Clinical trial results:
A Multi-center, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) in Symptomatic Subjects with Generalized Myasthenia Gravis

Summary

EudraCT number	2014-003997-18
Trial protocol	LT EE HU CZ DE BE
Global end of trial date	26 January 2018

Results information

Result version number	v1 (current)
This version publication date	08 February 2019
First version publication date	08 February 2019

Trial information

Trial identification

Sponsor protocol code	GTI1408

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02473952
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grifols Therapeutics LLC
Sponsor organisation address	79 TW Alexander Drive, Research Triangle Park, North Carolina, United States, NC 27709
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Scientific contact	Rhonda Griffin, Grifols Therapeutics 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	26 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) in subjects with generalized myasthenia gravis (MG) on standard of care treatment at study entry in terms of improvement in MG symptoms as measured by the mean change in Quantitative Myasthenia Gravis (QMG) total score from baseline (Week 0) to Week 24 as compared to placebo.

Protection of trial subjects:

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

Background therapy:

Standard of care treatment for MG included cholinesterase inhibitors, corticosteroid (CS) as an immunosuppressant/immunomodulator alone or in combination with other MG medications, any non-CS immunosuppressant/immunomodulator alone or in combination with other MG medications.

Evidence for comparator: -

Actual start date of recruitment	14 August 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: 15
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Lithuania: 4
Worldwide total number of subjects	62
EEA total number of subjects	39

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)	49
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Sixty two subjects with MG who were symptomatic on standard of care treatment with a QMG total score of at least 10 at screening were enrolled from August 2015 to January 2018 in this multicenter study.

Pre-assignment

Screening details:

Randomization was stratified according to baseline standard of care MG treatment at time of randomization: Cholinesterase inhibitors only; CS alone or with other MG medications and any non-CS immunosuppressant/immunomodulator alone or with other MG medications which may include CS.

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

Blinding implementation details:

To maintain blinding, the unblinded pharmacist or designee prepared all investigational product (IP) infusion bags with no visual differences between IGIV-C and placebo, which included covering the IP infusion with a non-transparent blinding bag cover. Results of the central laboratory analysis of immunoglobulin G (IgG) levels were not shared with the investigator, or other blinded study staff involved with study conduct.

Arms

Are arms mutually exclusive?	Yes
Arm title	IGIV-C

Arm description:

Subjects were randomized to receive IGIV-C. An initial loading dose of 2 grams per kilogram (g/kg) of body weight was administered after completing baseline assessments at the Baseline Visit (Week 0, Visit 1). Seven subsequent maintenance doses of 1 g/kg of body weight were administered every third week from Week 3 (Visit 2) to Week 21 (Visit 8).

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:

IGIV-C was administered as intravenous infusions with a limit of no more than 80 g/day, corresponding to body weight of 80 kg for a 1 g/kg per diem dosage. The loading dose of 2 g/kg was administered as divided doses over 2 consecutive days with an extension of up to 4 days to account for tolerability/weight in subjects weighing >80 kg. Maintenance doses of 1 g/kg were administered in 1 day with extension to 2 consecutive days to account for tolerability/weight in subjects weighing >80 kg.

Arm title	Placebo

Arm description:

Subjects were randomized to receive placebo. An initial loading dose using the same volume as would be required for the IGIV-C loading dose was administered after completing baseline assessments at the Baseline Visit (Week 0, Visit 1). Seven subsequent placebo maintenance doses were matched in volume to the IGIV-C maintenance doses, administered every third week from Week 3 (Visit 2) to Week 21 (Visit 8).

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:

Placebo consisting of sterile 0.9% sodium chloride was administered as intravenous infusion in a volume approximate to that required for the appropriate weight-based dose of IGIV-C.

Number of subjects in period 1	IGIV-C	Placebo
Started	30	32
Completed	28	24
Not completed	2	8
Consent withdrawn by subject	-	6
Adverse event, non-fatal	2	2

Baseline characteristics

Reporting groups	
Reporting group title	IGIV-C
Reporting group description:	
Subjects were randomized to receive IGIV-C. An initial loading dose of 2 grams per kilogram (g/kg) of body weight was administered after completing baseline assessments at the Baseline Visit (Week 0, Visit 1). Seven subsequent maintenance doses of 1 g/kg of body weight were administered every third week from Week 3 (Visit 2) to Week 21 (Visit 8).	
Reporting group title	Placebo
Reporting group description:	
Subjects were randomized to receive placebo. An initial loading dose using the same volume as would be required for the IGIV-C loading dose was administered after completing baseline assessments at the Baseline Visit (Week 0, Visit 1). Seven subsequent placebo maintenance doses were matched in volume to the IGIV-C maintenance doses, administered every third week from Week 3 (Visit 2) to Week 21 (Visit 8).	

Reporting group values	IGIV-C	Placebo	Total
Number of subjects	30	32	62
Age categorical Units: Subjects			
Age continuous Units: Years			
arithmetic mean	54.6	48.0	
standard deviation	± 17.06	± 13.66	-
Gender categorical Units: Subjects			
Female	14	19	33
Male	16	13	29
Standard of Care MG Treatment Regimen at Randomization Units: Subjects			
Only Cholinesterase Inhibitors	8	10	18
CS as Only Immunosuppressant/Immunomodulator	6	4	10
Any Non-CS Immunosuppressant/Immunomodulator	16	18	34

End points

End points reporting groups

Reporting group title	IGIV-C

Reporting group description:

Subjects were randomized to receive IGIV-C. An initial loading dose of 2 grams per kilogram (g/kg) of body weight was administered after completing baseline assessments at the Baseline Visit (Week 0, Visit 1). Seven subsequent maintenance doses of 1 g/kg of body weight were administered every third week from Week 3 (Visit 2) to Week 21 (Visit 8).

Reporting group title	Placebo

Reporting group description:

Subjects were randomized to receive placebo. An initial loading dose using the same volume as would be required for the IGIV-C loading dose was administered after completing baseline assessments at the Baseline Visit (Week 0, Visit 1). Seven subsequent placebo maintenance doses were matched in volume to the IGIV-C maintenance doses, administered every third week from Week 3 (Visit 2) to Week 21 (Visit 8).

Primary: Mean Change in QMG Total Score from Baseline to Week 24

End point title	Mean Change in QMG Total Score from Baseline to Week 24

End point description:

The efficacy of IGIV-C was evaluated in subjects with MG through the assessment of change from baseline (Week 0) to Week 24 in the QMG total score. The QMG consists of 13 test items, each graded according to level of symptoms with none=0, mild=1, moderate=2 or severe=3. The scores for each individual item are added together for the total score, ranging from 0 (least severe symptoms) to 39 (most severe symptoms).
Data is presented for the last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population. Baseline was defined as the last non-missing measurement taken prior to first dose of IP.

End point type	Primary

End point timeframe:

Baseline (Week 0) to Week 24.

End point values	IGIV-C	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Units on a scale				
arithmetic mean (standard deviation)	-4.6 (± 5.11)	-2.7 (± 6.23)		

Statistical analyses

Statistical analysis title	Treatment difference (IGIV-C - Placebo)

Statistical analysis description:

The analysis of covariance (ANCOVA) model included change from baseline in QMG total score as the dependent variable, with treatment and baseline standard of care treatment regimen as fixed factors, and baseline QMG total score as a covariate.

Comparison groups	IGIV-C v Placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.187
Method	ANCOVA
Parameter estimate	Least squares mean treatment difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	1

Secondary: Percentage of Subjects who Experienced a Clinical Improvement Assessed by QMG Total Score from Baseline to Week 24

End point title	Percentage of Subjects who Experienced a Clinical Improvement Assessed by QMG Total Score from Baseline to Week 24

End point description:

The percentage of subjects who experienced a clinical improvement as assessed by change in QMG total score from baseline (Week 0) to Week 24, where clinical improvement was defined as at least a 3-point decrease in QMG total score, is presented.
Data is presented for the LOCF in the mITT population. Baseline was defined as the last non-missing measurement taken prior to first dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) to Week 24.

End point values	IGIV-C	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Percentage of subjects				
number (not applicable)	70.0	59.4		

Statistical analyses

Statistical analysis title	IGIV-C versus Placebo

Statistical analysis description:

The ratio of the proportion of subjects experiencing a clinical improvement in the 2 treatment groups (IGIV-C relative to Placebo) is presented.

Comparison groups	IGIV-C v Placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.442 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.798
upper limit	1.683

Notes:

[1] - The Cochran-Mantel-Haenszel test was adjusted for baseline standard of care treatment regimen.

Secondary: Percentage of Subjects who Experienced a Clinical Improvement Assessed by the MG Composite Scale from Baseline to Week 24

End point title	Percentage of Subjects who Experienced a Clinical Improvement Assessed by the MG Composite Scale from Baseline to Week 24

End point description:

The percentage of subjects who experienced a clinical improvement as assessed by change in MG Composite score from baseline (Week 0) to Week 24, where clinical improvement was defined as at least a 3-point decrease in MG Composite total score, is presented.
The MG Composite scale consists of 10 items, and the total score ranges from 0 to 50, with a higher score indicating more severe symptoms.
Data is presented for the LOCF in the mITT population. Baseline was defined as the last non-missing measurement taken prior to first dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) to Week 24.

End point values	IGIV-C	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Percentage of subjects				
number (not applicable)	60.0	53.1		

Statistical analyses

Statistical analysis title	IGIV-C versus Placebo

Statistical analysis description:

The ratio of the proportion of subjects who experienced a clinical improvement in the 2 treatment groups (IGIV-C relative to Placebo) is presented.

Comparison groups	IGIV-C v Placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.61 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.123
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.728

Notes:

[2] - The Cochran-Mantel-Haenszel test was adjusted for baseline standard of care treatment regimen.

Secondary: Percentage of Subjects who Experienced a Clinical Improvement Assessed by the MG - Activities of Daily Living (MG-ADL) Questionnaire from Baseline to Week 24

End point title	Percentage of Subjects who Experienced a Clinical Improvement Assessed by the MG - Activities of Daily Living (MG-ADL) Questionnaire from Baseline to Week 24

End point description:

The percentage of subjects who experienced a clinical improvement as assessed by change in MG-ADL score from baseline to Week 24, where clinical improvement was defined as at least a 2-point decrease in MG-ADL total score, is presented.
The MG-ADL is an 8-item questionnaire, in which each item is graded from 0 to 3, and the total score ranges from 0 to 24, with a higher score indicating more severe symptoms.
Data is presented for the LOCF in the mITT population. Baseline was defined as the last non-missing measurement taken prior to first dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) to Week 24.

End point values	IGIV-C	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Percentage of subjects				
number (not applicable)	70.0	40.6		

Statistical analyses

Statistical analysis title	IGIV-C versus Placebo

Statistical analysis description:

The ratio of the proportion of subjects who experienced a clinical improvement in the 2 treatment groups (IGIV-C relative to Placebo) is presented.

Comparison groups	IGIV-C v Placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.025 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.701
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.061
upper limit	2.727

Notes:

[3] - The Cochran-Mantel-Haenszel test was adjusted for baseline standard of care treatment regimen.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were collected, defined as adverse events that started on or after the beginning of the first infusion of IP and prior to the final study visit.

Adverse event reporting additional description:

The safety population consisted of all randomized subjects who received any amount of IP, and subjects were classified according to treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects were randomized to receive placebo. An initial loading dose using the same volume as would be required for the IGIV-C loading dose was administered after completing baseline assessments at the Baseline Visit (Week 0, Visit 1). Seven subsequent placebo maintenance doses were matched in volume to the IGIV-C maintenance doses, administered every third week from Week 3 (Visit 2) to Week 21 (Visit 8).

Reporting group title	IGIV-C

Reporting group description:

Subjects were randomized to receive IGIV-C. An initial loading dose of 2 grams per kilogram (g/kg) of body weight was administered after completing baseline assessments at the Baseline Visit (Week 0, Visit 1). Seven subsequent maintenance doses of 1 g/kg of body weight were administered every third week from Week 3 (Visit 2) to Week 21 (Visit 8).

Serious adverse events	Placebo	IGIV-C	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 32 (12.50%)	5 / 30 (16.67%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 32 (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	
Cardiopulmonary failure			
subjects affected / exposed	0 / 32 (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	1 / 32 (3.13%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 32 (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	
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 32 (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 / 32 (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	
Septic shock			
subjects affected / exposed	0 / 32 (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	Placebo	IGIV-C	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 32 (37.50%)	18 / 30 (60.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 32 (6.25%)	3 / 30 (10.00%)	
occurrences (all)	3	5	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 32 (12.50%)	9 / 30 (30.00%)	
occurrences (all)	6	22	
Myasthenia gravis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Dizziness			
subjects affected / exposed	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	3	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	2 / 32 (6.25%)	3 / 30 (10.00%)	
occurrences (all)	2	4	
Nausea			
subjects affected / exposed	1 / 32 (3.13%)	3 / 30 (10.00%)	
occurrences (all)	1	13	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 32 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Catarrh			
subjects affected / exposed	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	3	
Dyspnoea			
subjects affected / exposed	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	3	
Neck pain			
subjects affected / exposed	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Pain in extremity			
subjects affected / exposed	2 / 32 (6.25%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	4 / 32 (12.50%)	3 / 30 (10.00%)	
occurrences (all)	4	3	
Upper respiratory tract infection			
subjects affected / exposed	3 / 32 (9.38%)	0 / 30 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2015	- Inclusion criteria modified including: prednisone requirement changed from 1 to 2 months prior to screening, methotrexate was included to accommodate current clinical practice patterns for MG. - Exclusion criteria modified including: clarification regarding subjects with evidence of malignancy within the past 5 years to be excluded from the study; extension of the timeframe of subjects receiving thymectomies from 3 months to 6 months; extension of timeframe of subjects receiving plasma exchange from 2 to 3 months. - The Independent Safety Review Committee was added. - Clarification provided that diphenhydramine, acetaminophen/ibuprofen, and nonsteroidal anti-inflammatory drugs were allowed as pre-medications. - Additional hemolysis laboratory assessments were added. - Hemolytic adverse reactions were defined as temporally associated with the study drug within 7 days post-infusion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported