Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Eculizumab in Subjects With Refractory Generalized Myasthenia Gravis (gMG)

Summary

EudraCT number	2013-003589-15
Trial protocol	SE IT GB DE ES BE NL DK GR FI HU CZ FR
Global end of trial date	01 June 2016

Results information

Result version number	v1 (current)
This version publication date	24 March 2017
First version publication date	24 March 2017

Trial information

Trial identification

Sponsor protocol code	ECU-MG-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01997229
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals
Sponsor organisation address	100 College Street, New Haven, United States, 06510
Public contact	Alexion Europe SAS, European Clinical Trial Information, +33 1 47 10 06 06, clinicaltrials.eu@alexion.com
Scientific contact	Alexion Europe SAS, European Clinical Trial Information, +33 1 47 10 06 06, 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	01 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 February 2016
Global end of trial reached?	Yes
Global end of trial date	01 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to assess the efficacy of eculizumab as compared with placebo in the treatment of refractory gMG based on the improvement in the Myasthenia Gravis-specific Activities of Daily Living profile (MG-ADL).

Protection of trial subjects:

Not Applicable

Background therapy:

Standard of care MG therapy, including cholinesterase inhibitors and immunosuppressive therapies, could be maintained at a stable dose during the study.

Evidence for comparator:

Matched placebo

Actual start date of recruitment	30 April 2014
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: 44
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Sweden: 1

Worldwide total number of subjects	125
EEA total number of subjects	46

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)	99
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with refractory generalized myasthenia gravis were screened to confirm study eligibility.

Pre-assignment

Screening details:

Prior to randomization, subjects continued on standard of care treatment and were vaccinated against Neisseria meningitidis, if not already vaccinated within the active coverage specified by the vaccine manufacturer or according to current medical/country guidelines. The washout period for IVIg and PE was 4 weeks prior to randomization.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravascular use

Dosage and administration details:

Induction phase: 3 vials of study drug (placebo) weekly for 4 doses (every 7 days ± 2 days) followed by 4 vials of study drug (placebo) 1 week later for the fifth dose (Week 4).
Maintenance phase: 4 vials of study drug (placebo) every 2 weeks (14 days ± 2 days) from the fifth dose onwards (Week 6 through Week 26).

Arm title	Eculizumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravascular use

Dosage and administration details:

Induction phase: 3 vials of study drug (equivalent to 900 mg of eculizumab) weekly for 4 doses (every 7 days ± 2 days) followed by 4 vials of study drug (equivalent to 1200 mg of eculizumab) 1 week later for the fifth dose (Week 4).
Maintenance phase: 4 vials of study drug (equivalent to 1200 mg of eculizumab) every 2 weeks (14 days ± 2 days) from the fifth dose onwards (Week 6 through Week 26).

Number of subjects in period 1	Placebo	Eculizumab
Started	63	62
Completed	61	57
Not completed	2	5
Consent withdrawn by subject	2	1
Adverse event, non-fatal	-	4

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Eculizumab
Reporting group description: -	

Reporting group values	Placebo	Eculizumab	Total
Number of subjects	63	62	125
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	46.9	47.5	
standard deviation	± 17.98	± 15.66	-
Gender categorical Units: Subjects			
Female	41	41	82
Male	22	21	43

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Eculizumab
Reporting group description: -	

Primary: Myasthenia Gravis Activities of Daily Living profile (MG-ADL): Change from Baseline in MG-ADL Total Score at Week 26 by Worst-Rank Analysis of Covariance (ANCOVA)	
End point title	Myasthenia Gravis Activities of Daily Living profile (MG-ADL): Change from Baseline in MG-ADL Total Score at Week 26 by Worst-Rank Analysis of Covariance (ANCOVA)
End point description:	
End point type	Primary
End point timeframe:	
End of study (Week 26)	

End point values	Placebo	Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: Worst-Rank score				
least squares mean (standard error)	68.3 (± 4.49)	56.6 (± 4.53)		

Statistical analyses

Statistical analysis title	MG-ADL Worst-Rank ANCOVA
Comparison groups	Placebo v Eculizumab
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0698
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.33
upper limit	0.96

Adverse events

Adverse events information

Timeframe for reporting adverse events:

26 weeks (Study Period) + 8 weeks (Follow-up Period for subjects who discontinued the Study Period or completed the Study Period but did not enroll in the ECU-MG-302 extension trial).

Adverse event reporting additional description:

Treatment-emergent adverse events were collected at every visit and during follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Eculizumab

Reporting group description: -

Serious adverse events	Placebo	Eculizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 63 (28.57%)	9 / 62 (14.52%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
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			

Intentional overdose			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Myasthenia gravis			
subjects affected / exposed	8 / 63 (12.70%)	5 / 62 (8.06%)	
occurrences causally related to treatment / all	0 / 17	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis crisis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (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	0 / 63 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			

subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (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			
Bacteraemia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 63 (3.17%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Eculizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 63 (84.13%)	52 / 62 (83.87%)	
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	2 / 63 (3.17%)	5 / 62 (8.06%)	
occurrences (all)	2	15	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 63 (7.94%)	5 / 62 (8.06%)	
occurrences (all)	10	5	
Headache			
subjects affected / exposed	12 / 63 (19.05%)	10 / 62 (16.13%)	
occurrences (all)	28	25	
Myasthenia gravis			
subjects affected / exposed	5 / 63 (7.94%)	1 / 62 (1.61%)	
occurrences (all)	6	1	
Paraesthesia			
subjects affected / exposed	4 / 63 (6.35%)	3 / 62 (4.84%)	
occurrences (all)	8	3	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	4 / 63 (6.35%)	1 / 62 (1.61%)	
occurrences (all)	9	2	
Oedema peripheral			
subjects affected / exposed	2 / 63 (3.17%)	4 / 62 (6.45%)	
occurrences (all)	2	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 63 (12.70%)	8 / 62 (12.90%)	
occurrences (all)	8	10	
Nausea			
subjects affected / exposed	9 / 63 (14.29%)	8 / 62 (12.90%)	
occurrences (all)	26	11	
Vomiting			
subjects affected / exposed	5 / 63 (7.94%)	3 / 62 (4.84%)	
occurrences (all)	6	5	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 63 (6.35%)	1 / 62 (1.61%)	
occurrences (all)	9	1	

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	5 / 63 (7.94%) 5	2 / 62 (3.23%) 2	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 6 / 63 (9.52%) 6 2 / 63 (3.17%) 2 2 / 63 (3.17%) 2	 5 / 62 (8.06%) 6 5 / 62 (8.06%) 6 4 / 62 (6.45%) 4	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 10 / 63 (15.87%) 13 0 / 63 (0.00%) 0 10 / 63 (15.87%) 12 5 / 63 (7.94%) 7	 9 / 62 (14.52%) 13 5 / 62 (8.06%) 5 10 / 62 (16.13%) 14 4 / 62 (6.45%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2014	A global amendment included the following significant changes: (1) extended the follow-up period to 8 weeks based on pharmacokinetic characteristics and to align the protocol with other ongoing eculizumab studies that also have an 8-week follow-up period; (2) modified the washout period for intravenous immunoglobulin and plasma exchange from 4 weeks prior to screening to 4 weeks prior to randomization; (3) modified the inclusion criteria to require that patients have an MG-ADL total score of ≥6 at screening and randomization.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported