



Clinical trial results:

A Multi-Center, Open-Label, Single-Arm Trial to Evaluate Efficacy, Pharmacokinetics, and Safety and Tolerability of IGSC 20% in Subjects with Primary Immunodeficiency

Summary

EudraCT number	2015-003290-15
Trial protocol	GB CZ ES DE PL HU FR
Global end of trial date	15 May 2019

Results information

Result version number	v1 (current)
This version publication date	13 March 2020
First version publication date	13 March 2020

Trial information

Trial identification

Sponsor protocol code	GTI1503
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02806986
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 Therapeutics LLC, rhonda.griffin@grifols.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001853-PIP01-15
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	15 May 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether weekly administered Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) over a one year period achieved less than 1 serious bacterial infection (SBI) per subject per year in primary immunodeficiency (PI) subjects.

Protection of trial subjects:

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

Background therapy:

Subjects must have been on immunoglobulin G (IgG) replacement therapy prior to enrolling in the study and continued to receive the same therapy during the Screening/Previous Regimen Phase. The previous regimen could be either intravenous immune globulin (IVIG) or subcutaneous immune globulin (SCIG).

Evidence for comparator: -

Actual start date of recruitment	29 June 2016
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	Australia: 6
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	61
EEA total number of subjects	55

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	18
Adolescents (12-17 years)	13
Adults (18-64 years)	27
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible participants for this study included male or female subjects who were 2 to 75 years of age and had a diagnosis of PI requiring IgG replacement treatment. A total of 61 subjects entered Treatment Stage 1 and received treatment with IGSC 20%. The study was conducted in 8 countries from June 2016 to May 2019.

Pre-assignment

Screening details:

Subjects had no SBI within last 3 months prior to Screening and were on IgG replacement therapy (stable regimen via intravenous [IV] or subcutaneous [SC] infusion) for ≥ 3 consecutive months prior to Screening. Subjects receiving IVIG prior to study entry must have received a dosage of ≥ 200 milligram/kilogram (mg/kg) per infusion.

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	IGSC 20%
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Arm description:

Treatment Stage 1: Subjects received 13 IGSC 20% infusions at weekly intervals from Baseline (Week 1) up to Week 13. Subjects were infused with IGSC 20% at a 1:1 dose-equivalent regimen from their previous regimen (or a minimum IGSC 20% dose of 100 mg/kg/week if the derived 1:1 dose from the previous regimen was lower). Dose adjustments were permitted in this phase per the study protocol and the Investigator's discretion.

Treatment Stage 2: Subjects received 39 IGSC 20% infusions at weekly intervals from Week 14 up to Week 52. The IGSC 20% dose (mg/kg) remained constant with no dose adjustment permitted in this phase, unless it was absolutely medically necessary to change the dose, and such change required prior consultation with the Sponsor Medical Monitor.

A final follow-up visit occurred at Week 53.

Arm type	Experimental
Investigational medicinal product name	IGSC 20%
Investigational medicinal product code	GRF6017
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

IGSC 20% is a sterile liquid formulation of immunoglobulin purified from human plasma. IGSC 20% was supplied in a 20 or 50 milliliter (mL) vial size containing a 20% solution of immunoglobulin (i.e. a concentration of 20 grams/100 mL, with a nominal 4 or 10 grams immunoglobulin per vial). Subjects received a total of 52 weekly SC infusions of IGSC 20% (13 weekly SC infusions in Treatment Stage 1 and 39 weekly SC infusions in Treatment Stage 2).

Number of subjects in period 1	IGSC 20%
Started	61
Entered Treatment Stage 1	61
Entered Treatment Stage 2	60
Completed	55
Not completed	6
Consent withdrawn by subject	2
Adverse event, non-fatal	4

Baseline characteristics

Reporting groups

Reporting group title	IGSC 20%
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Reporting group description:

Treatment Stage 1: Subjects received 13 IGSC 20% infusions at weekly intervals from Baseline (Week 1) up to Week 13. Subjects were infused with IGSC 20% at a 1:1 dose-equivalent regimen from their previous regimen (or a minimum IGSC 20% dose of 100 mg/kg/week if the derived 1:1 dose from the previous regimen was lower). Dose adjustments were permitted in this phase per the study protocol and the Investigator's discretion.

Treatment Stage 2: Subjects received 39 IGSC 20% infusions at weekly intervals from Week 14 up to Week 52. The IGSC 20% dose (mg/kg) remained constant with no dose adjustment permitted in this phase, unless it was absolutely medically necessary to change the dose, and such change required prior consultation with the Sponsor Medical Monitor.

A final follow-up visit occurred at Week 53.

Reporting group values	IGSC 20%	Total	
Number of subjects	61	61	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	27.3		
standard deviation	± 19.97	-	
Gender categorical			
Units: Subjects			
Female	19	19	
Male	42	42	
Race			
Units: Subjects			
White	57	57	
American Indian or Alaska Native	2	2	
Unknown	2	2	
Ethnicity			
Units: Subjects			
Hispanic or Latino	10	10	
Not Hispanic or Latino	49	49	
Unknown or Not Reported	2	2	
Subject Entry Status			
Units: Subjects			
Subject entered on IVIG	40	40	
Subject entered on SCIG	21	21	

End points

End points reporting groups

Reporting group title	IGSC 20%
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Reporting group description:

Treatment Stage 1: Subjects received 13 IGSC 20% infusions at weekly intervals from Baseline (Week 1) up to Week 13. Subjects were infused with IGSC 20% at a 1:1 dose-equivalent regimen from their previous regimen (or a minimum IGSC 20% dose of 100 mg/kg/week if the derived 1:1 dose from the previous regimen was lower). Dose adjustments were permitted in this phase per the study protocol and the Investigator's discretion.

Treatment Stage 2: Subjects received 39 IGSC 20% infusions at weekly intervals from Week 14 up to Week 52. The IGSC 20% dose (mg/kg) remained constant with no dose adjustment permitted in this phase, unless it was absolutely medically necessary to change the dose, and such change required prior consultation with the Sponsor Medical Monitor.

A final follow-up visit occurred at Week 53.

Subject analysis set title	IGSC 20% Treatment Stage 1
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received 13 IGSC 20% infusions at weekly intervals from Baseline (Week 1) up to Week 13.

Subject analysis set title	IGSC 20% Treatment Stage 2
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received 39 IGSC 20% infusions at weekly intervals from Week 14 up to Week 52.

Subject analysis set title	IGSC 20% Overall
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received a total of 52 IGSC 20% infusions at weekly intervals from Baseline (Week 1) up to Week 52.

Subject analysis set title	Previous Regimen
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects were required to attend the clinic for infusion with their previous ongoing ("previous regimen") IVIG/SCIG regimen (pIV/pSC) to obtain 2 trough IgG levels (obtained prior to each pIV/pSC infusion) on each subject's "previous regimen". Trough levels for total IgG determined during the Previous Regimen Phase were used to confirm final eligibility for subjects entering the study to receive treatment with IGSC 20% (must be ≥ 500 milligrams per deciliter [mg/dL]).

Subject analysis set title	Recommended Standard Historical Control Rate
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subject analysis included to represent the recommended standard historical control rate of 1 SBI per person per year. This was used as part of the statistical analysis for comparison with rate of SBI events per subject per year during IGSC 20% treatment.

Primary: Rate of SBIs Per Subject Per Year

End point title	Rate of SBIs Per Subject Per Year
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End point description:

The rate of SBI events per subject per year during IGSC 20% treatment was calculated as the total number of SBI events divided by the total duration of exposure in years across all subjects. The 2-sided 98% confidence interval (CI) was determined from a generalized linear model for Poisson regression for the log-transformed number of events with log-transformed duration of exposure in years as an offset variable. Analysis was performed on the Efficacy Evaluable population which included all subjects who received at least 1 dose of IGSC 20%. Note: 999999 (or any variant thereof) indicates that a value could not be calculated.

End point type	Primary
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End point timeframe:

Baseline (Week 1) up to Final Visit (Week 53)

End point values	IGSC 20% Treatment Stage 1	IGSC 20% Treatment Stage 2	IGSC 20% Overall	Recommended Standard Historical Control Rate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	60	61	1 ^[1]
Units: Rate of events per subject per year				
number (confidence interval 98%)	0.000 (-999999 to 999999)	0.023 (0.008 to 0.049)	0.017 (0.006 to 0.036)	999999 (999999 to 999999)

Notes:

[1] - Subject analysis set included only to permit selection as a comparison arm for statistical analysis.

Statistical analyses

Statistical analysis title	IGSC 20% Overall vs Recommended Standard SBI Rate
Statistical analysis description:	
The generalized linear model for Poisson regression with log link was used to estimate SBI rate and its 1-sided 99% upper confidence limit (CL), then compared with the recommended standard control rate of 1 SBI per person per year. Person-year during IGSC 20% treatment was calculated for each subject as (duration of exposure in days/365.25), and natural log-transformed person-year was used in the model as an offset variable. No covariates but the intercept term were included in the model.	
Comparison groups	IGSC 20% Overall v Recommended Standard Historical Control Rate
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other ^[2]
Parameter estimate	Generalized linear model
Point estimate	0.017
Confidence interval	
level	Other: 99 %
sides	1-sided
upper limit	0.036

Notes:

[2] - If the 1-sided 99% upper CL was <1, the null hypothesis that the SBI rate per person per year was ≥ 1 would be rejected at the 1-sided $\alpha = 0.01$ level.

The given number for 'Number of subjects included in analysis' is automatically calculated and states 62. This is incorrect and the number included in the analysis = 61 subjects.

Secondary: Mean Trough Total IgG Concentration

End point title	Mean Trough Total IgG Concentration
End point description:	
Mean trough total IgG concentration during the Previous Regimen Phase was calculated as the average of the trough concentrations at the pIV#1 and pIV#2 visits for subjects entering the study on a previous IVIG regimen, or at the pSC#1 and Baseline/SC#1 visits for subjects entering the study on a previous SCIG regimen. Mean trough total IgG concentration during the IGSC 20% phase was calculated as the average of all steady state trough concentrations measured during the IGSC 20% Treatment Stage 2 at the visits corresponding to Weeks 17, 18, 20, 24, 28, 32, 36, 40, 44, 48, 52 and 53. Analysis was performed on the IgG population which consisted of all subjects who received any amount of IGSC 20% and had total IgG concentration data to facilitate the comparison of mean trough IgG concentration during the IGSC 20% phase versus the pre-treatment phase.	
End point type	Secondary

End point timeframe:

Previous Regimen Phase: 2 timepoints pre-dose of pIV or pSC between Screening and Baseline (up to 8 weeks).

IGSC 20% Phase: Pre-dose of IGSC 20% at Baseline (Week 1), Weeks 2, 5, 9, 13, 17, 18, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at Week 53.

End point values	IGSC 20% Overall	Previous Regimen		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	59		
Units: mg/dL				
arithmetic mean (standard deviation)	947.64 (± 150.262)	891.37 (± 165.943)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Infection of Any Kind Per Subject Per Year

End point title	Rate of Infection of Any Kind Per Subject Per Year
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End point description:

The total number of infections of any kind (serious/non-serious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the investigator were evaluated. The rate of infection events per subject per year during IGSC 20% treatment was calculated as the total number of infection events divided by the total duration of exposure in years across all subjects. The 2-sided 95% CI was determined from a generalized linear model for Poisson regression for the log-transformed number of events with log-transformed duration of exposure in years as an offset variable. Analysis was performed on the Efficacy Evaluable population which included all subjects who received at least 1 dose of IGSC 20%.

End point type	Secondary
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End point timeframe:

Baseline (Week 1) up to Final Visit (Week 53)

End point values	IGSC 20% Treatment Stage 1	IGSC 20% Treatment Stage 2	IGSC 20% Overall	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed				
Units: Rate of events per subject per year				
number (confidence interval 95%)	2.524 (1.720 to 3.547)	2.353 (1.736 to 3.102)	2.397 (1.824 to 3.079)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Days on Antibiotics Per Subject Per Year

End point title	Rate of Days on Antibiotics Per Subject Per Year
End point description: The rate of days on antibiotics per subject per year during IGSC 20% treatment was calculated as the total number of days on antibiotic divided by the total duration of exposure in years across all subjects. The 2-sided 95% CI was determined from a generalized linear model for Poisson regression for the log-transformed number of days with log-transformed duration of exposure in years as an offset variable. Analysis was performed on the Efficacy Evaluable population which included all subjects who received at least 1 dose of IGSC 20%.	
End point type	Secondary
End point timeframe: Baseline (Week 1) up to Final Visit (Week 53)	

End point values	IGSC 20% Treatment Stage 1	IGSC 20% Treatment Stage 2	IGSC 20% Overall	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61	60	61	
Units: Rate of days per subject per year				
number (confidence interval 95%)				
Prophylactic Antibiotics	43.240 (24.786 to 69.152)	44.846 (26.197 to 70.755)	44.432 (26.351 to 69.339)	
Therapeutic Antibiotics	13.085 (7.777 to 20.387)	7.451 (4.843 to 10.861)	8.904 (5.949 to 12.705)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Hospitalization Due to Infection Per Subject Per Year

End point title	Rate of Hospitalization Due to Infection Per Subject Per Year
End point description: The rate of hospitalization due to infection events per subject per year during IGSC 20% treatment was calculated as the total number of hospitalization due to infection events divided by the total duration of exposure in years across all subjects. The 2-sided 95% CI was determined from a generalized linear model for Poisson regression for the log-transformed number of events with log-transformed duration of exposure in years as an offset variable. Analysis was performed on the Efficacy Evaluable population which included all subjects who received at least 1 dose of IGSC 20%. Note: 999999 (or any variant thereof) indicates that a value could not be calculated.	
End point type	Secondary
End point timeframe: Baseline (Week 1) up to Final Visit (Week 53)	

End point values	IGSC 20% Treatment Stage 1	IGSC 20% Treatment Stage 2	IGSC 20% Overall	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61	60	61	
Units: Rate of events per subject per year				
number (confidence interval 95%)	0.000 (-999999 to 999999)	0.023 (0.010 to 0.044)	0.017 (0.008 to 0.033)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Days of Work/School/Daily Activities Missed Per Subject Year Due to Infections and Related Treatment

End point title	Rate of Days of Work/School/Daily Activities Missed Per Subject Year Due to Infections and Related Treatment
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End point description:

The rate of days of work, school or daily activities missed per subject per year during IGSC 20% treatment was calculated as the total number of days of work/school/daily activities missed divided by the total duration of exposure in years across all subjects. The 2-sided 95% CI was determined from a generalized linear model for Poisson regression for the log-transformed number of days with log-transformed duration of exposure in years as an offset variable. Analysis was performed on the Efficacy Evaluable population which included all subjects who received at least 1 dose of IGSC 20%.

End point type	Secondary
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End point timeframe:

Baseline (Week 1) up to Final Visit (Week 53)

End point values	IGSC 20% Treatment Stage 1	IGSC 20% Treatment Stage 2	IGSC 20% Overall	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61	60	61	
Units: Rate of days missed per person per year				
number (confidence interval 95%)	4.118 (2.270 to 6.769)	5.283 (3.192 to 8.132)	4.983 (3.064 to 7.572)	

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 the beginning of treatment administration with IGSC 20% (Baseline/Week 1) until the Final Visit (Week 53). Up to 1 year overall.

Adverse event reporting additional description:

TEAEs are presented for the Safety population which included all subjects who received any amount of IGSC 20%.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	IGSC 20% Treatment Stage 1
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Reporting group description:

Subjects received 13 IGSC 20% infusions at weekly intervals from Baseline (Week 1) up to Week 13.

Reporting group title	IGSC 20% Treatment Stage 2
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Reporting group description:

Subjects received 39 IGSC 20% infusions at weekly intervals from Week 14 up to Week 52.

Reporting group title	IGSC 20% Overall
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Reporting group description:

Subjects received a total of 52 IGSC 20% infusions at weekly intervals from Baseline (Week 1) up to Week 52.

Serious adverse events	IGSC 20% Treatment Stage 1	IGSC 20% Treatment Stage 2	IGSC 20% Overall
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 61 (3.28%)	5 / 60 (8.33%)	7 / 61 (11.48%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Medical device site joint pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	IGSC 20% Treatment Stage 1	IGSC 20% Treatment Stage 2	IGSC 20% Overall
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 61 (54.10%)	44 / 60 (73.33%)	49 / 61 (80.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 61 (6.56%)	5 / 60 (8.33%)	7 / 61 (11.48%)
occurrences (all)	6	15	21
General disorders and administration site conditions			

Infusion site erythema subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 16	4 / 60 (6.67%) 10	10 / 61 (16.39%) 26
Infusion site pruritus subjects affected / exposed occurrences (all)	7 / 61 (11.48%) 17	2 / 60 (3.33%) 2	8 / 61 (13.11%) 19
Pyrexia subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2	5 / 60 (8.33%) 5	7 / 61 (11.48%) 7
Infusion site pain subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3	2 / 60 (3.33%) 2	5 / 61 (8.20%) 5
Infusion site swelling subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3	2 / 60 (3.33%) 8	4 / 61 (6.56%) 11
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 5	2 / 60 (3.33%) 2	6 / 61 (9.84%) 7
Vomiting subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	4 / 60 (6.67%) 6	5 / 61 (8.20%) 7
Nausea subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3	2 / 60 (3.33%) 3	4 / 61 (6.56%) 6
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4	5 / 60 (8.33%) 6	9 / 61 (14.75%) 10
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3	3 / 60 (5.00%) 3	5 / 61 (8.20%) 6
Back pain subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	4 / 60 (6.67%) 5	4 / 61 (6.56%) 5

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 61 (11.48%) 8	7 / 60 (11.67%) 15	12 / 61 (19.67%) 23
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 6	7 / 60 (11.67%) 11	9 / 61 (14.75%) 17
Bronchitis subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	8 / 60 (13.33%) 8	8 / 61 (13.11%) 9
Rhinitis subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3	6 / 60 (10.00%) 7	7 / 61 (11.48%) 10
Sinusitis subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3	6 / 60 (10.00%) 7	7 / 61 (11.48%) 10
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	6 / 60 (10.00%) 6	6 / 61 (9.84%) 6
Lower respiratory tract infection subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4	1 / 60 (1.67%) 2	5 / 61 (8.20%) 6
Influenza subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	3 / 60 (5.00%) 3	4 / 61 (6.56%) 4
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2	1 / 60 (1.67%) 1	3 / 61 (4.92%) 3
Viral infection subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	3 / 60 (5.00%) 3	4 / 61 (6.56%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2015	<p>Amendment 1 provided a number of clarifications to the original protocol:</p> <ul style="list-style-type: none">• Re-designation of other efficacy variables to secondary efficacy variables.• Proteinuria eligibility range was changed to a single value.• Clarification on handling study drug added, recording concomitant medications, to collect only relevant medication history.• Corrections made to subject numbering and administrative updates.• Updates added to clarify urine pregnancy test will be performed at the investigative sites.• Provided procedures for pregnancy reporting and follow-up.
22 July 2016	<p>Amendment 2 provided a number of clarifications to the original protocol:</p> <ul style="list-style-type: none">• Edited text to keep text consistent with European Medicines Agency guideline wording.• Increased criterion window to allow for varying institutional standards.• Revised visit day when recording of diary data begins.• Clarification of blood draw occurring at the Baseline visit does not apply to the pSC#2 trough as results are reported after first investigational product dose.• Added explanation of intent of criterion "The subject has known Selective Immunoglobulin A (IgA) Deficiency (with or without antibodies to IgA)."• Revised to exclude other IgG products as it is unnecessary to wait 3 months prior to screening a subject if they have received another investigational IgG product.• Revision to define a minimum time frame and human immunodeficiency virus screening results based on updated information from the Central Lab results timing.• Clarification of delegated medical monitor role.• "SC" added as it was intended only to be applicable to the investigational product Treatment Phase.• Expansion of visit window added for subject scheduling accommodation.• Expanded adverse event reporting criterion to include potential systemic infusion reactions.• Removed X-ray requirement during Screening for pediatric subjects to limit radiation exposure and comply with local requirements for adult subjects.• Moved initial use of the SC infusion diary from Screening to Baseline visit.• Removed requirement to repeat Screening safety labs as Screening/Previous Regimen Phase window is limited to 8 weeks and such lab parameters are not anticipated to significantly change in this timeframe for the targeted study population.• Revised for clarification on timing of withdrawal due to pregnancy.• Revisions made for internal consistency.• Removed IgG row to avoid an additional blood draw for certain subjects.

21 March 2017	<p>Amendment 3 provided a number of clarifications to the original protocol:</p> <ul style="list-style-type: none"> • Added requirement of assent as both consent and assent are required for inclusion. • Removed weight measurement at every clinic visit as it was not accurate. • The restriction to local infusion site reaction (ISRs) was removed to allow for the collection of all ISRs. • Added additional vial size of 20 mL that contains 4 grams of immune globulin. • Infusion rates were revised to reflect recently published data supporting the safety of higher infusion rates. • Clarification that the delegated medical monitor role may be consulted for such cases. • Deleted beginning time period of 4 weeks for clarity due to variable dosing intervals. • Added timing for consistency within the protocol. • Heading was revised as Visit #2 only applies to pIV dosing. • Expanded IgG trough sample collection window to accommodate subject visit logistics across sites • Added criterion for removal of subjects who develop an SBI prior to first dose of IGSC 20%.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported