Clinical trial results:
A Multicenter Study of Long-Term Clinical Outcomes of Immune Globulin Subcutaneous (Human) (SCIG) IgPro20 in Subjects with Primary Immunodeficiency

Summary

EudraCT number	2014-003409-13
Trial protocol	Outside EU/EEA
Global end of trial date	22 July 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	18 February 2015

Trial information

Trial identification

Sponsor protocol code	IgPro20_3006

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	CSL Behring K.K.
Sponsor organisation address	KDX Toyosu Grandsquare, 1-7-12 Shinonome, Koto-ku, Tokyo, Japan, 135-0062
Public contact	Trial Registration Co-ordinator, CSL Behring, clinicaltrials@cslbehring.com
Scientific contact	Trial Registration Co-ordinator, CSL Behring, clinicaltrials@cslbehring.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term efficacy, tolerability, and safety of IgPro20 in subjects with primary immunodeficiency (PID) as an extension to the preceding follow-up study ZLB07_001CR.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Ministry of Health, Labor, and Welfare (Japan, MHLW) Notification #28 (Good Clinical Practice [GCP], 27 March 1997), YakuShokuShinsaHatsu Notification #1001001 (01 October 2010), and the Declaration of Helsinki (version of 2008). The study was also carried out in keeping with requirements set forth in the Pharmaceutical Affairs Law 14-3 and 80-2. In addition, this study was conducted in accordance with the International Conference on Harmonisation (ICH) GCP guidelines, and Standard Operating Procedures (SOPs) for clinical research and development at CSL Behring and the clinical research organizations involved. The study protocol and all amendments were approved by an Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs). Before undergoing screening procedures for possible enrollment into the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 October 2011
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	Japan: 22
Worldwide total number of subjects	22
EEA total number of subjects	0

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)	5
Adolescents (12-17 years)	5
Adults (18-64 years)	12
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study enrolled subjects at 9 study centers in Japan who had participated in the preceding follow-up study ZLB07_001CR (CT.gov identifier: NCT01458171).

Pre-assignment

Screening details:

Only subjects participating in the preceding follow-up study ZLB07_001CR were eligible. Enrolment visit of this study was on same day as completion visit of the preceding follow-up study ZLB07_001CR.

Period 1

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

Arms

Arm title	IgPro20

Arm description:

IgPro20 is a 20% (weight per volume [w/v]) liquid formulation of human immunoglobulin for subcutaneous (SC) use.

Arm type	Experimental
Investigational medicinal product name	Hizentra®
Investigational medicinal product code	
Other name	Human Normal Immunoglobulin, Immune globulin subcutaneous (Human)
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IgPro20 is a 20% (weight per volume [w/v]) liquid formulation of human immunoglobulin for subcutaneous (SC) use.

Number of subjects in period 1	IgPro20
Started	22
Completed	19
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Pregnancy	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	22	22	
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)	5	5	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	12	12	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	21.6		
standard deviation	± 13.98	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	13	13	

End points

End points reporting groups

Reporting group title	IgPro20

Reporting group description:

IgPro20 is a 20% (weight per volume [w/v]) liquid formulation of human immunoglobulin for subcutaneous (SC) use.

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

Subject analysis set description:

The FAS comprised all subjects receiving at least 1 IgPro20 infusion.

Subject analysis set title	PPS (Per protocol set)
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS population comprised all subjects with the disease under study who a) received uniformly repeated IgPro20 infusions at weeks intervals and b) who had at least 1 documented total serum IgG trough level.

Primary: Annualized rate of infection episodes (serious and non-serious)

End point title	Annualized rate of infection episodes (serious and non-

End point description:

The annualized rate of infection episodes (serious and non-serious) was based on the total number of infection episodes and the total number of subject study days for all subjects in the FAS and the PPS and adjusted to 365 days.

End point type	Primary

End point timeframe:

Up to 36 months

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: Variables were descriptively summarised. No formal statistical tests were planned or performed.

End point values	FAS (Full analysis set)	PPS (Per protocol set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	17		
Units: infections per subject year				
number (not applicable)	2.42	1.91		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with newly developing or worsening adverse events (AEs)

End point title	Number of subjects with newly developing or worsening adverse events (AEs)

End point description:

Number of subjects with newly developing or worsening AEs, overall and classified (i) by severity (mild, moderate, severe) and (ii) by causal relationship to study medication (at least possibly related [i.e.,

possibly related, probably related, or related]).

End point type	Secondary

End point timeframe:

Up to 36 months

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: subjects				
All AEs	22			
Mild AEs	22			
Moderate AEs	4			
Severe AEs	2			
At least possibly related	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with newly developing or worsening adverse events (AEs)

End point title	Percentage of subjects with newly developing or worsening adverse events (AEs)

End point description:

Percentage of subjects with newly developing or worsening AEs, overall and classified (i) by severity (mild, moderate, severe) and (ii) by causal relationship to study medication (at least possibly related [i.e., possibly related, probably related, or related]).

End point type	Secondary

End point timeframe:

Up to 36 months

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage of subjects				
number (not applicable)				
All AEs	100			
Mild AEs	100			
Moderate AEs	18.2			
Severe AEs	9.1			
At least possibly related	59.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of AEs per infusion

End point title	Rate of AEs per infusion

End point description:

Rate of adverse events per infusion, overall and classified (i) by severity (mild, moderate, severe) and (ii) by causal relationship to study medication (not related or unlikely related; at least possibly related [i.e., possibly related, probably related, or related]).

End point type	Secondary

End point timeframe:

Up to 36 months

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: AE rate per infusion				
number (not applicable)				
All AEs	0.248			
Mild AEs	0.244			
Moderate AEs	0.003			
Severe AEs	0.001			
Not related or unlikely related	0.098			
At least possibly related	0.15			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate of clinically documented serious bacterial infections (SBIs)

End point title	Annualized rate of clinically documented serious bacterial infections (SBIs)

End point description:

SBIs are defined as bacterial pneumonia, bacteremia and septicemia, osteomyelitis/septic arthritis, bacterial meningitis, or visceral abscess. The annualized rate was based on the total number of SBIs and the total number of subject study days for all subjects in the FAS (N=22) and PPS (N=17) and adjusted to 365 days.

End point type	Secondary

End point timeframe:

Up to 36 months

End point values	FAS (Full analysis set)	PPS (Per protocol set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	17		
Units: SBIs per subject year				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections

End point title	Annualized rate of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections

End point description:

The annualized rate was based on the total number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections and the total number of subject study days for all subjects in the FAS and PPS and adjusted to 365 days.

End point type	Secondary

End point timeframe:

Up to 36 months

End point values	FAS (Full analysis set)	PPS (Per protocol set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	17		
Units: Annualized rate of days				
number (not applicable)	3.24	3.26		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate of days of hospitalization due to infections

End point title	Annualized rate of days of hospitalization due to infections

End point description:

The annualized rate was based on the total number of days hospitalized and the total number of subject study days for all subjects in the FAS and PPS and adjusted to 365 days.

End point type	Secondary

End point timeframe:

Up to 36 months

End point values	FAS (Full analysis set)	PPS (Per protocol set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	17		
Units: Annualized rate of days hospitalized				
number (not applicable)	0.27	0.34		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of use of antibiotics for infection prophylaxis and treatment

End point title	Duration of use of antibiotics for infection prophylaxis and treatment

End point description:

The annualized rate was based on the total number of days treated with antibiotics and the total number of subject study days for all subjects in the FAS and PPS and adjusted to 365 days.

End point type	Secondary

End point timeframe:

Up to 36 months

End point values	FAS (Full analysis set)	PPS (Per protocol set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	17		
Units: Annualized rate of days treated				
number (not applicable)	170.1	199.42		

Statistical analyses

No statistical analyses for this end point

Secondary: Median serum IgG concentration

End point title	Median serum IgG concentration

End point description:

End point type	Secondary

End point timeframe:

Up to 36 months

End point values	FAS (Full analysis set)	PPS (Per protocol set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	17		
Units: g/L				
median (full range (min-max))	8.32 (5.64 to 11.08)	8.13 (5.64 to 11.08)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the duration of the study, that is, up to 36 months per subject.

Adverse event reporting additional description:

Only AEs starting at or after the first study drug infusion are included. A total of 2660 infusions of IgPro20 were administered to 22 subjects.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	IgPro20

Reporting group description:

IgPro20 is a 20% (weight per volume [w/v]) liquid formulation of human immunoglobulin for subcutaneous (SC) use.

Serious adverse events	IgPro20		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis bacterial			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis aseptic			
subjects affected / exposed	1 / 22 (4.55%)		
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	IgPro20		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	7		
Arthropod bite			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 22 (36.36%)		
occurrences (all)	14		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	150		
Injection site haematoma			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Infusion site pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	108		
Injection site haemorrhage			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	8		
Abdominal pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	6		

Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 2 2 / 22 (9.09%) 2 2 / 22 (9.09%) 2		
Respiratory, thoracic and mediastinal disorders Rhinitis allergic subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 5 / 22 (22.73%) 7 4 / 22 (18.18%) 6 3 / 22 (13.64%) 9		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) Acne subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 5 / 22 (22.73%) 9 2 / 22 (9.09%) 2 2 / 22 (9.09%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 4 / 22 (18.18%) 6		
Infections and infestations Upper respiratory tract infection			

subjects affected / exposed	8 / 22 (36.36%)			
occurrences (all)	14			
Influenza				
subjects affected / exposed	6 / 22 (27.27%)			
occurrences (all)	6			
Gastroenteritis				
subjects affected / exposed	5 / 22 (22.73%)			
occurrences (all)	5			
Acute sinusitis				
subjects affected / exposed	3 / 22 (13.64%)			
occurrences (all)	8			
Conjunctivitis infective				
subjects affected / exposed	3 / 22 (13.64%)			
occurrences (all)	3			
Otitis media				
subjects affected / exposed	3 / 22 (13.64%)			
occurrences (all)	3			
Pharyngitis				
subjects affected / exposed	3 / 22 (13.64%)			
occurrences (all)	3			
Sinusitis				
subjects affected / exposed	3 / 22 (13.64%)			
occurrences (all)	3			
Bronchitis				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences (all)	2			
Cystitis				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences (all)	2			
Dermatitis infected				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences (all)	2			
Impetigo				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences (all)	2			
Nasopharyngitis				

subjects affected / exposed occurrences (all)	11 / 22 (50.00%) 44		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2013	There was 1 amendment to the original study protocol that was implemented during the study. The main changes were: 1. Change in regulatory status of the study from "phase 3 study" to "post-marketing approval study" after approval of IgPro20 in Japan, in compliance with Japanese regulations. 2. Extension of expected maximum study duration from "30" to "36" months, until availability of IgPro20 on the market in Japan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported