



## Clinical trial results:

### A Multicenter, Prospective, Open-Label, Non-Controlled Clinical Trial to Assess the Efficacy and Safety of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) in Patients With Myasthenia Gravis Exacerbations

#### Summary

EudraCT number	2013-005098-28
Trial protocol	CZ HU BE RO PL EE LV
Global end of trial date	17 April 2018

#### Results information

Result version number	v1 (current)
This version publication date	03 April 2019
First version publication date	03 April 2019

#### Trial information

##### Trial identification

Sponsor protocol code	GTI1305
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02413580
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
Public contact	Rhonda Griffin, Grifols Therapeutics LLC, rhonda.griffin@grifols.com
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Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 April 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of an intravenous (IV) infusion of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) (total dose of 2 grams per kilogram [g/kg] administered over 2 consecutive days at a dose of 1 g/kg per day) in subjects with myasthenia gravis (MG) exacerbations (not attributable to an infection or change in medication) by assessing the change in score of MG symptoms as measured by the Quantitative Myasthenia Gravis (QMG) scale from Baseline to Day 14.

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: -

Evidence for comparator: -

Actual start date of recruitment	01 June 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	Argentina: 3
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Latvia: 10
Worldwide total number of subjects	49
EEA total number of subjects	31

Notes:

<b>Subjects enrolled per age group</b>	
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)	42
From 65 to 84 years	7
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Forty-nine subjects with MG exacerbations falling in the class IVb-V of the disease severity staging proposed by the Myasthenia Gravis Foundation of America (MGFA) were enrolled. MG exacerbations were characterized by worsening muscle weakness causing swallowing difficulty, acute respiratory failure or major functional disability.

### Pre-assignment

Screening details:

There was no separate screening visit; screening evaluations were performed at the Baseline Visit (Day 0).

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	All subjects
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Arm description:

Subjects with MG exacerbations not attributable to an infection or change in medication were planned to receive 2 g/kg of IGIV-C on Day 0 (Baseline) and on Day 1 (dosed as 1 g/kg per day), followed by 28 days of post-infusion assessments.

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

Dosage and administration details:

1 g/kg of IGIV-C was administered as IV infusions over 2 consecutive days so that subjects received a total dose of 2 g/kg.

Number of subjects in period 1	All subjects
Started	49
Received IGIV-C on Day 0	49
Received IGIV-C on Day 1	46
Completed	46
Not completed	3
Adverse event, non-fatal	3

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Study
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Reporting group description:

Subjects with MG exacerbations not attributable to an infection or change in medication were planned to receive 2 g/kg of IGIV-C on Day 0 (Baseline) and on Day 1 (dosed as 1 g/kg per day), followed by 28 days of post-infusion assessments.

Reporting group values	Overall Study	Total	
Number of subjects	49	49	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	42	42	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	47.3		
standard deviation	± 15.22	-	
Gender categorical			
Units: Subjects			
Female	34	34	
Male	15	15	
MGFA classification at enrollment			
MGFA class IVb includes symptoms predominantly affecting oropharyngeal, respiratory muscles, or both. There may also be a lesser or equal involvement of limb, axial muscles or both. MGFA class V is defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management.			
Units: Subjects			
Class IVb	49	49	
Class V	0	0	

## End points

### End points reporting groups

Reporting group title	All subjects
Reporting group description: Subjects with MG exacerbations not attributable to an infection or change in medication were planned to receive 2 g/kg of IGIV-C on Day 0 (Baseline) and on Day 1 (dosed as 1 g/kg per day), followed by 28 days of post-infusion assessments.	

### Primary: Mean Change in QMG Scale Score from Baseline (Day 0) to Day 14

End point title	Mean Change in QMG Scale Score from Baseline (Day 0) to Day 14 <sup>[1]</sup>
End point description: The mean change in the QMG score from Baseline to Day 14 in the Evaluable population is presented. The QMG scale consists of 13 test items, each of which was given a score of either 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms) or 3 (severe symptoms). The Evaluable population was defined as all subjects who received the entire dose of investigational product (IP) (2 g/kg over 2 consecutive days) and had valid Baseline and Day 14 QMG score measurements. The change in QMG score from Baseline to Day 14 was analyzed using the paired t-test ( $p < 0.001$ , 95% confidence interval [CI]: -7.957 to -4.787).	
End point type	Primary
End point timeframe: From Baseline (Day 0) to Day 14.	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: As data is presented for a single reporting arm, the analysis of the change from Baseline to Day 14 is reported within the end point description.	

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Score on a Scale				
arithmetic mean (standard deviation)	-6.4 ( $\pm$ 5.15)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Clinical Improvement as Assessed by at Least a 3-Point Decrease in the QMG Scale from Baseline (Day 0) to Day 14

End point title	Percentage of Subjects with Clinical Improvement as Assessed by at Least a 3-Point Decrease in the QMG Scale from Baseline (Day 0) to Day 14
End point description: The percentage of subjects with clinical improvement at Day 14 as assessed by the QMG scale in the Evaluable population is presented. The QMG scale consists of 13 test items, each of which was given a score of either 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms) or 3 (severe symptoms). Subjects with clinical improvement had at least a 3-point decrease from Baseline in QMG score. The Evaluable population was defined as all subjects who received the entire dose of IP (2 g/kg over 2 consecutive days) and had valid Baseline and Day 14 QMG score measurements.	

End point type	Secondary
End point timeframe:	
Baseline (Day 0) to Day 14.	

<b>End point values</b>	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Percentage of subjects				
number (not applicable)	76.7			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Clinical Improvement as Assessed by at Least a 2-Point Decrease in the MG-Activities of Daily Living (MG-ADL) from Baseline (Day 0) to Day 14

End point title	Percentage of Subjects with Clinical Improvement as Assessed by at Least a 2-Point Decrease in the MG-Activities of Daily Living (MG-ADL) from Baseline (Day 0) to Day 14
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End point description:

The percentage of subjects with clinical improvement at Day 14 as assessed by the MG-ADL in the Evaluable population is presented. The MG-ADL is an 8-item, patient-reported questionnaire that is completed to assess the symptoms and activities of MG. Each item is scored from 0 (normal/no symptoms) to 3 (severe symptoms). Clinical improvement was defined as at least a 2-point decrease in the MG-ADL score. The Evaluable population was defined as all subjects who received the entire dose of IP (2 g/kg over 2 consecutive days) and had valid Baseline and Day 14 QMG score measurements.

End point type	Secondary
End point timeframe:	
From Baseline (Day 0) to Day 14.	

<b>End point values</b>	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Percentage of subjects				
number (not applicable)	88.4			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Clinical Improvement as Assessed by at Least a 3-Point Decrease in the MG Composite Scale from Baseline (Day 0) to Day 14

End point title	Percentage of Subjects with Clinical Improvement as Assessed by at Least a 3-Point Decrease in the MG Composite Scale from Baseline (Day 0) to Day 14
End point description:	
The percentage of subjects with clinical improvement at Day 14 as assessed by the MG Composite scale in the Evaluable population is presented. The MG Composite scale is a quantitative measure for determining improvement and worsening for subjects with generalized MG. It consists of 3 ocular, 3 bulbar, 1 respiratory, 1 neck and 2 limb items. The total score ranges from 0 to 50, with a higher score indicating more severe symptoms. Clinical improvement was defined as at least a 3-point decrease in the MG-ADL score. The Evaluable population was defined as all subjects who received the entire dose of IP (2 g/kg over 2 consecutive days) and had valid Baseline and Day 14 QMG score measurements.	
End point type	Secondary
End point timeframe:	
From Baseline (Day 0) to Day 14.	

<b>End point values</b>	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Percentage of subjects				
number (not applicable)	86.0			

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline (Day 0) up to Day 28.

Adverse event reporting additional description:

Adverse events are reported for the Safety population which consisted of all subjects who received any amount of IP.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	All subjects
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Reporting group description:

Subjects with MG exacerbations not attributable to an infection or change in medication were planned to receive 2 g/kg of IGIV-C on Day 0 (Baseline) and on Day 1 (dosed as 1 g/kg per day), followed by 28 days of post-infusion assessments.

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 49 (61.22%)		
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 49 (38.78%)		
occurrences (all)	21		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Pyrexia			

subjects affected / exposed occurrences (all)	8 / 49 (16.33%) 9		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3		
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)  Rash subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4  3 / 49 (6.12%) 4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2014	<ul style="list-style-type: none"><li>-The percentage of subjects with clinical improvement was included and was defined by 3-point decreases in QMG and MG Composite scores and by 2-point decreases in MG-ADL scores.</li><li>-MGFA post-intervention status was removed from Days 7, 21 and 28.</li><li>-The time frame for long-term corticosteroid (CS) treatment for MG was 8 weeks.</li><li>-Inclusion and exclusion criteria were updated with respect to use of contraception to prevent pregnancy during the course of the clinical study.</li><li>-CS treatment newly initiated within 8 weeks and any IPs received within 3 months prior to study participation were prohibited.</li><li>-Instructions for restricted concomitant medications during the clinical study were updated to prohibit cholinesterase inhibitors within 12 hours prior to assessment, and within 24 hours prior to assessment for subjects receiving slow-release cholinesterase inhibitors.</li><li>-Thromboembolic events and hemolysis were added as AEs of special interest, and assessments were added on Days 1, 7 and 21 for additional safety monitoring.</li></ul>
03 September 2015	<ul style="list-style-type: none"><li>- Biomarker testing for peripheral blood mononucleated cells was removed from the clinical study.</li><li>- The central laboratory could have been used if the local laboratory was unable to perform hemolysis laboratory testing.</li><li>- Blood testing included serum or plasma free hemoglobin.</li><li>- Instructions were provided that MG assessments should be performed by the same clinical staff member, if possible.</li><li>- The definition of 'infection' was updated to be defined as 'evident infection' which included, but was not limited to, the presence of at least one of the following diagnostic features: axillary temperature <math>\geq 38^{\circ}\text{C}</math>, positive blood culture of infective microorganism, white blood cell (WBC) count <math>&gt;12 \times 10^9/\text{L}</math> and differential WBC count of <math>&gt;10\%</math> band neutrophils (<math>&gt;1.2 \times 10^9/\text{L}</math>), and pulmonary infiltrate with consolidation on chest X-ray. Alternatively, other signs and symptoms could have been considered for the diagnosis of evident infection according to the investigator's judgement.</li><li>- Use of prophylactic anti-coagulant therapy would not be considered 'exceptional' when administered during hospitalization as prophylactic treatment as part of standard of care for deep vein thrombosis prevention.</li><li>- Prohibited medications were updated to include systemic antibiotic therapy.</li><li>- Physical examinations did not include breast and genitourinary areas.</li><li>- The Baseline Visit was to occur after the subject was stabilized according to the investigator's judgement.</li></ul>
30 March 2016	<ul style="list-style-type: none"><li>- There was no screening visit in this clinical study.</li><li>- Subjects with hemoglobin levels <math>&lt;9</math> grams/deciliter were not eligible for clinical study participation.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

As subjects may have been intubated or otherwise compromised, and the assessments may have been performed in extenuating circumstances, it was necessary to standardize methodology to obtain consistent scoring across study centers.

Notes: