Clinical trial results:
Comparison of 2 Infusion Devices with Respect to Pharmacokinetics, Safety, and Tolerability of Hizentra®: Investigational Wearable Infusor and the Crono S-PID-50 Infusion Pump

Summary

EudraCT number	2016-003798-16
Trial protocol	Outside EU/EEA
Global end of trial date	19 August 2019

Results information

Result version number	v1 (current)
This version publication date	05 March 2020
First version publication date	05 March 2020

Trial information

Trial identification

Sponsor protocol code	IgPro20_1001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	CSL Behring
Sponsor organisation address	Emil-von-Behring-Str. 76, Marburg, Germany,
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	17 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the AUC0-7 days of IgG during the last week of each study period (Weeks 4 & 8) after subcutaneous (SC) infusion of the same IgPro20 dose with the Investigational Wearable Infusor (IWI) vs Crono S-PID-50 Infusion Pump (CP) in PID patients.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and standard operating procedures for clinical research and development at CSL Behring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2018
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	United States: 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)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	15
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 30 subjects were screened, of which 23 subjects were enrolled. This is a crossover study in which subjects were then randomized into either Sequence 1 or Sequence 2.
• Sequence 1: IgPro20 administered with CP in Period 1 and with IWI in Period 2.
• Sequence 2: IgPro20 administered with IWI in Period 1 and with CP in Period 2.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Crono S-PID50 Pump (CP)

Arm description:

A liquid formulation of normal human IgG at a concentration of 20% administered via the Crono S-PID50 Pump as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Arm type	Active comparator
Investigational medicinal product name	Hizentra
Investigational medicinal product code	
Other name	IgPro20, Human normal immunoglobulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

A liquid formulation of normal human IgG at a concentration of 20% administered as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Arm title	Investigational Wearable Infusor (IWI)

Arm description:

A liquid formulation of normal human IgG at a concentration of 20% administered via the Investigational Wearable Infusor (IWI) as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Arm type	Experimental
Investigational medicinal product name	Hizentra
Investigational medicinal product code	
Other name	IgPro20, Human normal immunoglobulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

A liquid formulation of normal human IgG at a concentration of 20% administered as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Number of subjects in period 1	Crono S-PID50 Pump (CP)	Investigational Wearable Infusor (IWI)
Started	11	12
Completed	10	12
Not completed	1	0
Failure to meet randomization criteria	1	-

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Crono S-PID50 Pump (CP)

Arm description:

A liquid formulation of normal human IgG at a concentration of 20% administered via the Crono S-PID50 Pump as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Arm type	Active comparator
Investigational medicinal product name	Hizentra
Investigational medicinal product code	
Other name	IgPro20, Human normal immunoglobulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

A liquid formulation of normal human IgG at a concentration of 20% administered as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Arm title	Investigational Wearable Infusor (IWI)

Arm description:

A liquid formulation of normal human IgG at a concentration of 20% administered via the Investigational Wearable Infusor (IWI) as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Arm type	Experimental
Investigational medicinal product name	Hizentra
Investigational medicinal product code	
Other name	IgPro20, Human normal immunoglobulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

A liquid formulation of normal human IgG at a concentration of 20% administered as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Number of subjects in period 2	Crono S-PID50 Pump (CP)	Investigational Wearable Infusor (IWI)
Started	10	12
Completed	10	12

Baseline characteristics

Reporting groups	
Reporting group title	Period 1

Reporting group description:

This is a crossover study so subjects were randomized into either Sequence 1 or into Sequence 2.
- Sequence 1: IgPro20 administered with CP in Period 1 and with IWI in Period 2.
- Sequence 2: IgPro20 administered with IWI in Period 1 and with CP in Period 2.

Reporting group values	Period 1	Total	
Number of subjects	23	23	
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)	0	0	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	15	15	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	50.7		
standard deviation	± 16.84	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	5	5	

End points

End points reporting groups

Reporting group title	Crono S-PID50 Pump (CP)

Reporting group description:

A liquid formulation of normal human IgG at a concentration of 20% administered via the Crono S-PID50 Pump as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Reporting group title	Investigational Wearable Infusor (IWI)

Reporting group description:

A liquid formulation of normal human IgG at a concentration of 20% administered via the Investigational Wearable Infusor (IWI) as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Reporting group title	Crono S-PID50 Pump (CP)

Reporting group description:

A liquid formulation of normal human IgG at a concentration of 20% administered via the Crono S-PID50 Pump as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Reporting group title	Investigational Wearable Infusor (IWI)

Reporting group description:

A liquid formulation of normal human IgG at a concentration of 20% administered via the Investigational Wearable Infusor (IWI) as a weekly subcutaneous infusion at the subject's individual pre-study steady-state therapeutic dose

Subject analysis set title	CP (PKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Pharmacokinetic Analysis Set (PKS) comprised of all evaluable subjects who used the correct device in each treatment period, completed all the IgPro20 infusions with dosing within ±◦20% of an average prescribed weekly dose, and had at least 1 quantifiable PK measurement after CP infusions.

Subject analysis set title	CP (SPKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK Sensitivity Analysis Set (SPKS) comprised of all evaluable subjects who had used the correct device in each treatment period had at least 1 quantifiable PK measurement after CP infusions.

Subject analysis set title	CP (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set (SAF) comprised of all subjects in the FAS who received at least 1 complete or partial dose of IgPro20 with CP infusions. The Full Analysis Set (FAS) comprised of all subjects who provided informed consent/assent and who were randomized.

Subject analysis set title	IWI (PKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Pharmacokinetic Analysis Set (PKS) comprised of all evaluable subjects who used the correct device in each treatment period, completed all the IgPro20 infusions with dosing within ±◦20% of an average prescribed weekly dose, and had at least 1 quantifiable PK measurement after IWI infusions.

Subject analysis set title	IWI (SPKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK Sensitivity Analysis Set (SPKS) comprised of all evaluable subjects who had used the correct device in each treatment period had at least 1 quantifiable PK measurement after IWI infusions.

Subject analysis set title	IWI (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set (SAF) comprised of all subjects in the FAS who received at least 1 complete or partial dose of IgPro20 with IWI infusions. The Full Analysis Set (FAS) comprised of all subjects who

provided informed consent/assent and who were randomized.

Primary: Area under IgG concentration-time curve (AUC0-7 days) of IgG during the last weekly dosing interval for each period for each device group for IgPro20

End point title	Area under IgG concentration-time curve (AUC0-7 days) of IgG during the last weekly dosing interval for each period for each device group for IgPro20

End point description:

End point type	Primary

End point timeframe:

Up to 7 days after infusion

End point values	CP (PKS)	IWI (PKS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[1]	12[2]		
Units: h*g/L				
geometric mean (standard deviation)				
Period 1 (CP, n=8; IWI, n=12)	1767 (± 1.12)	1864 (± 1.23)		
Period 2 (CP, n=12; IWI, n=8)	1871 (± 1.21)	1724 (± 1.09)		

Notes:

[1] - Due to crossover: CP (n=20)

[2] - Due to crossover: IWI (n=20)

Statistical analyses

Statistical analysis title	IWI vs CP
Comparison groups	CP (PKS) v IWI (PKS)
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3378
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.01

Secondary: Maximum IgG serum concentration (Cmax) of IgPro20

End point title	Maximum IgG serum concentration (Cmax) of IgPro20

End point description:

End point type	Secondary

End point timeframe:
Up to 7 days

End point values	CP (PKS)	IWI (PKS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[3]	12[4]		
Units: g/L				
geometric mean (standard deviation)	11.7 (± 1.24)	11.4 (± 1.20)		

Notes:
[3] - Due to crossover: CP (n=20)
[4] - Due to crossover: IWI (n=20)

Statistical analyses

Statistical analysis title	IWI vs CP
Comparison groups	CP (PKS) v IWI (PKS)
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2917
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.91
upper limit	1.02

Secondary: Trough IgG serum concentration (Ctrough) of IgPro20

End point title	Trough IgG serum concentration (Ctrough) of IgPro20

End point description:

End point type	Secondary

End point timeframe:
Up to 7 days

End point values	CP (PKS)	IWI (PKS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[5]	12[6]		
Units: g/L				
geometric mean (standard deviation)	10.9 (± 1.25)	10.3 (± 1.17)		

Notes:
[5] - Due to crossover: CP (n=20)
[6] - Due to crossover: IWI (n=20)

Statistical analyses

Statistical analysis title	IWI vs CP
Comparison groups	CP (PKS) v IWI (PKS)
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1188
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.94
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.87
upper limit	1

Secondary: Weekly trough IgG serum concentration (Ctrough) of IgPro20

End point title	Weekly trough IgG serum concentration (Ctrough) of IgPro20
End point description:	
End point type	Secondary
End point timeframe:	
Before each infusion	

End point values	CP (SAF)	IWI (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[7]	12[8]		
Units: g/L				
arithmetic mean (standard deviation)				
Week 1 (CP,n=10;IWI,n=12)	10.6 (± 3.46)	11.0 (± 2.24)		
Week 2 (CP,n=10;IWI,n=12)	9.87 (± 0.699)	10.6 (± 2.28)		
Week 3 (CP,n=10;IWI,n=12)	9.74 (± 0.807)	10.8 (± 2.13)		
Week 4 (CP,n=10;IWI,n=12)	11.0 (± 3.66)	10.8 (± 1.98)		
Week 5 (CP,n=12;IWI,n=10)	10.9 (± 2.26)	9.73 (± 0.884)		
Week 6 (CP,n=12;IWI,n=10)	10.9 (± 2.18)	9.87 (± 0.730)		
Week 7 (CP,n=12;IWI,n=10)	11.0 (± 2.14)	9.87 (± 0.634)		
Week 8 (CP,n=12;IWI,n=10)	11.0 (± 2.03)	9.83 (± 0.944)		

Notes:
[7] - Due to crossover: CP (n=22)
[8] - Due to crossover: IWI (n=22)

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with treatment-emergent adverse events (TEAEs)

End point title	Subjects with treatment-emergent adverse events (TEAEs)

End point description:

End point type	Secondary

End point timeframe:
Up to 8 weeks

End point values	CP (SAF)	IWI (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[9]	12[10]		
Units: Subjects				
number (not applicable)				
Number of subjects	16	12		
Percent of subjects	69.6	54.5		

Notes:
[9] - Due to crossover: CP (n=23)
[10] - Due to crossover: IWI (n=22)

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with TEAEs related to IgPro20 only

End point title	Subjects with TEAEs related to IgPro20 only

End point description:

End point type	Secondary

End point timeframe:
Up to 8 weeks

End point values	CP (SAF)	IWI (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[11]	12[12]		
Units: Subjects				
number (not applicable)				
Number of subjects	7	5		
Percent of subjects	30.4	22.7		

Notes:

[11] - Due to crossover: CP (n=23)

[12] - Due to crossover: IWI (n=22)

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with TEAEs related to devices only

End point title	Subjects with TEAEs related to devices only

End point description:

End point type	Secondary

End point timeframe:

Up to 8 weeks

End point values	CP (SAF)	IWI (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[13]	12[14]		
Units: Subjects				
number (not applicable)				
Number of subjects	3	2		
Percent of subjects	13.0	9.1		

Notes:

[13] - Due to crossover: CP (n=23)

[14] - Due to crossover: IWI (n=22)

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with TEAEs related to IgPro20/device combination

End point title	Subjects with TEAEs related to IgPro20/device combination

End point description:

End point type	Secondary

End point timeframe:

Up to 8 weeks

End point values	CP (SAF)	IWI (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[15]	12[16]		
Units: Subjects				
number (not applicable)				
Number of subjects	3	2		
Percent of subjects	13.0	9.1		

Notes:

[15] - Due to crossover: CP (n=23)

[16] - Due to crossover: IWI (n=22)

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with serious TEAEs

End point title	Subjects with serious TEAEs

End point description:

End point type	Secondary

End point timeframe:

Up to 8 weeks

End point values	CP (SAF)	IWI (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[17]	12[18]		
Units: Subjects				
number (not applicable)				
Number of subjects	0	0		
Percent of subjects	0	0		

Notes:

[17] - Due to crossover: CP (n=23)

[18] - Due to crossover: IWI (n=22)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset and Duration of injection site reactions (ISRs)

End point title	Time to Onset and Duration of injection site reactions (ISRs)

End point description:

Time to onset (h) of injection site reactions will be calculated as: Date and time of start of ISR after infusion - date and time of start of preceding infusion.
Duration (h) of injection site reactions will be calculated as: Date and time of stop of event - date and time of
start of event.

End point type	Secondary

End point timeframe:

Up to 8 weeks

End point values	CP (SAF)	IWI (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[19]	12[20]		
Units: hours				
arithmetic mean (standard deviation)				
Time to onset	0.49 (± 0.730)	0.47 (± 0.295)		
Duration	19.32 (± 29.381)	26.90 (± 40.500)		

Notes:

[19] - Due to crossover: CP (n=23). Number of injection site reactions = 35.

[20] - Due to crossover: IWI (n=22). Number of injection site reactions = 26.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 8 weeks for each subject	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	CP (SAF)
Reporting group description: -	
Reporting group title	IWI (SAF)
Reporting group description: -	

Serious adverse events	CP (SAF)	IWI (SAF)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 22 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	CP (SAF)	IWI (SAF)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 23 (47.83%)	6 / 22 (27.27%)	
General disorders and administration site conditions			
Injection site induration			
subjects affected / exposed	5 / 23 (21.74%)	5 / 22 (22.73%)	
occurrences (all)	17	17	
Injection site pain			
subjects affected / exposed	3 / 23 (13.04%)	1 / 22 (4.55%)	
occurrences (all)	8	5	
Injection site erythema			
subjects affected / exposed	3 / 23 (13.04%)	1 / 22 (4.55%)	
occurrences (all)	6	1	
Injection site pruritus			

subjects affected / exposed	3 / 23 (13.04%)	1 / 22 (4.55%)	
occurrences (all)	4	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 23 (13.04%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Sinusitis			
subjects affected / exposed	3 / 23 (13.04%)	0 / 22 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2018	Removal of testing for HIV-2; Change to timing of vital signs after end of infusion from 2h ± 5 min after start of infusion to 10 ± 5 min after end of infusion
05 June 2019	Modification of the PKS dataset; addition of the SPKS dataset; correction of the dosing accuracy for the IWI and CP residual volume calculation

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported