EU Clinical Trials Register

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

Summary

EudraCT number	2014-003608-61
Trial protocol	Outside EU/EEA
Global end of trial date	24 November 2011

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	ZLB06_002CR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01199705
WHO universal trial number (UTN)	U1111-1116-6379

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	17 May 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 November 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to assess the efficacy, safety, tolerability, and pharmacokinetics of a subcutaneous immune globulin (SCIG; IgPro20) in subjects with primary immunodeficiency (PID). In addition, the study assessed the health-related quality of life and pharmacoeconomic aspects related to treatment with IgPro20.

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 (1 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) Good Clinical Practice (GCP) guidelines, and standard operating procedures for clinical research and development at CSL Behring and the Clinical Research Organisations involved. GCP compliance was assessed during data review and confirmed in the Data Review Meeting. 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	06 September 2010
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: 25
Worldwide total number of subjects	25
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)	7
Adolescents (12-17 years)	5
Adults (18-64 years)	13
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study enrolled subjects at nine of the participating study centers in Japan.

Pre-assignment

Screening details:

Screening took place 3 to 4 weeks prior to or at the first intravenous immunoglobulin (IVIG) infusion in the IVIG period of the study.

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	Overall trial

Arm description:

The study consisted of an intravenous immunoglobulin (IVIG) treatment period with 3 infusions, a 12-week subcutaneous immunoglobulin (SCIG) wash-in/washout period, and a 12-week SCIG efficacy period (i.e. 24 weeks of SCIG treatment with IgPro20):
 • IVIG treatment: Study subjects continued their previous IVIG therapy regimen with 3- or 4-weekly schedules for 3 dosing cycles (9 to 12 weeks; before being switched to SCIG treatment with IgPro20).
 • SCIG treatment (wash-in/wash-out; weeks 1 to 12): IgPro20 was administered subcutaneously with the first subcutaneous (SC) IgPro20 infusion starting 1 week after the last IVIG dose. Subjects were treated with weekly SC IgPro20 infusions for a 12-week wash-in/wash-out period.
 • SCIG treatment (efficacy; weeks 13 to 24): After the SCIG wash-in/wash-out treatment, subjects were treated with weekly SC IgPro20 infusions for a 12-week efficacy period.

Arm type	Experimental
Investigational medicinal product name	Immune Globulin Subcutaneous (Human) (SCIG)
Investigational medicinal product code	IgPro20
Other name	Hizentra, Human Normal Immunoglobulin
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. Subjects receive weekly infusions of IgPro20 at a weekly dosage calculated based on previous IVIG treatment.

Number of subjects in period 1	Overall trial
Started	25
IVIG Treatment	25
SCIG Treatment (Wash-in/Wash-out)	25
SCIG Treatment (Efficacy)	24
Completed	24
Not completed	1
'Transfer of Residence '	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

The study consisted of an intravenous immunoglobulin (IVIG) treatment period with 3 infusions, a 12-week subcutaneous immunoglobulin (SCIG) wash-in/washout period, and a 12-week SCIG efficacy period (i.e. 24 weeks of SCIG treatment with IgPro20):
 • IVIG treatment: Study subjects continued their previous IVIG therapy regimen with 3- or 4-weekly schedules for 3 dosing cycles (9 to 12 weeks; before being switched to SCIG treatment with IgPro20).
 • SCIG treatment (wash-in/wash-out; weeks 1 to 12): IgPro20 was administered subcutaneously with the first subcutaneous (SC) IgPro20 infusion starting 1 week after the last IVIG dose. Subjects were treated with weekly SC IgPro20 infusions for a 12-week wash-in/wash-out period.
 • SCIG treatment (efficacy; weeks 13 to 24): After the SCIG wash-in/wash-out treatment, subjects were treated with weekly SC IgPro20 infusions for a 12-week efficacy period.

Reporting group values	Overall trial	Total	
Number of subjects	25	25	
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)	7	7	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	13	13	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	20.6		
standard deviation	± 13.23	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	16	16	
Primary Immunodeficiency Type			
Units: Subjects			
Common Variable Immunodeficiency (CVID)	10	10	
X-Linked Agammaglobulinemia (XLA)	13	13	
Autosomal Recessive Agammaglobulinemia (ARAG)	1	1	
Hyper-Immunoglobulin M (IgM) Syndrome	1	1	

End points

End points reporting groups

Reporting group title	Overall trial

Reporting group description:

The study consisted of an intravenous immunoglobulin (IVIG) treatment period with 3 infusions, a 12-week subcutaneous immunoglobulin (SCIG) wash-in/washout period, and a 12-week SCIG efficacy period (i.e. 24 weeks of SCIG treatment with IgPro20):
 • IVIG treatment: Study subjects continued their previous IVIG therapy regimen with 3- or 4-weekly schedules for 3 dosing cycles (9 to 12 weeks; before being switched to SCIG treatment with IgPro20).
 • SCIG treatment (wash-in/wash-out; weeks 1 to 12): IgPro20 was administered subcutaneously with the first subcutaneous (SC) IgPro20 infusion starting 1 week after the last IVIG dose. Subjects were treated with weekly SC IgPro20 infusions for a 12-week wash-in/wash-out period.
 • SCIG treatment (efficacy; weeks 13 to 24): After the SCIG wash-in/wash-out treatment, subjects were treated with weekly SC IgPro20 infusions for a 12-week efficacy period.

Subject analysis set title	IgPro20 - Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS data set comprised all subjects with the disease under study who fulfilled the protocol-specified criteria for a) uniformly repeated immunoglobulin treatment prior to and during the study, b) availability of evaluable serum IgG levels, and c) dose stability.

Subject analysis set title	IgPro20 - Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS comprised all subjects treated with IgPro20 during the SCIG efficacy period (weeks 13 to 24) who had the disease under study.

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

Subject analysis set description:

Study subjects were treated with their IVIG therapy with 3- or 4-weekly schedules for 3 dosing cycles (9 to 12 weeks). The PPS data set comprised all subjects with the disease under study who fulfilled the protocol-specified criteria for a) uniformly repeated immunoglobulin treatment prior to and during the study, b) availability of evaluable serum IgG levels, and c) dose stability.

Subject analysis set title	SCIG Treatment (Wash-in/Wash-out)(PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

Weekly SC IgPro20 infusions for a 12-week wash-in/wash-out period (weeks 1 to 12). The IgPro20 dose was to be equal to the weekly equivalent dose of the previous IVIG therapy. The PPS data set comprised all subjects with the disease under study who fulfilled the protocol-specified criteria for a) uniformly repeated immunoglobulin treatment prior to and during the study, b) availability of evaluable serum IgG levels, and c) dose stability.

Subject analysis set title	SCIG Treatment (Efficacy)(PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

Weekly SC IgPro20 infusions for a 12-week efficacy period (weeks 13 to 24). The IgPro20 dose was to be equal to the weekly equivalent dose of the previous IVIG therapy. The PPS data set comprised all subjects with the disease under study who fulfilled the protocol-specified criteria for a) uniformly repeated immunoglobulin treatment prior to and during the study, b) availability of evaluable serum IgG levels, and c) dose stability.

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

Subject analysis set description:

Subjects were treated with their IVIG therapy with 3- or 4-weekly schedules for 3 dosing cycles (9 to 12 weeks). The FAS comprised all subjects treated with IgPro20 during the SCIG efficacy period (weeks 13 to 24) who had the disease under study.

Subject analysis set title	SCIG Treatment (Wash-in/Wash-out)(FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Weekly SC IgPro20 infusions for a 12-week wash-in/wash-out period (weeks 1 to 12). The IgPro20 dose was to be equal to the weekly equivalent dose of the previous IVIG therapy. The FAS comprised all subjects treated with IgPro20 during the SCIG efficacy period (weeks 13 to 24) who had the disease under study.

Subject analysis set title	SCIG Treatment (Efficacy)(FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Weekly SC IgPro20 infusions for a 12-week efficacy period (weeks 13 to 24). The IgPro20 dose was to be equal to the weekly equivalent dose of the previous IVIG therapy. The FAS comprised all subjects treated with IgPro20 during the SCIG efficacy period (weeks 13 to 24) who had the disease under study.

Subject analysis set title	IVIG Treatment (SDS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Study subjects were treated with their IVIG therapy with 3- or 4-weekly schedules for 3 dosing cycles (9 to 12 weeks). The safety data set (SDS) comprised all subjects treated with the study drug.

Subject analysis set title	SCIG Treatment (SDS)
Subject analysis set type	Safety analysis

Subject analysis set description:

IgPro20 was administered subcutaneously with the first SC IgPro20 infusion starting 1 week after the last IVIG dose. Subjects were treated with weekly SC IgPro20 infusions for a 12-week wash-in/wash-out period followed by a 12-week efficacy period. The IgPro20 dose was to be equal to the weekly equivalent dose of the previous IVIG IgG treatment. The safety data set (SDS) comprised all subjects treated with the study drug.

Primary: IgG Trough Level

End point title	IgG Trough Level[1]

End point description:

Geometric means of trough levels measured before 3 intravenous immunoglobulin (IVIG) infusions was compared with those of trough levels measured at steady-state for 3 subcutaneous immunoglobulin (SCIG) infusions (weeks 16, 20 and 24). The ratio of these geometric means was the primary outcome measure.

End point type	Primary

End point timeframe:

During IVIG period (IV 1, IV 2, IV 3) and during SCIG period at weeks 16, 20, and 24

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 statistical analysis for this endpoint, being the comparison of the geometric mean trough level of the IVIG and SCIG groups, calculated as a ratio with an associated 90% confidence interval and presented herein, was the primary endpoint.

End point values	IgPro20 - Per Protocol Set (PPS)	IgPro20 - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	24		
Units: ratio of geometric means				
number (confidence interval 90%)	1.09 (1.06 to 1.13)	1.11 (1.08 to 1.15)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Infection Episodes (Serious and Non-serious) by Study Period

End point description:

Number of infection episodes (serious and non-serious) presented by study period:
•IVIG treatment: Study subjects were treated with their IVIG therapy with 3- or 4-weekly schedules for 3 dosing cycles (9 to 12 weeks; before being switched to SCIG treatment with IgPro20).
•SCIG treatment (wash-in/wash-out; weeks 1 to 12): IgPro20 was administered subcutaneously with the first subcutaneous (SC) IgPro20 infusion starting 1 week after the last IVIG dose. Subjects were treated with weekly SC IgPro20 infusions for a 12-week wash-in/wash-out period. The IgPro20 dose was to be equal to the weekly equivalent dose of the previous IVIG therapy.
•SCIG treatment (efficacy; weeks 13 to 24): After the SCIG wash-in/wash-out treatment, subjects were treated with weekly SC IgPro20 infusions for a 12-week efficacy period. The IgPro20 dose was to be equal to the weekly equivalent dose of the previous IVIG therapy.

End point type	Secondary

End point timeframe:

Up to 36 weeks

End point values	IgPro20 - Per Protocol Set (PPS)	IgPro20 - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	24		
Units: number of infection episodes				
IVIG Treatment	19	22		
SCIG IgPro20 Treatment (Wash-in/Wash-out)	28	32		
SCIG IgPro20 Treatment (Efficacy)	15	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Infection Episodes (Serious and Non-serious) by Study Period, PPS Population

End point title	Rate of Infection Episodes (Serious and Non-serious) by Study Period, PPS Population

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 specified study periods (listed below) and analysis population and adjusted to 365 days.

Study periods:
•IVIG treatment (up to 12 weeks)
•SCIG IgPro20 treatment (wash-in/wash-out period) (12 weeks)
•SCIG IgPro20 treatment (efficacy) (12 weeks)

End point type	Secondary

End point timeframe:

Up to 36 weeks

End point values	IVIG Treatment (PPS)	SCIG Treatment (Wash-in/Wash-out)(PPS)	SCIG Treatment (Efficacy)(PPS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21[2]	21[3]	21[4]	
Units: infections per subject year				
number (not applicable)	5.74	5.79	2.98	

Notes:

[2] - Number of Subject Study Days Analyzed: 1209

[3] - Number of Subject Study Days Analyzed: 1764

[4] - Number of Subject Study Days Analyzed: 1840

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Infection Episodes (Serious and Non-serious) by Study Period, FAS Population

End point title	Rate of Infection Episodes (Serious and Non-serious) by Study Period, FAS Population

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 specified study periods (listed below) and analysis population and adjusted to 365 days.

Study periods:
•IVIG treatment (up to 12 weeks)
•SCIG IgPro20 treatment (wash-in/wash-out period) (12 weeks)
•SCIG IgPro20 treatment (efficacy) (12 weeks)

End point type	Secondary

End point timeframe:

Up to 36 weeks

End point values	IVIG Treatment (FAS)	SCIG Treatment (Wash-in/Wash-out)(FAS)	SCIG Treatment (Efficacy)(FAS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24[5]	24[6]	24[7]	
Units: Infections per subject year				
number (not applicable)	5.75	5.79	3.14	

Notes:

[5] - Number of Subject Study Days Analyzed = 1396

[6] - Number of Subject Study Days Analyzed = 2016

[7] - Number of Subject Study Days Analyzed = 2095

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 by Study Period

End point title	Number of Days Out of Work/School/Kindergarten/Day Care or Unable to Perform Normal Daily Activities Due to Infections by Study Period

End point description:

Median number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections, presented by study period: IVIG treatment (up to 12 weeks), SCIG IgPro20 treatment (wash-in/wash-out; 12 weeks), and SCIG IgPro20 treatment (efficacy; 12 weeks).

End point type	Secondary

End point timeframe:

Up to 36 weeks

End point values	IgPro20 - Per Protocol Set (PPS)	IgPro20 - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	24		
Units: days				
median (full range (min-max))				
IVIG Treatment	0 (0 to 8)	0 (0 to 8)		
SCIG IgPro20 Treatment (Wash-in/Wash-out)	0 (0 to 9)	0 (0 to 9)		
SCIG IgPro20 Treatment (Efficacy)	0 (0 to 8)	0 (0 to 8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days of Hospitalization Due to Infections by Study Period

End point title	Number of Days of Hospitalization Due to Infections by Study Period

End point description:

Median number of days of hospitalization due to infections, presented by study period: IVIG treatment (up to 12 weeks), SCIG IgPro20 treatment (wash-in/wash-out; 12 weeks), and SCIG IgPro20 treatment (efficacy; 12 weeks).

End point type	Secondary

End point timeframe:

Up to 36 weeks

End point values	IgPro20 - Per Protocol Set (PPS)	IgPro20 - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	24		
Units: days				
median (full range (min-max))				
IVIG Treatment	0 (0 to 1)	0 (0 to 1)		
SCIG IgPro20 Treatment (Wash-in/Wash-out)	0 (0 to 0)	0 (0 to 0)		
SCIG IgPro20 Treatment (Efficacy)	0 (0 to 3)	0 (0 to 3)		

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, presented by study period: IVIG treatment (up to 12 weeks), SCIG IgPro20 treatment (wash-in/wash-out; 12 weeks), and SCIG IgPro20 treatment (efficacy; 12 weeks).

End point type	Secondary

End point timeframe:

Up to 36 weeks

End point values	IgPro20 - Per Protocol Set (PPS)	IgPro20 - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	24		
Units: days				
median (full range (min-max))				
IVIG Treatment	48.5 (2 to 64)	48 (2 to 64)		
SCIG IgPro20 Treatment (Wash-in/Wash-out)	49 (3 to 86)	35.5 (2 to 86)		
SCIG IgPro20 Treatment (Efficacy)	71 (6 to 85)	71 (6 to 85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of All Adverse Events by Relatedness and Seriousness

End point title	Rate of All Adverse Events by Relatedness and Seriousness

End point description:

The rate of adverse events (AEs) was the number of treatment-emergent AEs over the number of infusions administered. At least possibly related AEs included possibly related AEs, probably related AEs, and related AEs.

End point type	Secondary

End point timeframe:

For the duration of the study, up to 36 weeks

End point values	IVIG Treatment (SDS)	SCIG Treatment (SDS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25[8]	25[9]		
Units: AEs per infusion				
number (not applicable)				
All AEs	0.653	0.457		
At Least Possibly Related AEs	0.027	0.296		
Serious AEs	0	0.002		
At Least Possibly Related and Serious AEs	0	0		

Notes:

[8] - Number of infusions analyzed: 75

[9] - Number of infusions analyzed: 584

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Mild, Moderate, or Severe Local Reactions

End point title	Rate of Mild, Moderate, or Severe Local Reactions

End point description:

In addition to the standard MedDRA System Organ Class (SOC) AE assignments, the category of 'local reactions' was defined to provide the possibility for a combined analysis of local reactions and included AEs of: infusion site discomfort, infusion site erythema, infusion site haemorrhage, infusion site induration, infusion site inflammation, infusion site pain, infusion site pruritus, infusion site swelling, injection site erythema, injection site extravasation, injection site induration, injection site irritation, injection site pain, injection site pruritus, injection site swelling, and puncture site reaction.

Mild AE: Symptoms are easily tolerated and there is no interference with daily activities; Moderate AE: Discomfort enough to cause some interference with daily activities; Severe AE: Incapacitating with inability to work or do usual activity.

End point type	Secondary

End point timeframe:

For the duration of the study, up to 36 weeks

End point values	IVIG Treatment (SDS)	SCIG Treatment (SDS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25[10]	25[11]		
Units: AEs per infusion				
number (not applicable)				
Mild Local Reactions	0	0.274		
Moderate Local Reactions	0	0		
Severe Local Reactions	0	0		

Notes:

[10] - Number of infusions analyzed: 75

[11] - Number of infusions analyzed: 584

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Annualized Rate of Serious Bacterial Infections (SBIs), PPS Population

End point title	Annualized Rate of Serious Bacterial Infections (SBIs), PPS Population

End point description:

The annualized rate was based on the total number of SBIs and the total number of subject study days for all subjects in the specified study periods (listed below) and analysis population and adjusted to 365 days.
Study periods:
•IVIG treatment (up to 12 weeks)
•SCIG IgPro20 treatment (wash-in/wash-out; 12 weeks)
•SCIG IgPro20 treatment (efficacy; 12 weeks)

End point type	Other pre-specified

End point timeframe:

Up to 36 weeks

End point values	IVIG Treatment (PPS)	SCIG Treatment (Wash-in/Wash-out)(PPS)	SCIG Treatment (Efficacy)(PPS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21[12]	21[13]	21[14]	
Units: SBIs per subject year				
number (not applicable)	0	0	0	

Notes:

[12] - Number of subject days analyzed: 1209

[13] - Number of subject days analyzed: 1764

[14] - Number of subject days analyzed: 1840

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Annualized Rate of Serious Bacterial Infections (SBIs), FAS

Population

End point title	Annualized Rate of Serious Bacterial Infections (SBIs), FAS Population

End point description:

The annualized rate was based on the total number of SBIs and the total number of subject study days for all subjects in the specified study periods (listed below) and analysis population and adjusted to 365 days.
Study periods:
•IVIG treatment (up to 12 weeks)
•SCIG IgPro20 treatment (wash-in/wash-out; 12 weeks)
•SCIG IgPro20 treatment (efficacy; 12 weeks)

End point type	Other pre-specified

End point timeframe:

Up to 36 weeks

End point values	IVIG Treatment (FAS)	SCIG Treatment (Wash-in/Wash-out)(FAS)	SCIG Treatment (Efficacy)(FAS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24[15]	24[16]	24[17]	
Units: SBIs per subject year				
number (not applicable)	0	0	0	

Notes:

[15] - Number of subject days analyzed: 1396

[16] - Number of subject days analyzed: 2016

[17] - Number of subject days analyzed: 2095

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, up to 36 weeks	
Adverse event reporting additional description:	
Safety data set (SDS) comprised all subjects treated with the study drug. All SAEs are presented including a pre-treatment SAE of gastroenteritis. In Other AEs, non-serious AEs starting at or after the first study drug infusion are presented. A total of 75 IVIG and 584 SCIG infusions of IgPro20 were administered to 25 subjects during the study.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	IVIG Treatment (SDS)
Reporting group description:	
Study subjects were treated with their IVIG therapy with 3- or 4-weekly schedules for 3 dosing cycles (9 to 12 weeks). The safety data set (SDS) comprised all subjects treated with the study drug.	
Reporting group title	SCIG Treatment (SDS)
Reporting group description:	
IgPro20 was administered subcutaneously with the first SC IgPro20 infusion starting 1 week after the last IVIG dose. Subjects were treated with weekly SC IgPro20 infusions for a 12-week wash-in/wash-out period followed by a 12-week efficacy period. The IgPro20 dose was to be equal to the weekly equivalent dose of the previous IVIG IgG treatment. The safety data set (SDS) comprised all subjects treated with the study drug.	

Serious adverse events	IVIG Treatment (SDS)	SCIG Treatment (SDS)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis	Additional description: This SAE occurred between screening and the first IVIG dose and was thus non-treatment-emergent.		
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IVIG Treatment (SDS)	SCIG Treatment (SDS)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 25 (80.00%)	24 / 25 (96.00%)	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	7	
Contusion			
subjects affected / exposed	2 / 25 (8.00%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 25 (12.00%)	1 / 25 (4.00%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Local reactions	Additional description: Local reactions cover MedDRA PTs: infusion site: discomfort, erythema, haemorrhage, induration, inflammation, pain, pruritus, swelling; injection site: erythema, extravasation, induration, irritation, pain, pruritus, swelling; puncture site reaction.		
subjects affected / exposed	0 / 25 (0.00%)	20 / 25 (80.00%)	
occurrences (all)	0	160	
Malaise			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	1 / 25 (4.00%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Vomiting			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	9	
Infections and infestations			

Bronchitis		
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	3
Conjunctivitis infective		
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)
occurrences (all)	1	2
Gastroenteritis		
subjects affected / exposed	1 / 25 (4.00%)	3 / 25 (12.00%)
occurrences (all)	1	5
Influenza		
subjects affected / exposed	4 / 25 (16.00%)	4 / 25 (16.00%)
occurrences (all)	4	4
Nasopharyngitis		
subjects affected / exposed	5 / 25 (20.00%)	11 / 25 (44.00%)
occurrences (all)	8	21
Sinusitis		
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	3
Upper respiratory tract infection		
subjects affected / exposed	4 / 25 (16.00%)	5 / 25 (20.00%)
occurrences (all)	4	8
Pharyngitis		
subjects affected / exposed	3 / 25 (12.00%)	1 / 25 (4.00%)
occurrences (all)	3	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2010	The first amendment (i.e., version 2.0) was dated 09 June 2010. The rationale for this amendment were changes based on discussions with the PMDA, updates to the original study concept to reflect the current scientific knowledge in PID treatment, and experience from ongoing or completed CSL Behring studies with IgPro20 in regions outside of Japan.
09 September 2010	The rationale for the 2nd and final amendment (i.e., version 3.0) was to incorporate changes based on further discussions with the PMDA during the 30-days review period. All subjects in the study were treated according to this study protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25236916

http://www.ncbi.nlm.nih.gov/pubmed/24504846