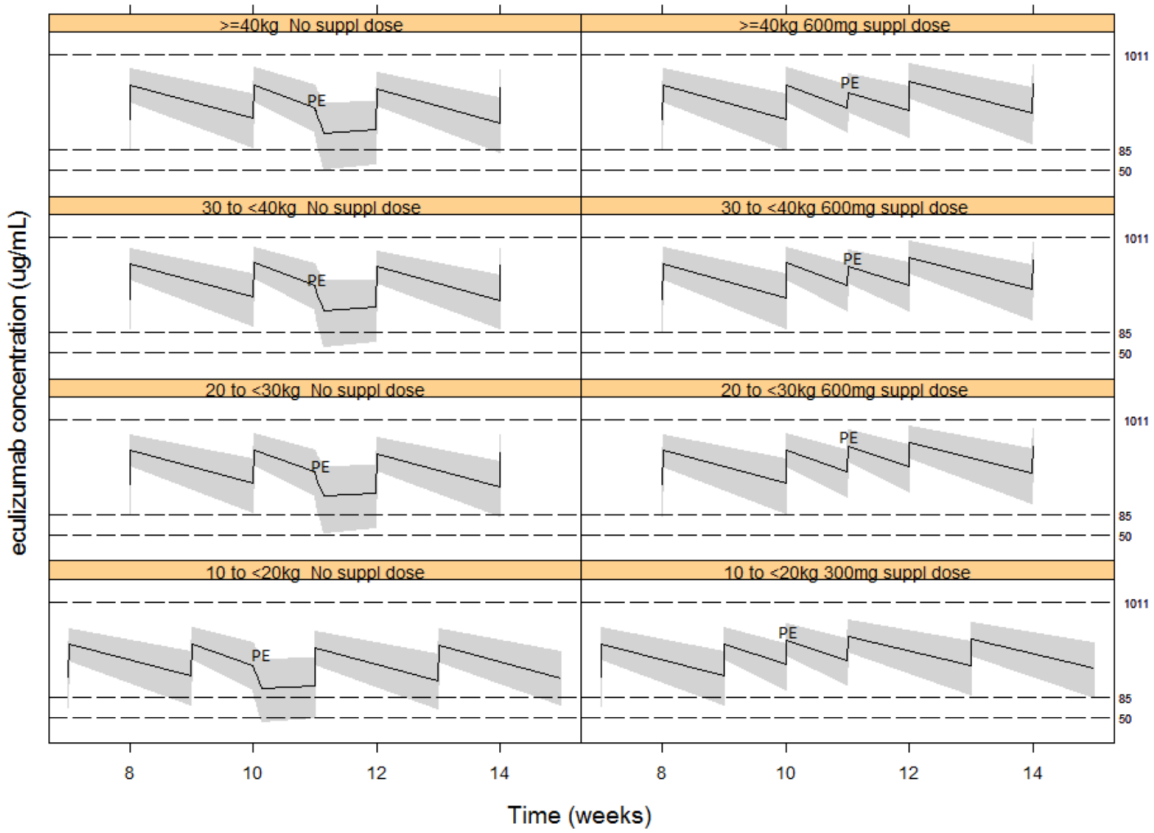
The supplemental eculizumab dose needs to be administered within 1 to 2 hours following each PE intervention (Table 17).

Table 16: Supplemental Dosing Regimen of Eculizumab after Plasma Exchange/Plasma Infusion

Type of Intervention	**Most Recent Eculizumab Dose**	**Supplemental Eculizumab Dose With Each PE/Plasma Infusion Intervention**	**Timing of Supplemental Eculizumab dose**
Plasmapheresis, plasma exchange	300 mg	300 mg per each plasmapheresis, plasma exchange	Within1 – 2 hours after each plasmapheresis, plasma exchange,
	600 mg or more	600 mg per each plasmapheresis, plasma exchange	
Fresh frozen plasma infusion	300 mg or more	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Because PE intervention is a 'transient' event that alters PK, simulations are conducted comparing the concentration-time profile without (Figure 14 left panels) and with (Figure 14 right panels) a supplemental dose following PE intervention.

Figure 14: Comparison of Concentration-Time Profiles During Plasma Exchange Intervention Without (Left Panels) and With (Right Panels) a Supplemental Dose of Eculizumab – Semilog Plot



Note: Gray region represents the 90% prediction interval, i.e., 5% to 95% range; black solid line is the median of the simulated concentration-time profiles; the horizontal dashed line is the ACF-scaled value at the predicted threshold concentration from Study ECU-MG-301 (85 µg/mL). The PE intervention is denoted by PE. Left panels show PE intervention with no supplemental dose and the right panels show PE intervention with a supplemental dose administered after the PE intervention is completed. Abbreviations: PE = plasma exchange, suppl = supplemental

Simulation of Supplemental Dosing Regimens of Eculizumab Following IVIg Treatment

Simulations with and without the proposed supplemental eculizumab dose regimens (Table 18) were conducted. When IVIg was given after eculizumab treatment initiation, it was assumed that the effect of IVIg on eculizumab CL would immediately reach maximum (50% increase). This represented a worst-case scenario.

Table 17: Supplemental Dosing Regimen of Eculizumab Following Intravenous Immunoglobulin

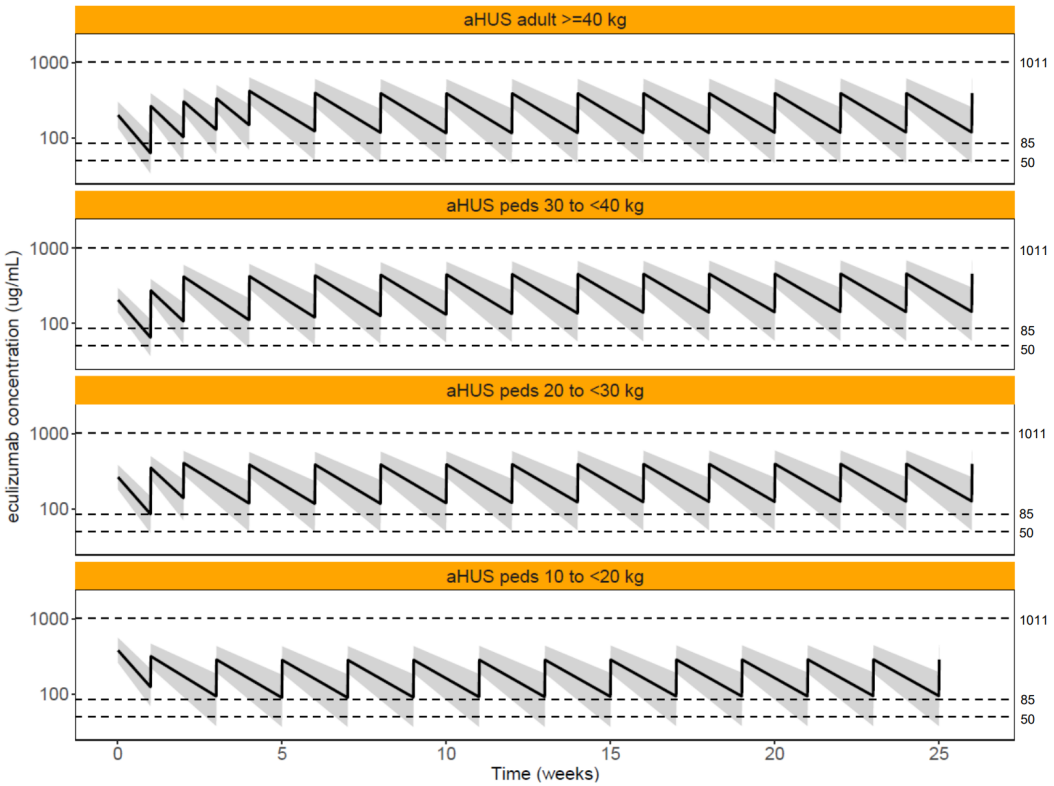
Weight Group	Dose Type	Induction Phase	Maintenance Phase
≥ 40 kg	Scheduled Dose	900 mg weekly for 4 weeks	1200 mg at Week 5; then every 2 weeks
	Supplemental Dose	600 mg	600 mg
30 to < 40 kg	Scheduled Dose	600 mg weekly for 2 weeks	900 mg at Week 3; then every 2 weeks
	Supplemental Dose	300 mg	600 mg
20 to < 30 kg	Scheduled Dose	600 mg weekly for 2 weeks	600 mg at Week 3; then every 2 weeks
	Supplemental Dose	300 mg	300 mg
10 to < 20 kg	Scheduled Dose	600 mg once	300 mg at Week 2; then every 2 weeks
	Supplemental Dose	300 mg	300 mg

Notes: If a patient receives IVIg treatment within 4 weeks prior to receiving the first dose of eculizumab, a supplemental dose of eculizumab will be administered at the same time the first dose of eculizumab is administered (the total dose is supplemental dose plus regular dose). If a patient continues to receive IVIg at a dose interval up to every 4 weeks during eculizumab treatment, a supplemental dose will be administered at the same time each regular dose of ecu is administered. If a patient receives IVIg treatment at a dose interval greater than every 4 weeks during eculizumab treatment, a supplemental dose will be administered following the last dose of IVIg infusion cycle at the next scheduled regular eculizumab dose

Based on literature data, IVIg treatment is likely to increase eculizumab clearance 50%, resulting in lowered trough eculizumab concentrations. Simulations were conducted comparing:

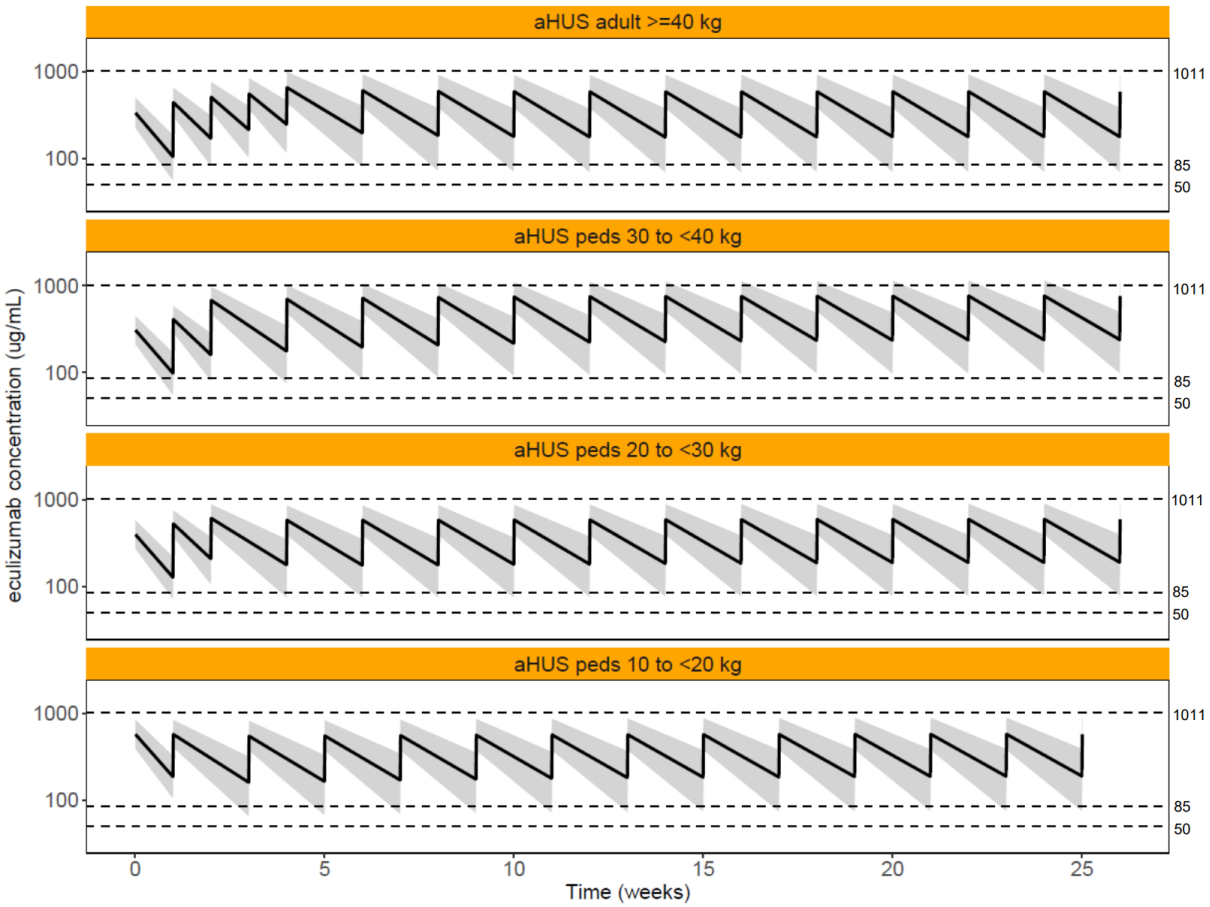
1) The eculizumab concentration-time profile without (Figure 15) and with (Figure 16) eculizumab supplemental doses following stable IVIg treatment, i.e, IVIg treatment initiated before eculizumab treatment
2) The eculizumab concentration-time profile without (Figure 17) and with (Figure 18) eculizumab supplemental doses when IVIg treatment started after eculizumab treatment.

Figure 15: Simulated Pharmacokinetic Profiles (Semilog Plot) for Adult and Paediatric Patients with Stable Dose of Intravenous Immunoglobulin in the Absence of Eculizumab Supplemental Doses



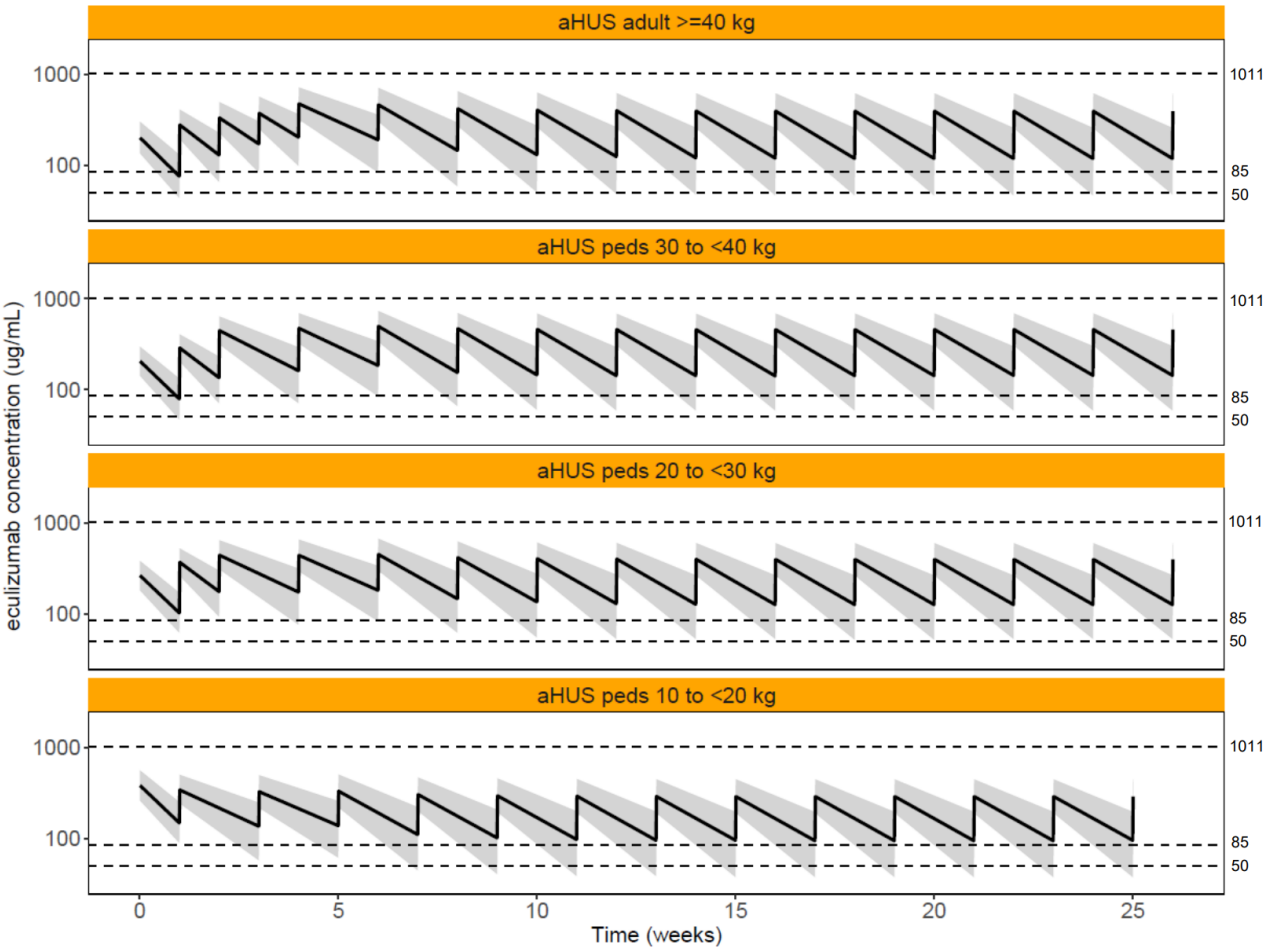
Abbreviation: aHUS = atypical haemolytic uremic syndrome, peds = pediatric patients

Figure 16: Simulated Pharmacokinetic Profiles (Semilog Plot) for Adult and Paediatric with Stable Dose of Intravenous Immunoglobulin and the Proposed Supplemental Dosing Regimens of Eculizumab



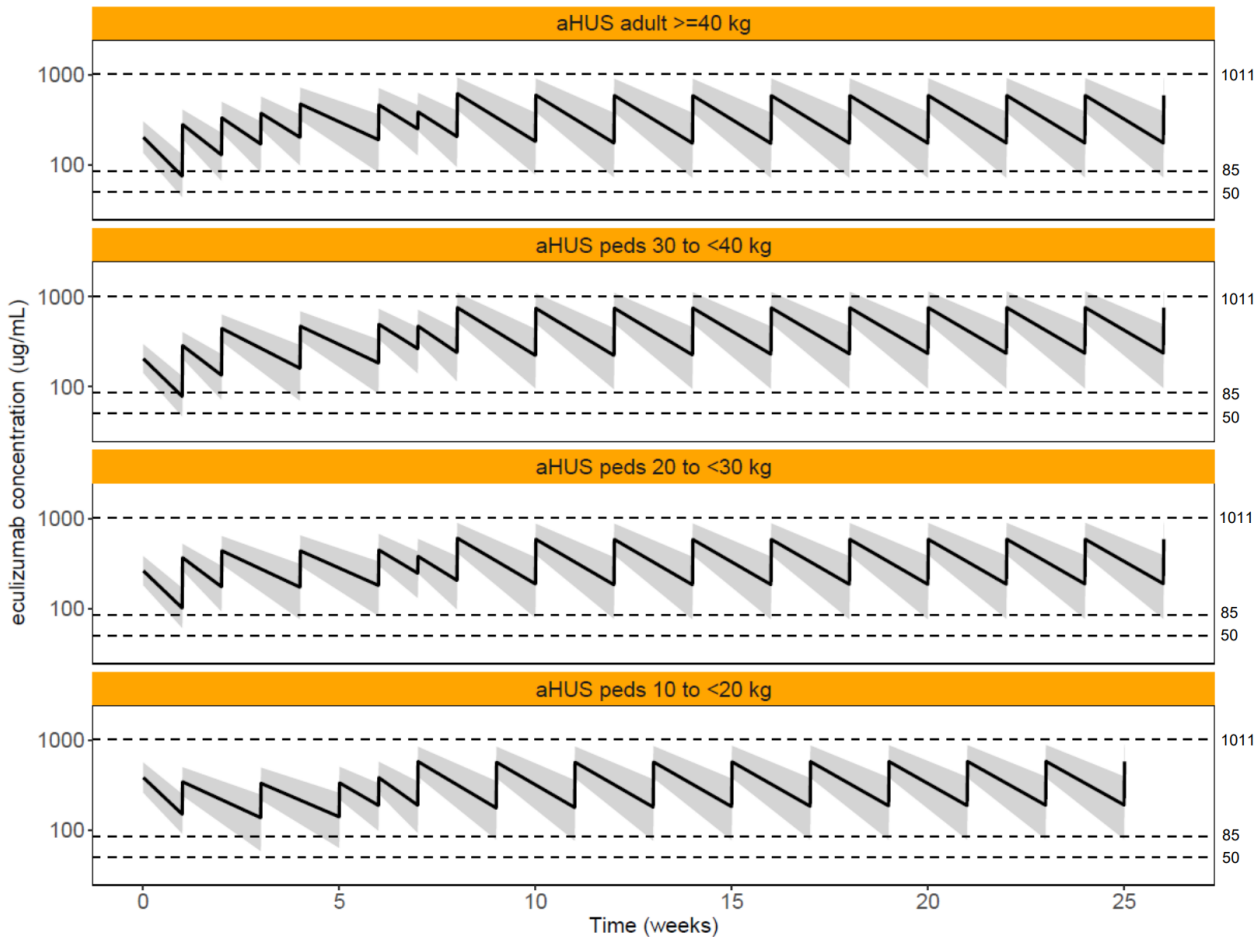
Note: Grey region represents the 90% prediction interval, i.e., 5% to 95% range; black solid line is the median of the simulated concentration-time profiles; horizontal dashed lines represent the ACF-scaled values of the highest observed concentration in Study ECU-MG-301 (1011 µg/mL) and the predicted threshold concentration from Study ECU-MG-301 (85 µg/mL) for complete and sustained terminal complement inhibition. Abbreviations: aHUS = atypical haemolytic syndrome, peds = paediatric patients

Figure 17: Simulated PK Profiles (Semilog Plot) for Adult and Paediatric Patients when IVIg Treatment Started After Eculizumab Treatment at the Absence of Eculizumab Supplemental Doses



Note: Grey region represents the 90% prediction interval, i.e., 5% to 95% range; black solid line is the median of the simulated concentration-time profiles; horizontal dashed lines represent the ACF-scaled values of the highest observed concentration in Study ECU-MG-301 (1011 µg/mL) and the predicted threshold concentration from Study ECU-MG-301 (85 µg/mL) for complete and sustained terminal complement inhibition. Abbreviations: aHUS = atypical haemolytic syndrome, peds = paediatric patients

Figure 18: Simulated PK Profiles (Semilog Plot) for Adult and Paediatric Patients when Intravenous Immunoglobulin Treatment Started After Eculizumab Treatment



Note: Grey region represents the 90% prediction interval, i.e., 5% to 95% range; black solid line is the median of the simulated concentration-time profiles; horizontal dashed lines represent the ACF-scaled values of the highest observed concentration in Study ECU-MG-301 (1011 µg/mL) and the predicted threshold concentration from Study ECU-MG-301 (85 µg/mL) for complete and sustained terminal complement inhibition. Abbreviations: aHUS = atypical haemolytic syndrome, peds = paediatric patients

Immunogenicity

No treatment-emergent ADA responses were observed following eculizumab treatment as of data cut-off date.

2.3.3. Pharmacodynamics

Mechanism of action

Eculizumab is a humanized monoclonal antibody that specifically binds to the human terminal complement component C5, inhibiting C5 enzymatic cleavage and thereby preventing the generation of the proinflammatory/prothrombotic complement activation products C5a and the cytolytic and proinflammatory/prothrombotic MAC C5b-9 that are responsible for the inflammatory consequences of terminal complement activation. Given that terminal complement-mediated cell damage and inflammation at the neuromuscular junction play a central role in the pathophysiology of autoimmune-mediated MG, the mechanism of action of eculizumab as a terminal complement inhibitor supports its use in the management of refractory gMG mediated by complement-activating antibodies directed against the NMJ.

2.3.4. PK/PD modelling

Exploratory Analysis of PK-PD relationship for Free C5 and Haemolysis

To exploratory assess the similarity of the relation of free C5 and haemolytic activity versus eculizumab concentrations in paediatric and adult subjects with refractory gMG, scatter plots were generated showing free C5 and haemolysis observations versus time-matched eculizumab concentrations colour coded by age group.

Data Summary

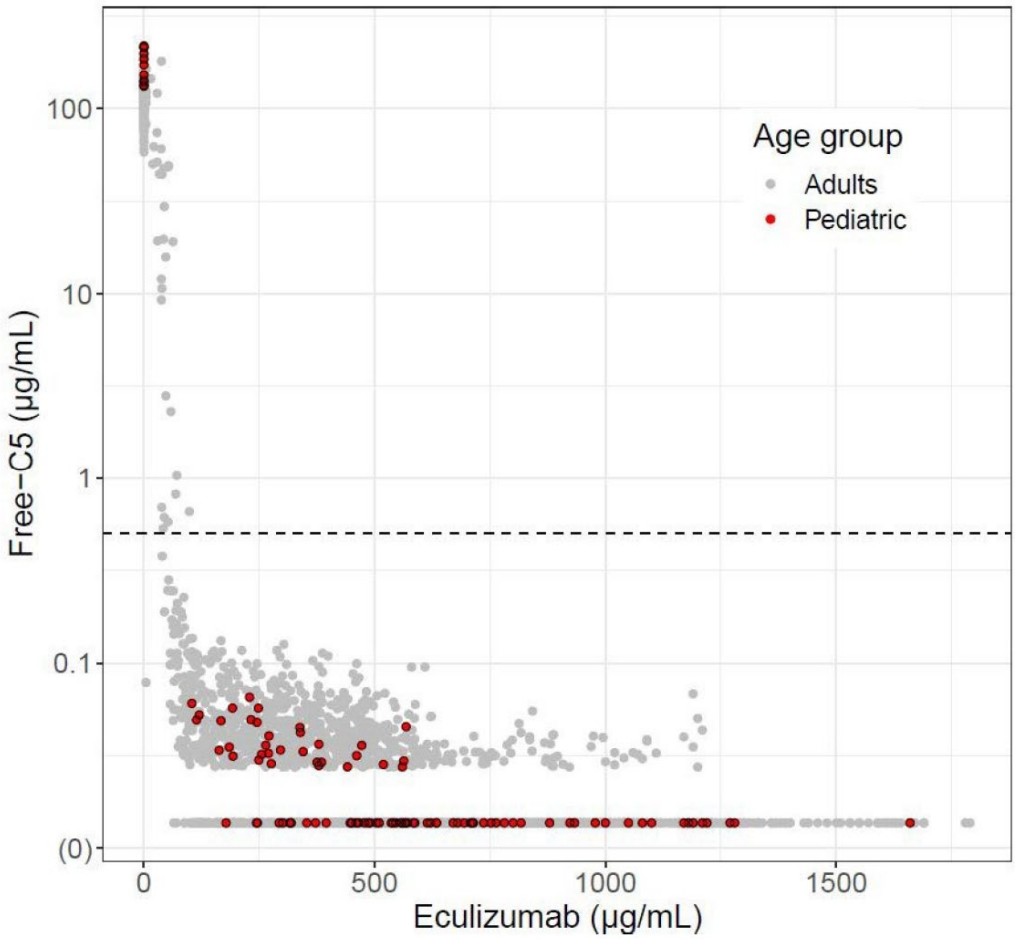
The analysis dataset for the PK-PD free C5 analysis of eculizumab comprised of 122 adult subjects from Studies ECU-MG-301 and ECU-MG-302 and 11 paediatric subjects from Study ECU-MG-303 for which evaluable free C5 with time-matched observations of eculizumab were available.

The analysis dataset for the PK-PD haemolysis analysis of eculizumab comprised of 135 adult subjects from Studies C08-001, ECU-MG-301 and ECU-MG-302 and 11 paediatric subjects from Study ECU-MG-303 for which evaluable haemolysis with time-matched observations of eculizumab were available.

Free C5

The free C5 responses versus time-matched eculizumab concentrations for adult subjects from Studies ECU-MG-301 and ECU-MG-302 and paediatric subjects from Study ECU-MG-303 are presented in presented in Figure 19. Subjects were color-coded by age group.

Figure 19: Eculizumab Concentration Versus Time Matched Free C5 Concentration for Paediatric and Adult Subjects

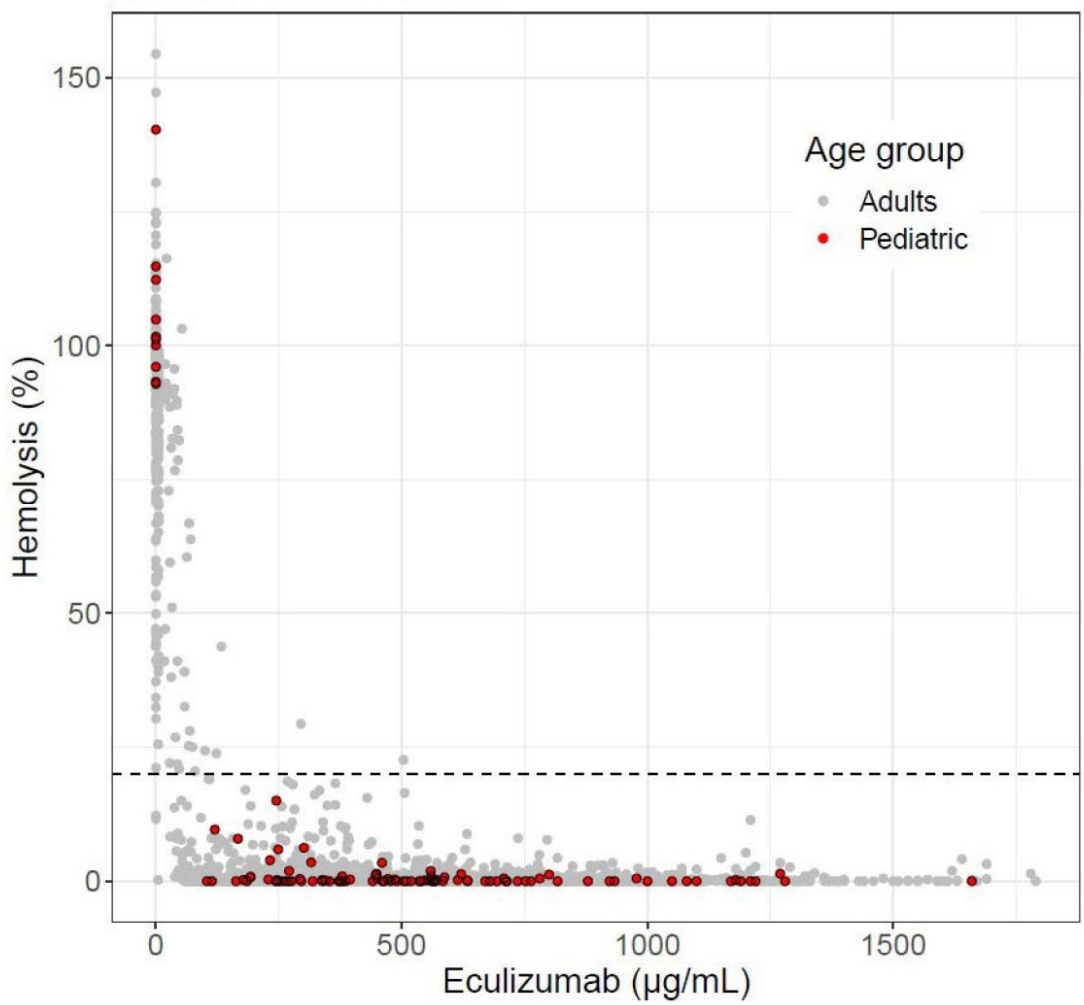


Note: Adult data from Studies ECU-MG-301 and ECU-MG-302. Pediatric data from Study ECU-MG-303.
Abbreviation: C5 = complement component 5

Haemolysis

The haemolysis responses versus time-matched eculizumab concentrations for adult subjects from Studies C08-001, ECU-MG-301, ECU-MG-302 and paediatric subjects from Study ECU-MG-303 are presented in presented in Figure 20. Subjects were color-coded by age group.

Figure 20: Eculizumab Concentration Versus Time Matched Haemolysis for Paediatric and Adult Subjects

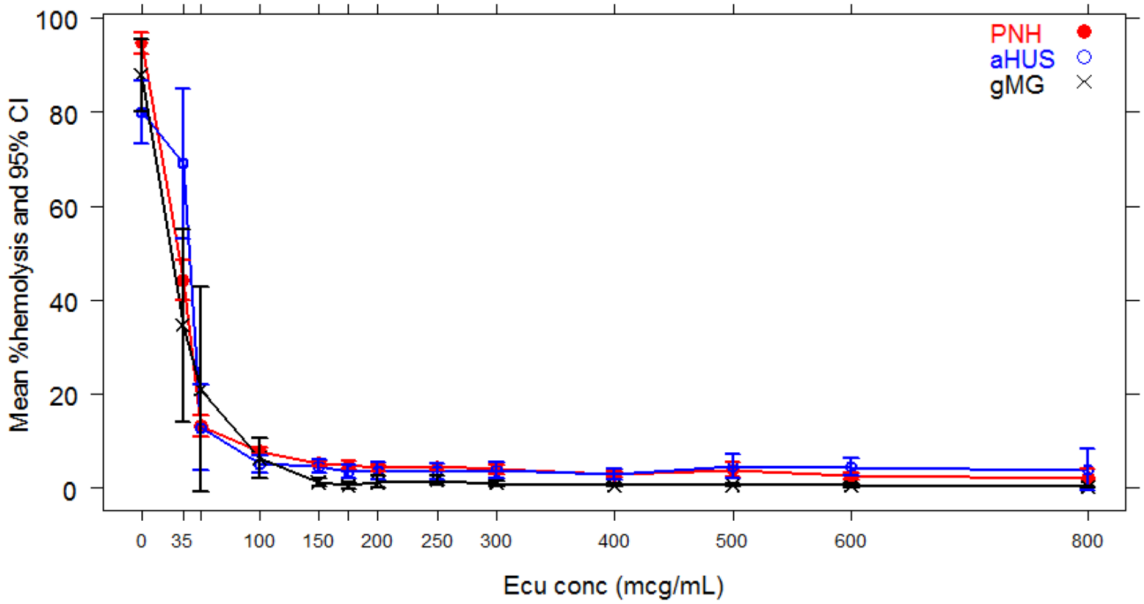


Note: Adult data from Studies ECU-MG-301 and ECU-MG-302. Pediatric data from Study ECU-MG-303.
Abbreviation: C5 = complement component 5

PD/Response Bridging Between aHUS and gMG Patients

Figure 21 establishes a threshold eculizumab concentration range using PK and PD data from aHUS, PNH, and refractory gMG patients. An analysis of haemolytic activity versus eculizumab concentration determined that a concentration range of 50 to 100 µg/mL resulted in complete inhibition of haemolysis (< 20%) regardless of indication.

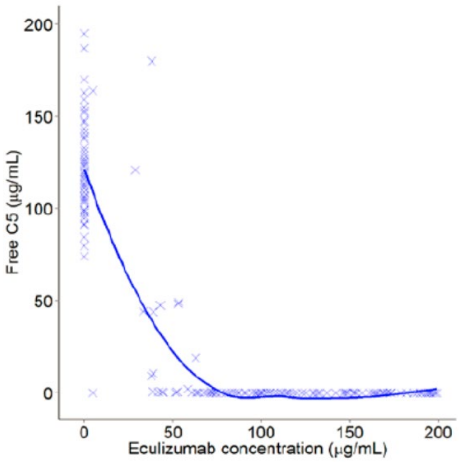
Figure 21: Comparison of Exposure-Response for %Haemolysis using Pooled PNH, aHUS, and Refractory gMG Trial Data



Note: Predose eculizumab concentrations below the lower limit of quantitation were set to 0 µg/mL. Post-dose eculizumab concentrations below the lower limit of quantitation were set to 5 µg/mL. For gMG study, ECU-MG-301, eculizumab concentrations were scaled by the assay conversion factor ie, Scaled=Cecu (1/1.07), where Cecu is the eculizumab concentration. Abbreviations: aHUS = atypical haemolytic uremic syndrome, gMG = generalized myasthenia gravis, PNH = paroxysmal nocturnal haemoglobinuria

Figure 22 shows the free C5-concentration time profile from Study ECU-MG-301 in adult refractory gMG patients. Treatment with eculizumab produced inhibition of the PD endpoint, free C5, as demonstrated using a highly reliable and accurate free C5 assay. Simulation using the free C5 model developed with the Study ECU-MG-301 data determined that a 116 µg/mL eculizumab concentration provides immediate and complete inhibition of free C5. When applying the inverse of the ACF, this value is 85 µg/mL. Free C5 data were not compared between PNH, aHUS and refractory gMG patients since free C5 was not measured in PNH studies and the aHUS studies (C08-002 and C08-003) used an earlier and more variable version of the assay.

Figure 22: Exposure-Response for Free C5 in Study ECU-MG-301



Observations within 0-200 ug/mL eculizumab concentration range, including a loess trend line.

2.3.5. Discussion on clinical pharmacology

Eculizumab for refractory gMG treatment in children was evaluated in the pivotal Phase 3 study ECU-MG-303. Eleven patients were included and treated in the study with eculizumab. The dosing regimens studied were those previously approved for paediatric patients with aHUS and PNH. However, the study did not include patients younger than 12 years old and there was only 1 patient in the body weight range 30 to 40 kg and 10 patients in the weight cohort ≥ 40 kg, which indicates that 10 out of 11 subjects received the dosing regimen for adult patients.

The pop-PK analysis was based on a pooled dataset from 4 studies, which includes data of eculizumab from studies in adult patients with refractory gMG (C08-001, ECU-MG-301, ECU-MG-302) and from the pivotal phase 3 study ECU-MG-303 in children. The final dataset for the current Pop-PK model development included 2674 observation records (133 BLQ) from 135 adult patients and 107 (11 BLQ) records from 11 children patients. PK samples of eculizumab below the lower limit of quantification (LLQ) were low and were excluded from the analysis. M1 method for handling BLQ-data is considered acceptable.

A pop-PK model update was conducted incorporating paediatric data from Study ECU-MG-303 with 11 paediatric subjects to the adult dataset, which comprised 135 adult subjects (Studies 08-001, ECU-MG-301 and ECU-MG-302). The exploratory analysis suggests an adequate correspondence between exposure levels of eculizumab in adult and paediatric patients with gMG. The re-estimation analysis of the pop-PK parameters shows very similar PK values and an adequate model performance of the experimental data. Model evaluation was conducted through (i) graphical assessment of the prediction intervals of the updated pop-PK model and the experimental paediatric data and (ii) a bootstrap analysis of the PK parameter estimates. Both analyses demonstrate the adequacy of the updated pop-PK model to capture the longitudinal PK data of eculizumab in paediatric gMG patients from 12 years of age and adult gMG patients although the model seems to slightly under-predict the median PK trend of eculizumab in paediatric patients. This could be explained by the unbalanced distribution of adult and paediatric patients, which could affect the estimated value of the allometric exponents on CL/Q (1.11) and V1/V2 (0.609) since both are not even close to the reference/standard values (0.75 and 1, respectively).

The experimental PD evidence collected in paediatric patients with gMG regarding the free-C5 and haemolysis suggests a similar PK/PD relationship between both populations. The efficacy threshold of 116 micrograms/mL is endorsed.

Then, a model-based extrapolation analysis was conducted using the estimates from the updated pop-PK model (gMG adult and paediatric patients) to evaluate the eculizumab concentration-time profiles in different sub-population of paediatric patients with different body weight ranges (5-<10 kg, 10-<20 kg, 20-<30 kg, 30-<40 kg, >=40 kg). Although simulated exposure with the proposed dosing regimens for each sub-group of paediatric patients predicted eculizumab levels at steady-state within the therapeutic range, a relevant increase in the exposure (1.5-2 fold) in paediatric patients from 5 to 10 kg is observed with the proposed dosing regimen.

A parallel analysis was provided evaluating the PK bridging of the pop-PK model developed in aHUS/PNH paediatric and adult patients. This latter model incorporates a wider body weight range (4.4-127 kg), which could be relevant for PK prediction in patients with very low body weight. Simulated eculizumab exposure in adult patients ≥40 kg using the pop-PK model in paediatric/adult aHUS/PNH patients demonstrates a 30-50% increase in the exposure in gMG adult patients compared to aHUS patients. Therefore, there is no clear similarity in predicted exposure between the indications. Furthermore, the correspondence of 1.3-1.5-fold increase in exposure in adults is not directly transferable to the different weight groups of the paediatric population. In this sense, the selection of dosing regimens in the paediatric population should be established using the predictions made with the pop-PK model developed in adults with gMG.

In order to characterize the PK properties of eculizumab in paediatric patients, taking into account that model predictions are highly dependent on allometric exponents values, but very little information (n=11) was available to fully characterize the relationship between body weight and disposition parameters (CL/Q and V1/V2) in paediatric patients with gMG, the Applicant was requested to provide a simulation-based analysis of the exposure at steady state across the different body-weight subgroups of paediatric patients using the pop-PK model in gMG patients and the allometric exponents obtained in the pop-PK model in aHUS/PNH, showing the proportion of patients below the efficacy threshold for each subgroup of body weight. The simulated exposure with the proposed dosing regimens for each sub-group of paediatric patients predicted eculizumab levels at steady-state within the therapeutic range. Thus, this issue was considered solved.

The Applicant has justified the absence of exposure safety analysis indicating that the exposure safety analysis performed in adults did not show any exposure-response relationship and the low small sample size of paediatric patients did not allow a proper analysis. A preliminary exposure safety assessment has been performed using data from ECU-MG-303. Any TEAE occurring in 3 or more patients was studied, the simulated exposure was calculated based on *post hoc* estimates for each patient and data was divided by two different exposure groups (94000 to 126000 µg.h/mL, and 126000 to 267000 µg.h/mL). It is agreed that no new trends have been detected. However, no definitive conclusions can be drawn from this analysis.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology properties of eculizumab in paediatric patients with gMG have been characterized using a previously developed pop-PK model in adult gMG patients and updating pop-PK parameters with the experimental evidence collected in study ECU-MG-303. The data analysis, model development and model evaluation are endorsed. Then, a simulation analysis has been conducted in paediatric gMG patients below 37 kg, which supports the dose recommendation in this sub-group of patients.

2.4. Clinical efficacy

2.4.1. Main study

Title of Study: An Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Eculizumab in Paediatric Patients with Refractory Generalized Myasthenia Gravis

Study ECU-MG-303 is an open-label, multicenter study to evaluate the efficacy, safety, PK, PD, and immunogenicity of eculizumab for the treatment of paediatric patients aged 6 to < 18 years with AChR-Ab+ refractory gMG.

The MAH has submitted the primary efficacy analysis results of the 26-week primary evaluation treatment period for all patients who were enrolled in the study.

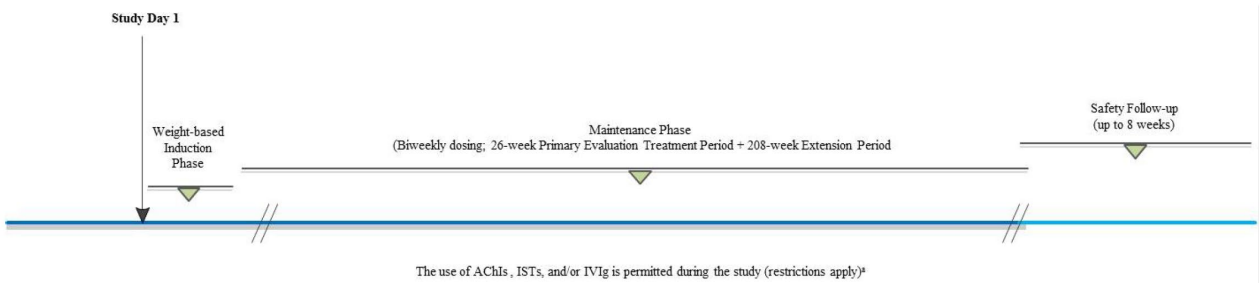
Methods

The study consists of a Screening Period of 2 to 4 weeks, a 26-week primary evaluation treatment period, an extension period of up to 208 weeks, and a Follow-up Period of 8 weeks.

The primary evaluation treatment period of 26 weeks defines the time period for the assessment of the study endpoints. There is also a screening period of 2 to 4 weeks and an extension period of up to an additional 208 weeks still ongoing.

In case of withdrawal or discontinuation from the study or eculizumab treatment at any time, the patient is required to complete an Early Termination Visit at the time of withdrawal and a Follow-up Visit 8 weeks after the last dose of eculizumab. The overall study duration for an individual patient is estimated to be up to 246 weeks (from Screening through the end of the Safety Follow-up).

Figure 23: Flow Diagram for Study Design



a Patients could continue to receive AChI, IST, and/or IVIg during the study where applicable under certain restrictions. For patients who entered the study receiving any background therapy, the dose/schedule could not be changed during the Primary Evaluation Treatment Period before Week 12, unless deemed necessary per the Investigator based on clinical safety evaluation and if Sponsor approval was obtained. Dose change with background medication was permitted after Week12 at the Investigator's discretion and with Sponsor notification.
During the Extension Period, changes in background medications are permitted at the Investigator's discretion and with Sponsor notification.
Abbreviations: AChI = acetylcholinesterase inhibitor; IST = immunosuppressant therapy; IVIg = intravenous immunoglobulin

Study participants

To be eligible for this study, study participants must have met all of the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

1. Male or female paediatric participants 6 to <18 years of age at time of assent/consent.
2. Vaccinated against *Neisseria meningitidis.*
3. Documented vaccination against *Haemophilus influenzae* and *Streptococcus pneumoniae* infections prior to dosing as per local and country specific immunization guidelines for the appropriate age group.
4. Diagnosis of MG confirmed by positive serologic test for anti-acetylcholine receptor antibodies at Screening, and 1 of the following: (a) history of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation; (b) history of positive anticholinesterase test (for example, edrophonium chloride or neostigmine test); or (c) participant demonstrated improvement in MG signs on oral acetylcholinesterase inhibitors, as assessed by the Investigator.
5. Presence of refractory gMG, defined as participants with gMG who have 1 or more of the following: (a) failed treatment ≥1 year with at least 1 IST, defined as follows: (1) persistent weakness with impairment of activities of daily living; (2) MG exacerbation and/or crisis while on treatment; or (3) intolerance to ISTs due to side effect or comorbid condition(s). (b) Require maintenance PE or IVIg to control symptoms; and/or (c) in the opinion of the Investigator, MG poses a significant functional burden despite current MG treatment.

6. MGFA Clinical Classification of Class II to IV at Screening.
7. In patients aged 12 to 18 years, Quantitative Myasthenia Gravis (QMG) total score ≥ 12 at Screening; in patients aged 6 to 11 years, no minimum QMG is required for inclusion; however, patients must have documented limb weakness in at least one limb.
8. All MG-specific treatment has been administered at a stable dosing regimen of adequate duration prior to Screening.

Exclusion criteria

1. Parent or legal guardian is an Alexion employee.
2. Any active or untreated thymoma. History of thymic carcinoma or thymic malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥5 years before Screening.
3. History of thymectomy within 12 months prior to Screening.
4. Are pregnant or lactating.
5. Any unresolved acute, or chronic, systemic bacterial or other infection, which is clinically significant in the opinion of the Investigator and has not been treated with appropriate antibiotics.
6. Use of PE within 4 weeks prior to first dose.
7. Use of rituximab within 6 months prior to first dose.
8. Patients who are under 15 kg and are receiving maintenance IVIg.
9. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater.
10. Have previously received treatment with eculizumab or other complement inhibitors.

Treatments

Eculizumab was initiated with a weekly weight-based induction regimen. Thereafter, patients are dosed every 2 weeks. Dosing was initiated with a weekly weight-based induction regimen; thereafter, patients are dosed every 2 weeks. The dosage regimen was based on the paediatric patient's body weight:

Table 18: Dosage regimen

Weight Cohort[a,b]	Induction Phase[c]	Maintenance Phase[c]
≥ 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 Dosage regimen is based on the current visit's recorded body weight. If site/institution policies prohibit study drug to be prepared on the day of visit, the weight from the most recent study visit is to be used.
b During the initial Induction Phase, if a patient's weight increased or decreased resulting in a change in weight cohort, the Alexion Medical Monitor had to be contacted prior to dosing.
c Induction and Maintenance Phase dosage regimens are identical to that of approved dosing

For patients who enter the study on maintenance IVIg treatment, a series of supplemental doses of eculizumab were administered to account for the anticipated approximately 50% increase in eculizumab clearance:

Table 19: Supplemental doses of eculizumab for patients on maintenance intravenous immunoglobulin (IVIg) treatment

Weight Cohort[a,b]	Induction Phase Supplemental Dose	Induction Phase Total Dose	Maintenance Phase Supplemental Dose	Maintenance Phase Total Dose
≥ 40 kg	600 mg	1500 mg	600 mg	1800 mg
30 to < 40 kg	300 mg	900 mg	600 mg	1500 mg
20 to < 30 kg	300 mg	900 mg	300 mg	900 mg
10 to < 20 kg	300 mg	900 mg	300 mg	600 mg

Notes: The timing of supplemental eculizumab dosing varied by IVIg frequency and is provided below:
• If a patient continues to receive IVIg treatment at a dose cycle interval equal to or more frequent than every 4 weeks during eculizumab treatment, a supplemental dose is to be administered at the same time that each scheduled dose of eculizumab is administered.
• If a patient receives IVIg treatment at a dose cycle interval less frequent than every 4 weeks during eculizumab treatment, a supplemental dose is to be administered following the last dose of the IVIg infusion cycle at the next scheduled eculizumab dose.
• If a patient receives IVIg treatment within 4 weeks prior to receiving the first dose of eculizumab, a supplemental dose of eculizumab is to be administered at the same time that the first dose of eculizumab is administered (ie, the total dose is the supplemental dose plus the first scheduled dose).
a Dosage regimen is based on the current visit's recorded body weight. If site/institution policies prohibit study drug to be prepared on the day of visit, the weight from the most recent study visit is to be used.
b During the initial Induction Phase, if a patient's weight increased or decreased resulting in a change in weight cohort, the Alexion Medical Monitor had to be contacted prior to dosing.
c Only patients in 15 – 20 kg weight category are to be included in this group.
Abbreviation: IVIg = intravenous immunoglobulin

Objectives and Endpoints

Table 20: Objectives and Endpoints. Study ECU-MG-303

Objectives	Endpoints
Primary	
To evaluate the efficacy of eculizumab in the treatment of pediatric refractory gMG based on change from Baseline in the QMG total score for disease severity	Primary Endpoint: • Change from Baseline in the QMG total score over time regardless of rescue treatment Secondary Endpoints: • Proportion of patients with ≥ 5-point reduction in the QMG total score from Baseline over time with no rescue treatment • Proportion of patients with ≥ 5-point reduction in the QMG total score from Baseline over time regardless of rescue treatment
Secondary	
To evaluate the safety and tolerability of eculizumab in the treatment of pediatric refractory gMG	• Frequency of AEs and SAEs • Frequency of AEs leading to discontinuation • Change from Baseline in laboratory assessments • Change from Baseline in vital signs • Change from Baseline in ECG parameters • Physical examination assessments • Incidence of ADAs
To evaluate the efficacy of eculizumab in the treatment of pediatric refractory gMG based on change from Baseline in the following measures: – MG-ADL total score – MGC total score	• Change from Baseline in the MG-ADL total score over time regardless of rescue treatment • Proportion of patients with ≥ 3-point reduction in the MG-ADL total score from Baseline over time with no rescue treatment • Proportion of patients with ≥ 3-point reduction in the MG-ADL total score from Baseline over time regardless of rescue treatment • Change from Baseline in the MGC total score over time regardless of rescue treatment
To evaluate the effect of eculizumab on the following quality of life measures: – EQ-5D-Y Questionnaire – EQ-5D-Y Proxy for patients < 8 years of age or EQ-5D-Y for patients ≥ 8 years of age – Neuro-QoL Pediatric Fatigue Questionnaire for patients ≥ 8 years of age – PROMIS Parent Proxy Item Bank v2.0 – Fatigue – Short Form 10a for patients < 8 years of age	• Change from Baseline in EQ-5D-Y over time regardless of rescue treatment • Change from Baseline in Neuro-QoL Pediatric Fatigue over time regardless of rescue treatment (for patients ≥ 8 years of age) • Change from Baseline in PROMIS Parent Proxy Item Bank v2.0 – Fatigue – Short Form 10a over time regardless of rescue treatment (for patients < 8 years of age)

Objectives	Endpoints
To evaluate MGFA Post-Interventional Status over time	• MGFA Post-Interventional Status over time regardless of rescue treatment
To describe total number and percentage of patients with clinical deteriorations, myasthenic crisis, and rescue therapy use over time	• Total number and percentage of patients with clinical deteriorations, myasthenic crisis, and rescue therapy use over time
To describe the PK and PD of eculizumab treatment in pediatric refractory gMG patients to confirm the pediatric dosing selected through modeling and simulation following 26 weeks of eculizumab treatment	• PK/PD parameters including maximum observed serum eculizumab concentration (C_{max}), terminal half-life ($t_{½}$), trough (C_{trough}), clearance, free C5, and in vitro hemolytic assay assessed at Baseline and various timepoints including 24 hours (Day 2), Week 12, and Week 26 during the treatment
Extension Period	
To characterize long-term safety beyond 26 weeks of eculizumab treatment in pediatric patients with refractory gMG	• Frequency of AEs and SAEs • Frequency of AEs leading to discontinuation • Incidence of ADAs • Physical examination assessments • Changes from Baseline in vital signs • Change from Baseline in ECG parameters • Change from Baseline in laboratory assessments
To characterize long-term efficacy beyond 26 weeks of eculizumab treatment in pediatric patients with refractory gMG	• Total number and percentage of patients with clinical deteriorations and/or myasthenic crisis during the study • Total number and percentage of patients needing rescue therapy during the study • Change from Baseline in the QMG total score regardless of rescue treatment • Change from Baseline in the MG-ADL total score regardless of rescue treatment • Change from Baseline in the MGC total score regardless of rescue treatment • Change from Baseline in EQ-5D-Y regardless of rescue treatment • Change from Baseline in Neuro-QoL Pediatric Fatigue regardless of rescue treatment • Change from Baseline in PROMIS Parent Proxy Item Bank v2.0 – Fatigue – Short Form 10a regardless of rescue treatment (for patients < 8 years of age) • Change from Baseline in MGFA Post-Interventional Status regardless of rescue treatment

Abbreviations: ADA = antidrug antibody; AE = adverse event; C5 = complement component 5; Cmax = maximum observed serum eculizumab concentration; Ctrough = serum eculizumab trough concentration; ECG = electrocardiogram; EQ-5D-Y = European Quality of Life 5-Dimension Youth version; gMG = generalized myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MGFA = Myasthenia Gravis Foundation of America; Neuro-QoL = Quality of Life in Neurological Disorders; PD = pharmacodynamics; PK = pharmacokinetics; PROMIS = Patient-Reported Outcomes Measurement Information System; QMG = Quantitative Myasthenia Gravis; SAE = serious adverse event

Sample size

Paediatric patients 6 to < 18 years of age were planned to be enrolled. At least 12 eligible patients aged 12 to < 18 years were planned to be enrolled in the study and receive eculizumab infusion to obtain at least 10 evaluable patients aged 12 to < 18 years for the primary endpoint analysis. There was not a minimum number of patients aged 6 to < 12 years required.

Randomisation

This was a single-group study.

Blinding (masking)

This was an open-label study.

Statistical methods

The definition of the populations analysed are provided below:

- The Safety Analysis Set is the population on which all safety analyses were performed and consists of all patients who received at least 1 dose of eculizumab.
- The Full Analysis Set (FAS) is the population on which all efficacy analyses were performed and consists of all patients who received at least 1 dose of eculizumab.
- The Modified Full Analysis Set (mFAS) is a subset of the Full Analysis Set and includes older patients (12 to < 18 years of age) only and was used for analyses of the primary and secondary endpoints during the 26-week Primary Evaluation Treatment Period.
- The PK analyses Set is the population on which all PK analyses were performed and consists of all patients how have PK data assessments during the study.
- The extension analysis set consists of all patients who received at least 1 dose of eculizumab during the extension period.

Efficacy Analyses

The primary efficacy endpoint is the change from baseline in the QMG total score over time regardless of rescue treatment, using the mFAS Population. A repeated measures model was used to analyse observed change in QMG with baseline QMG score and visits as covariates. The least-squares (LS) mean at week 12 was used to test the primary hypothesis (2-sided) at a significance level of 5%. The least-squares mean at Week 26 was used to test the PDCO-specific primary hypothesis at a significance level of 5%. The p-value, standard error of the mean, and 95% confidence interval (CI) were produced.

As for QMG responders measured as secondary efficacy endpoints the proportion of patients with a ≥ 5-point reduction in the QMG total score from baseline with no rescue therapy prior to the given visits as well as without regard to rescue therapy were summarized by visit. Exact (Clopper-Pearson) CIs for true proportion and p-values were presented by visit.

The following secondary efficacy endpoints that involve changes from baseline regardless of rescue treatment during the primary 26-week treatment period were summarized and analysed in a similar way as was described for the primary efficacy endpoint QMG using the mFAS Population: Myasthenia Gravis Activities of Daily Living (MG-ADL) total score, Myasthenia Gravis Composite (MGC) total score, European Quality of Life 5-Dimension Youth version (EQ-5D-Y) and Quality of Life in Neurological Disorders (Neuro-QoL) Paediatric Fatigue

Also, the proportion of patients with a ≥ 3-point reduction in the MG-ADL total score from baseline with no rescue therapy prior to the given visits as well as without regard to rescue therapy were summarized by visit. CIs and p-values were presented by visit.

MGFA post-interventional status during the first 26 weeks was summarized.

The number and percentage of patients with at least 1 on-study clinical deterioration and/or MG crisis during the first 26 weeks were summarized. Use of rescue therapy during the first 26 weeks was also summarized.

For the analysis of the primary and secondary efficacy endpoints, summary statistics were provided of actual results and changes from baseline results at each visit by the status of maintenance IVIg at study entry [yes, no], and overall patients in the mFAS.

For the summary efficacy analyses, there were no planned imputation of missing or partially missing baseline or post-baseline assessments, regardless of the efficacy endpoint analysed.

Results

Participant flow

A total of 16 patients were screened, and 12 (75.0%) patients were enrolled in the study. Four (25%) patients failed to meet the inclusion/exclusion criteria.

One patient in the age group < 12 years withdrew from the study before study drug administration. In total, 11 patients received study drug. Of which, 10 patients completed the primary evaluation treatment period and continued into the extension period.

Table 21: Patient Disposition (Full Analysis Set)

	Age ≥ 12 years (N = 11) n (%)
Completed the Primary Evaluation Treatment Period	10 (90.9)
Discontinued during the Primary Evaluation Treatment Period	0
Ongoing during the Primary Evaluation Treatment Period	1 (9.1)
Continue to Extension Period	
Yes	10 (90.9)
No	0

Percentages are calculated based on the total number of patients in each group. A patient may contribute to more than one disposition category.

Recruitment

Patients were enrolled in 10 sites across 2 countries (3 centres in Japan and 7 centres in the US).

Date first patient enrolled: 28 Dec 2018

Data cut-off date: 06 Jan 2022

Conduct of the study

Since the original protocol (dated 07 Mar 2018), 3 global protocol amendments were made.

Table 22: Summary of Protocol Changes

Amendment Number (Country) Date	Summary of Significant Changes to the Study Protocol
Amendment 1 (Global) Dated 17 Sep 2018	The purpose of this amendment was: To enhance clarity of guidance around the supplemental dosage regimen of eculizumab in patients receiving maintenance IVIg. To enhance clarity of guidance around duration of study drug administration for adult and pediatric patients. To enhance clarity of guidance around duration of study drug administration in the event of an AE in adult and pediatric patients. To align the section regarding acceptable forms of contraception with the current guidance from Heads of Medicine Agency Clinical Trial Facilitation Group. To update the Quantitative Myasthenia Gravis (QMG) testing form to reflect current version.
Amendment 2 (Global) Dated 16 Jul 2019	The purpose of this amendment was: To change the "Neuro-QoL Pediatric Proxy" assessment to the "PROMIS Parent Proxy Short Form v2.0 – Fatigue 10a" assessment. To specify the proxy versions for Neuro-QoL Pediatric Fatigue and EQ5DY assessments in the SoAs. To update the vaccination requirement for *Neisseria meningitidis* to within 3 years of study start. To clarify the inclusion criterion regarding the QMG score at Screening. To add an exclusion criterion for patients weighing under 15 kg and receiving maintenance IVIg. To revise the SoAs for PK, hemolysis, and free C5 testing and to add clinical laboratory testing at 6 months intervals during the extension phase. To enhance clarity of guidance around collection of AEs throughout the protocol to clarify that all AEs (serious and nonserious) were to be collected from the signing of the ICF. To update the PK/PD sampling window times. To clarify that the overall duration of study drug administration should not exceed 4 hours from the start of infusion in patients aged ≥ 18 years receiving maintenance IVIg. To enhance clarity of guidance around adjustment of ISTs during the study. To add subcutaneous Ig under disallowed medications. To remove pulse oximetry from vital sign assessments. To enhance clarity around the process for reporting SAEs.
Amendment 3 (Global) Dated 28 Sep 2020	The purpose of this global amendment was: To increase the maximum number of patients aged 12 to < 18 years who may enter the study on maintenance IVIg from 4 to 6. To add text regarding the protection of patient data. To revise the SoAs to include study drug infusion at the End of Study Visit for the Primary Evaluation Treatment Period and throughout the 208-week Extension Period.

Important deviations were reported for 6 (54.5%) patients during the Primary Evaluation Treatment Period

Table 23: Patients with Important Protocol Deviations During Primary Evaluation Treatment Period (Full Analysis Set)

	Age ≥ 12 years (N = 11) n (%)
At least 1 deviation	6 (54.5)
Investigational product	1 (9.1)
Informed consent	2 (18.2)
Laboratory assessment	1 (9.1)
Study procedures/test	4 (36.4)

Baseline data

Overall, 81.8% of patients in the Full Analysis Set were female; 45.5% were Black or African American, and the mean age was 14.8 years at Screening. The majority (90.9%) of the patients were in the baseline weight category ≥ 40 kg.

Table 24: Demographics and Baseline Characteristics (Full Analysis Set)

	Age ≥ 12 years (N = 11)
Sex, n (%)	
Male	2 (18.2)
Female	9 (81.8)
Race, n (%)	
Asian	3 (27.3)
Black or African American	5 (45.5)
White	2 (18.2)
Other	1 (9.1)
Ethnicity, n (%)	
Hispanic or Latino	2 (18.2)
Not Hispanic or Latino	9 (81.8)
Japanese descent, n (%)	
Yes	3 (27.3)
No	7 (63.6)
Unknown	1 (9.1)
Age at Screening (years)	
Mean (SD)	14.8 (1.78)
Median	15.0
Q1, Q3	14.0, 16.0
Min, max	12, 17
Height (cm)	

Mean (SD)	158.3 (8.52)
Median	158.0
Q1, Q3	149.1, 165.5
Min, max	146.0, 170.2
Weight (kg)	
Mean (SD)	61.8 (18.61)
Median	59.7
Q1, Q3	45.8, 80.4
Min, max	37.2, 91.2
Weight (kg) category, n (%)	
≥ 40 kg	10 (90.9)
30 to < 40 kg	1 (9.1)
BMI (kg/m^2)	
Mean (SD)	24.5 (6.43)
Median	25.3
Q1, Q3	17.7, 29.4
Min, max	16.3, 36.5

Note: Percentages are based on number of patients with nonmissing values in each group.
Abbreviations: BMI = body mass index; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile

The most frequently reported conditions and procedures (reported in ≥ 20% of patients) included thymectomy (54.5%), gastroesophageal reflux disease (45.5%), diplopia (27.3%), and eyelid ptosis (27.3%).

Table 25: Baseline Disease Characteristics (Safety Analysis Set)

Variable	**Statistic**	**Age ≥ 12 Years (N = 11)**
Age at MG diagnosis (years)[a]	n	11
	Mean (SD)	11.37 (2.666)
	Median	10.60
	Min, max	6.7, 16.1
Type of first MG presentation		
Ocular MG (oMG)	n (%)	1 (9.1)
Generalized MG (gMG)	n (%)	10 (90.9)
Duration of MG (time from MG diagnosis to first IP dose date [years])[b]	n	11
	Mean (SD)	3.99 (2.909)
	Median	2.90
	Min, max	0.1, 8.8

Ever required ventilatory support prior to study entry?		
Yes	n (%)	3 (27.3)
No	n (%)	8 (72.7)
Any MG exacerbation including MG crisis?		
Yes	n (%)	7 (63.6)
Exacerbation	n (%)	6 (54.5)
MG crisis	n (%)	3 (27.3)
No	n (%)	4 (36.4)
MGFA clinical classification at screening		
IIa	n (%)	2 (18.2)
IIb	n (%)	3 (27.3)
IIIa	n (%)	3 (27.3)
IIIb	n (%)	0
IVa	n (%)	3 (27.3)
IVb	n (%)	0
Patients with any immunosuppressant therapies at Baseline[c]	n (%)	9 (81.8)
Corticosteroids	n (%)	8 (72.7)
Azathioprine	n (%)	1 (9.1)
Mycophenolate mofetil[d]	n (%)	2 (18.2)
Tacrolimus	n (%)	3 (27.3)

a Age at MG Diagnosis = MG Diagnosis Date - Birth Date.
b Duration of MG = Treatment Start Date - MG Diagnosis Date.
c Immunosuppressant therapies include corticosteroids, azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus. No patients received cyclosporine, cyclophosphamide, or methotrexate at Baseline.
d Mycophenolate mofetil includes mycophenolate mofetil and mycophenolic acid.
Abbreviations: IP = investigational product; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America

Per protocol, all patients were diagnosed with gMG and had an MGFA clinical classification that ranged from Classes IIa to IVa at Screening. The mean (SD) time from MG diagnosis to the first study drug dose was 3.99 (2.909) years.

Prior Therapy

Two (18.2%) patients had not used any ISTs prior to study treatment. Three (27.3%) patients had used only 1 IST and 6 (54.5%) patients had used 2 ISTs. Corticosteroids were the most common ISTs used prior to study treatment and were used by 9 (81.8%) patients.

Nine (81.8%) patients had previously been treated with cholinesterase inhibitors, and 7 (63.6%) patients had received long-term IVIg therapy.

All patients received the protocol-required vaccinations against *N. meningitidis* and *S. pneumoniae*. All but 1 patient was vaccinated against *H influenzae* prior to enrolling in the study; this patient did not require vaccination per national vaccination recommendations.

Concomitant Therapy

Table 26:Immunosuppressant Therapies Used During the Primary Evaluation Treatment Period (Safety Analysis Set)

	Age ≥ 12 years (N = 11) n (%)
Corticosteroids	8 (72.7)
Azathioprine	1 (9.1)
Mycophenolate mofetil	2 (18.2)
Cyclosporine	0
Tacrolimus	3 (27.3)
Methotrexate	0
Rituximab	0
Cyclophosphamide	0
Patients using no IST	2 (18.2)
Patients using only 1 IST	4 (36.4)
Corticosteroids	3 (27.3)
Tacrolimus	1 (9.1)
Patients using only 2 ISTs	5 (45.5)
Corticosteroids and azathioprine	1 (9.1)
Corticosteroids and mycophenolate mofetil	2 (18.2)
Corticosteroids and tacrolimus	2 (18.2)
Patients using only 3 ISTs	0
Patients using 4 or more ISTs	0

Note: Mycophenolate mofetil includes mycophenolate mofetil and mycophenolic acid.
Abbreviation: IST = immunosuppressant therapy

During the primary evaluation treatment period, 2 patients had a change in cholinesterase use: 1 patient stopped an existing treatment for a few days due to running out of medication and 1 patient decreased their daily dose of treatment due to improved MG symptoms. Three patients decreased their daily dose of corticosteroid, all due to improved MG symptoms. There were no changes in the use of ISTs other than corticosteroids during the primary evaluation treatment period.

During the extension period, corticosteroids, tacrolimus, mycophenolate mofetil, and azathioprine were used by 8 (80.0%) patients, 3 (30.0%) patients, 2 (20.0%) patients, and 1 (10.0%) patient, respectively. Other concomitant MG medications used during the extension period included cholinesterase inhibitors (pyridostigmine or pyridostigmine bromide) in 8 (80.0%) patients and immunoglobulins in 5 (50.0%) patients.

Numbers analysed

Of the 12 enrolled patients, 11 patients were included in the FAS, mFAS, and Safety Analysis Set; and 10 patients were included in the Extension Analysis Set.

The Extension Analysis Set (N = 10) included patients who received at least 1 dose of eculizumab during the Extension Period. One patient was ongoing in the Primary Evaluation Treatment Period as of the data cut-off date and was excluded from the Extension Analysis Set.

As stated above, a total of 16 patients were screened and 12 (75.0%) patients were enrolled in the study. One patient in the age group < 12 years withdrew from the study before study drug administration. In total, 11 patients received study drug. As of the data cut-off date (06 Jan 2022), 10 of the 11 patients had completed the primary evaluation treatment period and continued into the Extension Period. One patient was ongoing in the primary evaluation treatment period.

Outcomes and estimation

Primary Efficacy Endpoint (Primary Evaluation Treatment Period)

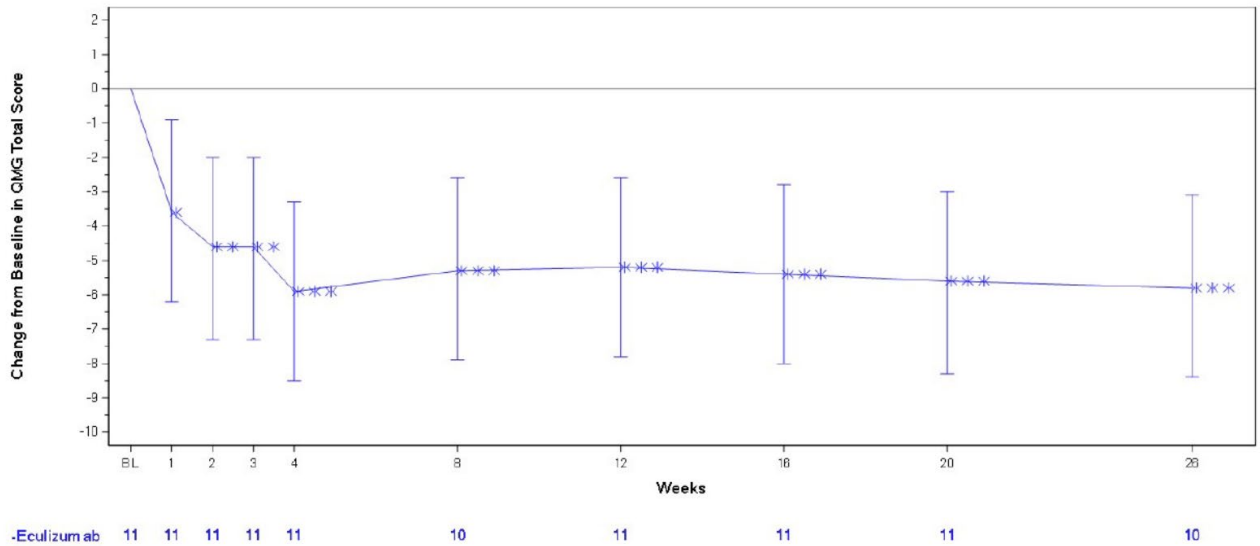
Results for the primary efficacy endpoint are provided for the primary evaluation treatment period based on data from 11 patients in the mFAS.

Change from Baseline in QMG Total Score

An improvement from baseline in QMG total score was observed at week 1 (LS mean [95% CI] change from baseline of -3.6 [-6.17, -0.94], p = 0.0116) and was maintained throughout the primary evaluation treatment period (LS mean [95% CI] change from Baseline at Week 12 of -5.2 [-7.81, -2.57], p = 0.0009; LS mean [95% CI] change from Baseline at week 26 of -5.8 [-8.40, -3.13], p = 0.0004).

At week 26, the median (min, max) change from baseline in QMG total score in patients with maintenance IVIg at baseline (n = 5) was -5.0 (-17, 0) and in patients without maintenance IVIg at Baseline (n = 5) was -6.0 (-8, -4).

Figure 24: Change from Baseline in QMG Total Score (LS Mean and 95% CI) During the Primary Evaluation Treatment Period Using a Repeated Measures Model (Modified Full Analysis Set)



Note: Baseline is defined as the last available assessment value prior to first study drug infusion. Estimates are based on MMRM that included terms of visit and baseline value. *, **, and *** represent two-sided nominal p-value is less than 0.05, 0.01, and 0.001 for testing whether the LS mean is equal to 0. A compound symmetry covariance structure was used.
Abbreviations: BL = baseline; CI = confidence interval; LS = least square; MMRM = mixed model for repeated measures; QMG = Quantitative Myasthenia Gravis

Secondary Efficacy Endpoints (Primary Evaluation Treatment Period)

QMG 5-Point Response

Overall, a ≥ 5-point reduction in QMG total score from baseline was observed in 6/11 (54.5%) patients at week 12 (p < 0.0001) and in 7/10 (70.0%) patients at week 26 (p < 0.0001).

Table 27: Proportion of Patients with at least a 5-Point Reduction in QMG Total Score from Baseline by Selected Study Visit During the Primary Evaluation Treatment Period (Modified Full Analysis Set)

Visit	Statistics	Maintenance IVIg (Yes) (N = 6)	Maintenance IVIg (No) (N = 5)	Total (N = 11)
Week 1	n/N (%)	1/6 (16.7)	2/5 (40.0)	3/11 (27.3)
	95% CI for %[a]	(0.4, 64.1)	(5.3, 85.3)	(6.0, 61.0)
	p-value[b]	-	-	0.0003
Week 12	n/N (%)	3/6 (50.0)	3/5 (60.0)	6/11 (54.5)
	95% CI for %[a]	(11.8, 88.2)	(14.7, 94.7)	(23.4, 83.3)
	p-value[b]	-	-	<0.0001
Week 26	n/N (%)	3/5 (60.0)	4/5 (80.0)	7/10 (70.0)
	95% CI for %[a]	(14.7, 94.7)	(28.4, 99.5)	(34.8, 93.3)
	p-value[b]	-	-	< 0.0001

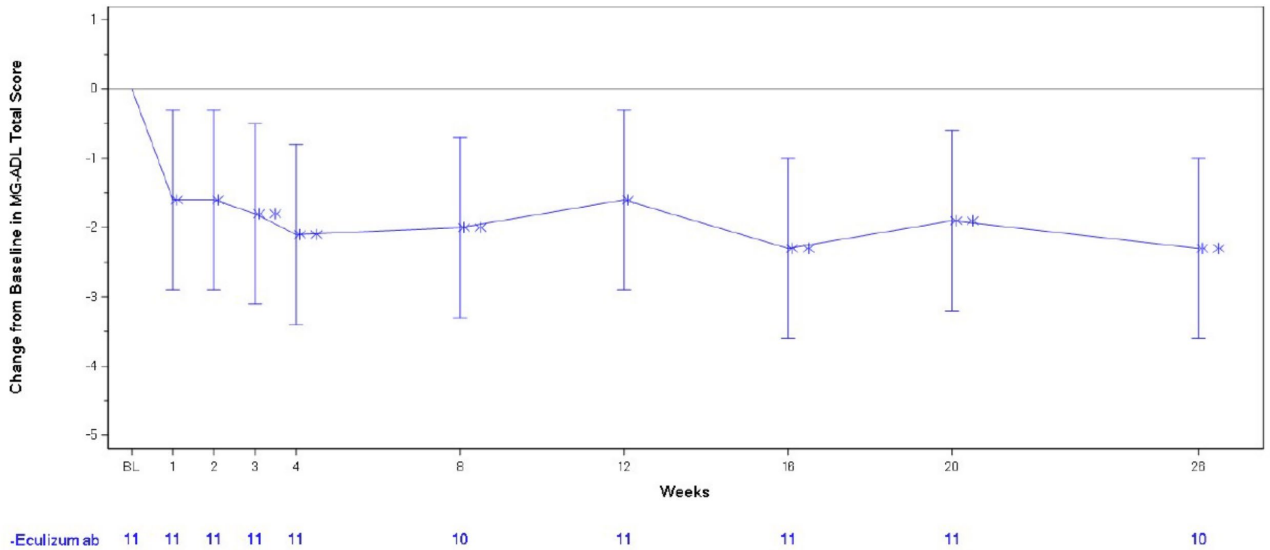
a Clopper-Pearson confidence interval.
b p-value of exact binomial test was calculated testing whether the sample proportion equals 0.
Abbreviations: CI = confidence interval; IVIg = intravenous immunoglobulin; QMG = Quantitative Myasthenia Gravis

Change from Baseline in MG-ADL Total Score

An improvement from baseline in MG-ADL total score was observed at week 1 (LS mean [95% CI] change from baseline of -1.6 [-2.92, -0.34], p = 0.0167) and was maintained throughout the primary evaluation treatment period (LS mean [95% CI] change from baseline at Week 12 of -1.6 [-2.92, -0.34], p = 0.0167; LS mean [95% CI] change from baseline at Week 26 of -2.3 [-3.63, -1.03], p = 0.0017).

At week 26, the median (min, max) change from baseline in MG-ADL total score in patients with maintenance IVIg at baseline (n = 5) was -3.0 (-5, -1) and in patients without maintenance IVIg at baseline (n = 5) was -2.0 (-5, 0).

Figure 25: Change from Baseline in MG-ADL Total Score (LS Mean and 95% CI) During the Primary Evaluation Treatment Period Using a Repeated Measures Model (Modified Full Analysis Set)



Note: Baseline is defined as the last available assessment value prior to first study drug infusion. Estimates are based on MMRM that included terms of visit and baseline value. *, **, and *** represent two-sided nominal p-value is less than 0.05, 0.01, and 0.001 for testing whether the LS mean is equal to 0. A compound symmetry covariance structure was used.
Abbreviations: BL = baseline; CI = confidence interval; LS = least square; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MMRM = mixed model for repeated measures

MG-ADL 3-Point Response

Overall, a ≥ 3-point reduction in MG-ADL total score from baseline was observed in 4/11 (36.4%) patients at week 12 ($p < 0.0001$) and in 5/10 (50.0%) patients at week 26 ($p < 0.0001$).

Table 28: Proportion of Patients with at least a 3-Point Reduction in MG-ADL Total Score from Baseline by Selected Study Visit During the Primary Evaluation Treatment Period (Modified Full Analysis Set)

Visit	Statistics	Maintenance IVIg (Yes) (N = 6)	Maintenance IVIg (No) (N = 5)	Total (N = 11)
Week 1	n/N (%)	1/6 (16.7)	1/5 (20.0)	2/11 (18.2)
	95% CI for %[a]	(0.4, 64.1)	(0.5, 71.6)	(2.3, 51.8)
	p-value[b]	-	-	0.0104
Week 12	n/N (%)	3/6 (50.0)	1/5 (20.0)	4/11 (36.4)
	95% CI for %[a]	(11.8, 88.2)	(0.5, 71.6)	(10.9, 69.2)
	p-value[b]	-	-	<0.0001
Week 26	n/N (%)	3/5 (60.0)	2/5 (40.0)	5/10 (50.0)
	95% CI for %[a]	(14.7, 94.7)	(5.3, 85.3)	(18.7, 81.3)
	p-value[b]	-	-	<0.0001

a Clopper-Pearson confidence interval.
b p-value of exact binomial test was calculated testing whether the sample proportion equals 0.
Abbreviations: CI = confidence interval; IVIg = intravenous immunoglobulin; MG-ADL = Myasthenia Gravis Activities of Daily Living profile

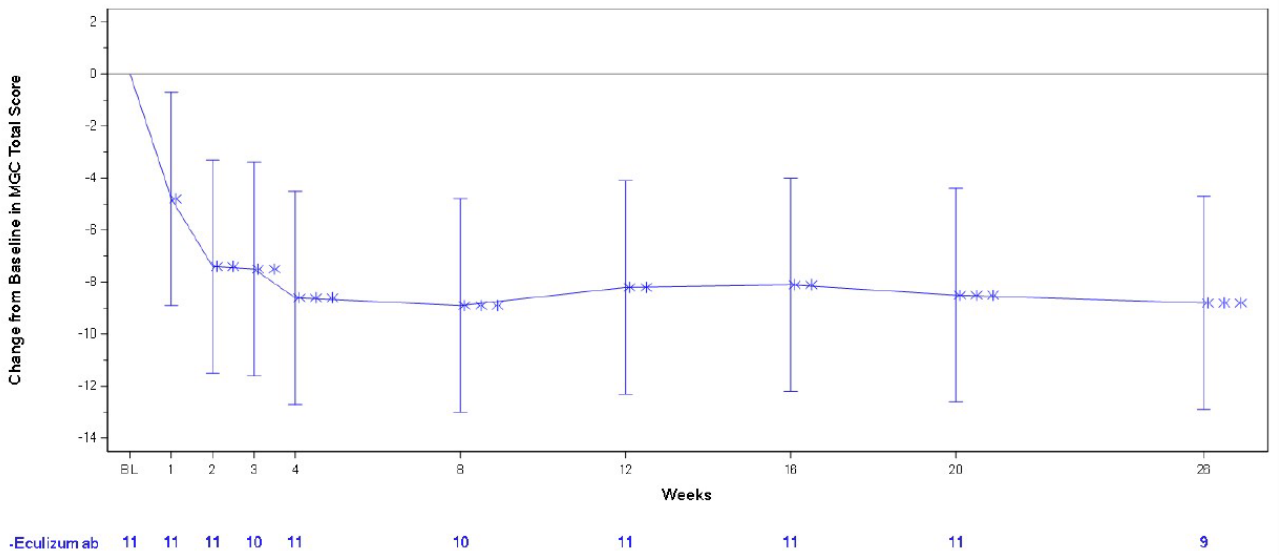
Abbreviations: gMG = generalized myasthenia gravis; ID = identification; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; NR = not reported; QMG = Quantitative Myasthenia Gravis

Change from Baseline in MGC Total Score

An improvement from baseline in MGC total score was observed at week 1 (LS mean [95% CI] change from baseline of -4.8 [-8.94, -0.73], $p = 0.0252$) and was maintained throughout the primary evaluation treatment period (LS mean [95% CI] change from baseline at week 12 of -8.2 [-12.30, -4.10], $p = 0.0012$; LS mean [95% CI] change from baseline at week 26 of -8.8 [-12.93, -4.69], $p = 0.0007$).

At week 26, the median (min, max) change from baseline in MGC total score in patients with maintenance IVIg at baseline (n = 4) was -4.0 (-21, 0) and in patients without maintenance IVIg at baseline (n = 5) was -11.0 (-13, -11).

Figure 26: Change from Baseline in MGC Total Score (LS Mean and 95% CI) During the Primary Evaluation Treatment Period Using a Repeated Measures Model (Modified Full Analysis Set)



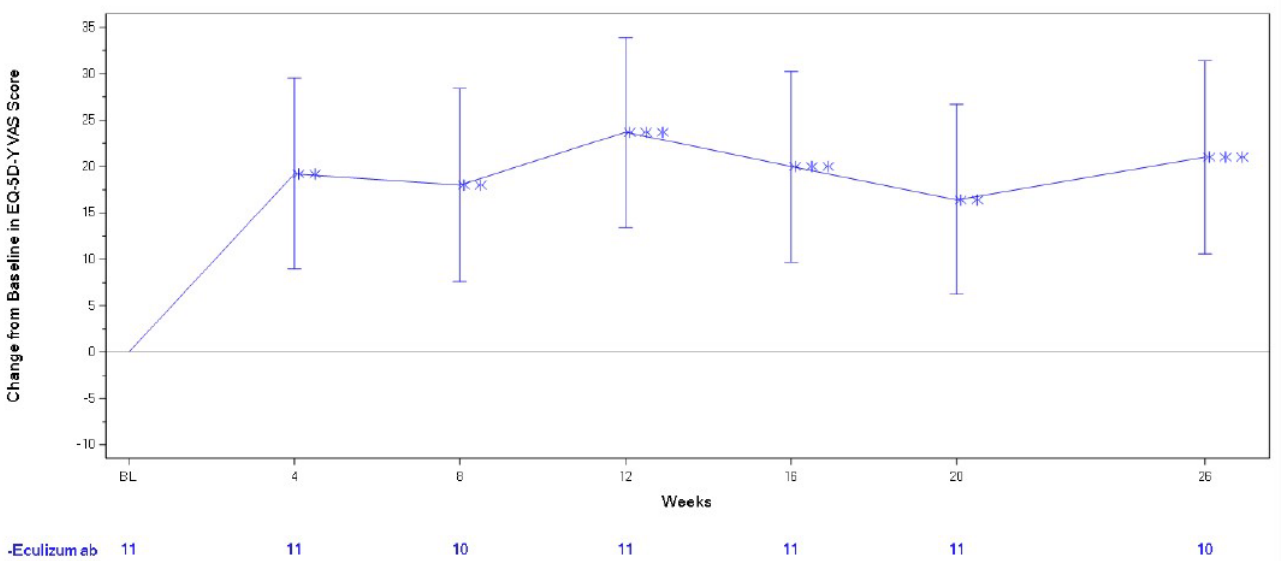
Note: Baseline is defined as the last available assessment value prior to first study drug infusion. Estimates are based on MMRM that included terms of visit and baseline value. *, **, and *** represent two-sided nominal p-value is less than 0.05, 0.01, and 0.001 for testing whether the LS mean is equal to 0. A compound symmetry covariance structure was used.
Abbreviations: BL = baseline; CI = confidence interval; LS = least square; MGC = Myasthenia Gravis Composite Scale; MMRM = mixed model for repeated measures

Change from Baseline in EQ-5D-Y VAS

An improvement from baseline in EQ-5D-Y VAS was observed at the first postbaseline timepoint (i.e. LS mean [95% CI] change from baseline at week 4 of 19.2 [8.99, 29.47], p = 0.0011) and was maintained throughout the primary evaluation treatment period (LS mean [95% CI] change from baseline at Week 12 of 23.7 [13.45, 33.93], p = 0.0002; LS mean [95% CI] change from baseline at week 26 of 21.0 [10.60, 31.39], p = 0.0005).

At Week 26, the median (min, max) change from baseline in EQ-5D-Y VAS in patients with maintenance IVIg at baseline (n = 5) was 5.0 (0, 60) and in patients without maintenance IVIg at baseline (n = 5) was 25.0 (0, 55).

Figure 27: Change from Baseline in EQ-5D-Y VAS (LS Mean and 95% CI) During the Primary Evaluation Treatment Period Using a Repeated Measures Model (Modified Full Analysis Set)



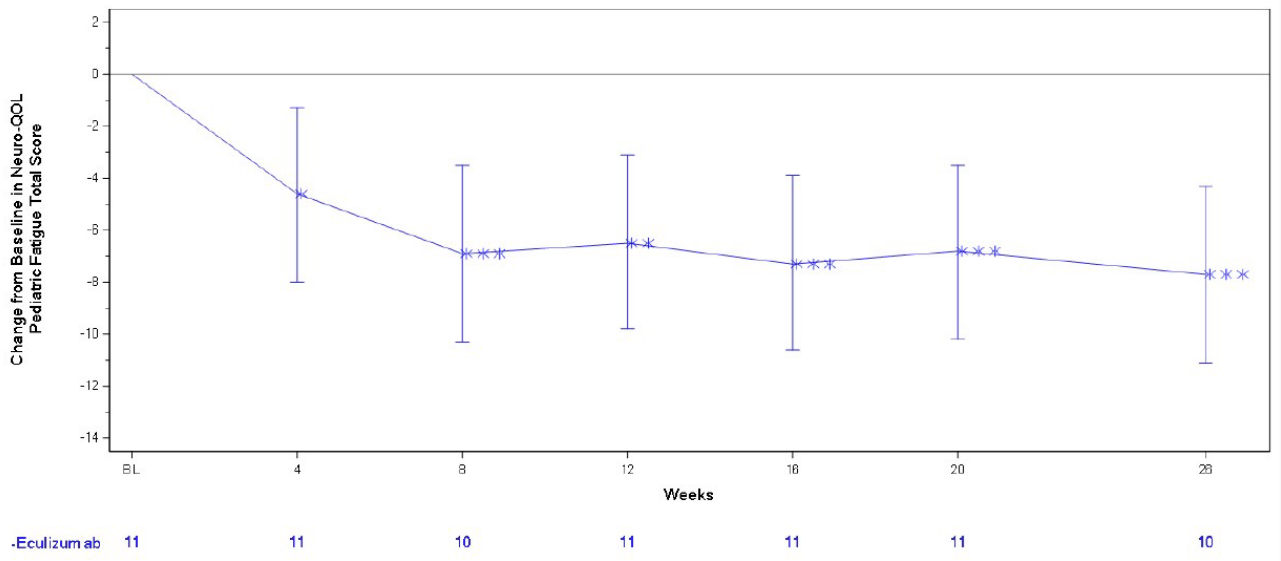
Note: Baseline is defined as the last available assessment value prior to first study drug infusion. Estimates are based on MMRM that included terms of visit and baseline value. *, **, and *** represent two-sided nominal p-value is less than 0.05, 0.01, and 0.001 for testing whether the LS mean is equal to 0. A compound symmetry covariance structure was used.
Abbreviations: BL = baseline; CI = confidence interval; EQ-5D-Y = European Quality of Life 5-Dimension Youth version; LS = least square; MMRM = mixed model for repeated measures; VAS = visual analogue scale

Change from Baseline in Neuro-QoL Paediatric Fatigue

An improvement from baseline in Neuro-QoL Paediatric Fatigue total score was observed at the first postbaseline timepoint (i.e. LS mean [95% CI] change from baseline at week 4 of -4.6 [-7.98, -1.30], p = 0.0103) and was maintained throughout the primary evaluation treatment period (LS mean [95% CI] change from baseline at week 12 of -6.5 [-9.80, -3.11], p = 0.0011; LS mean [95% CI] change from baseline at week 26 of -7.7 [-11.05, -4.31], p = 0.0003).

At week 26, the median (min, max) change from baseline in Neuro-QoL Paediatric Fatigue total score in patients with maintenance IVIg at baseline (n = 5) was -4.0 (-12, -2) and in patients without maintenance IVIg at baseline (n = 5) was -10.0 (-22, 0).

Figure 28: Change from Baseline in Neuro-QoL Paediatric Fatigue Total Score (LS Mean and 95% CI) During the Primary Evaluation Treatment Period Using a Repeated Measures Model (Modified Full Analysis Set)



Note: Baseline is defined as the last available assessment value prior to first study drug infusion. Estimates are based on MMRM that included terms of visit and baseline value. *, **, and *** represent two-sided nominal p-value is less than 0.05, 0.01, and 0.001 for testing whether the LS mean is equal to 0. A compound symmetry covariance structure was used.

Abbreviations: BL = baseline; CI = confidence interval; LS = least square; MMRM = mixed model for repeated measures; Neuro-QoL = Quality of Life in Neurological Disorders

MGFA post-interventional status

No patients showed worsening in MGFA post-interventional status during the primary evaluation treatment period and, at Week 26, 10/10 (100%) patients had improved MGFA post-interventional status (Table 31).

Table 29: Number (%) of Patients in Each Category of the MGFA PIS During the Primary Evaluation Treatment Period (Modified Full Analysis Set)

Timepoint	Total (N = 11)		
	Improved n/N (%)	Unchanged n/N (%)	Worse n/N (%)
Week 4[a]	8/11 (72.7)	3/11 (27.3)	0/11 (0)
Week 12	8/11 (72.7)	3/11 (27.3)	0/11 (0)
Week 26	10/10 (100)	0/10 (0)	0/10 (0)

Note: Percentage is based on the total number of patients in each group with non-missing data at a given visit.
a Week 4 was the first postbaseline assessment for MGFA PIS.
Abbreviations: MGFA = Myasthenia Gravis Foundation of America; PIS = Post-interventional Status

Clinical Deteriorations, Myasthenia Crises, and Use of Rescue Therapy

Per protocol, clinical deterioration requiring the use of on-study rescue therapy is defined as:

• Patients who experience an MG crisis, which is defined as weakness due to MG that is severe enough to necessitate intubation or to delay extubation following surgery; or,

• Significant symptomatic worsening that requires rescue medication in the opinion of the Investigator; or,

• Patients for whom the Investigator believes that the patients' health is in jeopardy if rescue therapy is not given.

One (9.1%) patient experienced clinical deterioration (MG crisis) during the primary evaluation treatment period. The patient was treated with plasmapheresis/PE that was administered between the week 22 and week 24 study visits.

Other Efficacy Analyses

MG-related Hospitalization

As of the data cut-off date, 3 patients experienced a total of 12 MG-related hospitalizations that were not due to eculizumab administration, representing a 49.3% reduction in MG-related hospitalizations relative to pre-study (Table 32).

Table 30: Summary of MG-related Hospitalization (Full Analysis Set)

	Patients/Events	Total Patient-Years	Observed Rate/100 PY[a]	% Reduction Compared to Pre-study
Age ≥ 12 years				
Prestudy (N = 11)	6/25	19.1	130.9	-
During treatment (N = 11)	4/14	18.1	77.4	40.9
MG-related hospitalization not due to study treatment administration[b]	3/12	18.1	66.3	49.3

Note: Hospitalizations that started before the first dosing date were excluded from the summary of "During treatment" hospitalization.
a Observed event rate per patient-year = Number of events/Total number of patient-years.

b MG-related hospitalization due to study treatment administration were excluded.
Abbreviations: MG = myasthenia gravis; PY = patient-years

Ancillary analyses

To supplement efficacy data generated in Study ECU-MG-303, efficacy data from the use of eculizumab in adult patients with gMG (Study ECU-MG-301) are also submitted.

Table 31: Demographic and Baseline Characteristics for Phase 3 Study ECU-MG-301 in Adult Patients with gMG

Variable	Study ECU-MG-301 (N= 125)			
	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Total (N = 125)
Age at first IP dose (years)[a]				
	Mean (SD)	46.9 (17.98)	47.5 (15.66)	47.2 (16.80)
	Median	48.0	44.5	46.0
	Min, max	19, 79	19, 74	19, 79
Sex				
Male	n (%)	22 (34.9)	21 (33.9)	43 (34.4)
Female	n (%)	41 (65.1)	41 (66.1)	82 (65.6)
Ethnicity				
Hispanic or Latino	n (%)	10 (15.9)	8 (12.9)	18 (14.4)
Not Hispanic or Latino	n (%)	50 (79.4)	51 (82.3)	101 (80.8)
Not Reported	n (%)	0 (0.0)	2 (3.2)	2 (1.6)
Unknown	n (%)	3 (4.8)	1 (1.6)	4 (3.2)
Race				
Asian	n (%)	16 (25.4)	3 (4.8)	19 (15.2)
Black or African American	n (%)	3 (4.8)	0 (0.0)	3 (2.4)
White	n (%)	42 (66.7)	53 (85.5)	95 (76.0)
Multiple	n (%)	0 (0.0)	1 (1.6)	1 (0.8)
Unknown	n (%)	0 (0.0)	1 (1.6)	1 (0.8)
Other	n (%)	2 (3.2)	4 (6.5)	6 (4.8)
Is the patient of Japanese descent?				
Yes	n (%)	9 (14.3)	3 (4.8)	12 (9.6)
No	n (%)	54 (85.7)	59 (95.2)	113 (90.4)
Region				
North America	n (%)	25 (39.7)	21 (33.9)	46 (36.8)
South America	n (%)	7 (11.1)	5 (8.1)	12 (9.6)
Europe	n (%)	18 (28.6)	33 (53.2)	51 (40.8)
Asia-Pacific	n (%)	5 (7.9)	0 (0.0)	5 (4.0)
Japan	n (%)	8 (12.7)	3 (4.8)	11 (8.8)
Weight (kg)				
	Mean (SD)	86.24 (28.072)	87.67 (28.190)	86.95 (28.026)
	Median	83.10	80.00	80.70
	Min, max	37.0, 155.5	42.9, 173.6	37.0, 173.6
Height (cm)				
	Mean (SD)	167.07 (9.383)	166.63 (9.684)	166.85 (9.497)
	Median	167.50	165.10	166.70
	Min, max	139.7, 184.2	150.1, 186.2	139.7, 186.2
BMI (kg/m^2)[b]				
	Mean (SD)	30.53 (8.373)	31.37 (8.997)	30.94 (8.663)
	Median	30.67	30.15	30.67
	Min, max	17.5, 51.1	14.8, 52.6	14.8, 52.6

The mean change from baseline to weeks 12 and 26 in the QMG, MG-ADL, and MGC total scores showed a consistent response across the paediatric and adult gMG patient populations.

Table 32: Efficacy Results in Paediatric and Adult Patients with gMG Treated with Eculizumab (Full Analysis Set) [Extrapolation Study-Study 3]

Key Efficacy Endpoints		ECU-MG-303 (Pediatric Patients with gMG)	ECU-MG-301 (Adult Patients with gMG)
QMG total score	Change from Baseline to Week 12 LS Mean (SEM) 5% CI for LS Mean	(N = 11) -5.2 (1.2) (-7.81, -2.57)	(N = 58) -4.1 (0.63) (-5.4, -2.9)
	Change from Baseline to Week 26 LS Mean (SEM) 95% CI for LS Mean	(N = 10) -5.8 (1.2) (-8.40, -3.13)	(N = 56) -4.6 (0.60) (-5.8, -3.4)
MG-ADL total score	Change from Baseline to Week 12 LS Mean (SEM) 95% CI for LS Mean	(N = 11) -1.6 (0.6) (-2.92, -0.34)	(N = 58) -3.7 (0.47) (-4.7, -2.8)
	Change from Baseline to Week 26 LS Mean (SEM) 95% CI for LS Mean	(N = 10) -2.3 (0.6) (-3.63, -1.03)	(N = 57) -4.2 (0.49) (-5.2, -3.3)
MGC total score	Change from Baseline to Week 12 LS Mean (SEM) 95% CI for LS Mean	(N = 11) -8.2 (1.9) (-12.30, -4.10)	(N = 58) -7.4 (0.93) (-9.3, -5.6)
	Change from Baseline to Week 26 LS Mean (SEM) 95% CI for LS Mean	(N = 9) -8.8 (1.9) (-12.93, -4.69)	(N = 57) -8.1 (0.96) (-10.0, -6.2)

Abbreviations: CI = confidence interval; gMG = generalized myasthenia gravis; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis Composite Scale; QMG = Quantitative Myasthenia Gravis; SEM = standard error of the mean

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial ECU-MG-303

Title: An Open-Label, Multicentre Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Eculizumab in Paediatric Patients with Refractory Generalized Myasthenia Gravis		
Study identifier	ECU-MG-303, EudraCT 2016-001384-37, NCT 03759366	
Design	Uncontrolled, open label, multicentre study	
	Duration of main phase: Duration of Extension phase: Duration of Safety Follow Up Phase:	26 weeks Up to 208 weeks 8 weeks
Hypothesis	Efficacy	
Treatment group	Eculizumab	Eculizumab was administered in a weight-based dosage regimen weekly during the initial Induction Phase followed by administration every 2 weeks during the Maintenance Phase and Extension period N = 11 patients

Endpoints and definitions	Primary endpoint	Change from Baseline in the QMG total score over time regardless of rescue treatment	A repeated measures model was used to analyse the observed change in QMG from Baseline with Baseline QMG score and visits as covariates. The least-squares (LS) mean at Week 12 was used to test the primary hypothesis (2-sided) at a significance level of 5%. The least-squares mean at Week 26 was used to test the Paediatric Committee of the European Medicines Agency (PDCO)-specific primary hypothesis at a significance level of 5%. The p-value, standard error of the mean, and 95% confidence interval (CI) were produced.
	Secondary endpoint	Proportion of patients with ≥ 5-point reduction in the QMG total score from Baseline over time regardless of rescue treatment	Proportion of patients with a ≥ 5-point reduction in the QMG total score from Baseline with no rescue therapy prior to the given visits without regard to rescue therapy were summarized by visit. Exact (Clopper-Pearson) CIs for true proportion and p-values were presented by visit.
	Secondary endpoint	Change from Baseline in MG-ADL total score over time regardless of rescue treatment Proportion of patients with ≥3-point reduction in the MG-ADL total score from Baseline over time regardless of rescue treatment	Change from Baseline was analyzed at a particular visit based on the repeated-measures models. CIs and p-values were presented by visit. The hypothesis testing was based on a 2-sided Type I error of 5%. Proportion of patients with a ≥ 3-point reduction in the MG-ADL total score from Baseline with no rescue therapy prior to the given visits as well as without regard to rescue therapy were summarized by visit. Cis and p-values were presented by visit.
Database lock	25 Mar 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Full Analysis Set (mFAS), which consists of all 12 to < 18 years of age patients who received at least 1 dose of eculizumab. Measured at Week 12 and Week 26		
Descriptive statistics and effect estimate	Treatment group	Eculizumab	
	Number of subjects	11	
	Change from Baseline in the QMG total score over time regardless of rescue treatment; Least squares mean	Week 12	Week 26
	Change from baseline in QMG total score	-5.2	-5.8
	95% CI for %	(-7.81, -2.57)	(-8.40, -3.13)
	p-value	p = 0.0009	p = 0.0004
Analysis description	**Secondary analysis**		

Analysis population and time point description	Modified Full Analysis Set (mFAS) which consists of all 12 to < 18 years of age patients who received at least 1 dose of eculizumab. Measured at Week 12 and Week 26		
Descriptive statistics and effect estimate	Treatment group	Eculizumab	
	Number of subjects	11	
	Proportion of patients with ≥ 5-point reduction in the QMG total score from Baseline over time regardless of rescue treatment n/N (%) 95% CI for % p-value	Week 12 6/11 (54.5) (23.4, 83.3) <0.0001	Week 26 7/10 (70.0) (34.8, 93.3) <0.0001
	Treatment group	Eculizumab	
	Number of subjects	11	
	Change from Baseline in MG-ADL total score over time regardless of rescue treatment Change from baseline in MG-ADL total score 95% CI for % p-value	Week 12 -1.6 (-2.92, -0.34) p = 0.0167	Week 26 -2.3 (-3.63, -1.03) p = 0.0017
	Proportion of patients with ≥3-point reduction in the MG-ADL total score from Baseline over time regardless of rescue treatment n/N (%) 95% CI for % p-value	Week 12 4/11 (36.4) (10.9, 69.2) p < 0.0001	Week 26 5/10 (50.0) (18.7, 81.3) p < 0.0001

2.4.2. Discussion on clinical efficacy

The evidence of the efficacy of Soliris (eculizumab) in the treatment of paediatric patients with refractory generalised Myasthenia Gravis and AChR-Ab (+) is provided by one phase 3 clinical trial (Study ECU-MG-303), still ongoing.

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. The majority of patients with MG have antibodies against AChR. These antibodies bind complement and initiate the complement cascade producing a complement-mediated lysis of the neuromuscular junction via formation of membrane attack complexes. Eculizumab targets the complement protein C5, inhibiting its cleavage into C5a and C5b and ultimately preventing the formation of terminal complement complex.

Design and conduct of clinical studies

This submission is based on data from Study ECU-MG-303, a Phase 3, multicentre, open-label study to evaluate the efficacy and safety of eculizumab for the treatment of paediatric patients aged 6 to < 18 years with refractory gMG AChR-Ab+. Data from the 26-week initial phase (the primary evaluation treatment period) have been submitted; the extension phase (extension period) is still ongoing and no efficacy results from this phase have been presented. The study was conducted in Japan and USA.

Patient population

Paediatric patients 6 to <18 years of age with confirmed gMG who were positive for AChR antibodies were eligible for the study. The study enrolled symptomatic patients (QMG total score ≥ 12) who have an insufficient clinical response to ongoing, stable standard of care therapy.

Eculizumab is approved in adult patients with refractory condition. Adult patients included in study ECU-MG-301 were required to have failed to at least 2 previous treatments according the international consensus[20]. This is not exactly the criteria applied to paediatric patients who were required to have refractory condition defined as having failed treatment ≥1 year with at least 1 immunosuppressive therapies or requiring PE or IVIg to control symptoms, or having a significant functional burden despite current MG treatment. The MAH has explained that a clear definition of refractoriness in MG in pediatric patients is not currently available. Considering the characteristics of the patients included in the study with respect to failure to previous treatments and the symptomatic condition in spite of the concomitant treatment received during the study (see below), it could be justified to consider pediatric patients in Study ECU-MG-303 as meeting the definition of refractory. This is accepted.

Patients could have been treated with acetylcholinesterase inhibitors, IVIg, and ISTs during the study at stable doses. Patients having received recent treatment with rituximab or PE were excluded as well as those who had been previously treated with eculizumab.

A total of 16 patients were screened and 12 (75.0%) patients were enrolled in the study. One patient in the age group < 12 years withdrew from the study before study drug administration. In total, 11 patients received the study drug. As of the data cut-off date (06 Jan 2022), a total of 10 patients entered the extension period. One patient has not completed the primary evaluation treatment period yet. The patient did not respond to treatment and experienced a clinical deterioration a month before their Week 26 visit. Rescue therapy was administered. By their week 26 visit (delayed), the patient contracted COVID-19 and did not continue into the extension period which is still ongoing.

The clinical outcome in childhood MG varies with age of onset, race, and sex[21]. Remission rates also appear to be influenced by ethnic origin.[22] African American children show lower remission rates than Caucasian children. In Asian population more than 70% of cases are restricted to ocular symptoms and benign course is common. White children with prepubertal onset have the best prognosis. The spontaneous remission rate is 44 percent in these children, and they respond well to early thymectomy.[26]

Most of the patients included in the study were female (81.8%). Only 18.2% of the recruited patients were White, being Black or African American (45.5%) followed by Asian (27.3%) patients the most represented groups. No EU patients were recruited. Mean age was 14.8 years (ranging from 12 to 17 years). The majority of patients (90.9%) were ≥40 kg. Thus, it was questioned whether the studied patients could be considered as representative of the intended population, that is, EU paediatric patients.

[20] Sanders DB., et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology 87.4 (2016): 419-425.
[21] Andrews PI, Massey JM, Howard JF Jr, Sanders DB. Race, sex, and puberty influence onset, severity, and outcome in juvenile myasthenia gravis. Neurology. 1994;44(7):120
[22] Marina AD, Trippe H, Lutz S, Schara U. Juvenile Myasthenia Gravis: Recommendations for Diagnostic Approaches and treatment. Neuropaediatrics 2014;45:75–83

With regards to the ethnicity, the MAH has explained that no significant impact on exposure and terminal complement inhibition has been observed in a Pop-PK analysis in adult gMG patients by ethnicity and no relevant differences in the treatment effect of eculizumab in adults has been reported in the literature when ethnic differences were explored. It can, therefore, be expected that the response in the target population would not be dissimilar to that observed in Study ECU-MG-303. This justification could be agreed.

No children less than 12 years of age participated in the study. Although limited (low patient availability), some data on PK, efficacy and safety were expected in this subset. Main differences in the disease between younger patients compared with adults are a less severe disease, often with an ocular phenotype and a better prognosis, with more frequent spontaneous remission. The diagnosis is difficult to be done in the very young age group. Positive acetylcholine receptor (AchR) antibodies are present only in 41% of cases presenting with ocular symptoms alone and 72% of those with generalized symptoms[23]. As the requested indication includes a subgroup of the broad paediatric MG population, - namely those with AChR Ab positive, treatment refractory, generalised MG-, patients without AChR antibodies, patients not converting from ocular to generalised MG, patients with mild disease that responds to already established treatments, and spontaneous remissions have already been excluded, regardless of age. With these restrictions already included in the indication, the differences between age populations might be reduced and it can be agreed that based on a similar pathophysiology and phenotype, extrapolation of efficacy to children aged ≥6 years is adequate. Of note, regarding the PIP, a waiver was granted in the paediatric population from birth to less than 6 years of age for the condition treatment of myasthenia gravis on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset. This explain the chosen cut-off.

The most common presenting type in the recruited patients was gMG (90.9%) with a mean duration of the condition of 4 years from diagnosis. Most of patients had a mild to moderate weakness affecting muscles other than the ocular muscles (45.5% MGFA Class II) and 27% presented a severe generalized MG (MGFA Class IV). A relevant percentage has had an exacerbation (63.6%) or had required ventilatory support (72.7%) in the past. Half of the patient underwent thymectomy (54.5%), which is expected since it is a recommended treatment in case of generalized weakness[24]. Acetylcholinesterase inhibitors (82%), corticosteroids (82%) and chronic IVIg (63.6%) were the most widely used MG treatments prior to the study. Two (18.2%) patients had not used any ISTs (including corticosteroids). Three (27.3%) patients had used only 1 IST and 6 (54.5%) patients had used 2 ISTs. Tacrolimus was the most frequently IST (different from corticosteroids) used followed by mycophenolate mofetil (27.3% and 18.2%, respectively).

At baseline, the mean (SD) MG-ADL total score was 5.0 (5.25), and the mean (SD) QMG total score was 16.7 (5.64) showing a relevant disease burden. During the study patients were concomitantly treated with cholinesterase inhibitors (81.8%), long-term IVIg (54.5%) and ISTs [4 (36.4%) 1 IST and 5 (45.5%) 2 ISTs]: corticosteroids (72.7%), tacrolimus (27.3%), mycophenolate mofetil (18.2%), and azathioprine (9.1%).

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 PNH based on the patient's body weight. Since the study did not include patients younger than 12 years of age and there was only 1 patient in the body weight range 30 to 40 kg, 10 out of 11 subjects received the dosing regimen for adult patients. Nevertheless, an acceptable estimation of the dose by weight for children, covering the weight of 6–12-year-olds could be agreed (see pharmacological section)

[23] Finnis MF, Jayawant S. Juvenile myasthenia gravis: a paediatric perspective. Autoimmune Dis. 2011;2011:404101.
[24]

Endpoints

Efficacy was based on the effect of eculizumab on the gMG signs and symptoms assessed by the physician (QMG scale; primary endpoint) and the patient (MG-ADL; secondary variable).

These endpoints and the rest of the selected efficacy variables are validated and widely used scales in the clinical development of medicinal product for the treatment of MG in adults. They are also used in clinical investigation in paediatric patients although with a limited experience (EudraCT Numbers: 2021-002460-46; 2021-002479-20).

Statistical analysis

A sample size of 12 patients older than 12 years of age was estimated. No predefined number of younger patients (6 to <12 years of age) was established. The sample size was defined by the low availability of patients given the rarity of the condition, which is acknowledged.

The primary analysis was based on the change from baseline in the QMG total score at 26 weeks regardless of whether patients received rescue therapy. A repeated measures model was used to analyse the observed change in QMG with baseline QMG score and visits as covariates. According to the MAH, the mFAS Population (including patients 12 to < 18 years of age who received at least 1 dose of eculizumab) was used for the analysis of the primary and secondary endpoints, whereas the FAS Population (including all patients who received at least 1 dose of eculizumab) was used for all other efficacy results summaries. Both analysis populations (FAS and mFAS) were identical.

The small number of subjects included in Study ECU-MG-303, the lack of a control arm and the observed variability as well as the fluctuating nature of the condition add uncertainty to the estimation of the magnitude of the effect with a potential of overestimating the effect.

IVIg treatment is likely to increase eculizumab clearance 50%, resulting in lowered trough eculizumab concentrations. For this reason, patients receiving maintenance IVIg receiving supplemental doses of eculizumab. However, patients who received maintenance IVIg therapy were shown to have higher mean eculizumab exposures than patients who did not receive maintenance IVIg therapy. The influence of the chronic treatment with IVIg was also analysed.

An extrapolation study (study 3) has been conducted by the MAH comparing the results obtained in eculizumab studies in adult patients with gMG (ECU-MG-301) and the data from Study ECU-MG-303 in paediatric gMG patients. The approach is based on the similarity in the dosage regimen administered in both studies and the efficacy variables measured. Given the differences between studies in population included, design of the studies and sample size only a qualitative comparison is performed, which is acceptable as supportive information.

Efficacy data and additional analyses

The evaluation of efficacy mainly relies on the assessment of the gMG signs and symptoms by the physician (QMG; primary endpoint) and the patient (MG-ADL; secondary endpoint).

The primary endpoint was the change from baseline in the QMG total score reported by the physician. At Week 26 a 5.8-point reduction was observed in comparison with baseline score (95% CI: -8.40, -3.13; p = 0.0004) (mFAS).

The effect of eculizumab was also assessed by the patient as a secondary endpoint. At Week 26 an improvement was observed in MG-ADL total score of -2.3 ([CI: -3.6, -1.03]; p=0.0017) (mFAS).

A relevant percentage of patients showed control of the disease: 70% of patients showed ≥ 5 point reduction in the QMG total score and 50% of patients showed ≥ 3 point reduction in the MG-ADL total score.

MGC Scale results are in line with those observed for MG-ADL and QMG total scores. At Week 26 patients experienced a 8.8-point reduction with respect to baseline ([95% CI: -12.9, -4.69; p=0.0007) (mFAS).

This improvement was also observed when the effect of eculizumab on health status (EQ-5D-Y VAS) and fatigue (Neuro-QoL Paediatric Fatigue) was measured.

One of the patients suffered a MG crisis during the primary evaluation treatment period and was treated with plasmapheresis/PE between the week 22 and week 24 study visits. It is said that the patient remained ongoing in the primary evaluation treatment period of the study as of the data cut-off date. A total of 4 patients (14 events) required hospitalization during this period, 3 of them (12 events) being considered MG-related, not due to study treatment.

The main effect was reached at Week 4 followed by a plateau phase maintained throughout the 26-week Primary Evaluation Treatment Period without further benefit. No efficacy data are available beyond this point so that the maintenance of the effect in this population is unknown. The study is still ongoing and results up to additional 208 Weeks are expected.

When the effect is analysed by the use or not of maintenance IVIg, it seems to be of lower magnitude in those patients chronically treated with IVIg. However, not all the efficacy results point in the same direction and the reduced number of patients prevents from drawing a conclusion on whether the efficacy may vary depending on the use of IVIg as maintenance IST. Of note, the reported PK data in patients receiving maintenance IVIg therapy and Soliris supplemental doses show an increased exposure of eculizumab (see clinical pharmacology section). The MAH has justified the need of supplemental doses of eculizumab when IVIg therapy is concomitantly administered, based on faster mAb clearance. Further, the MAH provided a new analysis for PK / PD modelling in which it can be agreed that the distribution of the Exposure of Eculizumab (PK) vs. inhibition of terminal complement (free C5 < 0.5 µg/mL) (PD) overlaps for those children using standard dose regimen (no IVIg-treatment) and standard dose regimen plus supplemental dosing (IVIg-treated patients). Whether the apparently reduced efficacy observed in those patients compared to those not receiving concomitant IVIg therapy can be (solely) explained from the PK perspective remains unclear. This information has been added to the SmPC.

The extrapolation study (study 3) conducted to supplement efficacy data from the use of eculizumab in adult patients with gMG (Study ECU-MG-301) suggests a similar trend in the efficacy results measured in the populations included in both studies. Further, as noted above, with these restrictions already included in the indication, the differences between age populations are sufficiently reduced and it can be agreed that based on a similar pathophysiology and phenotype, extrapolation of efficacy to children aged ≥6 years is adequate.

Assessment of paediatric data on clinical efficacy

See above

2.4.3. Conclusions on the clinical efficacy

The efficacy of eculizumab on the treatment of gMG in paediatric patients has been established in a single open label study (Study ECU-MG-303) including a total of 11 patients > 12 years of age. However, taken into account the target indication including paediatric patients with refractory gMG and anti-AChR antibodies positive, it can be agreed that based on a similar pathophysiology and phenotype, and the estimation of the dose recommendation in this sub-group of patients, the extrapolation of efficacy to children aged ≥6 years is adequate in light of the provided efficacy data.

Eculizumab has shown an effect on the control of symptoms assessed by the physician (QMG score; primary endpoint) and by the patient (MG-ADL score, secondary endpoint) in the studied patients after 26 weeks of treatment with respect to baseline values. However, the small number of subjects, the lack of a control arm, the observed variability as well as the fluctuating nature of the condition add uncertainty to the estimation of the magnitude of the effect with a potential of overestimating the effect. Further, long-term efficacy in paediatric gMG population is based on the effect of eculizumab during the extension period of the study, still ongoing. No efficacy results have been provided beyond the 26 Week time point.

2.5. Clinical safety

Introduction

The safety of eculizumab in paediatric patients with AChR-Ab + refractory gMG is based on data from Study ECU-MG-303 and supplementary data from other studies with eculizumab that were conducted in adult patients with refractory gMG, paediatric patients with PNH, and paediatric and adult patients with aHUS.

As for the data from Study ECU-MG-303 the MAH has submitted the safety analysis results from the 26-week primary evaluation treatment period and extension period up to the data cut-off date (safety and immunogenicity analyses) for all patients who were enrolled in the study.

Patient exposure

- **Study ECU-MG-303**: As of 06 Jan 2022 (data cut-off date for the interim clinical study report), a total of 11 patients aged 12 to < 18 years were enrolled and treated, including 6 patients who were on maintenance IVIg treatment at baseline (for at least 12 months and on a stable dose ≥ 3 months prior to Screening). Ten patients completed the primary evaluation treatment period and were ongoing during the extension period.

  The median treatment duration of the primary evaluation treatment period was 24.1 weeks (range 23.9 to 26.4 weeks). The median treatment duration of the primary evaluation treatment period and the extension period up to the data cut-off date (06 Jan 2022) was 95.1 weeks.

  One patient missed 1 scheduled maintenance dose at Week 8 during the primary evaluation treatment period due to coronavirus disease 2019 (COVID-19) exposure. Another patient missed 2 maintenance doses at Weeks 28 and 30 during the extension period due to COVID-19.

- **Supplementary Safety Data from Eculizumab Studies** in Adult Patients with Refractory gMG, Paediatric Patients with PNH, and Paediatric and Adult Patients with aHUS.

Table 33: Overview of Eculizumab Studies Contributing to Supplementary Safety Data

	Study in Adult Patients with Refractory gMG	Study in Pediatric Patients with PNH	Studies That Include Pediatric Patients with aHUS			
Study Number	**ECU-MG-301 N = 125[a]**	**M07-005 [b] N = 7**	**C08-002A/B Total: N = 17 Pediatric: n = 1**	**C08-003A/B Total: N = 20 Pediatric: n = 5**	**C09-001r Total: N = 30 Pediatric: n = 19**	**C10-003 N = 22**
Study design	Phase 3, randomized, double-blind, placebo-controlled, multicenter study	Postmarketing, open-label, multicenter study	Phase 2, open-label, single-arm, multicenter efficacy and safety study	Phase 2, open-label, single-arm, multicenter efficacy and safety study	Retrospective, observational, noninterventional study	Phase 2, open-label, single-arm, multicenter efficacy and safety study
Population	Diagnosis of MG confirmed by positive serologic test for anti-AChR-Ab	Pediatric patients (aged 2 to 17 years) with PNH	Pediatric patients (aged ≥ 12 to < 18 years [Study C08-002B]) with plasma therapy-resistant aHUS	Pediatric patients (aged ≥ 12 to < 18 years [Study C08-003B]) with plasma therapy-sensitive aHUS	Patients of any age who had been diagnosed with aHUS	Pediatric patients (< 18 years old) with aHUS

a Total number of patients (62 were randomized to the eculizumab group, and 63 were randomized to the placebo group).
b Substudy under the Soliris™ Safety Registry. At completion of the study, patients could continue treatment with commercially available Soliris TM and be followed in the Soliris™ Safety Registry.

Abbreviations: AChR-Ab = acetylcholine receptor antibody; aHUS = atypical hemolytic uremic syndrome; gMG = generalized myasthenia gravis; MG = myasthenia gravis; N = total number of patients in the study; n = number of paediatric patients in the study; PNH = paroxysmal nocturnal hemoglobinuria

The median duration of treatment in the studies in adult patients with refractory gMG, paediatric patients with PNH, and paediatric and adult patients with aHUS was as follows:

- Adult patients with refractory gMG (Study ECU-MG-301): 26.1 weeks
- Paediatric patients with PNH (Study M07-005): 12.1 weeks
- Paediatric and adult patients with aHUS (Study C08-002A/B, Primary Evaluation Treatment Period + Extension Period): 100.3 weeks
- Paediatric and adult patients with aHUS (Study C08-003A/B, Primary Evaluation Treatment Period + Extension Period): 155.6 weeks
- Paediatric and adult patients with aHUS (Study C09-001r): 27.5 weeks
- Paediatric patients with aHUS (Study C10-003): 25.3 weeks

Demographic and Other Characteristics

Study ECU-MG-303: Eleven paediatric patients treated with eculizumab were included in the interim analysis of Study ECU-MG-303. All patients were in the age category ≥ 12 to < 18 years at Screening. Overall, 81.8% of patients were female; 45.5% were Black or African American, and the mean age was 14.8 years at Screening. The majority (90.9%) of the patients were in the baseline weight category ≥ 40 kg.

Table 34: Demographic and Baseline Characteristics for Studies in Adult Patients with Refractory gMG, Paediatric Patients with PNH, and Paediatric and Adult Patients with aHUS

	Adult Patients with refractory gMG	Pediatric Patients with PNH	Pediatric and Adult Patients with aHUS			
	Study ECU-MG-301 (N = 62)[a]	Study M07-005 (N = 7)	Study C08-002A/B (N = 17)	Study C08-003A/B (N = 20)	Study C09-001r (N = 30)	Study C10-003 (N = 22)
Age at first dose (years)						
Median (min, max)	44.5 (19, 74)	15.6 (11.0, 17.1)	28 (17, 68)	28 (13, 63)	12 (0.17, 51.4)	6.5 (0.0, 17.0)
Population age category [n (%)]						
Children (< 12 years)	0	1 (14)	0	0	15 (50)	18 (82)
Adolescent (≥ 12 to < 18 years)	0	6 (86)	1 (5.9)	5 (25)	4 (13)	4 (18)
Adult (≥ 18 years)	62 (100.0)	0	16 (94.1)	15 (75)	11 (37)	0
Sex [n (%)]						
Female	41 (66.1)	4 (57)	12 (70.6)	12 (60)	16 (53)	10 (46)
Male	21 (33.9)	3 (43)	5 (29.4)	8 (40)	14 (47)	12 (55)
Race [n (%)]						
Asian	3 (4.8)	0	1 (5.8)	0	1 (3.3)	2 (9)
White or Caucasian	53 (85.5)	5 (71)	15 (88.2)	17 (85)	23 (76.7)	18 (82)
Black or African American	0	2 (29)	1 (5.8)	2 (10)	2 (6.7)	0
Other	4 (6.5)	0	0	1 (5)	4 (13.3)	2 (9)
Multiple or unknown	2 (3.2)	0	0	0	0	0

a Eculizumab treatment group.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; gMG = generalized myasthenia gravis; max = maximum; min = minimum; N = number of patients; n = number of patients in each category; PNH = paroxysmal nocturnal hemoglobinuria

Adverse events

Overall, AEs in studies with paediatric patients are presented by age subgroup: adolescents (≥ 12 to < 18 years of age). No other subgroup analysis was performed.

Overview of Treatment-emergent Adverse Events (TEAEs)

Study ECU-MG-303

During the first 12 weeks of the primary evaluation treatment period, 17 TEAEs were experienced by 6 (54.5%) patients. During the 26-week primary evaluation treatment period of Study ECU-MG-303, 40 TEAEs were experienced by 10 (90.9%) patients.

Table 35: Overview of All Treatment-Emergent Adverse Events and Serious Adverse Events as of Data Cutoff Date of Study ECU-MG-303 (Safety Analysis Set)

	Age ≥ 12 Years (N = 11)	
	n (%)	**E**
Any TEAE	11 (100)	127
Related TEAEs	5 (45.5)	16
Not related TEAEs	11 (100)	111
Mild TEAEs	11 (100)	118
Moderate TEAEs	6 (54.5)	9
Severe TEAEs	0 (0.0)	0
TEAEs leading to withdrawal of study drug	0 (0.0)	0
Any TESAE	3 (27.3)	6
Related TESAEs	1 (9.1)	1
Not related TESAEs	2 (18.2)	5
TESAEs leading to withdrawal of study drug	0 (0.0)	0
Deaths	0 (0.0)	0

Abbreviations: E = number of events; N = number of patients; n = number of patients in each category; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

The most frequently reported TEAEs (occurred in ≥ 10% of all patients) during the primary evaluation treatment period were nasopharyngitis (3 events reported for 2 [18.2%] patients), headache (3 events reported for 2[18.2%] patients), and palpitations (2 events reported for 2 [18.2%] patients)

Table 36: Treatment-emergent Adverse Events during the Primary Evaluation Treatment Period by MedDRA System Organ Class and Preferred Term in Study ECU-MG-303 (Safety Analysis Set)

	Day 1 to Day 85 (Week 12) Age ≥ 12 Years (N = 11) PY = 2.6			Day 1 to Day 183 (Week 26) Age ≥ 12 Years (N = 11) PY = 5.5		
System Organ Class Preferred Term	**n (%)**	**E**	**Rate**	**n (%)**	**E**	**Rate**
Any adverse event	6 (54.5)	17	664.1	10 (90.9)	40	724.0
Infections and infestations	1 (9.1)	1	39.1	4 (36.4)	6	108.6
Nasopharyngitis	1 (9.1)	1	39.1	2 (18.2)	3	54.3
Cellulitis	0	0	0	1 (9.1)	1	18.1
Pharyngitis	0	0	0	1 (9.1)	1	18.1
Upper respiratory tract infection	0	0	0	1 (9.1)	1	18.1
General disorders and administration site conditions	1 (9.1)	2	78.1	3 (27.3)	4	72.4
Fatigue	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Infusion site extravasation	0	0	0	1 (9.1)	1	18.1
Injection site bruising	0	0	0	1 (9.1)	1	18.1
Vaccination site pain	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Musculoskeletal and connective tissue disorders	3 (27.3)	4	156.3	3 (27.3)	5	90.5
Costochondritis	0	0	0	1 (9.1)	1	18.1
Muscle spasms	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Muscle twitching	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Myalgia	1(9.1)	1	39.1	1 (9.1)	1	18.1
Pain in extremity	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Nervous system disorders	1 (9.1)	1	39.1	3 (27.3)	4	72.4
Headache	0	0	0	2 (18.2)	3	54.3
Dizziness	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Blood and lymphatic system disorders	0	0	0	2 (18.2)	5	90.5
Iron deficiency anaemia	0	0	0	1 (9.1)	1	18.1
Leukopenia	0	0	0	1 (9.1)	1	18.1
Lymphocytosis	0	0	0	1 (9.1)	1	18.1
Monocytosis	0	0	0	1 (9.1)	1	18.1
Cardiac disorders	0	0	0	2 (18.2)	2	36.2
Palpitations	0	0	0	2 (18.2)	2	36.2

Injury, poisoning, and procedural complications	2 (18.2)	2	78.1	2 (18.2)	2	36.2
Arthropod bite	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Vaccination complication	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Skin and subcutaneous tissue disorders	2 (18.2)	5	195.3	2 (18.2)	6	108.6
Acne	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Eczema	1 (9.1)	3	117.2	1 (9.1)	4	72.4
Pruritus	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Gastrointestinal disorders	0	0	0	1 (9.1)	1	18.1
Abdominal pain	0	0	0	1 (9.1)	1	18.1
Investigations	0	0	0	1 (9.1)	1	18.1
Electrocardiogram PR prolongation	0	0	0	1 (9.1)	1	18.1
Metabolism and nutrition disorders	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Ketosis	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Psychiatric disorders	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Panic attack	1 (9.1)	1	39.1	1 (9.1)	1	18.1
Respiratory, thoracic, and mediastinal disorders	0	0	0	1 (9.1)	1	18.1
Oropharyngeal pain	0	0	0	1 (9.1)	1	18.1
Vascular disorders	0	0	0	1 (9.1)	1	18.1
Poor venous access	0	0	0	1 (9.1)	1	18.1

Note: In summarizing n (%), if a patient had multiple events for a particular SOC or Preferred Term, he/she is counted only once for that SOC or Preferred Term. Results were sorted by descending order of SOC percentage and then Preferred Term within SOC, and in case of equal percentage, sorted in alphabetical order. SOCs and Preferred Terms were coded using MedDRA version 24.1.
Rate = rate of TEAE adjusted by patient-years of exposure, defined as (number of events)/100 patient-years.
Abbreviations: E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; n = number of patients in each category; PY = patient-years; SOC = System Organ Class

As of the data cut-off date (06 Jan 2022, median study duration of 96 weeks), the most frequently reported TEAEs were headache (12 events reported by 4 [36.4%] patients), nasopharyngitis (5 events reported by 4 [36.4%] patients), pyrexia (5 events reported by 3 [27.3%] patients), and pain in extremity (4 events reported by 3 [27.3%] patients).

Table 37: Treatment-emergent Adverse Events Experienced by at least 10% of Patients as of Data Cut-off Date (Safety Analysis Set) Interim report

	Age ≥ 12 years (N = 11) PY = 18.1		
System Organ Class Preferred Term	**n (%)**	**E**	**Rate**
Any adverse event	11 (100)	127	702.2
General disorders and administration site conditions	6 (54.5)	13	71.9
Pyrexia	3 (27.3)	5	27.6
Fatigue	2 (18.2)	3	16.6
Infections and infestations	6 (54.5)	14	77.4
Nasopharyngitis	4 (36.4)	5	27.6
Upper respiratory tract infection	2 (18.2)	2	11.1
Musculoskeletal and connective tissue disorders	6 (54.5)	9	49.8
Pain in extremity	3 (27.3)	4	22.1

Nervous system disorders	6 (54.5)	18	99.5
Headache	4 (36.4)	12	66.3
Gastrointestinal disorders	5 (45.5)	27	149.3
Abdominal pain	2 (18.2)	2	11.1
Diarrhoea	2 (18.2)	2	11.1
Vomiting	2 (18.2)	2	11.1
Injury, poisoning and procedural complications	5 (45.5)	5	27.6
Thermal burn	2 (18.2)	2	11.1
Vaccination complication	2 (18.2)	2	11.1
Metabolism and nutrition disorders	3 (27.3)	4	22.1
Decreased appetite	2 (18.2)	2	11.1
Respiratory, thoracic, and mediastinal disorders	3 (27.3)	5	27.6
Nasal congestion	2 (18.2)	2	11.1
Skin and subcutaneous tissue disorders	3 (27.3)	13	71.9
Blood and lymphatic system disorders	2 (18.2)	5	27.6
Cardiac disorders	2 (18.2)	2	11.1
Palpitations	2 (18.2)	2	11.1
Investigations	2 (18.2)	2	11.1
Psychiatric disorders	2 (18.2)	2	11.1

Note: In summarizing n (%), if a patient had multiple events for a particular SOC or Preferred Term, the patient is counted only once for that SOC or Preferred Term. Results were sorted by descending order of SOC percentage and then Preferred Term within SOC, in case of equal percentage, sorted in alphabetical order. SOCs and Preferred Terms were coded using MedDRA 24.1. All applicable adverse events occurred during Primary Evaluation Treatment Period and Extension Period up to data cutoff date are included.
Abbreviations: E = total number of events; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-years; Rate = rate of TEAE adjusted by patient-years of exposure, defined as (number of events)/100 patient-years; SOC = System Organ Class

AEs of special interest

AEs of special interest for eculizumab include meningococcal infections, *Aspergillus* spp infections, sepsis, other serious infections, and infusion reactions. No events of sepsis, meningococcal, or *Aspergillus* spp infections were reported.

During the primary evaluation treatment period, 1 patient experienced 4 events of eczema. During the extension period (as of the data cutoff date), this same patient experienced 3 additional events of eczema and 1 event each of rash and urticaria. According to the medical history, this patient experienced recurrent rash due to IVIg. One patient experienced a serious infection (TESAE) during the Extension Period.

Adverse Events in Studies Providing Supplementary Safety Data

Paediatric and adult refractory gMG TEAE or TESAE data are similar to that from paediatric patients with PNH and paediatric and adult patients with aHUS. Overall, most TEAEs were mild or moderate in severity and assessed as unrelated to the study drug by the Investigator.

Table 38: Overview of All Treatment-emergent Adverse Events and Serious Adverse Events in Paediatric and Adult Patients with Refractory gMG, Paediatric Patients with PNH, and Paediatric and Adult Patients with aHUS (Safety Analysis Set, Extrapolation Analysis) (Extrapolation analysis Study 3)

Studies	Adult Patients with Refractory gMG		Pediatric Patients with Refractory gMG				Pediatric Patients with PNH		Pediatric and Adult Patients with aHUS							
	ECU-MG-301 Refractory gMG N = 62[a]		ECU-MG-303 Refractory gMG N = 11				M07-005 PNH N = 7		C08-002A/B[b] aHUS N = 17		C08-003A/B[b] aHUS N = 20		C09-001r[b] aHUS N = 30		C10-003 aHUS N = 22	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Data included in this analysis	26 weeks		26 weeks		Median 96 weeks		12 weeks		26 weeks		26 weeks		Median 27.5 weeks		26 weeks	
Any AE	53 (85.5)	361	10 (90.9)	40	11 (100)	127	7 (100.0)	69	17 (100.0)	-	20 (100.0)	-	22 (73.0)	-	20 (90.9)	-
Any SAE	9 (14.5)	17	0 (0.0)	0	3 (27.3)	6	2 (28.6)	12	17 (100.0)	-	13 (65.0)	-	7 (23.3)	-	13 (59.1)	-
Death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	-	1 (5.0)	-	2 (6.7)	-	0 (0.0)	-
AEs leading to discontinuation/withdrawal of study drug	4 (6.5)	-	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (5.9)	-	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-
SAEs leading to discontinuation/withdrawal of study drug	4 (6.5)	-	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (11.8)	-	0 (0.0)	-	0 (0.0)	-	1 (4.5)	-
AEs by relationship																
Related[c]	30 (48.4)	109	4 (36.4)	11	5 (45.5)	16	-	-	-	-	-	-	-	-	-	-
Definite	-	-			-	-	0 (0.0)	-	1 (5.9)	-	0 (0.0)	-	-	-	0 (0.0)	-
Probable	-	-			-	-	2 (28.6)	-	2 (11.8)	-	4 (20.0)	-	-	-	2 (9.1)	-
Possible	-	-				-	3 (42.9)	-	9 (52.9)	-	6 (30.0)	-	-	-	8 (36.4)	-
Unrelated/not related	49 (79.0)	252	10 (90.9)	29	11 (100)	111	2 (28.6)	-	5 (29.4)	-	10 (50.0)	-	-	-	10 (45.5)	-
AEs by severity																
Mild	49 (79.0)	264	10 (90.9)	39	11 (100)	118	4 (57.1)	-	0 (0.0)	-	1 (5.0)	-	-	-	5 (22.7)	-
Moderate	26 (41.9)	74	1 (9.1)	1	6 (54.5)	9	1 (14.3)	-	5 (29.4)	-	12 (60.0)	-	-	-	8 (36.4)	-
Severe	8 (12.9)	23	0	0	0	0	2 (28.6)	-	12 (70.6)	-	7 (35.0)	-	-	-	7 (31.8)	-
SAEs by relationship																
Related[c]	5 (8.1)	10	0 (0.0)	0	1 (9.1)	1	-	-	-		-	-	-	-	-	-
Definite	-	-	-	-	-	-	0 (0.0)	-	-	-	-	-	-	-	0 (0.0)	-
Probable	-	-	-	-	-	-	0 (0.0)	-	-	-	1 (5.0)	-	-	-	0 (0.0)	-
Possible	-	-	-	-	-	-	1 (14.3)	-	4 (23.5)	-	2 (10.0)	-	-	-	4 (18.2)	-
Unrelated/not related	5 (8.1)	7	0 (0.0)	0	2 (18.2)	5	1 (14.3)	-	13 (76.5)	-	10 (50.0)	-	-	-	9 (40.9)	-

a Eculizumab treatment group
b AEs were calculated with the overall population.
c Related AEs are defined as AEs that are possibly, probably, or definitely related to treatment.
Abbreviations: AE = adverse event; aHUS = atypical hemolytic uremic syndrome; E = number of events; gMG = generalized myasthenia gravis; N = number of patients; n = number of patients in each category; PNH = paroxysmal nocturnal hemoglobinuria; SAE = serious adverse event; - = not reported

Serious adverse event/deaths/other significant events

No TESAEs were reported during the primary evaluation treatment period.

During the extension period (as of the data cut-off date), 6 TESAEs were reported by 3 (27.3%) patients. Two patients had TESAEs that were related to MG. One patient experienced MG crisis and 1 patient experienced 3 episodes of MG worsening together with pyrexia during the first episode. One patient experienced a serious infection , which was assessed as related to study drug by the Investigator. None of the TESAEs resulted in a change in study drug dose or study drug discontinuation.

No patients died due to TEAEs in the paediatric and adult studies in refractory gMG, the paediatric study in PNH, and in 2 of the 4 paediatric and adult studies in aHUS (Studies C08-002A/B and C10-003). One (5%) adult patient with aHUS died in Study C08-003A/B, and 2 (6.7%) patients, (1 adult and 1 paediatric patient) with aHUS died in Study C09-001r (Table 40). Patients who discontinued from the study due to TEAEs were reported in Study ECU-MG-301 (adult patients with refractory gMG) (4 [6.5%] patients) and in 1 patient in Study C08-002A/B (paediatric and adult patients with aHUS) (1 [5.9%] patient).

Laboratory findings

As of the data cut-off date for the interim analysis, no clinically significant changes in clinical chemistry and haematology were observed. Shifts in laboratory parameters were infrequent, and none of the patients

experienced abnormalities that were moderate or severe in severity. Only mild laboratory-related TEAEs were reported during the study.

There were no clinically meaningful mean changes from Baseline in temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure at each postbaseline visit. The change from baseline in mean body weight values at any postbaseline visit was not clinically.

There were no relevant changes from baseline in ECGs for all parameters tested. Abnormalities in corrected QT interval (QTc), corrected QT interval by Bazett's formula (QTcB), and corrected QT interval by Fredericia's formula (QTcF) were infrequent. At week 12, changes from Baseline in QTc, QTcB, and QTcF of > 30 milliseconds to ≤ 60 milliseconds were recorded for 1 (9.1%) patient (QTc) and 2 (22.2%) patients (QTcB and QTcF) at week 12 and for 2 (20.0%) patients (QTc) at week 26. No patients had a change from Baseline in QTc, QTcB, and QTcF of > 60 milliseconds.

There were no clinically significant abnormal physical examination findings observed for any patient.

No treatment-emergent ADA responses were observed following eculizumab treatment.

Safety in special populations

No analysis of safety data by subgroups or situations (e.g. drug abuse, overdose, drug interactions) in Study ECU-MG-303 was performed due to the small sample size

Safety related to drug-drug interactions and other interactions

No drug interaction analyses with eculizumab were conducted in the eculizumab clinical development program.

Discontinuation due to adverse events

During primary evaluation treatment period, no patients died or discontinued the study due to a TEAE.

During the extension period (as of the data cut-off date), none of the TESAEs resulted in a change in study drug dose or study drug discontinuation.

Post marketing experience

Overall, the estimated postmarketing exposure to eculizumab since the first Marketing Authorization (16 Mar 2007) through 30 Sep 2021 was 70678.8 patient-years for all indications.

The MAH closely monitors the following risks for eculizumab in the postmarketing setting:

• Important identified risk: meningococcal infections, serious infections (including sepsis), Aspergillus spp infection, severe thrombotic microangiopathy complications due to drug discontinuation in aHUS patients, and infusion reactions

• Important potential risk: serious hemolysis after drug discontinuation in PNH patients, malignancies and hematologic abnormalities in PNH patients, immunogenicity, and serious infection in neonates after maternal exposure to eculizumab

• Missing information: none

Meningococcal Infection

As of 01 Oct 2021, the cumulative postmarketing reporting rate for meningococcal infection has remained stable at 0.25 per 100 patient-years (181 cases per 70678.8 patient-years). Of the 181 postmarketing cases, 16.6% (30 cases) of the meningococcal cases were reported in paediatric patients (age < 18 years).

Serious Infections (Including Sepsis)

As of 01 Oct 2021, the cumulative postmarketing rate of serious infections is approximately 9.83 per 100 patient-years (6945 cases per 70678.8 patient-years). Of the 6945 postmarketing cases, 8.6% (599 cases) of serious infections were reported in paediatric patients (age < 18 years).

Aspergillus spp Infection

As of 01 Oct 2021, the cumulative postmarketing rate of Aspergillus spp infection is approximately 0.10 per 100 patient-years (72 cases per 70678.8 patient-years). Of the 72 postmarketing cases, 15.3% (11 cases) of the Aspergillus spp infection cases were reported in paediatric patients (age < 18 years).

Infusion Reactions

As of 01 Oct 2021, the cumulative postmarketing rate of infusion reactions is approximately 0.73 per 100 patient-years (517 cases per 70678.8 patient-years). Of the 517 postmarketing cases, 19.9% (103 cases) of the infusion reactions were reported in paediatric patients (age < 18 years).

2.5.1. Discussion on clinical safety

Eculizumab is currently approved for the treatment of adult and paediatric patients with PNH and aHUS and for the treatment of adults with gMG and NMOSD. The first marketing authorization was granted on 20 Jun 2007. The safety profile of eculizumab is reasonably established.

The safety of eculizumab in paediatric patients with gMG has been evaluated in one phase 3 study (study ECU-MG-303) which includes a 26-week treatment period and an extension period still ongoing. The safety data are available up to the data cut-off date of 06 June 2022 (median study duration of 96 weeks).

A total of 11 patients aged ≥ 12 to < 18 years were exposed to eculizumab in the primary evaluation treatment period of Study ECU-MG-303. It represents a very limited safety database

These 11 patients have been exposed to eculizumab a median treatment duration of 95.1 weeks. The patients received a mean of 14.9 infusions per patient in this period. A total of 122 supplemental infusions were administered. As of the data cut-off date treatment compliance was 100% for 9 (81.8%) patients and ≥ 90% to < 100% for 2 (18.2%) patients.

As for the demographic and disease baseline characteristics, 81.8% of patients were women and the mean age was 14.8 years. All the patients treated in the study were > 12 years of age. The study was conducted in USA and Japan. Only 18.2% of the patients were White, being Black or African American (45.5%) followed by Asian (27.3%) patients the most represented groups. According to the MAH no differences in eculizumab's safety profile due to age, gender, race and ethnicity have been observed across the entirety of eculizumab clinical development program. This could be agreed.

In order to complete the safety profile in the paediatric population and provide some reference for comparison, supplementary data from eculizumab studies in adults with gMG and other paediatric indications (PNH, aHUS) have been also submitted. In paediatric patients with refractory gMG (aged 12 to less than 18 years) included in Study ECU MG 303, the safety profile appeared similar to that observed in adult patients with refractory gMG, based on an extrapolation study (study 3).

The safety database includes 20 adolescents (12 to 18 years of age) and 34 children (<12 years of age) with PNH/aHUS. This supportive safety population shows other demographic differences with respect to

that included in the Study ECU-MG-303, such as higher proportion of males and the predominance of White or Caucasian patients. In addition, paediatric PNH patients weighing >40 kg received lower induction and maintenance doses than patients in study ECU-MG-303. According to the MAH, there is no evidence suggesting a different safety profile in pediatric patients with refractory gMG. This could be agreed.

During the 26-week primary evaluation treatment period of Study ECU-MG-303, 40 TEAEs were experienced by 10 (90.9%) patients.

As of the data cut-off date, 127 TEAEs were reported by 11 (100%) patients. A total of 4 (36.4%) patients during primary evaluation treatment period of the study and 5 (45.5%) patients as of the data cut-off date reported a TEAE assessed to be related to study drug,

During the study the most frequently reported TEAEs were headache (4 [36.4%] patients), nasopharyngitis (4 [36.4%] patients), pyrexia (3 [27.3%] patients), and pain in extremity (3 [27.3%] patients). All these AEs are already included in the SmPC of Soliris.

During the initial period of treatment (first 12 weeks) none of the AEs was reported in more than 1 patient. The limited number of patients exposed prevent from an adequate characterisation of the safety profile in this population. The safety profile reported in the other paediatric indications (with a total database still limited even for frequent AEs) is deemed to be similar to that observed in adult patients.

No TESAEs were reported during the primary evaluation treatment period. During the extension period (as of the data cutoff date), 3 (27.3%) patients reported 6 TESAEs: 1 patient experienced MG crisis, 1 patient experienced 3 episodes of MG worsening (one of them with pyrexia). All these TESAEs were related to MG. One patient experienced a serious infection, which was assessed as related to study drug by the Investigator. None of the TESAEs resulted in a change in study drug dose or study drug discontinuation.

No events of sepsis, meningococcal, or *Aspergillu*s spp infections (considered as adverse events of special interest) were reported. No patients died or discontinued the study due to a TEAE. No clinically significant changes in clinical laboratory parameters, vital signs or ECG were observed. No ADA response was detected following eculizumab treatment.

One of the gMG patients reported several events of eczema, not currently included in the SmPC (MedRA Organ System Class of Skin and subcutaneous tissue disorders). However, eczema was reported as AEs in paediatric aHUS patients[25].

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

Assessment of paediatric data on clinical safety

See above

2.5.2. Conclusions on clinical safety

The safety database of eculizumab in the applied indication is considered very limited. Although the small size of the safety database is not unexpected considering the rarity of the condition, the limited number of patients included in the study ECU-MG-303 prevents from completely characterising the safety profile of eculizumab in this population. However, the limited safety database in paediatric gMG patients can be considered supported by safety data of eculizumab in paediatric patients with other conditions and safety data in adult patients with refractory gMG. In this regard, the safety data from paediatric patients with refractory gMG are consistent with the known safety profile of eculizumab in adult patients with refractory

[25] Greenbaum LA et al. Eculizumab is a safe and effective treatment in paediatric patients with atypical hemolytic uremic syndrome. Kidney International (2016) 89, 701–711.

gMG, paediatric patients with PNH, and paediatric and adult patients with aHUS. No new AEs have been reported in this new population. Further, the extension phase of the study is ongoing. The MAH is expected to submit the results when available in order to complete the long-term safety assessment.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP endorsed the Risk Management Plan version 20.3 with the following content:

Safety concerns

Table 39: Summary of 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
Missing information	None

Pharmacovigilance plan

Table 40: Planned and Ongoing Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – required additional pharmacovigilance activities				
"Atypical Hemolytic Uremic Syndrome (aHUS) Registry" (M11-001) 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 in aHUS patients receiving eculizumab treatment or other disease management.	Meningococcal infections Serious infections (including sepsis) *Aspergillus* infection Infusion reactions Severe TMA complications due to drug discontinuation in aHUS patients Immunogenicity	Interim data analysis	Every 2 years interim data analysis report

Abbreviation: TMA = thrombotic microangiopathy.

Risk minimisation measures

Table 41: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Meningococcal infections	**Routine risk minimisation measures**: – SmPC sections 4.3, 4.4, and 4.8 – 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, refractory gMG) – 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**: – 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 (PNH, aHUS, refractory gMG) – Patient safety card	**Additional pharmacovigilance activities**: – aHUS registry (M11-001)
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**: – 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**: – 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 (PNH, aHUS, refractory gMG, NMOSD) – Parent's information brochure (PNH, aHUS, refractory gMG)	**Additional pharmacovigilance activities**: – aHUS registry (M11-001)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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)	– None
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**: – 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 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the MAH has taken the opportunity to update section 4.8 of the SmPC in order to update the frequency of the list of adverse drug reactions (ADRs) based on cumulative safety data, to update the ATC code as per the new WHO guidelines and to introduce minor editorial changes to the PI.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of all MS as this was missing in the PL.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

• The content and format of information related to the paediatric population with refractory gMG are very similar to that of refractory gMG indication in the adult patient population, except for the additional efficacy results information related to the paediatric portion of refractory gMG indication;

• There were no specific or new risk added concerning the paediatric population with refractory gMG.

• The medicinal product is already approved for other paediatric indications (PNH, aHUS).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

gMG is an autoimmune disorder characterized by skeletal muscle weakness and fatigability caused by autoantibody-induced neurotransmission dysfunction at the neuromuscular junction.

Paediatric MG is rare, representing about 10–15% of total cases of MG. JMG is acquired MG not related to structural disorders, occurring in childhood or adolescence (i.e. <18 years of age)[26].

The purpose of this application is to extend the generalized myasthenia gravis indication for eculizumab to include paediatric patients with refractory AChR-Ab + gMG. The proposed indication is the following:

"Soliris is indicated in adults and children for the treatment of refractory generalized myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive."

3.1.2. Available therapies and unmet medical need

Treatment of JMG is similar to adult myasthenia gravis and typically involves a combination of symptomatic (anticholinesterase inhibitors), IST (steroids and other immunosuppressants), with thymectomy in appropriate cases. Maintenance PLEX or IVIg are alternatives to IST in JMG. Most of the current practice on diagnosis and treatment of JMG in children is extrapolated from adult trials and experience on the treatment of gMG. None of the available therapies are specifically approved for paediatric MG.

The condition may be life threatening due to swallowing and breathing muscle weakness. Over the longer term, it may be associated with significant disability and morbidity together with the AEs associated with the steroids and immunosuppressants use, in particular concerning growth and immune-system development in young children.

3.1.3. Main clinical studies

The eculizumab clinical development program in paediatric population with refractory gMG includes:

- Study ECU-MG-303: A Phase 3 open label, uncontrolled, multicentre study to evaluate efficacy, safety and PK/PD of eculizumab in paediatric patients from 6 to < 18 years of age with refractory AChR-Ab + gMG (ongoing).
- A modelling and simulation study to evaluate the use and support dosage regimen of eculizumab in paediatric patients from 6 to < 18 years of age with refractory AChRAb+ gMG.
- An extrapolation study to evaluate the efficacy, PK/PD, and safety of eculizumab in paediatric patients from 6 to < 18 years of age with refractory AChR-Ab+ gMG.

3.2. Favourable effects

Efficacy was based on the effect of eculizumab on the gMG signs and symptoms assessed by the physician (QMG scale; primary endpoint) and the patient (MG-ADL; secondary variable). At week 26 a 5.8-point reduction in the QMG total score reported by the physician was observed in comparison with baseline score (95% CI: -8.40, -3.13; p = 0.0004). When the effect was assessed from the patient perspective, an improvement was observed in MG-ADL total score of -2.3 ([95% CI: -3.6, -1.03]; p=0.0017). MGC Scale results are in line with those observed for MG-ADL and QMG total scores. At week 26 patients experienced an 8.8-point reduction with respect to baseline ([95% CI: -12.9, -4.69; p=0.0007) (mFAS).

A relevant percentage of patients showed control of the disease: 70% of patients showed ≥ 5 point reduction in the QMG total score and 50% of patients showed ≥ 3 point reduction in the MG-ADL total score.

This improvement was also observed when the effect of eculizumab on health status (EQ-5D-Y VAS) and fatigue (Neuro-QoL Paediatric Fatigue) was measured.

[26] Elsakka EE, Elmekky MH, Omar TE. Alex J Pediatr 2021,34:59–66

Similar to what was observed in adult gMG patients, the main effect was reached at Week 4 followed by a plateau phase maintained throughout the 26-week primary evaluation treatment period.

3.3. Uncertainties and limitations about favourable effects

Globally, the small number of subjects included in Study ECU-MG-303, the lack of a control arm and the observed variability as well as the fluctuating nature of the condition add uncertainty to the estimation of the magnitude of the effect with a potential of overestimating the effect.

The Study ECU-MG-03 was conducted in Japan and US. Most of the patients included were Black or African American (45.5%) followed by Asian (27.3%) patients. Only 18.2% were White. No EU patients were recruited. At request, the MAH has explained that no significant impact on exposure and terminal complement inhibition has been observed in a Pop-PK analysis in adult gMG patients by ethnicity and no relevant differences in the treatment effect of eculizumab in adults has been reported in the literature when ethnic differences were explored. It can, therefore, be expected that the response in the target population would not be dissimilar to that observed in Study ECU-MG-303. This can be agreed.

No children less than 12 years of age participated in the study. Mean age was 14.8 years (ranging from 12 to 17 years). Although limited (due to a low patient availability), some data on PK, efficacy and safety was expected in this young subset. While MG in adults and children have differences, it can be agreed that the paediatric target population including children with refractory gMG with anti-AChR antibodies is similar to the already approved adult population. Based on this similarity, the estimation of the dose recommendation in this sub-group of patients and the available efficacy results, extrapolation of efficacy to children aged ≥6 years can be agreed.

The majority of patients in study ECU-MG-303 (90%) were ≥40 kg. There was only 1 patient in the body weight range 30 to 40 kg and 10 patients in the weight cohort ≥ 40 kg, which indicates that 10 out of 11 subjects received the dosing regimen for adult gMG patients. Upon request, the Applicant presented a simulation-based analysis of the exposure at steady state across the different body-weight subgroups of paediatric patients using the pop-PK model in gMG patients and the allometric exponents obtained in the pop-PK model in aHUS/PNH that supports the dose recommendation in paediatric gMG patients below 37 kg.

Eculizumab is approved in adult patients with refractory gMG. Adult patients included in study ECU-MG-301 were required to have failed to at least 2 previous treatments according the international consensus[27]. In study ECU-MG-303, patients were required to have refractory condition defined as having failed treatment ≥1 year with at least 1 immunosuppressive therapies or requiring PE or IVIg to control symptoms or having a significant functional burden despite current MG treatment. The MAH has explained that a clear definition of refractoriness in MG in paediatric patients is not currently available. Considering the characteristics of the patients included in the study with respect to failure to previous treatments and the symptomatic condition in spite of the concomitant treatment received during the study, it could be justified to consider paediatric patients in Study ECU-MG-303 as meeting the definition of refractory.

When the effect is analysed by the use or not of maintenance IVIg, it seems to be of lower magnitude in those patients chronically treated with IVIg. However, not all the efficacy results point in the same direction and the reduced number of patients prevents from drawing a conclusion on whether the efficacy may vary depending on the use of IVIg as maintenance IST. Of note, the reported PK data in patients receiving maintenance IVIg therapy and Soliris supplemental doses show an increased exposure of eculizumab. The MAH has justified the need of supplemental doses of eculizumab when IVIg therapy is concomitantly administered, based on faster mAb clearance. Further, the MAH provided a new analysis for PK / PD

[27] Sanders DB., et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology 87.4 (2016): 419-425.

modelling in which it can be agreed that the distribution of the Exposure of Eculizumab (PK) vs. inhibition of terminal complement (free C5 < 0.5 µg/mL) (PD) overlaps for those children using standard dose regimen (no IVIg-treatment) and standard dose regimen plus supplemental dosing (IVIg-treated patients). Whether the apparently reduced efficacy observed in those patients compared to those not receiving concomitant IVIg therapy can be (solely) explained from the PK perspective remains unclear. This information has been added to the SmPC.

No efficacy data are available beyond week 26 so that the maintenance of the effect in this population is unknown. The study is still ongoing and results up to additional 208 Weeks are expected to be submitted, when available.

3.4. Unfavourable effects

Overall, headache (36.4%), nasopharyngitis (36.4%), pyrexia (27.3%) and pain in extremity (27.3%) were the most frequently reported during the 26-week primary evaluation treatment period of Study ECU-MG-303. All these AEs are already included in the SmPC of the product.

No TESAEs were reported during the primary evaluation treatment period. During the extension period (as of the data cutoff date), 3 (27.3%) patients reported 6 TESAEs: 1 patient experienced MG crisis, 1 patient experienced 3 episodes of MG worsening (one of them with pyrexia). All these TSAEs were related to MG. One patient experienced a serious infection, which was assessed as related to study drug by the Investigator. None of the TESAEs resulted in a change in study drug dose or study drug discontinuation.

No events of sepsis, meningococcal, or *Aspergillu*s spp infections (considered as adverse events of special interest) were reported. No patients died or discontinued the study due to a TEAE. No clinically significant changes in clinical laboratory parameters, vital signs or ECG were observed. No ADA response was detected following eculizumab treatment.

One of the gMG patients reported several events of eczema, not currently included in the SmPC. However, eczema was reported as AE in paediatric aHUS patients[28].

3.5. Uncertainties and limitations about unfavourable effects

The safety database of eculizumab in the applied indication is considered very limited. A total of 11 patients aged ≥ 12 to < 18 years were exposed to eculizumab in the primary evaluation treatment period ECU-MG-303. A total of 10 patients are being treated during the Extension period. The small size of the safety database is not unexpected considering the rarity of the condition. The limited safety database in paediatric gMG patients can be considered supported by safety data of eculizumab in paediatric patients with other conditions.

The study was conducted in USA and Japan. Only 18.2% of the patients were White, being Black or African American (45.5%) followed by Asian (27.3%) patients the most represented groups. There are no gMG patients <12 years treated with eculizumab.

Supplementary data from eculizumab studies in adults with gMG and other paediatric indications (PNH, aHUS) have been also submitted in order to complete the safety profile in the paediatric population. The safety database includes 34 children (<12 years of age) and 20 adolescents (12 to 18 years of age) with PNH/aHUS. This supportive safety population shows other demographic differences with respect to that included in the study ECU-MG-303 such as higher proportion of males and the predominance of White or Caucasian patients. In addition, paediatric PNH patients weighing >40 kg received lower induction and

[28] Greenbaum LA et al. Eculizumab is a safe and effective treatment in paediatric patients with atypical hemolytic uremic syndrome. Kidney International (2016) 89, 701–711.

maintenance doses than patients in study ECU-MG-303. The safety profile reported in these paediatric indications (with a total database still limited even for frequent adverse events) is deemed to be similar to that observed in adult patients. There is no evidence from this study suggesting a different safety profile in pediatric patients with refractory gMG. The extension phase of the study is ongoing. The MAH is expected to submit the results when available in order to complete the long-term safety assessment.

3.6. Effects Table

Table 42: Effects Table for Table for eculizumab for the treatment of paediatric refractory gMG (data cut-off: 06 Jan 2022)

Effect	Short description	Unit	Eculizumab	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint QMG Total Score	Change from Baseline in QMG Total Score	LS mean (95% CI) P-value	-5.8 (-8.40, -3.13) p= 0.0004		Lack of control arm N=11 patients 12-18y	Study ECU-MG-303 26-wk Primary Evaluation Period
Second endpoints MG-ADL	Change from Baseline in MG-ADL Total Score	LS mean	-2.3		Lack of control arm N=11 patients 12-18y (95% CI: -3.63, -1.03) P-value= 0.0017	Study ECU-MG-303 26-wk Primary Evaluation Period
Second endpoint QMG responder rate	QMG ≥5-point improvement	%	70.0%		Lack of control arm N=11 patients 12-18y (95% CI: 34.8, 93.3) P-value< 0.0001	Study ECU-MG-303 26-wk Primary Evaluation Period
Second endpoint MG-ADL responder rate	MG-ADL ≥5-point improvement	% P-value	50.0%		Lack of control arm N=11 patients 12-18y P-value< 0.0001	Study ECU-MG-303 26-wk Primary Evaluation Period
Second endpoint MGC Total Score	Change from Baseline in MGC Total Score	LS mean	-8.8		Lack of control arm N=11 patients 12-18y (95% CI: -12.93, -4.69) P-value= 0.0007	Study ECU-MG-303 26-wk Primary Evaluation Period
Second endpoint Neuro-QOL-fatigue	Change from Baseline in Neuro-QOL-fatigue Score	LS mean	-7.7		Lack of control arm N=11 patients 12-18y (95% CI: -11.05, -4.31) P-value= 0.0003	Study ECU-MG-303 26-wk Primary Evaluation Period
Unfavourable Effects						
AEs	Incidence of AEs regardless of causality	n(%)	10 (90.9)			Study ECU-MG-303 26-wk Primary Evaluation Period
Related AEs	Proportion	n(%)	4 (36.4)			Study ECU-MG-303 26-wk Primary Evaluation Period
AEs	Incidence of AEs regardless of causality	n(%)	11 (100)			Study ECU-MG-303 Data cut-off date
Related AEs	Proportion	n(%)	5 (45.5)			Study ECU-MG-303 Data cut-off date
Serious AEs	Proportion	n(%)	3 (27.3)			Study ECU-MG-303 Data cut-off date
Headache	Common TEAE	n(%)	4 (36.4)	-		Study ECU-MG-303
Nasopharyngitis	Common TEAE	n(%)	4 (36.4)			Study ECU-MG-303
Pyrexia	Common TEAE	n(%)	3 (27.3)			Study ECU-MG-303
Pain in extremity	Common TEAE	n(%)	3 (27.3)			Study ECU-MG-303

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of eculizumab on the treatment of gMG in paediatric patients has been established in a single open label study (study ECU-MG-303) that included a total of 11 patients > 12 years of age.

Overall, although the data suggest an effect of eculizumab in the studied population the available evidence is scarce. The rarity of the condition is acknowledged and these circumstances are more relevant in the paediatric population.. However, the study in adults may contribute to provide some reassurance, particularly due to the similarity of the phenotype and pathophysiology of the adult and paediatric population diagnosed as refractory gMG with anti-AChR antibodies positive. Additionally, an adequate estimation of the dose by weight for children covering the weight 6-12-year old is also supportive.

Therefore, the CHMP agreed on the inclusion of paediatric patients 6 years and above in the indication. The cut-off point is derived from the study 1 in the PIP, since a waiver was granted in the paediatric population from birth to less than 6 years of age.

The safety database of eculizumab in the applied indication is considered very limited which prevents from fully characterising the safety profile of eculizumab in this population. However, the safety data from paediatric patients with refractory gMG are consistent with the known safety profile of eculizumab in adult patients with refractory gMG, paediatric patients with PNH, and paediatric and adult patients with aHUS. There is no evidence from this study suggesting a different safety profile in paediatric patients with refractory gMG. Long-term efficacy and safety in paediatric gMG population is based on the effect of eculizumab during the extension period of the study, still ongoing. Results from this extension phase should be provided.

3.7.2. Balance of benefits and risks

Although the small number of subjects, the lack of a control arm, the observed variability as well as the fluctuating nature of the condition add uncertainty to the estimation of the magnitude of the effect with a potential of overestimating the effect, the CHMP noted that Eculizumab has shown an effect on the control of symptoms assessed by the physician (QMG score; primary endpoint) and by the patient (MG-ADL score, secondary endpoint) in the studied patients after 26 weeks of treatment, with respect to baseline values. The safety data are consistent with the known safety profile of eculizumab in adult patients with refractory gMG, and paediatric PNH and aHUS patients. The reduced safety database is the main limitation. The extension phase of the study is ongoing. The MAH is expected to submit the results when available in order to complete the long-term efficacy and safety assessment.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Soliris is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include treatment of paediatric patients with refractory generalised myasthenia gravis (gMG) for Soliris, based on interim results from study ECU-MG-303; this is an open-label, multicenter, phase 3 study to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of intravenous (IV) eculizumab in paediatric patients aged 6 to less than 18 years with acetylcholine receptor-antibody (AChR-Ab) positive (+) refractory gMG. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.3 of the RMP has been agreed. In addition, the MAH took the opportunity to update section 4.8 of the SmPC in order to update the frequency of the list of adverse drug reactions (ADRs) based on cumulative safety data and to introduce minor editorial changes to the PI. In addition, in line with the new WHO level alteration, the Marketing authorisation holder (MAH) took the opportunity to update the ATC code in the SmPC section 5.1. The list of local representatives in the Package Leaflet has been updated.

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

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/00074/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

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

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Soliris-H-C-000791-II-0126’