Clinical trial results:
An open-label multicenter study to evaluate the safety and tolerability of higher infusion parameters of immune globulin subcutaneous (human), 20% liquid (Hizentra®) in subjects with primary immunodeficiency

Summary

EudraCT number	2016-003799-33
Trial protocol	Outside EU/EEA
Global end of trial date	14 December 2018

Results information

Result version number	v1 (current)
This version publication date	16 June 2019
First version publication date	16 June 2019

Trial information

Trial identification

Sponsor protocol code	IgPro20_4004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03033745
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, 610 878-4000, clinicaltrials@cslbehring.com
Scientific contact	Trial Registration Coordinator, CSL Behring LLC, 610 878-4000, 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	09 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the responder rate at higher infusion parameters of IgPro20 under the following conditions:
• Pump-Assisted: Volume per injection site of 25 mL, 40 mL, and 50 mL;
• Pump-Assisted: Flow rate per injection site of 25 mL/h, 50 mL/h, 75 mL/h and 100 mL/h;
• Manual Push (manual infusion using syringe without a pump): Flow rate per injection site of 30 mL/h, 60 mL/h, and 120 mL/h (0.5 mL/min, 1 mL/min, and 2 mL/min, correspondingly).

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	01 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 40
Country: Number of subjects enrolled	Canada: 9
Worldwide total number of subjects	49
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)	5
Adults (18-64 years)	35

From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 55 subjects were screened. Of these, 49 subjects (including pediatric subjects ≤ 17 years of age and obese subjects with body mass index [BMI] of ≥30 kg/m2) with primary immune deficiency (PID) were enrolled and evaluated in 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

Are arms mutually exclusive?	Yes
Arm title	IgPro20 (Pump-Assisted Volume Cohort)

Arm description:

Weekly subcutaneous administration with maximum volumes per injection site of 25 mL up to 50 mL.

Arm type	Experimental
Investigational medicinal product name	Hizentra [human normal immunoglobulin (subcutaneous)]
Investigational medicinal product code	
Other name	IgPro20
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A liquid formulation of normal human IgG at a concentration of 20% administered as a subcutaneous infusion at a dose prescribed by subject's physician prior to study entry.

Arm title	IgPro20 (Pump Assisted Flow Rate Cohort)

Arm description:

Weekly subcutaneous administration with maximum flow rates per injection site of 25 mL/h up to 100 mL/h.

Arm type	Experimental
Investigational medicinal product name	Hizentra [human normal immunoglobulin (subcutaneous)]
Investigational medicinal product code	
Other name	IgPro20
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A liquid formulation of normal human IgG at a concentration of 20% administered as a subcutaneous infusion at a dose prescribed by subject's physician prior to study entry.

Arm title	IgPro20 (Manual Push Flow Rate Cohort)

Arm description:

Weekly (ie, 2-7 times per week) subcutaneous administration with maximum flow rates per injection site of 30 mL/h up to 120 mL/h.

Arm type	Experimental

Investigational medicinal product name	Hizentra [human normal immunoglobulin (subcutaneous)]
Investigational medicinal product code	
Other name	IgPro20
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A liquid formulation of normal human IgG at a concentration of 20% administered as a subcutaneous infusion at a dose prescribed by subject's physician prior to study entry.

Number of subjects in period 1	IgPro20 (Pump-Assisted Volume Cohort)	IgPro20 (Pump Assisted Flow Rate Cohort)	IgPro20 (Manual Push Flow Rate Cohort)
Started	15	18	16
Completed	14	17	14
Not completed	1	1	2
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	1	-	1
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	IgPro20 (Pump-Assisted Volume Cohort)
Reporting group description:	
Weekly subcutaneous administration with maximum volumes per injection site of 25 mL up to 50 mL.	
Reporting group title	IgPro20 (Pump Assisted Flow Rate Cohort)
Reporting group description:	
Weekly subcutaneous administration with maximum flow rates per injection site of 25 mL/h up to 100 mL/h.	
Reporting group title	IgPro20 (Manual Push Flow Rate Cohort)
Reporting group description:	
Weekly (ie, 2-7 times per week) subcutaneous administration with maximum flow rates per injection site of 30 mL/h up to 120 mL/h.	

Reporting group values	IgPro20 (Pump-Assisted Volume Cohort)	IgPro20 (Pump Assisted Flow Rate Cohort)	IgPro20 (Manual Push Flow Rate Cohort)
Number of subjects	15	18	16
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	6	0
Adolescents (12-17 years)	0	4	1
Adults (18-64 years)	14	6	15
From 65-84 years	1	2	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	49.1	26.7	47.9
standard deviation	± 14.18	± 24.52	± 13.28
Gender categorical Units: Subjects			
Female	9	10	10
Male	6	8	6

Reporting group values	Total		
Number of subjects	49		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	6		

Adolescents (12-17 years)	5		
Adults (18-64 years)	35		
From 65-84 years	3		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	29		
Male	20		

End points

End points reporting groups

Reporting group title	IgPro20 (Pump-Assisted Volume Cohort)
Reporting group description:	
Weekly subcutaneous administration with maximum volumes per injection site of 25 mL up to 50 mL.	
Reporting group title	IgPro20 (Pump Assisted Flow Rate Cohort)
Reporting group description:	
Weekly subcutaneous administration with maximum flow rates per injection site of 25 mL/h up to 100 mL/h.	
Reporting group title	IgPro20 (Manual Push Flow Rate Cohort)
Reporting group description:	
Weekly (ie, 2-7 times per week) subcutaneous administration with maximum flow rates per injection site of 30 mL/h up to 120 mL/h.	
Subject analysis set title	Safety Analysis Set (SAS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Analysis Set (SAS) comprised all subjects in the Full Analysis Set who received ≥ 1 dose or a partial dose of IgPro20 in the study.	

Primary: Percentage of Responders (pump-assisted volume)(SAS)

End point title	Percentage of Responders (pump-assisted volume)(SAS)[1][2]
End point description:	
A responder is a subject within the Pump-Assisted Cohorts that performs at least 3 out of 4 valid infusions at a certain infusion parameter level (weekly volumes per injection site of 25-50 mL). The infusion parameter level was considered successful if percentage of responders was ≥ 33%.	
End point type	Primary
End point timeframe:	
At the end of 4 weeks for each planned infusion volume.	

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: Descriptive statistics were used for this primary endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump-Assisted Volume Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	15[3]			
Units: Percent				
number (not applicable)				
25 mL	86.7			
40 mL	73.3			
50 mL	73.3			

Notes:

[3] - 25 mL (N=15), 40 mL (N=15), 50 mL (N=15)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Responders (pump-assisted flow rate)(SAS)

End point title	Percentage of Responders (pump-assisted flow rate)(SAS)[4][5]

End point description:

A responder is a subject within the Pump-Assisted Cohorts that performs at least 3 out of 4 valid infusions at a certain infusion parameter level (weekly flow rates per injection site of 25-100 mL/hour). The infusion parameter level was considered successful if percentage of responders was ≥ 33%.

End point type	Primary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

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: Descriptive statistics were used for this primary endpoint.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump Assisted Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	18[6]			
Units: Percent				
number (not applicable)				
25 mL/h	77.8			
50 mL/h	77.8			
75 mL/h	66.7			
100 mL/h	61.1			

Notes:

[6] - 25 mL/h (N=18), 50 mL/h (N=18), 75 mL/h (N=18), 100 mL/h (N=18)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Responders (manual-push flow rate)(SAS)

End point title	Percentage of Responders (manual-push flow rate)(SAS)[7][8]

End point description:

A responder within the Manual Push Cohort is a subject that performs a minimum number of valid infusions (ie, 5-17) during 4 weeks corresponding to a certain flow rate level ([ie, 2-7 times per week], flow rates per injection site of 30-120 mL/hour). The infusion parameter level was considered successful if percentage of responders was ≥ 33%.

End point type	Primary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[7] - 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: Descriptive statistics were used for this primary endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Manual Push Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	16[9]			
Units: Percent				
number (not applicable)				
30 mL/h	100.0			
60 mL/h	100.0			
120 mL/h	87.5			

Notes:

[9] - 30 mL/h (N=16), 60 mL/h (N=16), 120 mL/h (N=16)

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of treatment-emergent adverse events (TEAEs) per infusion (pump-assisted volume)(SAS)

End point title	Rate of treatment-emergent adverse events (TEAEs) per infusion (pump-assisted volume)(SAS)[10]

End point description:

Adverse event rate per infusion = number of adverse events/total number of infusions prior to subject's start date of non-response. Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion volume.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump-Assisted Volume Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	15[11]			
Units: AEs/infusion				
number (not applicable)				
25 mL (number of infusions = 60)	0.183			
40 mL (number of infusions = 48)	0.188			
50 mL (number of infusions = 44)	0.023			

Notes:

[11] - 25 mL (N=15), 40 mL (N=12), 50 mL (N=11)

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of TEAEs per infusion (pump-assisted flow rate)(SAS)

End point title	Rate of TEAEs per infusion (pump-assisted flow rate)(SAS)[12]

End point description:

Adverse event rate per infusion = number of adverse events/total number of infusions prior to subject's start date of non-response. Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump Assisted Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	18[13]			
Units: AEs/infusion				
number (not applicable)				
25 mL/h (number of infusions = 70)	0.329			
50 mL/h (number of infusions = 55)	0.255			
75 mL/h (number of infusions = 50)	0.140			
100 mL/h (number of infusions = 47)	0.085			

Notes:

[13] - 25 mL/h (N=18), 50 mL/h (N=14), 75 mL/h (N=13), 100 mL/h (N=12)

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of TEAEs per infusion (manual-push flow rate)(SAS)

End point title	Rate of TEAEs per infusion (manual-push flow rate)(SAS)[14]

End point description:

Adverse event rate per infusion = number of adverse events/total number of infusions prior to subject's start date of non-response. Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Manual Push Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	16[15]			
Units: AEs/infusion				
number (not applicable)				
30 mL/h (number of infusions = 220)	0.064			
60 mL/h (number of infusions = 208)	0.111			
100 mL/h (number of infusions = 198)	0.081			

Notes:

[15] - 30 mL/h (N=16), 60 mL/h (N=16), 120 mL/h (N=14)

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of local TEAEs (pump-assisted volume)(SAS)

End point title	Rate of local TEAEs (pump-assisted volume)(SAS)[16]

End point description:

Local adverse event rate per infusion = number of local adverse events/total number of infusions prior to subject's start date of non-response. Local Adverse Events: comprises all events reported within the MedDRA high level terms "administration site reactions NEC (Not Elsewhere Classified)", "infusion site reactions", and "injection site reactions". Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion volume.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump-Assisted Volume Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	15[17]			
Units: Local AEs/infusion				
number (not applicable)				
25 mL (number of infusions = 60)	0.150			
40 mL (number of infusions = 48)	0.063			
50 mL (number of infusions = 44)	0.0			

Notes:

[17] - 25 mL (N=15), 40 mL (N=12), 50 mL (N=11)

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of local TEAEs (pump-assisted flow rate)(SAS)

End point title	Rate of local TEAEs (pump-assisted flow rate)(SAS)[18]

End point description:

Local adverse event rate per infusion = number of local adverse events/total number of infusions prior to subject's start date of non-response. Local Adverse Events: comprises all events reported within the MedDRA high level terms "administration site reactions NEC", "infusion site reactions", and "injection site reactions". Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump Assisted Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	18[19]			
Units: Local AEs/infusion				
number (not applicable)				
25 mL/h (number of infusions = 70)	0.286			
50 mL/h (number of infusions = 55)	0.145			
75 mL/h (number of infusions = 50)	0.040			
100 mL/h (number of infusions = 47)	0.021			

Notes:

[19] - 25 mL/h (N=18), 50 mL/h (N=14), 75 mL/h (N=13), 100 mL/h (N=12)

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of local TEAEs (manual-push flow rate)(SAS)

End point title	Rate of local TEAEs (manual-push flow rate)(SAS)[20]

End point description:

Local adverse event rate per infusion = number of local adverse events/total number of infusions prior to subject's start date of non-response. Local Adverse Events: comprises all events reported within the MedDRA high level terms "administration site reactions NEC", "infusion site reactions", and "injection site reactions". Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Manual Push Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	16[21]			
Units: Local AEs/infusion				
number (not applicable)				
30 mL/h (number of infusions = 220)	0.027			
60 mL/h (number of infusions = 208)	0.082			
120 mL/h (number of infusions = 198)	0.025			

Notes:

[21] - 30 mL/h (N=16), 60 mL/h (N=16), 120 mL/h (N=14)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of local TEAEs (pump-assisted volume)(SAS)

End point title	Time to onset of local TEAEs (pump-assisted volume)(SAS)[22]

End point description:

Local Adverse Events: comprises all events reported within the MedDRA high level terms "administration site reactions NEC", "infusion site reactions", and "injection site reactions". Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion volume.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump-Assisted Volume Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	15[23]			
Units: Days				
arithmetic mean (standard deviation)				
25 mL (number of local TEAEs = 9)	1.3 (± 2.45)			
40 mL (number of local TEAEs = 3)	0 (± 0.0)			

Notes:

[23] - 25 mL (N=15), 40 mL (N=12), 50 mL (N=11): no local TEAEs, hence mean (SD) could not be calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of local TEAEs (pump-assisted flow rate)(SAS)

End point title	Time to onset of local TEAEs (pump-assisted flow rate)(SAS)[24]

End point description:

Local Adverse Events: comprises all events reported within the MedDRA high level terms "administration site reactions NEC", "infusion site reactions", and "injection site reactions". Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump Assisted Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	18[25]			
Units: Days				
arithmetic mean (standard deviation)				
25 mL/h (number of local TEAEs = 20)	1.7 (± 2.94)			
50 mL/h (number of local TEAEs = 8)	0.0 (± 0.04)			
75 mL/h (number of local TEAEs = 2)	0 (± 0.0)			

Notes:

[25] - 25 mL (N=18), 50 mL (N=14), 75 mL (N=13), 100 mL (N=12): mean(SD)=0(non-evaluable because events=1)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of local TEAEs (manual-push flow rate)(SAS)

End point title	Time to onset of local TEAEs (manual-push flow rate)(SAS)[26]

End point description:

Local Adverse Events: comprises all events reported within the MedDRA high level terms "administration site reactions NEC", "infusion site reactions", and "injection site reactions". Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Manual Push Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	16[27]			
Units: Days				

arithmetic mean (standard deviation)				
30 mL/h (number of local TEAEs = 6)	0.2 (± 0.41)			
60 mL/h (number of local TEAEs = 17)	0.3 (± 0.59)			
120 mL/h (number of local TEAEs = 5)	0.2 (± 0.45)			

Notes:

[27] - 30 mL (N=16), 60 mL (N=16), 120 mL (N=14)

Statistical analyses

No statistical analyses for this end point

Secondary: Intensity of local TEAEs (pump-assisted volume)(SAS)

End point title	Intensity of local TEAEs (pump-assisted volume)(SAS)[28]

End point description:

Mild = A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate = A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe = A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion volume.

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump-Assisted Volume Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	15[29]			
Units: Number of subjects				
number (not applicable)				
25 mL mild	3			
25 mL moderate	0			
25 mL severe	0			
40 mL mild	1			
40 mL moderate	0			
40 mL severe	0			
50 mL mild	0			
50 mL moderate	0			
50 mL severe	0			

Notes:

[29] - 25 mL (N=15), 40 mL (N=12), 50 mL (N=11)

Statistical analyses

No statistical analyses for this end point

Secondary: Intensity of local TEAEs (pump-assisted flow rate)(SAS)

End point title	Intensity of local TEAEs (pump-assisted flow rate)(SAS)[30]

End point description:

Mild = A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate = A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe = A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump Assisted Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	18[31]			
Units: Number of subjects				
number (not applicable)				
25 mL/h mild	4			
25 mL/h moderate	2			
25 mL/h severe	0			
50 mL/h mild	3			
50 mL/h moderate	0			
50 mL/h severe	0			
75 mL/h mild	1			
75 mL/h moderate	0			
75 mL/h severe	0			
100 mL/h mild	0			
100 mL/h moderate	0			
100 mL/h severe	1			

Notes:

[31] - 25 mL (N=18), 50 mL (N=14), 75 mL (N=13), 100 mL (N=12)

Statistical analyses

No statistical analyses for this end point

Secondary: Intensity of local TEAEs (manual-push flow rate)(SAS)

End point title	Intensity of local TEAEs (manual-push flow rate)(SAS)[32]

End point description:

Mild = A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate = A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe = A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Manual Push Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	16[33]			
Units: Number of subjects				
number (not applicable)				
30 mL/h mild	3			
30 mL/h moderate	0			
30 mL/h severe	0			
60 mL/h mild	4			
60 mL/h moderate	0			
60 mL/h severe	0			
120 mL/h mild	2			
120 mL/h moderate	0			
120 mL/h severe	0			

Notes:

[33] - 30 mL (N=16), 60 mL (N=16), 120 mL (N=14)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of local TEAEs (pump-assisted volume)(SAS)

End point title	Duration of local TEAEs (pump-assisted volume)(SAS)[34]

End point description:

Local Adverse Events: comprises all events reported within the MedDRA high level terms "administration site reactions NEC", "infusion site reactions", and "injection site reactions".

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion volume.

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump-Assisted Volume Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	15[35]			
Units: Days				
arithmetic mean (standard deviation)				
25 mL	2.2 (± 1.30)			
40 mL	2.7 (± 2.08)			

Notes:

[35] - 25 mL (N=15), 40 mL (N=12), 50 mL (N=11): no local TEAEs, hence mean (SD) could not be calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of local TEAEs (pump-assisted flow rate)(SAS)

End point title	Duration of local TEAEs (pump-assisted flow rate)(SAS)[36]

End point description:

Local Adverse Events: comprises all events reported within the MedDRA high level terms "administration site reactions NEC", "infusion site reactions", and "injection site reactions".

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump Assisted Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	18[37]			
Units: Days				
arithmetic mean (standard deviation)				
25 mL/h	1.2 (± 0.37)			
50 mL/h	1.6 (± 0.92)			
75 mL/h	1.0 (± 0.00)			

Notes:

[37] - 25 mL/h (N=18), 50 mL/h (N=14), 75 mL (N=13), 100 mL/h (N=12): mean (SD) = 1.0 (non-evaluable)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of local TEAEs (manual-push flow rate)(SAS)

End point title	Duration of local TEAEs (manual-push flow rate)(SAS)[38]

End point description:

Local Adverse Events: comprises all events reported within the MedDRA high level terms "administration site reactions NEC", "infusion site reactions", and "injection site reactions".

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Manual Push Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	16[39]			
Units: Days				
arithmetic mean (standard deviation)				
30 mL/h	2.2 (± 2.86)			
60 mL/h	5.6 (± 12.91)			
120 mL/h	3.0 (± 2.12)			

Notes:

[39] - 30 mL/h (N=16), 60 mL/h (N=16), 120 mL/h (N=14)

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability of infusions (pump-assisted volume)(SAS)

End point title	Tolerability of infusions (pump-assisted volume)(SAS)[40]

End point description:

Tolerability = number of infusions without severe local adverse events / total number of infusions. Severe = A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion volume.

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump-Assisted Volume Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	15[41]			
Units: Proportion				
number (not applicable)				
25 mL (number of infusions = 60)	1.00			
40 mL (number of infusions = 48)	1.00			
50 mL (number of infusions = 44)	1.00			

Notes:

[41] - For this end point, is not the number of subjects but the number of infusions being analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability of infusions (pump-assisted flow rate)(SAS)

End point title	Tolerability of infusions (pump-assisted flow rate)(SAS)[42]

End point description:

Tolerability = number of infusions without severe local adverse events / total number of infusions. Severe = A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Pump Assisted Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	18[43]			
Units: Proportion				
number (not applicable)				
25 mL/h (number of infusions = 70)	1.00			
50 mL/h (number of infusions = 55)	1.00			
75 mL/h (number of infusions = 50)	1.00			
100 mL/h (number of infusions = 47)	0.98			

Notes:

[43] - For this end point, is not the number of subjects but the number of infusions being analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability of infusions (manual-push flow rate)(SAS)

End point title	Tolerability of infusions (manual-push flow rate)(SAS)[44]

End point description:

Tolerability = number of infusions without severe local adverse events / total number of infusions. Severe = A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Only events are included which start prior to subject's start date of non-response.

End point type	Secondary

End point timeframe:

At the end of 4 weeks for each planned infusion flow rate.

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms were reported separately because the volumes and flow rates were different between the three arms.

End point values	IgPro20 (Manual Push Flow Rate Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	16[45]			
Units: Proportion				
number (not applicable)				
30 mL/h (number of infusions = 220)	1.00			
60 mL/h (number of infusions = 208)	1.00			
120 mL/h (number of infusions = 198)	1.00			

Notes:

[45] - For this end point, is not the number of subjects but the number of infusions being analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 17 weeks per participant	
Adverse event reporting additional description:	
Only events are included which start prior to subject's start date of non-response.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	IgPro20 (pump-assisted volume) 25 mL
Reporting group description: -	
Reporting group title	IgPro20 (pump-assisted volume) 40 mL
Reporting group description: -	
Reporting group title	IgPro20 (pump-assisted volume) 50 mL
Reporting group description: -	
Reporting group title	IgPro20 (pump-assisted flow rate) 25 mL/h
Reporting group description: -	
Reporting group title	IgPro20 (pump-assisted flow rate) 50 mL/h
Reporting group description: -	
Reporting group title	IgPro20 (pump-assisted flow rate) 75 mL/h
Reporting group description: -	
Reporting group title	IgPro20 (pump-assisted flow rate) 100 mL/h
Reporting group description: -	
Reporting group title	IgPro20 (manual push flow rate) 30 mL/h
Reporting group description: -	
Reporting group title	IgPro20 (manual push flow rate) 60 mL/h
Reporting group description: -	
Reporting group title	IgPro20 (manual push flow rate) 120 mL/h
Reporting group description: -	

Serious adverse events	IgPro20 (pump-assisted volume) 25 mL	IgPro20 (pump-assisted volume) 40 mL	IgPro20 (pump-assisted volume) 50 mL
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	IgPro20 (pump-assisted flow rate) 25 mL/h	IgPro20 (pump-assisted flow rate) 50 mL/h	IgPro20 (pump-assisted flow rate) 75 mL/h
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	IgPro20 (pump-assisted flow rate) 100 mL/h	IgPro20 (manual push flow rate) 30 mL/h	IgPro20 (manual push flow rate) 60 mL/h
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	IgPro20 (manual push flow rate) 120 mL/h		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	IgPro20 (pump-assisted volume) 25 mL	IgPro20 (pump-assisted volume) 40 mL	IgPro20 (pump-assisted volume) 50 mL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 15 (26.67%)	4 / 12 (33.33%)	1 / 11 (9.09%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
Injection site erythema			
subjects affected / exposed	1 / 15 (6.67%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Injection site pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Injection site extravasation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Injection site haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Injection site mass			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Injection site pruritus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Injection site bruising			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Injection site discolouration			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gait inability			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Foot fracture			

subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Trigeminal neuralgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Hypertonic bladder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0

Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Tinea infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			

subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	IgPro20 (pump-assisted flow rate) 25 mL/h	IgPro20 (pump-assisted flow rate) 50 mL/h	IgPro20 (pump-assisted flow rate) 75 mL/h
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 18 (38.89%)	4 / 14 (28.57%)	3 / 13 (23.08%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	2 / 18 (11.11%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	3	0	0
Injection site erythema			
subjects affected / exposed	3 / 18 (16.67%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	8	0	0
Injection site pain			
subjects affected / exposed	2 / 18 (11.11%)	2 / 14 (14.29%)	0 / 13 (0.00%)
occurrences (all)	7	5	0

Injection site extravasation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injection site haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Injection site mass			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	2 / 18 (11.11%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
Injection site bruising			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Injection site discolouration			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gait inability			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			

subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 18 (0.00%)	2 / 14 (14.29%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Trigeminal neuralgia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Hypertonic bladder			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 18 (5.56%)	0 / 14 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Respiratory tract infection viral			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Tinea infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			

subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	IgPro20 (pump-assisted flow rate) 100 mL/h	IgPro20 (manual push flow rate) 30 mL/h	IgPro20 (manual push flow rate) 60 mL/h
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	5 / 16 (31.25%)	8 / 16 (50.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypotension			

subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	0 / 12 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	3
Injection site erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	3
Injection site pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	1	4	4
Injection site extravasation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Injection site haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Injection site mass			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Injection site bruising			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Injection site discolouration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Injection site reaction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gait inability			

subjects affected / exposed	1 / 12 (8.33%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Trigeminal neuralgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Leukopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	0	3	1
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Hypertonic bladder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Bronchitis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Tinea infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	1 / 12 (8.33%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Vitamin D deficiency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	IgPro20 (manual push flow rate) 120 mL/h		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 14 (50.00%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injection site erythema			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injection site extravasation			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Injection site haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Injection site mass			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

Injection site pruritus subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injection site bruising subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 3		
Injection site discolouration subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injection site reaction subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Gait inability subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Fatigue subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Dyspnoea subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Investigations Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		

Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Trigeminal neuralgia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Renal and urinary disorders			

Hypertonic bladder			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Respiratory tract infection viral			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Tinea infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Oral candidiasis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2017	•Introduction section updated to include recent clinical trial data (safe infusion of SCIG at infusion flow rates of up to 60 mL/h/site). •Infusion frequency in the Manual Push Flow Rate Cohort changed from 5 to 7 infusions per week to 2 to 7 infusions per week. •Definition of responders modified to account for the changed infusion frequency in the Manual Push Flow Rate Cohort. •Use of Interactive Response Technology introduced for IgPro20 accountability. •The frequency of office visits changed from every 5 to 8 weeks to every 4 weeks. •Differential count added to the list of hematology assessments. •Window for Screening changed from "on Day −14 (± 2)" to "between Day −35 and −7". •Description of "valid infusion" criteria modified to include more details.
31 May 2017	•Study design updated to permit subjects who were unable to tolerate the respective infusion parameter level to continue study participation at the individually tolerable infusion parameter level for the remaining study duration. •Time window for collection of blood for serum IgG trough levels (Day 1, End of Study Visit) changed from "30 minutes before next infusion" to "within approximately 1 hour before next infusion". •Relevant safety sections were updated to state that subjects who discontinued without withdrawing consent were followed up by weekly phone calls by site personnel for the full duration of their planned study participation to collect AE information.
02 December 2017	•Definition of study population modified to clarify the number of enrolled pediatric and obese subjects as target number of enrolled subjects and not a minimum number of subjects. •Inclusion criterion 4 modified to define Primary Immunodeficiency by use of the International Union of Immunological Societies Expert Committee as additional reference. •Inclusion criterion 5 modified to clarify the required tolerated flow rate for the Pump Assisted Flow Rate Cohort during the month before Day 1 (allowable variance of 20% around the stated flow rate of 25 mL/h for constant pressure pumps). •Backup paper diary to be used when eDiary unavailable. •New section on reporting of unusual failure of efficacy was added to the Serious Event Reporting section to comply with Health Canada's Food and Drug Regulations (for Canadian sites only). •Definition of Full Analysis Set modified to include eligible subjects who provided informed consent and underwent study procedures after Screening. •Planned study duration increased from 9 to 18 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported