EU Clinical Trials Register

Clinical trial results:
A Multicenter Follow-up Study of Long-term Safety, Tolerability, and Efficacy of Immune Globulin Subcutaneous (Human) IgPro20 in Subjects With Primary Immunodeficiency

Summary

EudraCT number	2014-003609-14
Trial protocol	Outside EU/EEA
Global end of trial date	24 April 2012

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	ZLB07_001CR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01458171
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring K.K.
Sponsor organisation address	1-13-1 Kachidoki, Chuo-ku, Tokyo, Japan, 104-0054
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	23 May 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety, tolerability, and efficacy of IgPro20 in subjects with primary immunodeficiency (PID) as a follow-up to the pivotal study ZLB06_002CR (EUdraCT: 2014-003608-61, NCT01199705).

Protection of trial subjects:

The study was conducted in accordance with the principles of the Ministry of Health and Welfare notification #28 (GCP, 27 March 1997) and YakuShokuShinsaHatsu Notification #1001001 (01 October 2000). The study was also carried out in keeping with requirements set forth in 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. GCP compliance was assessed during data review and confirmed in the Data Review Meeting (DRM). Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki (version of 2008). The study was conducted under a protocol reviewed and approved by an Independent Ethics Committee/Institutional Review Board; the study was conducted by scientifically and medically qualified persons; the benefits of the study were in proportion to the risks; the rights and welfare of the subjects were respected; the physicians conducting the study did not find the hazards to outweigh the potential benefits; the results reported are accurate.
The investigator was responsible for obtaining written informed consent from the participating subject in accordance with Ministry of Health and Welfare notification #28 (GCP, 27 March 1997) and in compliance with the Declaration of Helsinki. Each subject and/or subject's parent or legal guardian gave his or her written informed consent before any protocol-driven tests or evaluations were performed. The investigator could cease study treatment and withdraw the subject, or the subject could withdraw themselves from participation in the study at any time. The decision to withdraw consent and discontinue participation in the study could not prejudice the subject's future medical treatment in any way.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 April 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: 23
Worldwide total number of subjects	23
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)	6
Adolescents (12-17 years)	6
Adults (18-64 years)	11
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study enrolled subjects at nine study centers in Japan who had participated in the preceding pivotal study ZLB06_002CR (EudraCT: 2014-003608-61, CT.gov identifier: NCT01199705).

Pre-assignment

Screening details:

Only subjects participating in the preceding pivotal study ZLB06_002CR were eligible. The enrolment visit of this study was on the same day as the completion visit of the preceding pivotal study ZLB06_002CR.

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	IgPro20

Arm description:

Immune globulin subcutaneous (Human): IgPro20 is a 20% (weight per volume [w/v]) liquid formulation of human immunoglobulin for subcutaneous (SC) use. Subjects will receive weekly infusions of IgPro20 for a total of 24 weeks at a dose based on the subject's IgPro20 dose in the pivotal study ZLB06_002CR (EudraCT 2014-003608-61, NCT01199705).

Arm type	Experimental
Investigational medicinal product name	Immune globulin subcutaneous (Human)
Investigational medicinal product code	
Other name	Hizentra, IgPro20
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 SCIG. Each subject was to receive 24 weekly IgPro20 subcutaneous infusions in total.   The weekly IgPro20 dose was equivalent to the subject's last dose, recommended by the investigator, from pivotal study ZLB06_002CR. The IgPro20 dose could be adjusted if medically indicated or to ensure adequate IgPro20 trough levels.

Number of subjects in period 1	IgPro20
Started	23
Completed	22
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	IgPro20

Reporting group description:

Immune globulin subcutaneous (Human): IgPro20 is a 20% (weight per volume [w/v]) liquid formulation of human immunoglobulin for subcutaneous (SC) use. Subjects will receive weekly infusions of IgPro20 for a total of 24 weeks at a dose based on the subject's IgPro20 dose in the pivotal study ZLB06_002CR (EudraCT 2014-003608-61, NCT01199705).

Reporting group values	IgPro20	Total	
Number of subjects	23	23	
Age categorical			
Units: Subjects			
Children (2-11 years)	6	6	
Adolescents (12-17 years)	6	6	
Adults (18-64 years)	11	11	
Age continuous			
Units: years			
arithmetic mean	20.8		
standard deviation	± 13.68	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	14	14	

End points

End points reporting groups

Reporting group title	IgPro20

Reporting group description:

Immune globulin subcutaneous (Human): IgPro20 is a 20% (weight per volume [w/v]) liquid formulation of human immunoglobulin for subcutaneous (SC) use. Subjects will receive weekly infusions of IgPro20 for a total of 24 weeks at a dose based on the subject's IgPro20 dose in the pivotal study ZLB06_002CR (EudraCT 2014-003608-61, NCT01199705).

Subject analysis set title	IgPro20 - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) comprised all subjects receiving at least 1 IgPro20 infusion.

Subject analysis set title	IgPro20 - PPS
Subject analysis set type	Per protocol

Subject analysis set description:

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

Primary: Median of the Individual Subject's Rate of Adverse Events (AEs) Per Infusion

End point title	Median of the Individual Subject's Rate of Adverse Events (AEs) Per Infusion[1]

End point description:

The rate was calculated by counting all newly developed or worsened AEs within a subject and dividing by the total number of IgPro20 infusions administered to this subject. Subsequently, the median of these individual AE rates per infusion was calculated. AE rates were 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	Primary

End point timeframe:

24 weeks

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	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	23[2]			
Units: AEs per infusion				
median (full range (min-max))				
All AEs	0.167 (0 to 1.71)			
Mild AEs	0.125 (0 to 1.71)			
Moderate AEs	0 (0 to 0.04)			
Severe AEs	0 (0 to 1)			
Not related or unlikely related AEs	0.125 (0 to 0.75)			
At least possibly related AEs	0 (0 to 1)			

Notes:

[2] - The All Treated (AT) set comprised all subjects receiving at least 1 IgPro20 infusion.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Rate of AEs Per Infusion

End point title	Overall Rate of AEs Per Infusion

End point description:

The rate was calculated by counting all newly developed or worsened AEs during the treatment period in all subjects and dividing the total number of AEs by the total number of IgPro20 infusions administered. In addition, individual AEs were 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]). The AE rates per infusion by severity and causal relationship to study medication were calculated by dividing the number of AEs in each category by the total number of IgPro20 infusions.

End point type	Secondary

End point timeframe:

24 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	23[3]			
Units: AEs per infusion				
number (not applicable)				
All AEs	0.346			
Mild AEs	0.342			
Moderate AEs	0.002			
Severe AEs	0.002			
Not related or unlikely related AEs	0.21			
At least possibly related AEs	0.136			

Notes:

[3] - The AT set = all subjects receiving at least 1 IgPro20 infusion.
Number of Infusions Analyzed = 529

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Newly Developing or Worsening AEs

End point title	Number of Subjects With Newly Developing or Worsening AEs

End point description:

Number of subjects with AEs, 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:
24 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	23[4]			
Units: participants				
All AEs	22			
Mild AEs	21			
Moderate AEs	1			
Severe AEs	1			
Not related or unlikely related	12			
At least possibly related	10			

Notes:

[4] - The AT set comprised all subjects receiving at least 1 IgPro20 infusion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Infusions With Subject-assessed Tolerability of at Least 'Good'

End point title	Percentage of Infusions With Subject-assessed Tolerability of at Least 'Good'

End point description:

Subjects assessed their overall perception of local tolerability at the infusion site throughout the study in the subject diary within a time window of 24 h to 72 h after the end of the latest infusion by assessing it as "very good", "good", "fair", or "poor". The reported end point represents the percentage of infusions for which subjects' overall perception of local tolerability was "very good" or "good" at any given study infusion.

End point type	Secondary

End point timeframe:
24 to 72 hours after infusion

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	23[5]			
Units: percentage of infusions				
number (not applicable)	85.4			

Notes:

[5] - The FAS comprised all subjects receiving at least 1 IgPro20 infusion.

Statistical analyses

No statistical analyses for this end point

Secondary: IgG Trough Level

End point title	IgG Trough Level
End point description:	
Serum IgG trough levels at the completion visit compared to the baseline visit of the follow-up study. IgG trough levels at baseline, at the completion visit, and the change from baseline to the completion visit are shown	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	IgPro20 - FAS	IgPro20 - PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	19		
Units: g/L				
arithmetic mean (standard deviation)				
Baseline	7.469 (± 1.3943)	7.586 (± 1.3363)		
Completion visit	8.914 (± 4.0502)	8.227 (± 1.5458)		
Change from baseline to the completion visit	1.445 (± 3.4379)	0.642 (± 0.7687)		

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 and PPS and adjusted to 365 days.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	IgPro20 - FAS	IgPro20 - PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[6]	19[7]		
Units: SBIs per subject year				
number (not applicable)	0	0		

Notes:

[6] - Number of total study days analyzed: 3739

[7] - Number of Total Study Days Analyzed: 3214

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Infection Episodes (Serious and Non-serious)

End point title	Number of Infection Episodes (Serious and Non-serious)
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	IgPro20 - FAS	IgPro20 - PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	19		
Units: infection episodes	43	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days Out of Work/School/Kindergarten/Day Care or Unable to Perform Normal Daily Activities Due to Infections

End point title	Number of Days Out of Work/School/Kindergarten/Day Care or Unable to Perform Normal Daily Activities Due to Infections
End point description:	
Median number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	IgPro20 - FAS	IgPro20 - PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	19[8]		
Units: days				
median (full range (min-max))	0 (0 to 12)	0 (0 to 9)		

Notes:

[8] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days of Hospitalization Due to Infections

End point title	Number of Days of Hospitalization Due to Infections
End point description:	
Median number of days of hospitalization due to infections.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	IgPro20 - FAS	IgPro20 - PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	19		
Units: days				
median (full range (min-max))	0 (0 to 11)	0 (0 to 0)		

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:	
Median number of days of use of antibiotics for infection prophylaxis and/or treatment.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	IgPro20 - FAS	IgPro20 - PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	19		
Units: days				
median (full range (min-max))	91.5 (6 to 170)	154 (6 to 170)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Rate of Infection Episodes (Serious and Non-serious)

End point title	Rate of Infection Episodes (Serious and Non-serious)
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 population and the PPS population and adjusted to 365 days.

End point type	Other pre-specified
End point timeframe:	

24 weeks

End point values	IgPro20 - FAS	IgPro20 - PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[9]	19[10]		
Units: infection episodes per subject year				
number (not applicable)	4.2	4.32		

Notes:

[9] - Number of total study days analyzed: 3739

[10] - Number of total study days analyzed: 3214

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, 24 weeks.	
Adverse event reporting additional description:	
Only AEs starting at or after the first study drug infusion are included. The AT set comprised all subjects receiving at least 1 IgPro20 infusion.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	IgPro20
Reporting group description:	
Immune globulin subcutaneous (Human): IgPro20 is a 20% (weight per volume [w/v]) liquid formulation of human immunoglobulin for subcutaneous (SC) use. Subjects will receive weekly infusions of IgPro20 for a total of 24 weeks at a dose based on the subject's IgPro20 dose in the pivotal study ZLB06_002CR (EudraCT 2014-003608-61, NCT01199705).	

Serious adverse events	IgPro20		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Encephalitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 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	20 / 23 (86.96%)		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	13		

Nervous system disorders			
Headache			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	8		
General disorders and administration site conditions			
Injection site induration			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Injection site pain			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	37		
Pyrexia			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	4		
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	6 / 23 (26.09%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	3		
Conjunctivitis infective			

subjects affected / exposed	2 / 23 (8.70%)
occurrences (all)	2
Nasopharyngitis	
subjects affected / exposed	6 / 23 (26.09%)
occurrences (all)	13
Pharyngitis	
subjects affected / exposed	2 / 23 (8.70%)
occurrences (all)	2
Sinusitis	
subjects affected / exposed	2 / 23 (8.70%)
occurrences (all)	2
Upper respiratory tract infection	
subjects affected / exposed	5 / 23 (21.74%)
occurrences (all)	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2011	There was 1 amendment to the original study protocol that was implemented prior to study start and to inclusion of any subjects. All subjects in the study were treated according to the final study protocol following Amendment 1 (i.e., CSP version 2.0) dated 11 February 2011. The main changes are summarized below: • An extension to the study objectives to include the HRQL and PhEc assessments. • Clearer illustration of the mode of administration. • A change to the number of planned subjects for enrollment into the study from "15" to "20 to 25" subjects. • Clearer subcategories for casual relationship and severity. • Change to the schedule for completion of the questionnaires.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported