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

Summary

EudraCT number	2016-001384-37
Trial protocol	DE NL
Global end of trial date	06 November 2023

Results information

Result version number	v2
This version publication date	28 July 2024
First version publication date	16 July 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	ECU-MG-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03759366
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	100 College Street, New Haven, CT, United States, 06510
Public contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 7 87148158, clinicaltrials.eu@alexion.com
Scientific contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 7 87148158, clinicaltrials.eu@alexion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000876-PIP05-15
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 February 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the efficacy of eculizumab in the treatment of pediatric refractory generalized Myasthenia Gravis (gMG) based on change from baseline in the Quantitative Myasthenia Gravis (QMG) total score for disease severity.

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following: • Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines • Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines • Applicable laws and regulations

Background therapy:

Participants could continue to receive acetylcholinesterase inhibitor (AChI), intravenous immunoglobulin (IVIg), and immunosuppressant therapies (ISTs) during the study, where applicable, under certain restrictions.

Evidence for comparator: -

Actual start date of recruitment	28 December 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Japan: 3
Worldwide total number of subjects	11
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	11
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study included a Primary Evaluation Treatment Period of 26 weeks, an Extension Period of up to an additional 208 weeks, and a Follow-up Period of 8 weeks.

Pre-assignment

Screening details:

All participants were offered participation in the Extension Period of the study.

Period 1

Period 1 title	Primary Evaluation Period (26 Weeks)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Eculizumab

Arm description:

Participants received eculizumab by intravenous (IV) infusion during the Primary Evaluation Treatment Period (26 weeks) and the Extension Period (up to 208 weeks). Dosing was initiated with a weekly weight-based induction regimen (Induction Phase) and, thereafter, participants were dosed every 2 weeks (Maintenance Phase). Eculizumab was administered at doses of 300, 600, 900, or 1200 milligrams (mg), based on the participant's current body weight.

Arm type	Experimental
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eculizumab was administered per dose and schedule specified in the protocol.

Number of subjects in period 1	Eculizumab
Started	11
Received at Least 1 Dose of Study Drug	11
Completed	10
Not completed	1
Physician decision	1

Period 2

Period 2 title	Extension Period (Up to 208 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Eculizumab

Arm description:

Participants received eculizumab by intravenous (IV) infusion during the Primary Evaluation Treatment Period (26 weeks) and the Extension Period (up to 208 weeks). Dosing was initiated with a weekly weight-based induction regimen (Induction Phase) and, thereafter, participants were dosed every 2 weeks (Maintenance Phase). Eculizumab was administered at doses of 300, 600, 900, or 1200 milligrams (mg), based on the participant's current body weight.

Arm type	Experimental
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eculizumab was administered per dose and schedule specified in the protocol.

Number of subjects in period 2	Eculizumab
Started	10
Received at Least 1 Dose of Study Drug	10
Completed	2
Not completed	8
Consent withdrawn by subject	2
Physician decision	1
Participant transferred to another study	1
Lost to follow-up	1
Participant transitioned to Soliris	1
Participant transitioned to Ultomiris	2

Baseline characteristics

Reporting groups	
Reporting group title	Eculizumab
Reporting group description:	
Participants received eculizumab by intravenous (IV) infusion during the Primary Evaluation Treatment Period (26 weeks) and the Extension Period (up to 208 weeks). Dosing was initiated with a weekly weight-based induction regimen (Induction Phase) and, thereafter, participants were dosed every 2 weeks (Maintenance Phase). Eculizumab was administered at doses of 300, 600, 900, or 1200 milligrams (mg), based on the participant's current body weight.	

Reporting group values	Eculizumab	Total	
Number of subjects	11	11	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	11	11	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	14.8		
standard deviation	± 1.78	-	
Gender Categorical Units: Subjects			
Female	9	9	
Male	2	2	
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	9	9	
Race Units: Subjects			
Asian	3	3	
Black or African American	5	5	
White	2	2	
Other	1	1	
QMG Total Score			
The QMG scoring system consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). Each item is graded from 0 to 3, (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The range of total QMG score is 0 to 39, with higher score indicating most severe disease.			
Units: units on a scale			
arithmetic mean	16.7		

standard deviation	± 5.64	-	

End points

End points reporting groups

Reporting group title	Eculizumab

Reporting group description:

Participants received eculizumab by intravenous (IV) infusion during the Primary Evaluation Treatment Period (26 weeks) and the Extension Period (up to 208 weeks). Dosing was initiated with a weekly weight-based induction regimen (Induction Phase) and, thereafter, participants were dosed every 2 weeks (Maintenance Phase). Eculizumab was administered at doses of 300, 600, 900, or 1200 milligrams (mg), based on the participant's current body weight.

Reporting group title	Eculizumab

Reporting group description:

Participants received eculizumab by intravenous (IV) infusion during the Primary Evaluation Treatment Period (26 weeks) and the Extension Period (up to 208 weeks). Dosing was initiated with a weekly weight-based induction regimen (Induction Phase) and, thereafter, participants were dosed every 2 weeks (Maintenance Phase). Eculizumab was administered at doses of 300, 600, 900, or 1200 milligrams (mg), based on the participant's current body weight.

Primary: Change From Baseline in the QMG Total Score at Week 26 Regardless of Rescue Treatment

End point title	Change From Baseline in the QMG Total Score at Week 26 Regardless of Rescue Treatment[1]

End point description:

The QMG scoring system consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). Each item is graded from 0 to 3, (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The range of total QMG score is 0 to 39, with higher score indicating more severe disease. A repeated measures model was used to analyse observed change in QMG with baseline QMG score and visits as covariates. The least square mean (95% confidence interval) change from baseline in QMG total score at Week 26 of was -5.8 (-8.40, -3.13), p=0.0004. Modified full analysis set (mFAS) included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline, Week 26

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the single-arm study model, statistical analysis is reported in the 'Reporting group description'.

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: units on a scale				
arithmetic mean (standard deviation)	-6.1 (± 4.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ≥3-Point Reduction in the MG-ADL Total

Score With No Rescue Treatment

End point title	Percentage of Participants With ≥3-Point Reduction in the MG-ADL Total Score With No Rescue Treatment

End point description:

The MG-ADL is an 8-point questionnaire that focuses on relevant symptoms and functional performance of activities of daily living in participants with MG. The 8 items of the MG-ADL are derived from symptom-based components of the original 13-item QMG to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects from MG. In this functional status instrument, each response is graded from 0 (normal) to 3 (most severe). The range of total MG-ADL score is 0 to 24, with higher score indicating more severe disease. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	50.0 (18.7 to 81.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ≥3-Point Reduction in the MG-ADL Total Score Regardless of Rescue Treatment

End point title	Percentage of Participants With ≥3-Point Reduction in the MG-ADL Total Score Regardless of Rescue Treatment

End point description:

The MG-ADL is an 8-point questionnaire that focuses on relevant symptoms and functional performance of activities of daily living in participants with MG. The 8 items of the MG-ADL are derived from symptom-based components of the original 13-item QMG to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects from MG. In this functional status instrument, each response is graded from 0 (normal) to 3 (most severe). The range of total MG-ADL score is 0 to 24, with higher score indicating more severe disease. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	50.0 (18.7 to 81.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ≥5-Point Reduction in the QMG Total Score With No Rescue Treatment

End point title	Percentage of Participants With ≥5-Point Reduction in the QMG Total Score With No Rescue Treatment

End point description:

The QMG scoring system consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). Each item is graded from 0 to 3, (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The range of total QMG score is 0 to 39, with higher score indicating more severe disease. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	70.0 (34.8 to 93.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ≥5-Point Reduction in the QMG Total Score Regardless of Rescue Treatment

End point title	Percentage of Participants With ≥5-Point Reduction in the QMG Total Score Regardless of Rescue Treatment

End point description:

The QMG scoring system consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). Each item is graded from 0 to 3, (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The range of total QMG score is 0 to 39, with higher score indicating more severe disease. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	70.0 (34.8 to 93.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Myasthenia Gravis Activities of Daily Living (MG-ADL) Total Score at Week 26 Regardless of Rescue Treatment

End point title	Change From Baseline in the Myasthenia Gravis Activities of Daily Living (MG-ADL) Total Score at Week 26 Regardless of Rescue Treatment

End point description:

The MG-ADL is an 8-point questionnaire that focuses on relevant symptoms and functional performance of activities of daily living in participants with myasthenia gravis (MG). The 8 items of the MG-ADL are derived from symptom-based components of the original 13-item QMG to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects from MG. In this functional status instrument, each response is graded from 0 (normal) to 3 (most severe). The range of total MG-ADL score is 0 to 24, with higher score indicating more severe disease. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: units on a scale				
arithmetic mean (standard deviation)	-2.5 (± 1.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Myasthenia Gravis Composite (MGC) Scale Total Score at Week 26 Regardless of Rescue Treatment

End point title	Change From Baseline in the Myasthenia Gravis Composite (MGC) Scale Total Score at Week 26 Regardless of Rescue Treatment

End point description:

The MGC is a validated assessment tool for measuring clinical status of participants with MG. The MGC assesses 10 important functional areas most frequently affected by MG: ocular (2 items), facial (1 item), bulbar (3 items), respiratory (1 item), axial (1 item), and gross motor (2 items). The scales are weighted for clinical significance that incorporates patient-reported outcomes. The MGC total score ranges from 0 to 50, with lower scores indicating less functional impairment and higher scores indicating greater functional impairment. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: units on a scale				
arithmetic mean (standard deviation)	-9.4 (± 5.91)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Serum Concentration Of Eculizumab

End point title	Pharmacokinetics (PK): Serum Concentration Of Eculizumab

End point description:

PK analysis set included participants who had PK data assessments during this study. Here, n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

24 hours postdose on Day 1; predose and 60 minutes postdose at Week 12; predose at Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: micrograms (µg)/millilitre (mL)				
arithmetic mean (standard deviation)				
Day 1, 24 hours postdose (n = 11)	359.6 (± 105.18)			
Week 12, Predose (n = 10)	382.8 (± 159.57)			

Week 12, 60 minutes postdose (n = 11)	910.5 (± 277.29)			
Week 26, Predose (n = 9)	433.9 (± 171.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Neurological Quality of Life-Fatigue Questionnaire (Neuro-QoL Pediatric Fatigue) Total Score at Week 26 Regardless of Rescue Treatment

End point title	Change From Baseline in the Neurological Quality of Life-Fatigue Questionnaire (Neuro-QoL Pediatric Fatigue) Total Score at Week 26 Regardless of Rescue Treatment

End point description:

The Neuro-QoL Pediatric Fatigue questionnaire is a reliable and validated brief 11-item survey of fatigue, completed by the participant for participants ≥12 years of age (at time of assessment) and completed by the participant's caregiver or with caregiver assistance for participants <12 years of age. Each item was scored on a scale of 1 to 5 (1=Not at all, 2=A little bit, 3=Somewhat, 4=Quite a bit, 5=Very much). Total score is the sum of each item's score and it ranges from 11 to 55. Higher scores indicate greater fatigue and greater impact of MG on activities. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: units on a scale				
arithmetic mean (standard deviation)	-7.9 (± 7.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the European Quality of Life 5-Dimension Youth version (EQ-5D-Y) Scale Score at Week 26 Regardless of Rescue Treatment

End point title	Change From Baseline in the European Quality of Life 5-Dimension Youth version (EQ-5D-Y) Scale Score at Week 26 Regardless of Rescue Treatment

End point description:

The EQ-5D-Y is a reliable and validated survey of health status in 5 areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each of which is completed by the participant for participants ≥12 years of age (at time of assessment) and completed by the participant's caregiver or with caregiver assistance for participant <12 years of age. Each area has 3 levels: Level 1 (no problems), Level 2 (some problems), and Level 3 (extreme problems). The EQ visual analogue scale

(VAS) records the participant's self-rated health on a vertical, 20 cm VAS where the endpoints are labelled 'Best imaginable health state, marked as 100' and 'Worst imaginable health state, marked as 0'. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: units on a scale				
arithmetic mean (standard deviation)	23.5 (± 23.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants in Each Category of the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFAPIS) Regardless of Rescue Treatment at Week 26

End point title	Number of Participants in Each Category of the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFAPIS) Regardless of Rescue Treatment at Week 26

End point description:

The MG clinical state (improved, unchanged, and worse) was assessed using the MGFAPIS. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants				
Improved	10			
Unchanged	0			
Worse	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Deteriorations, Myasthenic Crises, and Rescue Therapy Use

End point title	Percentage of Participants With Clinical Deteriorations, Myasthenic Crises, and Rescue Therapy Use

End point description:

Rescue therapy (for example, high dose corticosteroid, plasma exchange [PE], or intravenous immunoglobulin [IVIg]) was to be allowed when a participant experienced clinical deterioration. Clinical deterioration was defined as follows: Participants who experienced an MG crisis, which was defined as weakness due to MG that was severe enough to necessitate intubation or to delay extubation following surgery; or, Significant symptomatic worsening that required rescue medication in the opinion of the Investigator; or, Participants for whom the Investigator believed that the participants' health was in jeopardy if rescue therapy was not given. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percentage of participants				
number (not applicable)				
Clinical Deterioration	9.1			
MG Crisis	9.1			
Requiring Rescue Therapy	9.1			

Statistical analyses

No statistical analyses for this end point

Secondary: PD: Percentage of Hemolysis (In Vitro Assay)

End point title	PD: Percentage of Hemolysis (In Vitro Assay)

End point description:

PD analysis set included participants who had PD data assessments during this study. Here, 'Overall number of participants analysed' = participants evaluable for this endpoint. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline; 24 hours postdose on Day 1; predose and 60 minutes postdose at Week 12; predose at Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of hemolysis				
arithmetic mean (standard deviation)				
Baseline (n = 10)	105.8 (± 14.15)			
Day 1, 24 hours postdose (n = 10)	1.1 (± 2.01)			
Week 12, Predose (n = 10)	1.8 (± 4.67)			
Week 12, 60 minutes postdose (n = 10)	0.2 (± 0.45)			
Week 26, Predose (n = 9)	0.5 (± 1.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics (PD): Serum Free Complement Component 5 (C5) Concentrations

End point title	Pharmacodynamics (PD): Serum Free Complement Component 5 (C5) Concentrations

End point description:

PD analysis set included participants who had PD data assessments during this study. Here, n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline; 24 hours postdose on Day 1; predose and 60 minutes postdose at Week 12; predose at Week 26

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: µg/mL				
arithmetic mean (standard deviation)				
Baseline (n = 11)	172.7 (± 34.52)			
Day 1, 24 hours postdose (n = 11)	0.0 (± 0.01)			
Week 12, Predose (n = 11)	0.0 (± 0.01)			
Week 12, 60 minutes postdose (n = 11)	0.0 (± 0.01)			
Week 26, Predose (n = 10)	0.0 (± 0.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the QMG Total Score at Week 52 Regardless of

Rescue Treatment

End point title	Change From Baseline in the QMG Total Score at Week 52 Regardless of Rescue Treatment

End point description:

The QMG scoring system consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). Each item is graded from 0 to 3, (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The range of total QMG score is 0 to 39, with higher score indicating more severe disease. A repeated measures model was used to analyse observed change in QMG with baseline QMG score and visits as covariates. The least square mean (95% confidence interval) change from baseline in QMG total score at Week 52 of was -4.3 (-6.93, -1.65), p = 0.0033. mFAS included participants 12 to <18 years of age who received at least 1 dose of eculizumab. Overall number of participants analysed = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: units on a scale				
arithmetic mean (standard deviation)	-4.9 (± 4.26)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 5 years

Adverse event reporting additional description:

Safety analysis set included all participants who received at least 1 dose of eculizumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Eculizumab

Reporting group description:

Participants received eculizumab by IV infusion during the Primary Evaluation Treatment Period (26 weeks) and the Extension Period (up to 208 weeks). Dosing was initiated with a weekly weight-based induction regimen (Induction Phase) and, thereafter, participants were dosed every 2 weeks (Maintenance Phase). Eculizumab was administered at doses of 300, 600, 900, or 1200 mg, based on the participant's current body weight.

Serious adverse events	Eculizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Myasthenia gravis crisis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Suicide attempt			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Peritonsillar abscess			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Eculizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)		
Vascular disorders			
Poor venous access			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	5		
Injection site bruising			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vaccination site pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infusion site extravasation			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Asthenia			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Chronic fatigue syndrome			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gait disturbances			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infusion site discharge			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infusion site swelling			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	8		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed[1]	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Sinus congestion			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	4		
Nasal congestion			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	4		
Dyspnoea			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory disorder			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Sputum discoloured			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Psychiatric disorders			
Behaviour disorder			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Panic attack			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Product issues			
Device malfunction			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Investigations			
Glucose urine present			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Electrocardiogram PR prolongation			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood bicarbonate decreased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Immunisation reaction			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Arthropod bite			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Head injury			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 16		
Dizziness subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Tremor subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Myasthenia gravis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Post-traumatic headache subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Leukopenia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Lymphocytosis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Monocytosis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Neutropenia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Ear and labyrinth disorders			

Cerumen impaction			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Ear pain			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Eye pruritus			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Ocular hyperaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Abdominal distension			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Constipation			

subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	21		
Nausea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	4		
Abdominal discomfort			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	8		
Pruritus			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		

Urticaria			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Asteatosis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hand dermatitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Renal and urinary disorders			
Hypercalciuria			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	4		
Costochondritis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Muscle twitching			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Joint swelling			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 11 (54.55%)		
occurrences (all)	10		
Upper respiratory tract infection			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	4		
COVID-19			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Cellulitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Ketosis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypokalaemia			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Folate deficiency			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vitamin B12 deficiency			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This adverse event only affected female participants.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2018	The purpose of this amendment was: • To enhance clarity of guidance around the supplemental dosage regimen of eculizumab in participants receiving maintenance IVIg. • To enhance clarity of guidance around duration of study drug administration for adult and pediatric participants. • To enhance clarity of guidance around duration of study drug administration in the event of an adverse event (AE) in adult and pediatric participants. • 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 QMG testing form to reflect current version.
16 July 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 EQ-5D-Y assessments in the Schedule of Assessments (SoAs). • To update the vaccination requirement for N. 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 participants weighing under 15 kilograms (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 non-serious) were to be collected from the signing of the informed consent form (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 participants aged ≥18 years receiving maintenance IVIg. • To enhance clarity of guidance around adjustment of immunosuppressant therapies (ISTs) during the study. • To add subcutaneous immunoglobulin (Ig) under disallowed medications. • To remove pulse oximetry from vital sign assessments. • To enhance clarity around the process for reporting serious adverse events (SAEs).
28 September 2020	The purpose of this global amendment was: • To increase the maximum number of participants aged 12 to <18 years who may enter the study on maintenance IVIg from 4 to 6. • To add text regarding the protection of participant 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported