Clinical trial results:
A Multicenter Extension Study on the Safety and Efficacy of IgPro10 in Patients With Primary Immunodeficiency (PID)

Summary

EudraCT number	2014-003772-23
Trial protocol	Outside EU/EEA
Global end of trial date	16 April 2008

Results information

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

Trial information

Trial identification

Sponsor protocol code	ZLB05_006CR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00322556
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring AG
Sponsor organisation address	Wankdorfstrasse 10, Berne 22, Switzerland, CH-3000
Public contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com
Scientific contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 July 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and efficacy of IgPro10 in patients with PID, and to assess the tolerability of a high infusion rate.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, and standard operating procedures for clinical research and development at CSL Behring (CSLB). The study protocol and all amendments were approved by the Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs) of the participating centers. Before undergoing screening procedures for possible enrollment into the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

The investigator may cease study treatment and withdraw the subject, or the subject may withdraw himself from participation in the study at any time. If a subject is withdrawn from the study or further participation is declined, the subject will continue to have access to medical care and will be treated according to routine medical practice, but will no longer receive the investigational medicinal product (IMP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2005
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: 55
Worldwide total number of subjects	55
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)	13
Adolescents (12-17 years)	11
Adults (18-64 years)	27
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

For subjects joining from study ZLB03_002CR, Screening was done between the completion visit for that study and the first infusion for study ZLB05_006CR (2014-003772-23), including both days. For 'new' subjects, Screening was done 1 to 30 days before the first infusion with IgPro10 for study ZLB05_006CR.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IgPro10

Arm description:

A 10% liquid formulation of human immunoglobulin G (stabilized with 250 millimole per liter of L-proline) administered as an intravenous infusion, every 3 or 4 weeks for the duration of the study.

Arm type	Experimental
Investigational medicinal product name	IgPro10
Investigational medicinal product code	
Other name	human normal immunoglobulin, Privigen®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IgPro10 was administered every 3 or 4 weeks using an individualized regimen with a dose of 0.2 – 0.8 g IgG per kg body weight.

Number of subjects in period 1	IgPro10
Started	55
Completed	43
Not completed	12
Consent withdrawn by subject	1
Adverse event	1
Other reason	7
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	IgPro10

Reporting group description:

A 10% liquid formulation of human immunoglobulin G (stabilized with 250 millimole per liter of L-proline) administered as an intravenous infusion, every 3 or 4 weeks for the duration of the study.

Reporting group values	IgPro10	Total	
Number of subjects	55	55	
Age categorical Units: Subjects			
3 to < 12 years	13	13	
12 to < 16 years	8	8	
16 to < 65 years	30	30	
>= 65 years	4	4	
Age continuous Units: years			
arithmetic mean	30		
standard deviation	± 21	-	
Gender categorical Units: Subjects			
Female	29	29	
Male	26	26	

End points

End points reporting groups

Reporting group title	IgPro10
Reporting group description:	
A 10% liquid formulation of human immunoglobulin G (stabilized with 250 millimole per liter of L-proline) administered as an intravenous infusion, every 3 or 4 weeks for the duration of the study.	
Subject analysis set title	IgPro10 (≤ 4 mg/kg/Min)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
A 10% liquid formulation of human immunoglobulin G (stabilized with 250 millimole per liter of L-proline) administered as an intravenous infusion, every 3 or 4 weeks for the duration of the study, at the maximum infusion rate (≤ 4 mg/kg/min) for new subjects.	
Subject analysis set title	IgPro10 (≤ 8 mg/kg/Min)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
A 10% liquid formulation of human immunoglobulin G (stabilized with 250 millimole per liter of L-proline) administered as an intravenous infusion, every 3 or 4 weeks for the duration of the study, at the low maximum infusion rate (≤ 8 mg/kg/min) for old subjects.	
Subject analysis set title	IgPro10 (> 8 to ≤ 12 mg/kg/Min)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
A 10% liquid formulation of human immunoglobulin G (stabilized with 250 millimole per liter of L-proline) administered as an intravenous infusion, every 3 or 4 weeks for the duration of the study, at the high maximum infusion rate (> 8 and ≤ 12 mg/kg/min) for old subjects.	

Primary: Proportion of Infusions With One or More Temporally-associated Adverse Events (AEs)

End point title	Proportion of Infusions With One or More Temporally-associated Adverse Events (AEs)[1]
End point description:	
AEs were considered temporally-associated AEs if they occurred during the infusion or in the period from the start of the infusion until either 48 or 72 hours after the end of the infusion. The Safety Data Set (SDS) comprised all subjects treated with the study drug.	
End point type	Primary
End point timeframe:	
During each infusion, and within 48 or 72 hours after the end of each infusion.	

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 are reported for this end point.

End point values	IgPro10			
Subject group type	Reporting group			
Number of subjects analysed	55[2]			
Units: Proportion of infusions]				
number (not applicable)				
During infusion	0.073			
Within 48 hours after infusion	0.141			
Within 72 hours after infusion	0.15			

Notes:

[2] - Number of infusions analyzed: 771

Statistical analyses

No statistical analyses for this end point

Primary: Influence of Infusion Rate on Temporally-associated AEs

End point title	Influence of Infusion Rate on Temporally-associated AEs[3]

End point description:

The total and most frequent (1% or more) number of infusions for which subjects experienced temporally-associated AEs occurring within 72 hours of infusion, by infusion rate (≤ 4 mg/kg/min, ≤ 8 mg/kg/min, and > 8 and ≤ 12 mg/kg/min).

AEs were considered to be temporally-associated AEs if they occurred in the period from the start of the infusion until 72 hours after the end of the infusion.

'New subjects' could receive IgPro10 at up to 4 mg/kg/min. Subjects treated with the study drug who participated in a preceding, pivotal, Phase III clinical study with intravenous IgPro10 (study number ZLB03_002CR, NCT00168025) could receive IgPro10 at up to 12 mg/kg/min at the discretion of the Investigator.

End point type	Primary

End point timeframe:

Within 72 hours after each infusion

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: Descriptive statistics are reported for this end point.

End point values	IgPro10 (≤ 4 mg/kg/Min)	IgPro10 (≤ 8 mg/kg/Min)	IgPro10 (> 8 to ≤ 12 mg/kg/Min)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10[4]	22[5]	23[6]	
Units: infusions				
All temporally-associated AEs	23	153	30	
Headache	10	54	2	
Pyrexia	0	9	1	
Nausea	0	8	2	
Back pain	0	8	0	
Chills	0	7	0	
Pain	0	6	0	
Anaemia	1	0	0	
Constipation	2	0	0	
Fatigue	3	0	0	
Influenza like illness	3	1	0	
Myalgia	1	0	0	
Pharyngolaryngeal pain	1	1	2	
Eczema	1	0	0	
Night sweats	1	0	0	

Notes:

[4] - Number of infusions analyzed: 81

[5] - Number of infusions analyzed: 423

[6] - Number of infusions analyzed: 265

Statistical analyses

No statistical analyses for this end point

Primary: Rate of AEs by Severity and Relationship

End point title	Rate of AEs by Severity and Relationship[7]

End point description:

The AE rate was the number of AEs over the number of infusions administered.

Mild AEs: Did not interfere with daily activities; Moderate AEs: Interfered with routine daily activities; Severe AEs: Impossible to perform routine daily activities.

At least possibly related AEs included possibly related AEs, probably related AEs, and related AEs.

The SDS comprised all subjects treated with the study drug.

End point type	Primary

End point timeframe:

For the duration of the study, up to approximately 29 months

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 are reported for this end point.

End point values	IgPro10			
Subject group type	Reporting group			
Number of subjects analysed	55[8]			
Units: AEs per infusion				
number (not applicable)				
All mild AEs	0.467			
All moderate AEs	0.28			
All severe AEs	0.058			
Unrelated AEs	0.61			
Possibly related AEs	0.088			
Probably related AEs	0.048			
Related AEs	0.06			
At least possibly related mild AEs	0.121			
At least possibly related moderate AEs	0.062			
At least possibly related severe AEs	0.013			
Unrelated mild AEs	0.346			
Unrelated moderate AEs	0.218			
Unrelated severe AEs	0.045			

Notes:

[8] - Number of infusions analyzed: 771

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Vital Signs

End point title	Number of Subjects With Clinically Significant Changes in Vital Signs[9]

End point description:

Vital signs included heart rate, systolic blood pressure, diastolic blood pressure, and body temperature.

The SDS comprised all subjects treated with the study drug.

End point type	Primary

End point timeframe:

Before, during, and after each infusion.

Notes:

[9] - 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 are reported for this end point.

End point values	IgPro10			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Acute Serious Bacterial Infections

End point title	Annualized Rate of Acute Serious Bacterial Infections

End point description:

The annualized rate was based on the total number of infections and the total number of subject study days for all subjects in the specified analysis population and adjusted to 365 days.

Acute serious bacterial infections included pneumonia, bacteremia / septicemia, osteomyelitis / septic arthritis, bacterial meningitis, and visceral abscess.

The Intention-To-Treat (ITT) data set comprised all subjects treated with the study drug.

End point type	Secondary

End point timeframe:

For the duration of the study, up to approximately 29 months

End point values	IgPro10			
Subject group type	Reporting group			
Number of subjects analysed	55[10]			
Units: Infections per subject year				
number (not applicable)	0.018			

Notes:

[10] - Number of subject study days analyzed:20757

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days Out of Work / School / Kindergarten / Day Care or Inability to Perform Normal Activities Due to Illness

End point title	Number of Days Out of Work / School / Kindergarten / Day Care or Inability to Perform Normal Activities Due to Illness

End point description:

The ITT data set comprised all subjects treated with the study drug. The patient diary (in which the number of days was recorded) was not available for 1 subject so the analyzed population was reduced from 55 to 54 subjects for this outcome measure.

End point type	Secondary

End point timeframe:

For the duration of the study, up to approximately 29 months.

End point values	IgPro10			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: days				
median (full range (min-max))	8.5 (0 to 104)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days of Hospitalization

End point title	Number of Days of Hospitalization

End point description:

The ITT data set comprised all subjects treated with the study drug. The patient diary (in which the number of days was recorded) was not available for 1 subject so the analyzed population was reduced from 55 to 54 subjects for this outcome measure.

End point type	Secondary

End point timeframe:

For the duration of the study, up to approximately 29 months

End point values	IgPro10			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: days				
median (full range (min-max))	0 (0 to 17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Any Infection

End point title	Annualized Rate of Any Infection

End point description:

The annualized rate was based on the total number of infections and the total number of subject study days for all subjects in the specified analysis population and adjusted to 365 days.

Infections were classified as all AEs with the system organ class “infections and infestations” and AEs with the preferred term “conjunctivitis.”

The ITT data set comprised all subjects treated with the study drug.

End point type	Secondary

End point timeframe:

For the duration of the study, up to approximately 29 months.

End point values	IgPro10			
Subject group type	Reporting group			
Number of subjects analysed	55[11]			
Units: Infections per subject year				
number (not applicable)	1.6			

Notes:

[11] - Number of subject study days analyzed: 20757

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Levels of Total Immunoglobulin (IgG) Serum Concentrations

End point title	Trough Levels of Total Immunoglobulin (IgG) Serum Concentrations

End point description:

Mean IgG trough concentration. For this analysis, each subject's values were first aggregated to their median and the median values were then analyzed.

The ITT data set comprised all subjects treated with the study drug for which serum IgG information was available.

End point type	Secondary

End point timeframe:

Prior to each infusion; every 3 or 4 weeks depending upon the dosing schedule.

End point values	IgPro10			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: g/L				
arithmetic mean (full range (min-max))	9.72 (5.72 to 18.01)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the duration of the study, up to approximately 29 months

Adverse event reporting additional description:

Only AEs starting at or after the first study drug infusion were included. The SDS comprised all subjects treated with the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	IgPro10

Reporting group description:

A 10% liquid formulation of human immunoglobulin G (stabilized with 250 millimole per liter of L-proline) administered as an intravenous infusion, every 3 or 4 weeks for the duration of the study.

Serious adverse events	IgPro10		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 55 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Surgical and medical procedures			
Ileostomy closure			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Transient ischemic attack			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Gastrointestinal hemorrhage				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Angioedema				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Aggression				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Muscular weakness				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint effusion				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Clostridial infection				

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Giardiasis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis externa fungal			
subjects affected / exposed	1 / 55 (1.82%)		
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	IgPro10		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 55 (87.27%)		
Injury, poisoning and procedural complications			
Joint sprain			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	5		
Procedural pain			

subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 55 (38.18%)		
occurrences (all)	147		
Dizziness			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	22		
Fatigue			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	10		
Chest pain			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Chills			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	7		
Influenza-like illness			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	9		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		

Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	16		
Diarrhea			
subjects affected / exposed	10 / 55 (18.18%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	12		
Abdominal pain			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	5		
Toothache			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 55 (21.82%)		
occurrences (all)	17		
Pharyngolaryngeal pain			
subjects affected / exposed	9 / 55 (16.36%)		
occurrences (all)	11		
Epistaxis			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	9		
Rhinorrhea			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		

Asthma subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 4		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 6 / 55 (10.91%) 6 6 / 55 (10.91%) 7 3 / 55 (5.45%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 4 / 55 (7.27%) 4		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 6 / 55 (10.91%) 12		
Infections and infestations Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Bronchitis	 14 / 55 (25.45%) 15 6 / 55 (10.91%) 6 5 / 55 (9.09%) 5 3 / 55 (5.45%) 3		

subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Gastroenteritis viral			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2006	Recruitment for the study was expanded from an estimated 30 subjects to an estimated 40 to 60 subjects. The duration for the study was extended until the time when all sites were to be open for the ZLB04_009CR (2014-003607-30) study. This caused the study duration per subject to increase from < 9 months to a variable time dependent upon the time slot between a subject's last infusion within ZLB03_002CR and the regulatory and IRB approvals of the ZLB04_009CR study. Amendment 1 described the inclusion of new subjects who would later be enrolled into the pharmacokinetic (PK) substudy ZLB04_009CR. The PK endpoints, inclusion/exclusion criteria, subject identification, and dosing schedule were added. The study objectives were also updated to reflect the purpose of the PK inclusion.
29 March 2007	The time of duration for the study was extended from the time when all sites were opened for the ZLB04_009CR SCIG study to the time when IgPro10 was launched in the United States (US). Previously, subjects were only offered to switch to the subcutaneous Ig (SCIg) study. This change allowed current subjects on the study the alternative option to remain in the protocol until IgPro10 was launched in the US. The Sponsor name was changed to CSL Behring to keep in line with corporate changes. Changes in study personnel on both the Sponsor and contract research organization levels were reflected. Other changes to the clinical study protocol introduced an interim analysis and provided clarification of the scope of statistical analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported