Clinical trial results:
Study of immune deficiency patients treated with subcutaneous immunoglobulin (IgPro20, Hizentra®) on weekly and biweekly schedules

Summary

EudraCT number	2015-004977-34
Trial protocol	Outside EU/EEA
Global end of trial date	30 January 2018

Results information

Result version number	v1 (current)
This version publication date	09 August 2018
First version publication date	09 August 2018

Trial information

Trial identification

Sponsor protocol code	IgPro20_4005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02711228
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring, LLC
Sponsor organisation address	1020 First Avenue, King of Prussia, United States, 19406
Public contact	Trial Registration Coordinator, CSL Behring, LLC, clinicaltrials@cslbehring.com
Scientific contact	Trial Registration Coordinator, CSL Behring, LLC, 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	01 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To determine tolerability and safety of biweekly IgPro20 injection regimen
- To assess the pharmacokinetics of weekly and biweekly IgPro20 injections

Protection of trial subjects:

This study was carried out 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2016
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	Canada: 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)	8
Adolescents (12-17 years)	7
Adults (18-64 years)	9
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited between 15Mar2016 and 11Oct2016 from the Investigators' clinical practices.

Pre-assignment

Screening details:

Patients who have a documented diagnosis of primary immune deficiency (PID) and secondary immune deficiency (SID), who were on a stable dosing regimen of immunoglobulin (IgG) replacement therapy at screening.

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 (Hizentra)

Arm description:

Commercially available Hizentra was used for this study at doses that were consistent with the approved weekly and biweekly Hizentra therapy regimens for patients with immune deficiency.

Arm type	Experimental
Investigational medicinal product name	Hizentra, Subcutaneous Immune Globulin (Human) (SCIg)
Investigational medicinal product code	IgPro20
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Commercially available Hizentra was used for this study at doses that were consistent with the approved weekly and biweekly Hizentra therapy regimens for patients with immune deficiency. In Part 1, all subjects were observed for 12 weeks on a weekly Hizentra home infusion treatment regimen. In Part 2, subjects were observed for up to 52 weeks on a biweekly Hizentra home infusion treatment regimen. Part 2 of the study began immediately after the end of Part 1, with the first biweekly Hizentra infusion occurring 2 weeks after the last weekly infusion of Hizentra.

Number of subjects in period 1	IgPro20 (Hizentra)
Started	25
Completed	16
Not completed	9
Adverse event, non-fatal	1
Travel abroad	2
Refuse to continue to do 8 infusion sites	1
Patient schedule	1
Mother unable to come	2
Subject choice	1

Child does not accept to have 4 infusion sites	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

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)	8	8	
Adolescents (12-17 years)	7	7	
Adults (18-64 years)	9	9	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	23.6		
standard deviation	± 17.93	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	14	14	

End points

End points reporting groups

Reporting group title	IgPro20 (Hizentra)

Reporting group description:

Commercially available Hizentra was used for this study at doses that were consistent with the approved weekly and biweekly Hizentra therapy regimens for patients with immune deficiency.

Subject analysis set title	All Treated Subjects Analysis Set (ATS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All Treated Subjects Analysis Set (ATS): all subjects in the Enrolled analysis set who receive at least one dose of Hizentra, regardless of treatment regimen.

Subject analysis set title	Pharmacokinetic Analysis Set (PK)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pharmacokinetic Analysis Set (PK): all subjects in the PK subset who have at least 1 post-infusion sample taken and analyzed for 1 of the 2 PK parts

Subject analysis set title	Modified ITT Analysis Set (MITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified ITT Analysis Set (MITT): all subjects in the ITT analysis set who receive at least 1 dose of biweekly Hizentra and have at least 1 QoL questionnaire filled.

Primary: Annualized Rate of Treatment Emergent Adverse Events (TEAEs) (ATS)

End point title	Annualized Rate of Treatment Emergent Adverse Events (TEAEs) (ATS)[1]

End point description:

The annualized rate of TEAEs was calculated per subject as the number of TEAEs in the respective regimen divided by the days treated in the respective
treatment regimen multiplied by 365.25.

End point type	Primary

End point timeframe:

During biweekly treatment period, up to approximately 52 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: Only descriptive statistics were used for this endpoint.

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Rate per subject				
arithmetic mean (standard deviation)				
Local TEAEs	0.18 (± 0.509)			
Any TEAEs	4.14 (± 4.787)			

Statistical analyses

No statistical analyses for this end point

Primary: Area under the concentration-time curve [AUC(0-t)] for IgPro20 (PK)

End point title	Area under the concentration-time curve [AUC(0-t)] for IgPro20 (PK)[2]

End point description:

End point type	Primary

End point timeframe:

Up to 7 days after infusion during the weekly treatment period and up to 14 days after infusion during the biweekly treatment periods.

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: Only descriptive statistics were used for this endpoint.

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: h*g/L				
arithmetic mean (standard deviation)				
Weekly (n=17)	1770.62 (± 279.119)			
Biweekly (n=15)	3683.26 (± 655.535)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximal serum IgG concentration of IgPro20 (Cmax) for IgPro20 (PK)

End point title	Maximal serum IgG concentration of IgPro20 (Cmax) for IgPro20 (PK)[3]

End point description:

End point type	Primary

End point timeframe:

Up to 7 days after infusion during the weekly treatment period and up to 14 days after infusion during the biweekly treatment periods

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were used for this endpoint.

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: g/L				
arithmetic mean (standard deviation)				
Weekly (n=17)	11.09 (± 1.659)			
Biweekly (n=15)	11.97 (± 2.024)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to maximal serum IgG concentration (Tmax) for IgPro20 (PK)

End point title	Time to maximal serum IgG concentration (Tmax) for IgPro20 (PK)[4]

End point description:

End point type	Primary

End point timeframe:

Up to 7 days after infusion during the weekly treatment period and up to 14 days after infusion during the biweekly treatment periods.

Notes:

[4] - 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: Only descriptive statistics were used for this endpoint.

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: days				
median (full range (min-max))				
Weekly (n=17) Biweekly (n=15)	2.02 (0 to 5.1) 3.02 (2.0 to 7.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Trough serum IgG concentration (Ctrough) for IgPro20 (PK)

End point title	Trough serum IgG concentration (Ctrough) for IgPro20 (PK)[5]

End point description:

End point type	Primary

End point timeframe:

Up to 7 days after infusion during the weekly treatment period and up to 14 days after infusion during the biweekly treatment periods.

Notes:

[5] - 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: Only descriptive statistics were used for this endpoint.

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: g/L				
arithmetic mean (standard deviation)				
Weekly (n=17)	10.32 (± 1.573)			
Biweekly (n=15)	10.13 (± 1.940)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rate of infections per subject (ATS)

End point title	Annualized rate of infections per subject (ATS)

End point description:

End point type	Secondary

End point timeframe:

During weekly (up to 6 weeks) and biweekly treatment periods (up to 52 weeks)

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Rate per subject				
arithmetic mean (standard deviation)				
Weekly (n=25)	2.43 (± 3.146)			
Biweekly (n=24)	1.22 (± 1.641)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life using the SF-36 short form during weekly regimen (MITT)

End point title	Quality of life using the SF-36 short form during weekly regimen (MITT)

End point description:

End point type	Secondary

End point timeframe:

Week 6

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: scores				
arithmetic mean (standard deviation)				
Physical summary score	51.45 (± 6.480)			
Mental summary score	51.27 (± 7.807)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life using the SF-36 short form during biweekly regimen (MITT)

End point title	Quality of life using the SF-36 short form during biweekly regimen (MITT)

End point description:

End point type	Secondary

End point timeframe:

Week 52

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: scores				
arithmetic mean (standard deviation)				
Physical score	51.25 (± 7.056)			
Mental score	49.20 (± 8.727)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life using the CHQ-PF28 (Child Health Questionnaire Parent Form 28): for age < 10 years during weekly regimen (MITT)

End point title	Quality of life using the CHQ-PF28 (Child Health Questionnaire

	Parent Form 28): for age < 10 years during weekly regimen (MITT)

End point description:

End point type	Secondary

End point timeframe:

Week 6

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Scores				
arithmetic mean (standard deviation)				
Physical Summary Score	49.82 (± 4.631)			
Psychosocial summary score	41.99 (± 18.248)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life using the CHQ-PF28 (Child Health Questionnaire Parent Form 28): for age < 10 years during biweekly regimen (MITT)

End point title	Quality of life using the CHQ-PF28 (Child Health Questionnaire Parent Form 28): for age < 10 years during biweekly regimen (MITT)

End point description:

End point type	Secondary

End point timeframe:

Week 52

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Scores				
arithmetic mean (standard deviation)				
Physical summary score	43.98 (± 17.308)			
Psychosocial summary score	37.38 (± 5.336)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life using the CHQ-CF87 (Child Health Questionnaire Child Form 87): for age ≥ 10 years during weekly regimen (MITT)

End point title	Quality of Life using the CHQ-CF87 (Child Health Questionnaire Child Form 87): for age ≥ 10 years during weekly regimen (MITT)

End point description:

End point type	Secondary

End point timeframe:

Week 6

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: scores				
arithmetic mean (standard deviation)				
Global health	84.44 (± 15.501)			
Physical functioning	100 (± 0)			
Role/Social limitations-physical	98.77 (± 3.704)			
Bodily pain	76.67 (± 15.811)			
Behavior	89.12 (± 11.606)			
Global behavior	84.44 (± 15.501)			
Mental health	81.77 (± 13.166)			
Self esteem	81.35 (± 15.338)			
General health perceptions	73.01 (± 18.478)			
Change in health	4 (± 1)			
Family activities	92.59 (± 20.706)			
Family cohesion	84.44 (± 15.501)			
Role/Social limitations-emotional	98.77 (± 3.704)			
Role/Social limitations-behavioral	100 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life using the CHQ-CF87 (Child Health Questionnaire Child Form 87): for age ≥ 10 years during biweekly regimen (MITT)

End point title	Quality of Life using the CHQ-CF87 (Child Health Questionnaire Child Form 87): for age ≥ 10 years during biweekly regimen (MITT)

End point description:

End point type	Secondary

End point timeframe:

Week 52

End point values	IgPro20 (Hizentra)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Scores				
arithmetic mean (standard deviation)				
Global health	75 (± 13.693)			
Physical functioning	98.52 (± 3.313)			
Role/Social limitations-physical	100 (± 0)			
Bodily pain	78 (± 20.494)			
Behavior	88.88 (± 16.516)			
Global behavior	86 (± 16.355)			
Mental health	85.31 (± 16.850)			
Self esteem	87.14 (± 15.330)			
General health perceptions	65.83 (± 9.247)			
Change in health	3.4 (± 0.894)			
Family activities	95 (± 11.18)			
Family cohesion	89 (± 17.464)			
Role/Social limitations-emotional	97.78 (± 4.969)			
Role/Social limitations-behavioral	97.78 (± 4.969)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
1 year, 4 months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	IgPro20 (Hizentra)

Reporting group description:

Commercially available Hizentra was used for this study at doses that were consistent with the approved weekly and biweekly Hizentra therapy regimens for patients with immune deficiency.

Serious adverse events	IgPro20 (Hizentra)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 25 (4.00%)		
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 (Hizentra)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 25 (84.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	5		
Migraine			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Paraesthesia			

subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Injection site pain			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Tendonitis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Infections and infestations			
Ear infection			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	9 / 25 (36.00%)		
occurrences (all)	9		
Sinusitis			

subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported