Clinical trial results:
A multi-center, randomized, double-blind, placebo controlled, parallel group study to preliminarily evaluate the safety, tolerability, pharmacokinetics and efficacy of CFZ533 in patients with moderate to severe myasthenia gravis

Summary

EudraCT number	2015-000097-35
Trial protocol	DE DK
Global end of trial date	19 December 2017

Results information

Result version number	v1 (current)
This version publication date	28 December 2018
First version publication date	28 December 2018

Trial information

Trial identification

Sponsor protocol code	CCFZ533X2204

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	19 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main opbjective for the trial were :
- to evaluate the safety and tolerability of intravenous (IV) CFZ533 as an add-on therapy to standard of care in patients with moderate to severe MG throughout the study,
- and to evaluate the efficacy of IV CFZ533 as an add-on therapy to standard of care in patients with moderate to severe MG

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2015
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	Canada: 4
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Russian Federation: 24
Country: Number of subjects enrolled	Taiwan: 7
Worldwide total number of subjects	44
EEA total number of subjects	9

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)	40
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 44 patients were randomized to receive either IV CFZ533 or IV placebo, of which 34 patients (77%) completed the study.

Pre-assignment

Screening details:

Safety analysis set, and Full analysis: 44 patients (22 treated with CFZ533 and 22 with placebo)
PK analysis set : 20 patients treated with CFZ533
PD analysis set: 42 patients (20 treated with CFZ533 and 20 with placebo)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CFZ533

Arm description:

CFZ533 10 mg/kg

Arm type	Experimental
Investigational medicinal product name	CFZ533
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CFZ533 was provided as lyophilisate in vial (150 mg).

CFZ533 was administered as a 10 mg/kg IV infusion given over 2 hours, every 28 days (q4w), for a treatment duration of 24 weeks (six doses).

Arm title	Placebo

Arm description:

Placebo

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:

The CFZ533 matching placebo was provided as liquid in vials,
and was administered as IV infusion over 2 hours, every 28 days (q4w), for a treatment duration of 24 weeks (six doses).

Number of subjects in period 1	CFZ533	Placebo
Started	22	22
Completed	17	17
Not completed	5	5
Adverse event, serious fatal	-	2
Adverse event, non-fatal	1	-
subject / guardian decision	1	3
Lost to follow-up	1	-
abnormal lab value	2	-

Baseline characteristics

Reporting groups	
Reporting group title	CFZ533
Reporting group description: CFZ533 10 mg/kg	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	CFZ533	Placebo	Total
Number of subjects	22	22	44
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)	20	20	40
From 65-84 years	2	2	4
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	44.7	43.3	
standard deviation	± 13.54	± 13.92	-
Sex: Female, Male Units: Subjects			
Female	12	16	28
Male	10	6	16
Race/Ethnicity, Customized Units: Subjects			
caucasian|	19	16	35
Asian (Chinese)|	3	5	8
other|	0	1	1

End points

End points reporting groups

Reporting group title	CFZ533
Reporting group description: CFZ533 10 mg/kg	
Reporting group title	Placebo
Reporting group description: Placebo	

Primary: Mean change from baseline in the Quantitative Myastenia Gravis (QMG) score at week 25. Posterior Median was used as measure type.

End point title	Mean change from baseline in the Quantitative Myastenia Gravis (QMG) score at week 25. Posterior Median was used as measure type.

End point description:

The QMG score is an established and validated measure of disease severity used in MG trials (Jaretzki et al 2000). This scoring system is based on quantitative testing of sentinel muscle groups by means of a 4 point scale ranging from 0 (no symptoms) to 3 (severe symptoms). The scale measures ocular, bulbar, respiratory, and limb function, grading each finding, and the total score ranges from 0 (no myasthenic findings) to 39 (maximal myasthenic deficits). Its reliability and longitudinal validity have been demonstrated in several studies (Sharshar et al 2000, Bedlack et al 2005).

End point type	Primary
End point timeframe: week 25	

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: score				
median (confidence interval 90%)	-4.07 (-5.67 to -2.47)	-2.93 (-4.53 to -1.33)		

Statistical analyses

Statistical analysis title	Analysis primary objective

Statistical analysis description:

The changes from baseline in QMG scores at Week 25 were analyzed using a Bayesian model that investigated effects for CFZ533 or placebo and baseline QMG score. The prior of the difference in changes from baseline between CFZ533 and placebo at week 25 was used to obtain the posterior estimates. Bayesian posterior probabilities at Week 25 were ≥ 0 or ≥ 3 points. A difference of 3 points on the mean change in QMG score was deemed clinically meaningful.

Comparison groups	Placebo v CFZ533

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Method	bayesian
Parameter estimate	estimate of contrast posterior median
Point estimate	-1.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.41
upper limit	1.14

Secondary: Mean changes from baseline in the Myasthenia Gravis Composite (MGC) score. Posterior Median was used as measure type.

End point title	Mean changes from baseline in the Myasthenia Gravis Composite (MGC) score. Posterior Median was used as measure type.

End point description:

The MGC score is another key efficacy outcome measure. It is reliable and demonstrates concurrent and longitudinal construct validity in the MG practice care setting (Burns et al 2010). The MGC scale covers 10 important functional domains most frequently involved in patients with MG. The proportion of bulbar and respiratory items reflect the clinical importance of these domains in the disease, and are appropriately weighted. The assessment of each of the 10 test items provides immediate insight into the status of that particular functional domain.

End point type	Secondary

End point timeframe:

From baseline to week 49

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: score				
median (confidence interval 90%)	-8.00 (-9.83 to -6.16)	-5.62 (-7.45 to -3.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with improvement or worsening by ≥ 3 points in the QMG score

End point title	Proportion of patients with improvement or worsening by ≥ 3 points in the QMG score

End point description:

End point type	Secondary

End point timeframe:
at week 49

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: participants				
improvement by ≥ 3 points in the QMG score|	10	9		
worsening by ≥ 3 points in the QMG score|	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients intolerant to steroid taper

End point title	Proportion of patients intolerant to steroid taper

End point description:

End point type	Secondary

End point timeframe:
week 49

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[1]	22[2]		
Units: participants	0	0		

Notes:
[1] - this data was not collected
[2] - this data was not collected

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients who discontinued due to inefficacy or worsening

End point title	Proportion of patients who discontinued due to inefficacy or worsening

End point description:

End point type	Secondary

End point timeframe:
week 49

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in the Myasthenia Gravis-specific Activities of Daily Living scale (MG-ADL)

End point title	Mean change from baseline in the Myasthenia Gravis-specific Activities of Daily Living scale (MG-ADL)

End point description:

The MG-ADL is an 8-item survey to assess functional performance of daily activities that are sometimes impaired by MG e.g. talking, breathing, swallowing etc. (Muppidi et al 2011). The higher score on MG-ADL scale (0-24 points) indicates worse functional performance of daily activities.

End point type	Secondary

End point timeframe:

week 25

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	18		
Units: score				
arithmetic mean (standard deviation)	-2.6 (± 2.97)	-1.1 (± 3.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean changes from baseline in the QMG score at week 49

End point title	Mean changes from baseline in the QMG score at week 49

End point description:

End point type	Secondary

End point timeframe:

week 49

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: change from baseline				
arithmetic mean (standard deviation)	-2.9 (± 5.16)	-2.6 (± 4.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in the Myasthenia Gravis Quality of Life (MG QOL-15)

End point title	Mean change from baseline in the Myasthenia Gravis Quality of Life (MG QOL-15)

End point description:

The MG-QOL15 is a 15-item survey, completed by MG patients and it is designed to assess some aspects of quality of life (QoL) related to MG (Burns et al 2011) e.g. assesment of mood, eating, speaking, driving a car etc.. The higher score on MG-QOL15 scale (0-60 points) indicates worse QoL.

End point type	Secondary

End point timeframe:

week 25

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: score				
arithmetic mean (standard deviation)	-9.7 (± 11.0)	-6.7 (± 10.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Free CD40 on B cells

End point title	Free CD40 on B cells

End point description:

CD40 receptor occupancy by CFZ533 in peripheral blood was assessed by flow cytometry analysis, measuring free or total CD40 receptors on whole blood B cells. Free CD40 on CD19-positive B cells, using PE-conjugated CFZ533 whose binding was prevented by bound, unconjugated CFZ533 (drug bound to CD40 on peripheral blood B cells). The more CD40 was occupied by unlabeled CFZ533, the less binding of labeled CFZ533, manifest as a lower mean fluorescence intensity (MFI) of CD40 on B cells. MFI from free CD40 on B cells was converted into Molecules of Equivalent Soluble Fluorochrome (MESF) using PE-MESF beads.

End point type	Secondary

End point timeframe:

week 1, week 25

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[3]	22[4]		
Units: MESF				
arithmetic mean (standard deviation)				
week 1	34242.9 (± 18455.80)	31025.9 (± 16138.97)		
week 25	5259.1 (± 11341.57)	24908.3 (± 5022.03)		

Notes:

[3] - 14 participants at week 1, 8 participants at week 25

[4] - 17 participants at week 1, 12 participants at week 25

Statistical analyses

No statistical analyses for this end point

Secondary: Total soluble CD40 (sCD40) in plasma

End point title	Total soluble CD40 (sCD40) in plasma

End point description:

End point type	Secondary

End point timeframe:

week 1, week 25

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[5]	22[6]		
Units: ng/mL				
arithmetic mean (standard deviation)				
week 1	0.1778 (± 0.13077)	0.1577 (± 0.17243)		
week 25	191.1278 (± 69.67597)	0.1163 (± 0.18298)		

Notes:

[5] - 21 participants at week 1, 18 participants at week 25

[6] - 20 participants at week 1, 19 participants at week 25

Statistical analyses

No statistical analyses for this end point

Secondary: plasma CFZ533 concentration at steady state conditions

End point title	plasma CFZ533 concentration at steady state conditions

End point description:

End point type	Secondary

End point timeframe:

week 17

End point values	CFZ533	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22[7]		
Units: microg/mL				
arithmetic mean (standard deviation)				
week 17 (steady state)	120 (± 4.05)	0 (± 0)		

Notes:

[7] - only patients treated with CFZ533, therefore patients treated with placebo were not analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Placebo IV infusion
Reporting group description:	
Placebo IV infusion	
Reporting group title	CFZ533 10 mg/kg IV infusion
Reporting group description:	
CFZ533 10 mg/kg IV infusion	

Serious adverse events	Placebo IV infusion	CFZ533 10 mg/kg IV infusion	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)	7 / 22 (31.82%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Brachial plexopathy			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis crisis			

subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radial nerve palsy			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis toxic			

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo IV infusion	CFZ533 10 mg/kg IV infusion	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)	20 / 22 (90.91%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Chills			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Discomfort			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Fatigue			

subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	4	
Feeling cold			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Hyperthermia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Infusion site bruising			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Breast pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Cough			

subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Laryngeal inflammation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Sinus disorder			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Nervousness			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Panic attack			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Activated partial thromboplastin time shortened			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Blood bicarbonate decreased			

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Free haemoglobin present			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	
occurrences (all)	3	4	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Prothrombin time prolonged			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Muscle strain			

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Procedural headache			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Von Willebrand's disease			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dementia Alzheimer's type			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	
occurrences (all)	3	3	
Headache			
subjects affected / exposed	3 / 22 (13.64%)	4 / 22 (18.18%)	
occurrences (all)	5	7	
Migraine			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Myasthenia gravis			

subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Nerve compression			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Neuralgia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	2	
Post herpetic neuralgia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Leukocytosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Lymphocytosis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Neutropenia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	1	

Neutrophilia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Dental caries			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Food poisoning			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Gastroduodenitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Gingival bleeding			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 22 (9.09%)	3 / 22 (13.64%)	
occurrences (all)	3	6	
Pancreatitis chronic			

subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	2	
Hyperhidrosis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Arthritis reactive			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	5	0	
Muscular weakness			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	3	
Musculoskeletal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	2	
Neck pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Osteochondrosis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Tendonitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	2	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Bronchitis			

subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Ear infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Herpes virus infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Laryngitis viral			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	3 / 22 (13.64%)	2 / 22 (9.09%)	
occurrences (all)	4	2	
Oral candidiasis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Oral herpes			

subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	4	
Respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	
occurrences (all)	4	5	
Rhinitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Skin candida			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Systemic infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Tooth infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Tracheobronchitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	4 / 22 (18.18%)	1 / 22 (4.55%)	
occurrences (all)	7	1	
Urinary tract infection			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 22 (4.55%) 1	
Viral pharyngitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 22 (4.55%) 1	
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 22 (0.00%) 0	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 22 (4.55%) 1	
Dyslipidaemia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 22 (4.55%) 1	
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 22 (4.55%) 1	
Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 22 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2015	The purpose of this amendment was to incorporate a second screening visit (Visit 2) to allow safety laboratory results to be available prior to randomization at Day 1. Moreover, some inclusion/exclusion criteria were modified, in consultation with the investigators, to simplify recruitment.
29 July 2015	The purpose of this amendment was to incorporate requests following Health Authority and Ethic Committee review. Suggestions following investigators feedback were also implemented. Given the limited clinical safety data available to date, an independent DMC was instituted to routinely monitor the safety data as requested after Health Authority Review. The manual randomization process was replaced by using a validated Interactive response technology system for patient randomization.
19 May 2016	The purpose of this amendment was to make the optional autoantibodies (anti-AChR and anti-MuSK) diagnostic test at screening visit mandatory for all patients as an inclusion criterion to confirm eligibility. This assessment was already foreseen at screening, only in case of absence of AChR or MuSK autoantibodies with a positive medical history of MG. To allow consistency in all patients for AChR or MuSK autoantibodies assessment and a positive diagnosis of MG, the assessment was made mandatory at visit 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported