Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) as a Corticosteroid Sparing Agent in Corticosteroid Dependent Patients with Generalized Myasthenia Gravis

Summary

EudraCT number	2013-005099-17
Trial protocol	LT EE HU CZ DE BE
Global end of trial date	14 February 2019

Results information

Result version number	v1 (current)
This version publication date	28 February 2020
First version publication date	28 February 2020

Trial information

Trial identification

Sponsor protocol code	GTI1306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02473965
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grifols Therapeutics LLC
Sponsor organisation address	Research Triangle Park, North Carolina, United States, 27709
Public contact	Rhonda Griffin, Grifols Therapeutics LLC, rhonda.griffin@grifols.com
Scientific contact	Rhonda Griffin, Grifols Therapetuics LLC, rhonda.griffin@grifols.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	14 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of intravenous (IV) infusions of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) as compared to placebo in reducing the maintenance dosage of corticosteroids (CS) in CS-dependent subjects with myasthenia gravis (MG) when given as an initial loading dose (2 grams per kilogram [2 g/kg]) followed by 12 maintenance doses (1 g/kg) every 3 weeks through Week 36 by assessing the percent of subjects achieving a 50% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1).

Protection of trial subjects:

Standards for Good Clinical Practice were adhered to for all procedures in this clinical study. The investigators ensured the clinical study was conducted in full conformance with appropriate local laws and regulations and the Declaration of Helsinki.

Background therapy:

Subjects were on systemic CS treatment for at least 3 months and on a stable CS dose of ≥15 milligrams/day (mg/day) and ≤60 mg/day (prednisone equivalent) for the month prior to screening. Subjects on alternate day CS dosing were judged to be on a daily dose equivalent to half their alternate day dose.

Evidence for comparator: -

Actual start date of recruitment	04 November 2015
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: 11
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Poland: 16
Worldwide total number of subjects	60
EEA total number of subjects	36

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)	50
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Sixty subjects with a confirmed diagnosis of generalized MG historically meeting the clinical criteria for MG diagnosis Class II, III, IV or V of the Myasthenia Gravis Foundation of America were randomized. The study was conducted in 8 countries from November 2015 to February 2019.

Pre-assignment

Screening details:

Subjects had symptoms at screening controlled by CS, had been dependent on systemic CS for at least the preceding 3 months and who had received a stable dose of CS for at least 1 month immediately prior to the screening visit.

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	Subject, Investigator, Carer, Assessor

Blinding implementation details:

The investigational product (IP) was prepared by the unblinded site pharmacist or designee, and the infusion solution was visually masked to maintain the blind. The volume of placebo was approximate to that required for the appropriate weight-based dose of IGIV-C in order to maintain blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	IGIV-C

Arm description:

IP Run-in Maintenance Phase (Weeks 0-9): Subjects randomized to receive IGIV-C were given a loading dose of 2 g/kg at Baseline/Week 0 (Visit 1) and 2 maintenance doses of 1 g/kg at Weeks 3 and 6 (Visits 2 and 3). The CS dose remained stable in this phase.

CS Tapering/IP Maintenance Phase (Weeks 9-36): Subjects continued to receive maintenance doses (1 g/kg) every third week from Week 9 (Visit 4) up to Week 36 (Visit 13). Prescribed CS tapering began at Week 9 (Visit 4) after the third maintenance dose of IGIV-C was given. The last CS dose reduction was at Week 36 (Visit 13).

Safety/Follow-up Phase: Follow-up visits were at Weeks 39, 42 and 45 (Visits 14, 15 and 16). If considered medically indicated, the investigator could increase the CS dose after the Week 39 (Visit 14) assessments.

Arm type	Experimental
Investigational medicinal product name	IGIV-C
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The loading dose of 2 g/kg was divided over 2 days as standard infusion time, and extensions up to 4 days were allowed for tolerability issues or higher weight. The maintenance doses of 1 g/kg were infused in 1 day as standard, and extension was allowed for divided dosage over 2 days for tolerbility issues or higher weight. The limit for IGIV-C infusion was no more than 80 g/day.

Arm title	Placebo

Arm description:

IP Run-in Maintenance Phase (Weeks 0-9): Subjects randomized to receive placebo were given 3 doses of placebo matching IGIV-C at Baseline/Week 0 (Visit 1) and at Weeks 3 and 6 (Visits 2 and 3). The CS dose remained stable in this phase.

CS Tapering/IP Maintenance Phase (Weeks 9-36): Subjects continued to receive maintenance doses of placebo matching IGIV-C every third week from Week 9 (Visit 4) up to Week 36 (Visit 13). Prescribed CS tapering began at Week 9 (Visit 4) after the third maintenance dose of placebo was given. The last CS dose reduction was at Week 36 (Visit 13).

Safety/Follow-up Phase: Follow-up visits were at Weeks 39, 42 and 45 (Visits 14, 15 and 16). If considered medically indicated the investigator could increase the CS dose after the Week 39 (Visit 14) assessments.

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

Dosage and administration details:

Subjects received 0.9% sodium chloride injection, United States Pharmacopeia or equivalent, visually masked and at a volume approximate to that required for the appropriate weight-based dose of IGIV-C to maintain blinding.

Number of subjects in period 1	IGIV-C	Placebo
Started	30	30
Completed	18	20
Not completed	12	10
Adverse event, serious fatal	1	2
Consent withdrawn by subject	2	3
Physician decision	-	2
MG worsening	4	1
Adverse event, non-fatal	5	2

Baseline characteristics

Reporting groups	
Reporting group title	IGIV-C

Reporting group description:

IP Run-in Maintenance Phase (Weeks 0-9): Subjects randomized to receive IGIV-C were given a loading dose of 2 g/kg at Baseline/Week 0 (Visit 1) and 2 maintenance doses of 1 g/kg at Weeks 3 and 6 (Visits 2 and 3). The CS dose remained stable in this phase.

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Safety/Follow-up Phase: Follow-up visits were at Weeks 39, 42 and 45 (Visits 14, 15 and 16). If considered medically indicated, the investigator could increase the CS dose after the Week 39 (Visit 14) assessments.

Reporting group title	Placebo

Reporting group description:

IP Run-in Maintenance Phase (Weeks 0-9): Subjects randomized to receive placebo were given 3 doses of placebo matching IGIV-C at Baseline/Week 0 (Visit 1) and at Weeks 3 and 6 (Visits 2 and 3). The CS dose remained stable in this phase.

CS Tapering/IP Maintenance Phase (Weeks 9-36): Subjects continued to receive maintenance doses of placebo matching IGIV-C every third week from Week 9 (Visit 4) up to Week 36 (Visit 13). Prescribed CS tapering began at Week 9 (Visit 4) after the third maintenance dose of placebo was given. The last CS dose reduction was at Week 36 (Visit 13).

Safety/Follow-up Phase: Follow-up visits were at Weeks 39, 42 and 45 (Visits 14, 15 and 16). If considered medically indicated the investigator could increase the CS dose after the Week 39 (Visit 14) assessments.

Reporting group values	IGIV-C	Placebo	Total
Number of subjects	30	30	60
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 47.6 ± 16.99	 48.5 ± 14.51	 -
Gender categorical Units: Subjects			
Female	16	18	34
Male	14	12	26
Race (NIH/OMB) Units: Subjects			
White	27	27	54
Black or African American	0	1	1
Asian	3	2	5
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	0	2	2
Not Hispanic or Latino	30	28	58
Baseline Daily Prednisone Equivalent Dose Level Stratification Categories Units: Subjects			
15 mg to 40 mg/day	29	28	57
41 to 60 mg/day	1	2	3
Baseline QMG Total Score			
The Quantitative Myasthenia Gravis (QMG) total score was the sum of the 13 items used to measure spirometry and muscle strength and ranges from 0 to 39 (higher values indicate greater severity of illness). The QMG total scores were used to assess MG worsening.			
Units: units on a scale			
arithmetic mean	12.1	11.2	
standard deviation	± 6.98	± 6.48	-

End points

End points reporting groups

Reporting group title	IGIV-C

Reporting group description:

IP Run-in Maintenance Phase (Weeks 0-9): Subjects randomized to receive IGIV-C were given a loading dose of 2 g/kg at Baseline/Week 0 (Visit 1) and 2 maintenance doses of 1 g/kg at Weeks 3 and 6 (Visits 2 and 3). The CS dose remained stable in this phase.

CS Tapering/IP Maintenance Phase (Weeks 9-36): Subjects continued to receive maintenance doses (1 g/kg) every third week from Week 9 (Visit 4) up to Week 36 (Visit 13). Prescribed CS tapering began at Week 9 (Visit 4) after the third maintenance dose of IGIV-C was given. The last CS dose reduction was at Week 36 (Visit 13).

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Reporting group title	Placebo

Reporting group description:

IP Run-in Maintenance Phase (Weeks 0-9): Subjects randomized to receive placebo were given 3 doses of placebo matching IGIV-C at Baseline/Week 0 (Visit 1) and at Weeks 3 and 6 (Visits 2 and 3). The CS dose remained stable in this phase.

CS Tapering/IP Maintenance Phase (Weeks 9-36): Subjects continued to receive maintenance doses of placebo matching IGIV-C every third week from Week 9 (Visit 4) up to Week 36 (Visit 13). Prescribed CS tapering began at Week 9 (Visit 4) after the third maintenance dose of placebo was given. The last CS dose reduction was at Week 36 (Visit 13).

Safety/Follow-up Phase: Follow-up visits were at Weeks 39, 42 and 45 (Visits 14, 15 and 16). If considered medically indicated the investigator could increase the CS dose after the Week 39 (Visit 14) assessments.

Primary: Percent of Subjects Achieving a 50% or Greater Reduction in CS Dose (Prednisone or Equivalent) from Baseline to Week 39

End point title	Percent of Subjects Achieving a 50% or Greater Reduction in CS Dose (Prednisone or Equivalent) from Baseline to Week 39

End point description:

The average daily CS dose was derived for each subject at each scheduled visit based on the prescribed dose and the time interval taking into account any prescribed dose changes between routinely scheduled visits. Subjects who discontinued the study early with adverse outcomes related to MG were considered as not achieving a 50% or greater reduction. The missing dose reduction at Week 39 was imputed using the worst observation carried forward (WOCF) method. For subjects who did not have CS dose prescribed at Week 39 due to other reasons, the last observation carried forward (LOCF) method was used to impute the prescribed CS dose at Week 39. Baseline was defined as the last non-missing measurement taken prior to first dose of study medication. The percent of subjects achieving ≥50% reduction in CS dose from baseline to Week 39 is presented for each treatment group and for the baseline daily prednisone equivalent dose level stratification categories. mITT = modified intent-to-treat.

End point type	Primary

End point timeframe:

Baseline/Week 0 (Visit 1) and Week 39 (Visit 14).

End point values	IGIV-C	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: Percentage of subjects				
number (not applicable)				
All mITT subjects	60.0	63.3		
15 mg to 40 mg/day (n=29,28)	58.6	60.7		
41 mg to 60 mg/day (n=1,2)	100.0	100.0		

Statistical analyses

Statistical analysis title	Unstratified Analysis Using Fisher's Exact Test

Statistical analysis description:

The Fisher's exact test was used for treatment comparison without adjustment for startified baseline prednisone equivalent dose level due to the small cell size. The odds ratio and confidence intervals are calculated overall (i.e. all mITT subjects).

Comparison groups	IGIV-C v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.868
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	2.787

Secondary: Mean Percent Change in Daily CS Dose (Prednisone or Equivalent) from Baseline to Week 39

End point title	Mean Percent Change in Daily CS Dose (Prednisone or Equivalent) from Baseline to Week 39

End point description:

The average daily CS dose was derived for each subject at each scheduled visit based on the prescribed dose and the time interval taking into account any prescribed dose changes between routinely scheduled visits. For subjects who discontinued the study early with adverse outcomes related to MG, the missing dose reduction at Week 39 was imputed using the WOCF method. For subjects who had missing CS dose reduction at Week 39 due to other reasons, the missing CS dose was imputed using the LOCF method. Baseline was defined as the last non-missing measurement taken prior to first dose of study medication. The least squares (LS) mean percent change from baseline in daily CS dose to Week 39 is presented for each treatment group. Analysis was performed on the mITT population.

End point type	Secondary

End point timeframe:

Baseline/Week 0 (Visit 1) and Week 39 (Visit 14).

End point values	IGIV-C	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: Percent change in daily CS dose				
least squares mean (standard error)	-52.57 (± 8.835)	-54.15 (± 8.835)		

Statistical analyses

Statistical analysis title	IGIV-C versus Placebo

Statistical analysis description:

Treatment comparison of percent change in daily CS dose from baseline to Week 39. The Analysis of Covariance model included the percent change from baseline in daily CS dose as the dependent variable, treatment as a fixed effect and baseline daily CS dose as covariate.

Comparison groups	IGIV-C v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.52
upper limit	26.68
Variability estimate	Standard error of the mean
Dispersion value	12.536

Secondary: Median Time to First Episode of MG Worsening

End point title	Median Time to First Episode of MG Worsening

End point description:

The time to the first episode of MG worsening was defined as the time between baseline and the first instance of QMG total score increase by ≥4 points relative to Baseline/Week 0. The QMG total score is the sum of all 13 items and ranges from 0 to 39. Higher values represent greater severity of illness. If one or more items were missing at a given assessment, the total score was set to missing. The time to MG worsening was calculated based on Kaplan-Meier methodology. Baseline was defined as the last non-missing measurement taken prior to the first dose of study medication. Analysis was performed on the mITT population. '99999' indicates that the data is not available.

End point type	Secondary

End point timeframe:

From Baseline/Week 0 (Visit 1) to Week 39 (Visit 14).

End point values	IGIV-C	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[1]	30[2]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	99999 (33.10 to 99999)	99999 (30.10 to 99999)		

Notes:

[1] - The median and 75th percentile were non-estimable as >50% of subjects did not have MG worsening.
[2] - The median and 75th percentile were non-estimable as >50% of subjects did not have MG worsening.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) were collected from Baseline/Week 0 to Week 39 (approximately 9 months).

Adverse event reporting additional description:

TEAEs are presented for the Safety population which consisted of all randomized subjects who received any amount of study medication. Subjects were classified according to the treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	IGIV-C

Reporting group description:

Investigational Product (IP) Run-in Maintenance Phase (Weeks 0-9): Subjects randomized to receive IGIV-C were given a loading dose of 2 g/kg at Baseline/Week 0 (Visit 1) and 2 maintenance doses of 1 g/kg at Weeks 3 and 6 (Visits 2 and 3). The CS dose remained stable in this phase.

CS Tapering/IP Maintencance Phase (Weeks 9-36): Subjects continued to receive maintenance doses (1 g/kg) every third week from Week 9 (Visit 4) up to Week 36 (Visit 13). Prescribed CS tapering began at Week 9 (Visit 4) after the third maintenance dose of IGIV-C was given. The last CS dose reduction was at Week 36 (Visit 13).

Safety/Follow-up phase: Follow-up visits were at Weeks 39, 42 and 45 (Visits 14, 15 and 16). If considered medically indicated, the investigator could increase the CS dose after the Week 39 (Visit 14) assessments.

Reporting group title	Placebo

Reporting group description:

IP Run-in Maintenance Phase (Weeks 0-9): Subjects randomized to receive placebo were given 3 doses of placebo matching IGIV-C at Baseline/Week 0 (Visit 1) and at Weeks 3 and 6 (Visits 2 and 3). The CS dose remained stable in this phase.

CS Tapering/IP Maintenance Phase (Weeks 9-36): Subjects continued to receive maintenance doses of placebo matching IGIV-C every third week from Week 9 (Visit 4) up to Week 36 (Visit 13). Prescribed CS tapering began at Week 9 (Visit 4) after the third maintenance dose of placebo was given. The last CS dose reduction was at Week 36 (Visit 13).

Safety/Follow-up phase: Follow-up visits were at Weeks 39, 42 and 45 (Visits 14, 15 and 16). If considered medically indicated, the investigator could increase the CS dose after the Week 39 (Visit 14) assessments.

Serious adverse events	IGIV-C	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 30 (13.33%)	6 / 30 (20.00%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Myasthenia gravis			
subjects affected / exposed	4 / 30 (13.33%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myasthenia gravis crisis			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subcutaneous abscess			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
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: 5 %

Non-serious adverse events	IGIV-C	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 30 (70.00%)	24 / 30 (80.00%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	5	0	
Red blood cell count decreased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
White blood cell count decreased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 30 (33.33%)	3 / 30 (10.00%)	
occurrences (all)	15	3	
Myasthenia gravis			

subjects affected / exposed	7 / 30 (23.33%)	2 / 30 (6.67%)	
occurrences (all)	7	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Fatigue			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	2	3	
Non-cardiac chest pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	2 / 30 (6.67%)	3 / 30 (10.00%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 30 (16.67%)	1 / 30 (3.33%)	
occurrences (all)	6	1	
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 30 (10.00%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			

Urticaria			
subjects affected / exposed	3 / 30 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Rash			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 30 (13.33%)	6 / 30 (20.00%)	
occurrences (all)	4	7	
Arthritis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal pain			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	2	
Myalgia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Back pain			
subjects affected / exposed	0 / 30 (0.00%)	5 / 30 (16.67%)	
occurrences (all)	0	6	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 30 (20.00%)	3 / 30 (10.00%)	
occurrences (all)	7	3	
Influenza			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	5 / 30 (16.67%)	
occurrences (all)	2	6	

Pneumonia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Viral infection			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Bronchitis			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2015	- The WHO-5 Well-Being Index was added. - Number of study centers was increased. - Inclusion criteria clarifications included: a previous CS taper attempt must have been completed and the CS dose reduction must have been the greatest feasible to attain the lowest feasible CS dose based on observed MG signs and symptoms; intended subjects participating in the study to provide their own informed consent. - Exclusion criteria were modified to extend the timeframe of subjects receiving thymectomies to 6 months. - Clarification was provided that subjects with evidence of malignancy within the past 5 years (non-melanoma skin cancer, carcinoma in situ of cervix was allowed) or thymoma potentially requiring surgical intervention during the course of the study (intent to perform thymectomy) were to be excluded from study participation. - The Independent Safety Review Committee was added. - Clarifications were provided that diphenhydramine, acetaminophen/ibuprofen, and nonsteroidal anti-inflammatory drugs were allowed during the study as pre-medications for study drug infusions. - Concomitant Medications section was changed so that methotrexate at stable dose for 6 months prior to screening was acceptable. - Clarification was provided that each MG assessment should have been performed by the same clinical staff whenever possible. - Addition of waist circumference as a quantitative measure of centripetal obesity, a Cushingoid body habitus (possibly modifiable with CS dose reduction). - The assessment of 7 sentinel Cushingoid features were added at additional times to allow more frequent measures of corticosteroid manifestations and possible impact of CS dose reduction. - Text was added to describe the approach to missing data, for subjects who discontinued the study early due to other reasons, the LOCF method would be used to compute the missing CS dose and drive the primary efficacy endpoint. - Additional hemolysis assessments added for hemolysis surveillance.
23 December 2016	- Investigator discretion was introduced for final taper step from 5 mg prednisone equivalent daily to 0 mg prednisone equivalent daily as safety measure. - Exclusion criteria were updated to clarify that subjects with any episode of myasthenic crisis or hospitalization for MG exacerbation associated with a previous CS taper attempt and subjects whose only MG treatment was CS alone were not permitted to participate in the study. - Additional safety measures were added for subjects whose CS was tapered to 0 mg prednisone equivalent daily to assure rapid medical evaluation (recommended within 24 hours, allowed up to 48 hours), CS re-initiations and medical intervention. A 4-point QMG increase from Baseline/Week 0 was not required for re-initiating CS. - Clarifications were provided that MG treatment measures for MG crisis or hospitalization for MG exacerbation were always allowed for emergent medical need.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported