Clinical trial results:
CLINICAL PHASE III STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY, TOLERABILITY AND SAFETY OF SUBCUTANEOUS HUMAN IMMUNOGLOBULIN (OCTANORM 16.5%) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES

Summary

EudraCT number	2013-003877-87
Trial protocol	CZ HU PL SK
Global end of trial date	09 June 2020

Results information

Result version number	v1 (current)
This version publication date	07 April 2021
First version publication date	07 April 2021

Trial information

Trial identification

Sponsor protocol code	SCGAM-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01888484
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Octapharma Pharmazeutika Produktionsges.m.b.H.
Sponsor organisation address	Oberlaaer Strasse 235, Vienna, Austria, 1100
Public contact	clinical.department@octapharma.com, Octapharma Pharmazeutika Prod.Ges.m.b.H, +43 1610320 , clinical.department@octapharma.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	04 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The first primary objective of the study is to assess the efficacy of octanorm in preventing serious bacterial infections compared with historical control data.
The second primary objective is to evaluate the pharmacokinetic characteristics of octanorm and to compare the area under the curve (AUC) with that of IVIG.

Protection of trial subjects:

This trial was conducted in accordance to the principles of ICH- GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki and national regulatory requirements. 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.
Study safety was assessed such as monitoring of AEs and SAEs, monitoring of local injection site reactions, concomitant medication, physical examination, vital signs and safety lab parameters.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Russian Federation: 10
Worldwide total number of subjects	75
EEA total number of subjects	30

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)	26
Adolescents (12-17 years)	12
Adults (18-64 years)	35
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients with documented diagnosis primary immunodeficiency diseases as defined by the European Society for Immunodeficiencies (ESID) and Pan-American Group for Immunodeficiency and requiring immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia were screened according to predefined in- and exclusion criteria.

Period 1

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

Arms

Arm title	Octanorm

Arm description:

Octanorm 16.5%, human normal immunoglobulin for weekly (±2 days) subcutaneous (SC) administration.

Arm type	Experimental
Investigational medicinal product name	Octanorm 16.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Octanorm, a human normal immunoglobulin, had to be administered subcutaneously every week (±2 days). A minimum time of 4 days had to be kept in between two single SC infusions.

Number of subjects in period 1	Octanorm
Started	75
Completed	68
Not completed	7
patient's non-compliance	1
Withdrawal by subject	6

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	75	75	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	27.81		
full range (min-max)	2 to 72	-	
Gender categorical Units: Subjects			
Female	36	36	
Male	39	39	

End points

End points reporting groups

Reporting group title	Octanorm

Reporting group description:

Octanorm 16.5%, human normal immunoglobulin for weekly (±2 days) subcutaneous (SC) administration.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS is defined according to the intention-to-treat principle and consists of all patients of the Safety Analysis Set who satisfy all major eligibility criteria and for whom any postbaseline data are available; it is the set of eligible patients with treatment effects measured.

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol (PP) set consists of all patients of the FAS excluding those with major protocol violations which may have an impact on the analysis of the primary efficacy endpoint. This is the set of patients who participated in the study as intended and for whom the primary efficacy endpoint can be evaluated as planned.

Subject analysis set title	PK Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who had a full PK profile after the last administration of the previously used IVIG product before he was switched to octanorm (PKIV), a full PK profile at the end of the wash-in/wash-out phase (PKSC1) and a final PK profile after 28 administrations of octanorm (at steady state) to assess the bioavailability of total IgG with respect to the two administration methods (PKSC2).

Primary: Primary Efficacy Endpoint: Rate of Serious Bacterial Infections per person-year on treatment.

End point title	Primary Efficacy Endpoint: Rate of Serious Bacterial Infections per person-year on treatment.[1]

End point description:

The primary efficacy endpoint is the rate of SBI (defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess) per person-year on treatment. No SBIs were observed during the study. For this reason, it was not possible to calculate a CI using the originally planned compound Poisson process model. In the alternative analysis of CIs based on the standard Poisson distribution, overall the upper limit of the 2- sided 98% CI was 0.065 in the primary observation period and 0.054 in the total treatment period in both the FAS and PP analysis set.

End point type	Primary

End point timeframe:

Baseline to end of the study. (Every 4 weeks until the final evaluation at week 65)

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: The system does not permit reporting of statistical analyses for studies with only 1 arm/reporting group. Therefore, only results for this endpoint are provided.

End point values	Full analysis set (FAS)	Per Protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	75		
Units: Rate of SBI				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Primary Pharmacokinetic Endpoint: AUCτ at Steady-State Conditions

End point title	Primary Pharmacokinetic Endpoint: AUCτ at Steady-State Conditions[2]

End point description:

The AUCτ (i.e., AUC from time 0 (start of the infusion) to the end of the nominal dosing period, standardised to 1 week) at PKSC2 (steady-state conditions) In several cases, AUCτ could not be calculated due to very flat time-concentration profiles.
Geometric mean was 2166.13 h*g/L.

End point type	Primary

End point timeframe:

AUC from time 0 (start of the infusion) to the end of the nominal dosing period. Measured at Week 12 and Week 28.

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: The system does not permit reporting of statistical analyses for studies with only 1 arm/reporting group. Therefore, only results for this endpoint are provided.

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: AUCτ of IgG (h*g/L)				
arithmetic mean (standard deviation)	2232.61 (± 585.842)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total number (rate) of infections per person-year

End point title	Total number (rate) of infections per person-year

End point description:

The annual rate of all infections of any kind or seriousness.

End point type	Secondary

End point timeframe:

Baseline to end of the study, up to 65 weeks

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	75			
Units: Rate				
number (not applicable)				
Rate of other infections	3.414			

Statistical analyses

No statistical analyses for this end point

Secondary: Non-serious Infections

End point title	Non-serious Infections

End point description:

End point type	Secondary

End point timeframe:

Up to 65 weeks

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	75			
Units: infections				
number (not applicable)				
Ear infections	8			
Eye infections	3			
Infections of the GI tract	25			
Infections of the genitourinary tract	24			
Upper respiratory tract infections	179			
Lower respiratory tract infections	32			
Infections of the skin	6			
Infections not (elsewhere) classified	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Total IgG and IgG Subclasses

End point title	Cmax of Total IgG and IgG Subclasses

End point description:

Cmax of Total IgG and IgG Subclasses

End point type	Secondary

End point timeframe:
Up to 28 days

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: g/L				
arithmetic mean (standard deviation)				
IgG Total Cmax	13.47 (± 3.655)			
IgG1 Cmax	8.56 (± 1.858)			
IgG2 Cmax	3.88 (± 1.532)			
IgG3 Cmax	0.32 (± 0.127)			
IgG4 Cmax	0.40 (± 0.567)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Total IgG and IgG Subclasses

End point title	Tmax of Total IgG and IgG Subclasses

End point description:

End point type	Secondary

End point timeframe:
Up to 28 days

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: hours				
arithmetic mean (full range (min-max))				
Tmax Total IgG	49.62 (0.8 to 98.3)			
Tmax IgG1	50.50 (1.5 to 167.7)			
Tmax IgG2	72.20 (0.5 to 167.7)			
Tmax IgG3	49.62 (1.8 to 98.1)			
Tmax IgG4	47.50 (0.6 to 167.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC of Total IgG and IgG Subclasses

End point title	AUC of Total IgG and IgG Subclasses

End point description:

End point type	Secondary

End point timeframe:

Up to 28 days

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: h*g/L				
number (not applicable)				
IgG Total AUC Number Patients Analyzed	24			
IgG Total AUC Mean	2232.61			
IgG Total AUC SD	585.842			
IgG1 AUC Number Patients Analyzed	22			
IgG1 AUC Mean	1424.69			
IgG1 AUC SD	298.776			
IgG2 AUC Number Patients Analyzed	23			
IgG2 AUC Mean	659.57			
IgG2 AUC SD	262.295			
IgG3 AUC Number Patients Analyzed	25			
IgG3 AUC Mean	48.65			
IgG3 AUC SD	18.455			
IgG4 AUC Number Patients Analyzed	25			
IgG4 AUC Mean	71.40			
IgG4 AUC SD	102.578			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Levels of Serum IgG

End point title	Trough Levels of Serum IgG

End point description:

Trough levels of serum IgG, IgG1, IgG2, IgG3, IgG4 at PK 7 days after 28th infusion of octanorm.

End point type	Secondary

End point timeframe:

Up to 65 weeks

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: g/L				
median (inter-quartile range (Q1-Q3))				
Total IgG	11.85 (10.00 to 13.70)			
IgG1	7.51 (6.58 to 9.00)			
IgG2	3.12 (2.69 to 3.85)			
IgG3	0.27 (0.20 to 0.34)			
IgG4	0.15 (0.11 to 0.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: IVIG to Octanorm DCF (Based on the Area Under the Concentration-time Curve [AUCτ])

End point title	IVIG to Octanorm DCF (Based on the Area Under the Concentration-time Curve [AUCτ])

End point description:

IVIG to octanorm Dose Conversion Factor (based on the area under the concentration-time curve [AUCτ]) - Regression Model without Restriction.

End point type	Secondary

End point timeframe:

Up to 29 weeks

End point values	PK Set			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: Ratio				
arithmetic mean (standard deviation)	1.278 (± 0.9401)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the whole study from Visit 1 up to Visit 22 (Termination visit)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Safety Population (SAF)

Reporting group description: -

Serious adverse events	Safety Population (SAF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 75 (12.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid neoplasm			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Grand mal convulsion			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Asperger's disorder			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute odontogenic jaw osteomyelitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus bronchiolitis			

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population (SAF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 75 (81.33%)		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	9 / 75 (12.00%)		
occurrences (all)	10		
Excoriation			
subjects affected / exposed	5 / 75 (6.67%)		
occurrences (all)	6		
Fall			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 75 (8.00%)		
occurrences (all)	14		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	11 / 75 (14.67%)		
occurrences (all)	14		
Infusion site erythema			
subjects affected / exposed	7 / 75 (9.33%)		
occurrences (all)	12		
Infusion site reaction			

subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 10		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 5 / 75 (6.67%) 5 4 / 75 (5.33%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 11 / 75 (14.67%) 18 6 / 75 (8.00%) 8		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Asthma subjects affected / exposed occurrences (all)	 12 / 75 (16.00%) 22 7 / 75 (9.33%) 7 6 / 75 (8.00%) 8		
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 5 / 75 (6.67%) 5 4 / 75 (5.33%) 6		
Renal and urinary disorders Dysuria			

subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	4		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	21 / 75 (28.00%)		
occurrences (all)	33		
Nasopharyngitis			
subjects affected / exposed	17 / 75 (22.67%)		
occurrences (all)	37		
Sinusitis			
subjects affected / exposed	15 / 75 (20.00%)		
occurrences (all)	25		
Rhinitis			
subjects affected / exposed	11 / 75 (14.67%)		
occurrences (all)	17		
Bronchitis			
subjects affected / exposed	7 / 75 (9.33%)		
occurrences (all)	14		
Urinary tract infection			
subjects affected / exposed	6 / 75 (8.00%)		
occurrences (all)	11		
Acute sinusitis			
subjects affected / exposed	5 / 75 (6.67%)		
occurrences (all)	13		
Rhinovirus infection			
subjects affected / exposed	5 / 75 (6.67%)		
occurrences (all)	7		
Influenza			

subjects affected / exposed	5 / 75 (6.67%)		
occurrences (all)	5		
Gastroenteritis viral			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	6		
Laryngitis			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	5		
Otitis media			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2015	Protocol Version 7: incorporates the change of the maximal number of patients in the age group ≥16 years: amended from 28 to a maximum of 39. In the PK substudy, the number of enrolled patients was changed from 24 to maximum of 34 patients. Exclusion criterion no. 3 was amended allowing the upper level of the BMI to be <40 (previously BMI ≤30). The method of subcutaneous administration for adult patients was amended: increase of maximal volume to 40 mL per site, and the total flow rate of max. 100mL per hour together for all sites after the 40th s.c. administration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported