



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Trial to Evaluate the Safety and Efficacy of Eculizumab in Patients With Relapsing Neuromyelitis Optica (NMO)

Summary

EudraCT number	2013-001150-10
Trial protocol	DE IT GB ES AT CZ DK FR HR
Global end of trial date	17 July 2018

Results information

Result version number	v1 (current)
This version publication date	21 June 2019
First version publication date	21 June 2019

Trial information

Trial identification

Sponsor protocol code	ECU-NMO-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01892345
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, MA, United States, 02210
Public contact	European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100615, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100615, clinicaltrials.eu@alexion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
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	17 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objectives of this time-to-event study were to assess the efficacy and safety of eculizumab as compared with placebo in participants with neuromyelitis optica spectrum disorder (NMOSD) who were anti-aquaporin-4 (AQP4) antibody-positive.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Japan: 14
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 13
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Thailand: 7
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United States: 38

Worldwide total number of subjects	143
EEA total number of subjects	27

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)	0
Adults (18-64 years)	134
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Main inclusion criteria for the study were: participants aged ≥ 18 years old with NMO/NMOSD AQP4 antibody-positive, receiving stable maintenance dose of immunosuppressive therapies, historical relapse of at least 2 in last 12 months or 3 in last 24 months with at least 1 in 12 months prior to screening, Expanded Disability Status Scale score ≤ 7 .

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Eculizumab

Arm description:

Induction Period: Participants received eculizumab (900 milligrams [mg]) via intravenous (IV) infusion once a week (every 7 ± 2 days) for 4 weeks followed by eculizumab 1200 mg for the fifth dose (Week 4).

Maintenance Period: Participants received eculizumab (1200 mg) via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose (Week 6) onwards.

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

Dosage and administration details:

Induction Phase: 900 mg IV weekly for 4 weeks, followed by 1200 mg for the fifth dose; Maintenance Phase: 1200 mg IV every 2 weeks.

Arm title	Placebo
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Arm description:

Induction Period: Participants received matching placebo (900 mg) via IV infusion once a week (every 7 ± 2 days) for 4 weeks, followed by matching placebo (1200 mg) for the fifth dose (Week 4).

Maintenance Period: Participants received matching placebo (1200 mg) via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose (Week 6) onwards.

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

Dosage and administration details:

Placebo contains the same buffer components without the active ingredient. Induction Phase: matching placebo (900 mg) IV weekly for 4 weeks, followed by matching placebo (1200 mg) for the fifth dose; Maintenance Phase: matching placebo (1200 mg) IV every 2 weeks.

Number of subjects in period 1	Eculizumab	Placebo
Started	96	47
Received at least 1 dose of study drug	96	47
Completed	80	44
Not completed	16	3
Consent withdrawn by subject	12	1
Adverse event, non-fatal	-	2
Death	1	-
Lost to follow-up	3	-

Baseline characteristics

Reporting groups

Reporting group title	Eculizumab
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Reporting group description:

Induction Period: Participants received eculizumab (900 milligrams [mg]) via intravenous (IV) infusion once a week (every 7 ± 2 days) for 4 weeks followed by eculizumab 1200 mg for the fifth dose (Week 4).

Maintenance Period: Participants received eculizumab (1200 mg) via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose (Week 6) onwards.

Reporting group title	Placebo
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Reporting group description:

Induction Period: Participants received matching placebo (900 mg) via IV infusion once a week (every 7 ± 2 days) for 4 weeks, followed by matching placebo (1200 mg) for the fifth dose (Week 4).

Maintenance Period: Participants received matching placebo (1200 mg) via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose (Week 6) onwards.

Reporting group values	Eculizumab	Placebo	Total
Number of subjects	96	47	143
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	90	44	134
65 years and over	6	3	9
Age continuous			
Age at first dose (years)			
Units: years			
median	43.9	45.0	
standard deviation	± 13.32	± 13.29	-
Gender categorical			
Units: Subjects			
Female	88	42	130
Male	8	5	13
Race			
Units: Subjects			
Asian	37	15	52
Black or African American	9	8	17
White	46	24	70
Unknown or Not Reported	4	0	4
Ethnicity			
Units: Subjects			
Hispanic or Latino	13	3	16
Not Hispanic or Latino	78	41	119

Unknown or Not Reported	5	3	8
Overall Stratification Groupings (4 strata) at Randomization			
EDSS = Expanded Disability Status Scale; IST = Immunosuppressive Therapy High EDSS (≥ 2.5 to ≤ 7): Same IST = High EDSS (≥ 2.5 to ≤ 7) and Continuing on the Same IST(s) since last relapse High EDSS (≥ 2.5 to ≤ 7): Change in IST = High EDSS (≥ 2.5 to ≤ 7) and Changes in IST(s) since last relapse			
Units: Subjects			
Low EDSS (≤ 2.0)	11	5	16
High EDSS (≥ 2.5 to ≤ 7) and Treatment Naive	12	5	17
High EDSS (≥ 2.5 to ≤ 7): Same IST	44	22	66
High EDSS (≥ 2.5 to ≤ 7): Change in IST	29	15	44

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who were randomized to treatment and who received at least 1 dose of study drug.	

Reporting group values	Full Analysis Set (FAS)		
Number of subjects	143		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	134		
65 years and over	9		
Age continuous			
Age at first dose (years)			
Units: years			
median	44.3		
standard deviation	± 13.27		
Gender categorical			
Units: Subjects			
Female	130		
Male	13		
Race			
Units: Subjects			
Asian	52		
Black or African American	17		
White	70		
Unknown or Not Reported	4		
Ethnicity			

Units: Subjects			
Hispanic or Latino	16		
Not Hispanic or Latino	119		
Unknown or Not Reported	8		
Overall Stratification Groupings (4 strata) at Randomization			
EDSS = Expanded Disability Status Scale; IST = Immunosuppressive Therapy High EDSS (≥ 2.5 to ≤ 7): Same IST = High EDSS (≥ 2.5 to ≤ 7) and Continuing on the Same IST(s) since last relapse High EDSS (≥ 2.5 to ≤ 7): Change in IST = High EDSS (≥ 2.5 to ≤ 7) and Changes in IST(s) since last relapse			
Units: Subjects			
Low EDSS (≤ 2.0)	16		
High EDSS (≥ 2.5 to ≤ 7) and Treatment Naive	17		
High EDSS (≥ 2.5 to ≤ 7): Same IST	66		
High EDSS (≥ 2.5 to ≤ 7): Change in IST	44		

End points

End points reporting groups

Reporting group title	Ecuzumab
Reporting group description:	
Induction Period: Participants received ecuzumab (900 milligrams [mg]) via intravenous (IV) infusion once a week (every 7 ± 2 days) for 4 weeks followed by ecuzumab 1200 mg for the fifth dose (Week 4).	
Maintenance Period: Participants received ecuzumab (1200 mg) via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose (Week 6) onwards.	
Reporting group title	Placebo
Reporting group description:	
Induction Period: Participants received matching placebo (900 mg) via IV infusion once a week (every 7 ± 2 days) for 4 weeks, followed by matching placebo (1200 mg) for the fifth dose (Week 4).	
Maintenance Period: Participants received matching placebo (1200 mg) via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose (Week 6) onwards.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who were randomized to treatment and who received at least 1 dose of study drug.	

Primary: Participants With An Adjudicated On-trial Relapse

End point title	Participants With An Adjudicated On-trial Relapse
End point description:	
An On-trial Relapse was defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on neurologic examination that persisted for more than 24 hours as confirmed by the treating physician. An adjudicated On-trial Relapse was defined by the protocol and positively adjudicated by the relapse adjudication committee.	
End point type	Primary
End point timeframe:	
Baseline, Up To 211 Weeks (End of Study)	

End point values	Ecuzumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96 ^[1]	47 ^[2]		
Units: Participants	3	20		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	Analysis of Adjudicated On-trial Relapse
Statistical analysis description:	
HR based on a stratified Cox proportional hazards model. Confidence interval = Wald confidence interval. HR for ecuzumab compared with placebo represented a 94.2% reduction in the risk of relapse, 95% Wald confidence interval (80.3%, 98.3%).	
Comparison groups	Ecuzumab v Placebo

Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	< 0.0001
Method	Stratified Log-Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.197

Notes:

[3] - Treatment Effect

Secondary: Adjudicated On-trial Annualized Relapse Rate (ARR)

End point title	Adjudicated On-trial Annualized Relapse Rate (ARR)
End point description:	
The adjudicated On-trial ARR was computed as the total number of relapses divided by the total number of patient years in the study period. A central independent committee was used to adjudicate all On-trial Relapses as determined by the treating physician. Results reported as adjusted adjudicated On-trial ARR based on a Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to Screening.	
End point type	Secondary
End point timeframe:	
Baseline, Up To 211 Weeks (End of Study)	

End point values	Ecuzumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96 ^[4]	47 ^[5]		
Units: Relapses/years on study				
number (confidence interval 95%)	0.016 (0.005 to 0.050)	0.350 (0.199 to 0.616)		

Notes:

[4] - FAS

[5] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In EDSS At End Of Study

End point title	Change From Baseline In EDSS At End Of Study
End point description:	
Disease-related disability was measured by the EDSS. The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. A decrease in score indicates improvement.	
End point type	Secondary
End point timeframe:	
Baseline, Up To 211 Weeks (End of Study)	

End point values	Ecuzumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96 ^[6]	47 ^[7]		
Units: Units on a Scale				
arithmetic mean (standard deviation)	-0.18 (± 0.814)	0.12 (± 0.945)		

Notes:

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Modified Rankin Scale (mRS) Score At End Of Study

End point title	Change From Baseline In Modified Rankin Scale (mRS) Score At End Of Study
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End point description:

Disease-related disability was measured by the mRS score. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered from a neurological disability. The scale ranges from 0 (no disability) to 6 (death) in whole-point increments. A decrease in score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline, Up To 211 Weeks (End of Study)

End point values	Ecuzumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96 ^[8]	47 ^[9]		
Units: Units on a Scale				
arithmetic mean (standard deviation)	-0.2 (± 0.72)	0.1 (± 0.75)		

Notes:

[8] - FAS

[9] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Hauser Ambulation Index (HAI) Score At End of Study

End point title	Change From Baseline In Hauser Ambulation Index (HAI) Score At End of Study
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End point description:

The HAI evaluates gait and was used to assess the time and effort used by the participant to walk 25 feet (8 meters). The scale ranges from 0 to 9, with 0 being the best score (asymptomatic; fully ambulatory with no assistance) and 9 being the worst (restricted to wheel chair; unable to transfer self

independently). A decrease in score indicates improvement.

End point type	Secondary
End point timeframe:	
Baseline, Up To 211 Weeks (End of Study)	

End point values	Eculizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96 ^[10]	47 ^[11]		
Units: Units on a Scale				
arithmetic mean (standard deviation)	-0.4 (± 1.08)	0.5 (± 1.61)		

Notes:

[10] - FAS

[11] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In European Quality Of Life (EuroQoL) Health 5-Dimension Questionnaire (EQ-5D) Visual Analogue Scale At End Of Study

End point title	Change From Baseline In European Quality Of Life (EuroQoL) Health 5-Dimension Questionnaire (EQ-5D) Visual Analogue Scale At End Of Study
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End point description:

The EuroQoL EQ-5D is a generic, standardized, self-administered instrument that provides a simple, descriptive profile and a single index value for health status. Assessments were made using the EQ-5D Visual Analogue Scale, which captures the self-rating of current health status using a visual "thermometer" with the endpoints of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom. An increase in score indicates improvement.

End point type	Secondary
End point timeframe:	
Baseline, Up To 211 Weeks (End of Study)	

End point values	Eculizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96 ^[12]	47 ^[13]		
Units: Units on a Scale				
arithmetic mean (standard deviation)	5.4 (± 18.53)	0.6 (± 16.39)		

Notes:

[12] - FAS

[13] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In EuroQoL EQ-5D Index Score At End Of Study

End point title	Change From Baseline In EuroQoL EQ-5D Index Score At End
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End point description:

The EuroQoL EQ-5D is a generic, standardized, self-administered instrument that provides a simple, descriptive profile and a single index value for health status. Index scores range from less than 0 to 1, with higher scores representing a better health status.

End point type

Secondary

End point timeframe:

Baseline, Up To 211 Weeks (End of Study)

End point values	Ecuzumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96 ^[14]	47 ^[15]		
Units: Units on a Scale				
arithmetic mean (standard deviation)	0.05 (\pm 0.179)	-0.04 (\pm 0.212)		

Notes:

[14] - FAS

[15] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 to End of Study (211 Weeks)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Eculizumab
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Reporting group description:

Induction Period: Participants received eculizumab (900 mg) via IV infusion once a week (every 7 ± 2 days) for 4 weeks followed by eculizumab 1200 mg for the fifth dose (Week 4).

Maintenance Period: Participants received eculizumab (1200 mg) via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose (Week 6) onwards.

Reporting group title	Placebo
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Reporting group description:

Induction Period: Participants received matching placebo (900 mg) via IV infusion once a week (every 7 ± 2 days) for 4 weeks, followed by matching placebo (1200 mg) for the fifth dose (Week 4).

Maintenance Period: Participants received matching placebo (1200 mg) via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose (Week 6) onwards.

Serious adverse events	Eculizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 96 (31.25%)	26 / 47 (55.32%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior mesenteric artery syndrome			

subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous occlusion			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheterisation venous			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			

subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Contusion			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Myelitis transverse			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuromyelitis optica spectrum disorder			
subjects affected / exposed	7 / 96 (7.29%)	16 / 47 (34.04%)	
occurrences causally related to treatment / all	0 / 7	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctival haemorrhage			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 96 (1.04%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 96 (3.13%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 96 (1.04%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 96 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 96 (1.04%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 96 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 96 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholin's abscess			

subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder empyema			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumococcal infection			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
subjects affected / exposed	1 / 96 (1.04%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 96 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Eculizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 96 (89.58%)	43 / 47 (91.49%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 96 (7.29%)	5 / 47 (10.64%)	
occurrences (all)	16	5	
Pyrexia			
subjects affected / exposed	6 / 96 (6.25%)	4 / 47 (8.51%)	
occurrences (all)	9	5	
Pain			
subjects affected / exposed	4 / 96 (4.17%)	4 / 47 (8.51%)	
occurrences (all)	4	7	
Oedema peripheral			
subjects affected / exposed	4 / 96 (4.17%)	3 / 47 (6.38%)	
occurrences (all)	4	3	
Asthenia			
subjects affected / exposed	5 / 96 (5.21%)	1 / 47 (2.13%)	
occurrences (all)	6	1	
Chest discomfort			
subjects affected / exposed	2 / 96 (2.08%)	3 / 47 (6.38%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 96 (10.42%)	7 / 47 (14.89%)	
occurrences (all)	12	9	
Oropharyngeal pain			
subjects affected / exposed	7 / 96 (7.29%)	2 / 47 (4.26%)	
occurrences (all)	11	3	
Rhinitis allergic			
subjects affected / exposed	3 / 96 (3.13%)	3 / 47 (6.38%)	
occurrences (all)	3	3	
Nasal congestion			

subjects affected / exposed occurrences (all)	2 / 96 (2.08%) 6	3 / 47 (6.38%) 3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 96 (6.25%)	4 / 47 (8.51%)	
occurrences (all)	6	4	
Depression			
subjects affected / exposed	1 / 96 (1.04%)	4 / 47 (8.51%)	
occurrences (all)	1	5	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 96 (1.04%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	9 / 96 (9.38%)	2 / 47 (4.26%)	
occurrences (all)	10	8	
Fall			
subjects affected / exposed	3 / 96 (3.13%)	4 / 47 (8.51%)	
occurrences (all)	4	9	
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 96 (22.92%)	11 / 47 (23.40%)	
occurrences (all)	95	20	
Dizziness			
subjects affected / exposed	14 / 96 (14.58%)	6 / 47 (12.77%)	
occurrences (all)	19	6	
Paraesthesia			
subjects affected / exposed	8 / 96 (8.33%)	3 / 47 (6.38%)	
occurrences (all)	9	4	
Hypoaesthesia			
subjects affected / exposed	2 / 96 (2.08%)	4 / 47 (8.51%)	
occurrences (all)	2	5	
Blood and lymphatic system disorders			
Leukopenia			

subjects affected / exposed	5 / 96 (5.21%)	1 / 47 (2.13%)	
occurrences (all)	8	1	
Lymphopenia			
subjects affected / exposed	5 / 96 (5.21%)	0 / 47 (0.00%)	
occurrences (all)	7	0	
Eye disorders			
Cataract			
subjects affected / exposed	6 / 96 (6.25%)	2 / 47 (4.26%)	
occurrences (all)	8	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	16 / 96 (16.67%)	12 / 47 (25.53%)	
occurrences (all)	29	19	
Diarrhoea			
subjects affected / exposed	15 / 96 (15.63%)	7 / 47 (14.89%)	
occurrences (all)	23	19	
Vomiting			
subjects affected / exposed	9 / 96 (9.38%)	8 / 47 (17.02%)	
occurrences (all)	9	10	
Constipation			
subjects affected / exposed	9 / 96 (9.38%)	3 / 47 (6.38%)	
occurrences (all)	9	3	
Dyspepsia			
subjects affected / exposed	6 / 96 (6.25%)	4 / 47 (8.51%)	
occurrences (all)	31	4	
Abdominal pain upper			
subjects affected / exposed	5 / 96 (5.21%)	3 / 47 (6.38%)	
occurrences (all)	5	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 96 (5.21%)	3 / 47 (6.38%)	
occurrences (all)	5	5	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 96 (4.17%)	4 / 47 (8.51%)	
occurrences (all)	4	4	
Alopecia			

subjects affected / exposed	5 / 96 (5.21%)	2 / 47 (4.26%)	
occurrences (all)	6	2	
Pruritus			
subjects affected / exposed	3 / 96 (3.13%)	4 / 47 (8.51%)	
occurrences (all)	3	8	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	14 / 96 (14.58%)	6 / 47 (12.77%)	
occurrences (all)	16	9	
Pain in extremity			
subjects affected / exposed	10 / 96 (10.42%)	10 / 47 (21.28%)	
occurrences (all)	12	11	
Arthralgia			
subjects affected / exposed	11 / 96 (11.46%)	5 / 47 (10.64%)	
occurrences (all)	12	10	
Myalgia			
subjects affected / exposed	6 / 96 (6.25%)	3 / 47 (6.38%)	
occurrences (all)	8	3	
Muscle spasms			
subjects affected / exposed	5 / 96 (5.21%)	2 / 47 (4.26%)	
occurrences (all)	5	2	
Musculoskeletal pain			
subjects affected / exposed	6 / 96 (6.25%)	0 / 47 (0.00%)	
occurrences (all)	7	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	28 / 96 (29.17%)	6 / 47 (12.77%)	
occurrences (all)	54	10	
Nasopharyngitis			
subjects affected / exposed	20 / 96 (20.83%)	9 / 47 (19.15%)	
occurrences (all)	50	15	
Urinary tract infection			
subjects affected / exposed	11 / 96 (11.46%)	10 / 47 (21.28%)	
occurrences (all)	43	13	
Conjunctivitis			

subjects affected / exposed	9 / 96 (9.38%)	4 / 47 (8.51%)	
occurrences (all)	10	8	
Pharyngitis			
subjects affected / exposed	10 / 96 (10.42%)	3 / 47 (6.38%)	
occurrences (all)	13	3	
Influenza			
subjects affected / exposed	11 / 96 (11.46%)	1 / 47 (2.13%)	
occurrences (all)	18	1	
Bronchitis			
subjects affected / exposed	9 / 96 (9.38%)	2 / 47 (4.26%)	
occurrences (all)	11	2	
Cystitis			
subjects affected / exposed	8 / 96 (8.33%)	1 / 47 (2.13%)	
occurrences (all)	8	1	
Hordeolum			
subjects affected / exposed	7 / 96 (7.29%)	0 / 47 (0.00%)	
occurrences (all)	8	0	
Sinusitis			
subjects affected / exposed	6 / 96 (6.25%)	0 / 47 (0.00%)	
occurrences (all)	8	0	
Pneumonia			
subjects affected / exposed	0 / 96 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 96 (5.21%)	1 / 47 (2.13%)	
occurrences (all)	5	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2013	<p>Assumptions for sample size and event-driven power calculations were updated following further consideration of the Investigator-sponsored study with eculizumab and incorporating new and unpublished information from 2 academic databases.</p> <p>Updated the anticipated sample size based on power calculations requiring 24 relapses in 24 distinct participants.</p> <p>Updated the IST status randomization strata from:</p> <p>a. Treatment naïve participants versus prior IST and are receiving IST at randomization participants versus prior IST and are not receiving IST at randomization participants</p> <p>to</p> <p>b. Treatment naïve participants versus participants continuing on the same IST(s) since last relapse versus participants with changes in IST(s) since last relapse.</p> <p>Expanded on the clinical information to be collected for historical relapses to aid in describing the participants, their disease severity, prior treatments, and more accurate subgroup assignment based on their treatment history.</p> <p>Safety follow-up was extended from 4 weeks to 8 weeks.</p> <p>Updated the inclusion criterion around historical relapses to be less restrictive.</p> <p>Updated the inclusion criterion around concomitant IST use during the study to be less restrictive and better aligned with current clinical practice.</p> <p>Added exclusion criteria for participants receiving high doses of corticosteroid since this may decrease the relapse rate in some participants, confounding the interpretation of study results.</p>

25 February 2015	<p>Changed the inclusion criterion "NMO-IgG seropositive at Screening Visit" to "NMO-IgG seropositive" to allow historically seropositive participants.</p> <p>Allowed qualified non-physician healthcare professionals (for example, nurses) to conduct the EDSS rating with the Sponsor's approval.</p> <p>Removed an interim analysis, in alignment with recommendations from regulatory agencies.</p> <p>Removed text emphasizing reporting the IST use "within 24 months prior to the Screening Visit" to encourage obtaining all available history on IST use for relapse prevention.</p> <p>Clarified that supportive ISTs are for relapse prevention, so as not to be confused with ISTs administered for relapse treatment or other medical reasons.</p> <p>Extended the Screening Period from 1-3 weeks to 1-6 weeks to allow more time for all screening procedures to be completed and for participants to be vaccinated at least 2 weeks prior to study drug administration, as required by the protocol.</p> <p>Provided some flexibility for the supplemental study drug dose administration time from "within 60 minutes" to "preferably within 1-2 hours" after each PE cycle to address operational challenges.</p> <p>Changed the definition of the Per Protocol Set from participants who have "no major protocol deviations or inclusion/exclusion criteria deviations" to "no major protocol deviations or key inclusion/exclusion criteria deviations that might potentially affect efficacy" to prevent the exclusion of participants from the Per Protocol Set with deviations not relevant for assessing the efficacy and safety of eculizumab.</p>
01 July 2016	<p>Established the Relapse Adjudication Committee for adjudication of all On-trial Relapses.</p> <p>Updated the primary end point of the study from "time to first Relapse" to "time to first adjudicated On-trial Relapse".</p> <p>Added a sensitivity analysis of time to first On-trial Relapse using a log-rank test including strata for the randomization stratification variables.</p> <p>The secondary efficacy end point was changed from ARR to adjudicated ARR.</p> <p>Added a sensitivity analysis for ARR using all On-trial Relapses in a Poisson regression analysis with treatment group, stratification variables, and baseline ARR as covariates in the model, and the log of time in the study was used as the offset variable.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

After rigorous review of blinded study data, the Sponsor terminated the study at 23 adjudicated events, not the protocol-specified 24. This was not driven by safety or efficacy concerns, but rather by uncertainty in estimating final event occurrence.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23623397>

<http://www.ncbi.nlm.nih.gov/pubmed/31050279>