Clinical trial results:
A randomised, cross-over study to compare quality of life and satisfaction in primary immunodeficient patients treated with subcutaneous injections of Gammanorm® 165 mg/mL administered with two different delivery devices: injections using pump or rapid push.

Summary

EudraCT number	2014-003746-27
Trial protocol	DE GB
Global end of trial date	11 December 2017
Results information	
Result version number	v1 (current)
This version publication date	16 February 2019
First version publication date	16 February 2019

Trial information

Trial identification	
Sponsor protocol code	GAN-06
Additional study identifiers	
ISRCTN number	ISRCTN55938644
ClinicalTrials.gov id (NCT number)	NCT02503293
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00008784

Notes:

Sponsors	
Sponsor organisation name	Octapharma Pharmazeutika Produktionsges.m.b.H.
Sponsor organisation address	Oberlaaer Strasse 235, Vienna, Austria, 1100
Public contact	Clinical Research and Development, Octapharma Pharmazeutika Produktionsges.m.b.H., tatiana.lavrova@octapharma.com
Scientific contact	Clinical Research and Development, Octapharma Pharmazeutika Produktionsges.m.b.H., tatiana.lavrova@octapharma.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	27 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare satisfaction (LQI questionnaire, factor I: treatment interference) in PID patients receiving subcutaneous injections of Gammanorm 165 mg/mL by delivery device used.

Protection of trial subjects:

This trial was conducted in accordance to the principles of GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki.
Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and risk factors associated with the investigational medicinal product. Throughout the study safety was assessed, such as occurrence of AEs and safety labs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 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 Kingdom: 13
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Australia: 5
Worldwide total number of subjects	30
EEA total number of subjects	25

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)	27
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male or female patients suffering from PID and having received subcutaneous injections of immunoglobulin at home using an automatic pump or syringe for at least 1 month at the time of inclusion were eligible for study inclusion.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Gammanorm 165 mg/mL

Arm description:

Each patient received Gammanorm using each of the two studied delivery devices according to the sequence randomly assigned based on a cross-over design in a 1:1 ratio to one of two following sequences: Pump and then syringe, or syringe and then pump.

Arm type	Experimental
Investigational medicinal product name	Gammanorm 165 mg/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

The usual dose was 0.6 mL (100 mg) of Gammanorm 165 mg/mL per kg of body weight per week, which could be administered at several infusion sites.
Pump: Initial recommended infusion rate was 15 mL per hour per site. For subsequent infusions, the flow rate could be gradually increased at a rate of 1-2 mL/hour/site to 25 mL/hour/site, as tolerated. The maximum flow rate administered, if tolerated, could have been 100 mL/hour at all sites.
Syringe: The usual dose was 0.6 mL (100 mg) of Gammanorm 165 mg/mL per kg of body weight/ week. The weekly dose could have been divided into three injections administered every other day. Maximum infusion rate was set at approximately 1 2 mL/minute. The maximum volume to be infused per injection site was not to exceed 25 mL.
If, in general, higher infusion rates and volumes were determined by the routine practice of the site, then higher infusion volumes and higher infusion rates could be administered, if well tolerated by the patient.

Number of subjects in period 1	Gammanorm 165 mg/mL
Started	30
Completed	28
Not completed	2
Adverse event, non-fatal	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	30	30	
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)	27	27	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	46.2		
full range (min-max)	20 to 73	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	15	15	

End points

End points reporting groups

Reporting group title	Gammanorm 165 mg/mL

Reporting group description:

Each patient received Gammanorm using each of the two studied delivery devices according to the sequence randomly assigned based on a cross-over design in a 1:1 ratio to one of two following sequences: Pump and then syringe, or syringe and then pump.

Subject analysis set title	FAS Population
Subject analysis set type	Full analysis

Subject analysis set description:

Analysis of all randomised patients who have received at least one infusion of immunoglobulin and with at least one baseline evaluation (V1) and one evaluation on treatment (V2 or V3) regarding their treatment satisfaction using the LQI scale.

Subject analysis set title	PP Population
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects in the ITT analysis population who completed the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the evaluation of the primary endpoint.

Primary: Lsmean Endpoint Pump Sequence

End point title	Lsmean Endpoint Pump Sequence[1]

End point description:

Assessment of patient satisfaction regarding the treatment delivery device using the LQI I patient satisfaction score (factor I: treatment interference) at the end of the 3-month treatment period with pump.

End point type	Primary

End point timeframe:

at the end of the 3 months treatment period for delivery device pump

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: One reporting group only, therefore only results of this endpoint (treatment interference) can be documented.

End point values	FAS Population	PP Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	26		
Units: Score				
least squares mean (confidence interval 95%)	84.32 (79.80 to 89.09)	83.21 (78.60 to 88.08)		

Statistical analyses

No statistical analyses for this end point

Primary: Lsmean Endpoint Syringe Sequence

End point title	Lsmean Endpoint Syringe Sequence[2]

End point description:

Assessment of patient satisfaction regarding the treatment delivery device using the LQI I patient satisfaction score (factor I: treatment interference) at the end of the 3-month treatment period with syringe.

End point type	Primary

End point timeframe:

at the end of the 3 months treatment period for delivery device syringe

Notes:

[2] - 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: One reporting group only, therefore only results of this endpoint (treatment interference) can be documented.

End point values	FAS Population	PP Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	26		
Units: Score				
least squares mean (confidence interval 95%)	78.85 (74.74 to 83.18)	78.68 (74.33 to 83.29)		

Statistical analyses

No statistical analyses for this end point

Primary: Ratio of Lsmeans Syringe/Pump

End point title	Ratio of Lsmeans Syringe/Pump[3]

End point description:

Ratio of Lsmeans Syringe and Lsmeans Pump.

End point type	Primary

End point timeframe:

at the end of the 3 months treatment period for each delivery device.

Notes:

[3] - 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: Study tested that LQI Factor I (treatment interference) for administration of IMP with syringe is not inferior to pump.
Non-inferiority threshold for the ratio LQI Factor I syringe / LQI Factor I pump was set at 0.9. Results were expressed as mean of ratios and two-sided 95% CI. The lower limit of the CI was compared to the non-inferiority threshold of 0.90.n of ratios and two-sided 95% CI. The lower limit of the CI was compared to the non-inferiority threshold of 0.90.

End point values	FAS Population	PP Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	26		
Units: Ratio				
least squares mean (confidence interval 95%)	93.51 (87.58 to 99.84)	94.56 (88.53 to 100.99)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Throughout the whole study from V1 up to V3.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	Safety Set Total
Reporting group description: Patients who received at least one dose of IMP.	
Reporting group title	Safety Set Pump
Reporting group description: -	
Reporting group title	Safety Set Syringe
Reporting group description: -	

Serious adverse events	Safety Set Total	Safety Set Pump	Safety Set Syringe
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 30 (10.00%)	1 / 29 (3.45%)	3 / 30 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Multiple Thromboembolic Event			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
C6 nerve impingement			
subjects affected / exposed	1 / 30 (3.33%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain in multiple sites			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal bleed			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Exacerbation of Asthma			
subjects affected / exposed	1 / 30 (3.33%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sinusitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	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	Safety Set Total	Safety Set Pump	Safety Set Syringe
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 30 (90.00%)	24 / 29 (82.76%)	23 / 30 (76.67%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 30 (6.67%)	2 / 29 (6.90%)	1 / 30 (3.33%)
occurrences (all)	3	2	1
Nervous system disorders			
Headache			

subjects affected / exposed	6 / 30 (20.00%)	4 / 29 (13.79%)	2 / 30 (6.67%)
occurrences (all)	13	11	2
Dizziness			
subjects affected / exposed	3 / 30 (10.00%)	2 / 29 (6.90%)	2 / 30 (6.67%)
occurrences (all)	6	4	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 30 (16.67%)	4 / 29 (13.79%)	3 / 30 (10.00%)
occurrences (all)	10	4	6
Chills			
subjects affected / exposed	4 / 30 (13.33%)	3 / 29 (10.34%)	2 / 30 (6.67%)
occurrences (all)	41	7	34
Fatigue			
subjects affected / exposed	3 / 30 (10.00%)	3 / 29 (10.34%)	1 / 30 (3.33%)
occurrences (all)	9	8	1
Feeling Cold			
subjects affected / exposed	2 / 30 (6.67%)	2 / 29 (6.90%)	1 / 30 (3.33%)
occurrences (all)	47	8	39
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 30 (16.67%)	4 / 29 (13.79%)	2 / 30 (6.67%)
occurrences (all)	15	10	5
Abdominal discomfort			
subjects affected / exposed	2 / 30 (6.67%)	1 / 29 (3.45%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Abdominal pain			
subjects affected / exposed	2 / 30 (6.67%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	3	3	0
Abdominal pain upper			
subjects affected / exposed	2 / 30 (6.67%)	1 / 29 (3.45%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Diarrhoea			
subjects affected / exposed	2 / 30 (6.67%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	2	2	0
Vomiting			

subjects affected / exposed	2 / 30 (6.67%)	1 / 29 (3.45%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 30 (16.67%)	5 / 29 (17.24%)	1 / 30 (3.33%)
occurrences (all)	7	6	1
Cough			
subjects affected / exposed	4 / 30 (13.33%)	5 / 29 (17.24%)	2 / 30 (6.67%)
occurrences (all)	7	6	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 30 (13.33%)	2 / 29 (6.90%)	2 / 30 (6.67%)
occurrences (all)	12	2	10
Arthralgia			
subjects affected / exposed	3 / 30 (10.00%)	1 / 29 (3.45%)	2 / 30 (6.67%)
occurrences (all)	13	1	12
Myalgia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 29 (0.00%)	2 / 30 (6.67%)
occurrences (all)	16	0	16
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 30 (23.33%)	7 / 29 (24.14%)	2 / 30 (6.67%)
occurrences (all)	11	9	2
Nasopharyngitis			
subjects affected / exposed	7 / 30 (23.33%)	3 / 29 (10.34%)	4 / 30 (13.33%)
occurrences (all)	7	3	4
Lower respiratory tract infection			
subjects affected / exposed	4 / 30 (13.33%)	2 / 29 (6.90%)	3 / 30 (10.00%)
occurrences (all)	6	3	3
Sinusitis			
subjects affected / exposed	4 / 30 (13.33%)	2 / 29 (6.90%)	4 / 30 (13.33%)
occurrences (all)	8	2	6
Oral candidiasis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 29 (0.00%)	2 / 30 (6.67%)
occurrences (all)	3	0	3
Pharyngitis			

subjects affected / exposed	2 / 30 (6.67%)	2 / 29 (6.90%)	1 / 30 (3.33%)
occurrences (all)	3	2	1
Rhinitis			
subjects affected / exposed	2 / 30 (6.67%)	1 / 29 (3.45%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Urinary tract infection			
subjects affected / exposed	2 / 30 (6.67%)	0 / 29 (0.00%)	2 / 30 (6.67%)
occurrences (all)	2	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2015	Amendment 1 - Implementation of the requested changes regarding biostatistics by the authorities in Germany and clarifications to the protocol
02 June 2015	Amendment 3: - Higher infusion rates and higher volumes may be administered if determined by the routine practice of the site. - Unscheduled Visits were added.
07 December 2015	Amendment 4: - Clarification of Adverse Events documentation - Addition of study sites in Australia
10 October 2016	Amendment 10: - Prolongation of study duration - maximum number of patients enrolled increased from 30 to 40

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported