Clinical trial results:
A phase II, open, study to assess the immunogenicity and reactogenicity of GlaxoSmithKline (GSK) Biologicals' combined DTPa-HBV-IPV/Hib vaccine when administered as a booster dose to children aged 16-20 months, previously primed with GSK Biologicals' combined DSSITGDPa-HBV-IPV/Hib vaccine, containing diphtheria toxoid from the Statens Serum Institute (SSI) of Denmark and tetanus toxoid from GSK Biologicals' Kft [GD] or with GSK Biologicals licensed DTPa-HBV-IPV/Hib vaccine (Infanrix hexa™) in the primary vaccination study DTPa-HBV-IPV-116 (106786).

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2007-005343-16
Trial protocol	FI
Global end of trial date	18 August 2008

Results information

Result version number	v2
This version publication date	08 July 2016
First version publication date	28 June 2015
Version creation reason	• Correction of full data set Data correction due to a system error in EudraCT – Results

Trial information

Trial identification

Sponsor protocol code	111344

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00627458
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.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	29 March 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2008
Global end of trial reached?	Yes
Global end of trial date	18 August 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the immunogenicity of the DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free or preservative-containing), in terms of persistence of the antibodies to all vaccine antigens at the time of the booster vaccination.
To assess the immunogenicity of a booster dose of DTPa-HBV-IPV/Hib vaccine given after primary vaccination with the DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free or preservative-containing), in terms of response to all vaccine antigens.

Protection of trial subjects:

All subjects were supervised after vaccination/product administration with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	19 February 2008
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	Finland: 403
Worldwide total number of subjects	403
EEA total number of subjects	403

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	403
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Preservative-free Group

Arm description:

Subjects received the preservative-free (PF) formulation of DSSITGDPa-HBV-IPV/Hib in the primary phase and a booster dose of DTPa-HBV-IPV/Hib in the booster phase.

Arm type	Experimental
Investigational medicinal product name	Preservative-free Infanrix hexa™
Investigational medicinal product code	
Other name	DSSI-TGD-Pa-HBV-IPV/Hib
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received one vaccine dose administered intramuscularly into the anterolateral quadrant of the right thigh.

Investigational medicinal product name	Infanrix hexa™
Investigational medicinal product code	
Other name	DTPa-HBV-IPV/Hib
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received one booster dose of study vaccine, intramuscularly into the anterolateral right thigh.

Arm title	Preservative-containing Group

Arm description:

Subjects received the preservative-containing (PC) formulation of DSSITGDPa-HBV-IPV/Hib in the primary phase and a booster dose of DTPa-HBV-IPV/Hib in the booster phase.

Arm type	Experimental
Investigational medicinal product name	Preservative-containing Infanrix hexa™
Investigational medicinal product code	
Other name	DSSI-TGD-Pa-HBV-IPV/Hib
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received one vaccine dose administered intramuscularly into the anterolateral quadrant of the right thigh.

Investigational medicinal product name	Infanrix hexa™
Investigational medicinal product code	
Other name	DTPa-HBV-IPV/Hib
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received one booster dose of study vaccine, intramuscularly into the anterolateral right thigh.

Arm title	Control Group

Arm description:

Subjects received the licensed formulation of DTPa-HBV-IPV/Hib in the primary phase and a booster dose in the booster phase.

Arm type	Active comparator
Investigational medicinal product name	Licensed Infanrix hexa™
Investigational medicinal product code	
Other name	DTPa-HBV-IPV/Hib
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received one vaccine dose administered intramuscularly into the anterolateral quadrant of the right thigh, in the primary phase and one booster dose of the same vaccine in the booster phase.

Number of subjects in period 1	Preservative-free Group	Preservative-containing Group	Control Group
Started	127	137	139
Completed	123	130	133
Not completed	4	7	6
Consent withdrawn by subject	2	6	5
Migrated from study area	1	-	1
Lost to follow-up	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Preservative-free Group
Reporting group description:	
Subjects received the preservative-free (PF) formulation of DSSITGDPa-HBV-IPV/Hib in the primary phase and a booster dose of DTPa-HBV-IPV/Hib in the booster phase.	
Reporting group title	Preservative-containing Group
Reporting group description:	
Subjects received the preservative-containing (PC) formulation of DSSITGDPa-HBV-IPV/Hib in the primary phase and a booster dose of DTPa-HBV-IPV/Hib in the booster phase.	
Reporting group title	Control Group
Reporting group description:	
Subjects received the licensed formulation of DTPa-HBV-IPV/Hib in the primary phase and a booster dose in the booster phase.	

Reporting group values	Preservative-free Group	Preservative-containing Group	Control Group
Number of subjects	127	137	139
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: months			
arithmetic mean	17.9	18	17.8
standard deviation	± 1.12	± 1.03	± 1.11
Gender categorical Units: Subjects			
Female	56	66	59
Male	71	71	80

Reporting group values	Total		
Number of subjects	403		
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)	0		

Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: months			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	181		
Male	222		

End points

End points reporting groups

Reporting group title	Preservative-free Group
Reporting group description:	
Subjects received the preservative-free (PF) formulation of DSSITGDPa-HBV-IPV/Hib in the primary phase and a booster dose of DTPa-HBV-IPV/Hib in the booster phase.	
Reporting group title	Preservative-containing Group
Reporting group description:	
Subjects received the preservative-containing (PC) formulation of DSSITGDPa-HBV-IPV/Hib in the primary phase and a booster dose of DTPa-HBV-IPV/Hib in the booster phase.	
Reporting group title	Control Group
Reporting group description:	
Subjects received the licensed formulation of DTPa-HBV-IPV/Hib in the primary phase and a booster dose in the booster phase.	

Primary: Number of subjects with anti-diphtheria and anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/mL

End point title	Number of subjects with anti-diphtheria and anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/mL[1][2]
End point description:	

End point type	Primary
End point timeframe:	
Before (PRE) and one month after the booster vaccination [PI(M1)]	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	119		
Units: Subjects				
Anti-D, PRE [N=112,117]	22	35		
Anti-D, PI(M1) [N=113,119]	112	118		
Anti-T, PRE [N=112,117]	93	103		
Anti-T, PI(M1) [N=113,119]	113	118		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with anti-Hepatitis B surface antigen (HBs) antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL

End point title	Number of subjects with anti-Hepatitis B surface antigen (HBs) antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL[3][4]

End point description:

End point type	Primary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[4] - 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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	118		
Units: Subjects				
Anti-HBs ≥ 10 mIU/mL, PRE [N=111,117]	106	112		
Anti-HBs ≥ 10 mIU/mL, PI(M1) [N=111,118]	110	117		
Anti HBs ≥ 100 mIU/mL, PRE [N=111,117]	55	54		
Anti HBs ≥ 100 mIU/mL, PI(M1) [N=111,118]	105	113		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with anti-poliovirus type 1, type 2 and type 3 antibody titers ≥ 8

End point title	Number of subjects with anti-poliovirus type 1, type 2 and type 3 antibody titers ≥ 8[5][6]

End point description:

End point type	Primary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[6] - 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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	117		
Units: Subjects				
Anti-polio 1, PRE [N=110,117]	67	76		
Anti-polio 1, PI(M1) [N=111,117]	110	117		
Anti-polio 2, PRE [N=111,117]	48	51		
Anti-polio 2, PI(M1) [N=112,117]	110	117		
Anti-polio 3, PRE [N=111,117]	58	77		
Anti-polio 3, PI(M1) [N=112,117]	111	117		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) concentrations ≥ 5 EL.U/mL

End point title	Number of subjects with anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) concentrations ≥ 5 EL.U/mL[7][8]

End point description:

End point type	Primary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	119		
Units: Subjects				
Anti-PT, PRE [N=109,112]	80	81		
Anti-PT, PI(M1) [N=111,119]	111	118		
Anti-FHA, PRE [N=110,112]	106	107		
Anti-FHA, PI(M1) [N=112,119]	112	118		
Anti-PRN, PRE [N=112,117]	81	86		
Anti-PRN, PI(M1) [N=113,118]	113	117		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-diphtheria and anti-tetanus toxoids antibody concentrations

End point title	Anti-diphtheria and anti-tetanus toxoids antibody concentrations[9][10]

End point description:

End point type	Primary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	119		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-D, PRE [N=112,117]	0.064 (0.058 to 0.071)	0.069 (0.062 to 0.076)		
Anti-D, PI(M1) [N=113,119]	2.237 (1.877 to 2.666)	2.242 (1.868 to 2.689)		
Anti-T, PRE [N=112,117]	0.216 (0.184 to 0.254)	0.248 (0.213 to 0.289)		
Anti-T, PI(M1) [N=113,119]	9.799 (8.39 to 11.444)	9.136 (7.838 to 10.648)		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-PT, anti-FHA, anti-PRN antibody concentrations

End point title	Anti-PT, anti-FHA, anti-PRN antibody concentrations[11][12]

End point description:

End point type	Primary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	119		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PT, PRE [N=109,112]	7.8 (6.7 to 9.1)	7 (6.1 to 8.1)		
Anti-PT, PI(M1) [N=111,119]	150.9 (132.9 to 171.2)	117.1 (101.5 to 135)		
Anti-FHA, PRE [N=110,112]	21.7 (18.1 to 25.9)	22.1 (18.5 to 26.2)		
Anti-FHA, PI(M1) [N=112,119]	609.6 (534.1 to 695.7)	533.7 (463 to 615.1)		
Anti-PRN, PRE [N=112,117]	8.6 (7.1 to 10.3)	8.7 (7.3 to 10.2)		
Anti-PRN, PI(M1) [N=113,118]	308.5 (261.3 to 364.2)	311.7 (260.3 to 373.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-HBs antibody concentrations

End point title	Anti-HBs antibody concentrations[13][14]

End point description:

End point type	Primary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	118		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs, PRE [N=111,117]	84.3 (65.7 to 108.2)	86.2 (67.8 to 109.6)		
Anti-HBs, PI(M1) [N=111,118]	3291.7 (2373.6 to 4565)	3528.1 (2546.1 to 4888.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-poliovirus type 1, type 2 and type 3 antibody titers

End point title	Anti-poliovirus type 1, type 2 and type 3 antibody titers[15][16]

End point description:

End point type	Primary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[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 results in this study were tabulated by treatment group. Hence for each related

endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	117		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-polio 1, PRE [N=110,117]	12.9 (10.3 to 16.3)	15.2 (12.3 to 18.9)		
Anti-polio 1, PI(M1) [N=111,117]	726.3 (560.4 to 941.4)	942.4 (734.1 to 1209.7)		
Anti-polio 2, PRE [N=111,117]	9.1 (7.3 to 11.3)	8.7 (7.2 to 10.5)		
Anti-polio 2, PI(M1) [N=112,117]	712.8 (529.1 to 960.4)	812.9 (632.8 to 1044.3)		
Anti-polio 3, PRE [N=111,117]	9.5 (7.9 to 11.6)	16 (12.6 to 20.4)		
Anti-polio 3, PI(M1) [N=112,117]	780 (591 to 1029.3)	1145.8 (891.6 to 1472.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-PRP antibody concentrations

End point title	Anti-PRP antibody concentrations[17][18]

End point description:

End point type	Primary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	119		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PRP, PRE [N=111,117]	0.249 (0.199 to 0.31)	0.314 (0.252 to 0.392)		
Anti-PRP, PI(M1) [N=112,119]	36.866 (28.61 to 47.504)	35.318 (27.447 to 45.445)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with a vaccine response to PT, FHA and PR

End point title	Number of subjects with a vaccine response to PT, FHA and

End point description:

Vaccine response was defined as appearance of antibodies in subjects who were initially seronegative (i.e. with concentrations < cut-off value) or at least doubling of pre-vaccination antibody concentrations in subjects who were initially seropositive (i.e. with concentrations > cut-off value).

End point type	Primary

End point timeframe:

One month after the booster dose

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	116		
Units: Subjects				
Anti-PT, S- [N=29,31]	29	30		
Anti-PT, S+ [N=78,81]	78	81		
Anti-PT, Total [N=107,112]	107	111		
Anti-FHA, S- [N=4,5]	4	4		
Anti-FHA, S+ [N=105,107]	104	106		
Anti-FHA, Total [N=109,112]	108	110		
Anti-PRN, S- [N=31,31]	31	30		
Anti-PRN, S+ [N=81,85]	81	85		

Anti-PRN, Total [N=112,116]	112	115		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL

End point title	Number of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL[21][22]

End point description:

End point type	Primary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

[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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Preservative-free Group	Preservative-containing Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	119		
Units: Subjects				
Anti-PRP ≥ 0.15µg/mL, PRE [N=111,117]	71	87		
Anti-PRP ≥ 0.15µg/mL, PI(M1) [N=112,119]	112	119		
Anti-PRP ≥ 1.0µg/mL, PRE [N=111,117]	15	23		
Anti-PRP ≥ 1.0µg/mL, PI(M1) [N=112,119]	111	117		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms

End point title	Number of subjects with solicited local symptoms

End point description:

Assessed solicited local symptoms were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade.

End point type	Secondary

End point timeframe:

During the 4-day (Day 0–Day 3) follow-up period after the booster vaccination

End point values	Preservative-free Group	Preservative-containing Group	Control Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	136	138	
Units: Subjects				
Any Pain	74	76	82	
Any Redness	66	79	94	
Any Swelling	44	53	60	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited general symptoms

End point title	Number of subjects with solicited general symptoms

End point description:

Assessed solicited general symptoms were drowsiness, fever [defined as rectal temperature equal to or above 38.0 degrees Celsius (°C)], irritability and loss of appetite. Any = occurrence of the symptom regardless of intensity grade.

End point type	Secondary

End point timeframe:

During the 4-day (Day 0–Day 3) follow-up period after the booster vaccination

End point values	Preservative-free Group	Preservative-containing Group	Control Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	136	138	
Units: Subjects				
Any Drowsiness	50	48	58	
Any Fever (Rectal)	22	34	31	
Any Irritability	68	86	78	
Any Loss of Appetite	37	46	45	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with unsolicited adverse events (AEs)

End point title	Number of subjects with unsolicited adverse events (AEs)

End point description:

An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product and reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as the occurrence of any unsolicited AE regardless of intensity grade or relation to vaccination.

End point type	Secondary

End point timeframe:

During the 31-day (Day 0–Day 30) follow-up period after the booster vaccination

End point values	Preservative-free Group	Preservative-containing Group	Control Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127	137	139	
Units: Subjects				
Any AEs	51	54	61	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with serious adverse events (SAEs)

End point title	Number of subjects with serious adverse events (SAEs)

End point description:

Assessed SAEs include medical occurrences that result in death, are life-threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity.

End point type	Secondary

End point timeframe:

From study vaccine administration during the study period

End point values	Preservative-free Group	Preservative-containing Group	Control Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127	137	139	
Units: Subjects				
Any SAEs	1	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting concomitant medications

End point title	Number of subjects reporting concomitant medications

End point description:

End point type	Secondary

End point timeframe:

During the 4-day follow-up period

End point values	Preservative-free Group	Preservative-containing Group	Control Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127	137	139	
Units: Subjects				
Any concomitant medication	105	111	116	
Any antipyretic	34	35	33	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-diphtheria and anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/mL

End point title	Number of subjects with anti-diphtheria and anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/mL[23]

End point description:

End point type	Secondary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[23] - 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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: Subjects				
Anti-D, PRE [N=111]	40			
Anti-D, PI(M1) [N=119]	119			
Anti-T, PRE [N=111]	95			
Anti-T, PI(M1) [N=119]	119			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-Hepatitis B surface antigen (HBs) antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL

End point title	Number of subjects with anti-Hepatitis B surface antigen (HBs) antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL[24]

End point description:

End point type	Secondary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Subjects				
Anti-HBs ≥ 10 mIU/mL, PRE [N=110]	106			
Anti-HBs ≥ 10 mIU/mL, PI(M1) [N=118]	118			
Anti HBs ≥ 100 mIU/mL, PRE [N=110]	67			
Anti HBs ≥ 100 mIU/mL, PI(M1) [N=118]	114			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-poliovirus type 1, type 2 and type 3 antibody titers ≥ 8

End point title	Number of subjects with anti-poliovirus type 1, type 2 and type 3 antibody titers ≥ 8[25]

End point description:

End point type	Secondary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[25] - 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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Subjects				
Anti-polio 1, PRE [N=109]	84			
Anti-polio 1, PI(M1) [N=113]	112			
Anti-polio 2, PRE [N=109]	56			
Anti-polio 2, PI(M1) [N=113]	112			
Anti-polio 3, PRE [N=109]	82			
Anti-polio 3, PI(M1) [N=113]	113			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-PT, anti-FHA and anti-PRN concentrations ≥ 5 EL.U/mL

End point title	Number of subjects with anti-PT, anti-FHA and anti-PRN concentrations ≥ 5 EL.U/mL[26]

End point description:

End point type	Secondary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: Subjects				
Anti-PT, PRE [N=110]	93			
Anti-PT, PI(M1) [N=119]	119			
Anti-FHA, PRE [N=109]	109			

Anti-FHA, PI(M1) [N=119]	119			
Anti-PRN, PRE [N=111]	99			
Anti-PRN, PI(M1) [N=119]	119			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-diphtheria and anti-tetanus toxoids antibody concentrations

End point title	Anti-diphtheria and anti-tetanus toxoids antibody concentrations[27]

End point description:

End point type	Secondary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[27] - 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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-D, PRE [N=111]	0.084 (0.073 to 0.097)			
Anti-D, PI(M1) [N=119]	3.952 (3.365 to 4.642)			
Anti-T, PRE [N=111]	0.261 (0.219 to 0.31)			
Anti-T, PI(M1) [N=119]	10.833 (9.505 to 12.347)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-PT, anti-FHA, anti-PRN antibody concentrations

End point title	Anti-PT, anti-FHA, anti-PRN antibody concentrations[28]

End point description:

End point type	Secondary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PT, PRE [N=110]	8.9 (7.7 to 10.3)			
Anti-PT, PI(M1) [N=119]	153.7 (135.1 to 174.9)			
Anti-FHA, PRE [N=109]	33.7 (27.6 to 41.1)			
Anti-FHA, PI(M1) [N=119]	791.9 (708.8 to 884.8)			
Anti-PRN, PRE [N=111]	15.3 (12.6 to 18.5)			
Anti-PRN, PI(M1) [N=119]	564.1 (489.5 to 650.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HBs antibody concentrations

End point title	Anti-HBs antibody concentrations[29]

End point description:

End point type	Secondary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[29] - 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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs, PRE [N=110]	139.8 (107.2 to 182.3)			
Anti-HBs, PI(M1) [N=118]	6132.7 (4587.8 to 8197.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-poliovirus type 1, type 2 and type 3 antibody titers

End point title	Anti-poliovirus type 1, type 2 and type 3 antibody titers[30]

End point description:

End point type	Secondary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-polio 1, PRE [N=109]	21.6 (17.1 to 27.4)			
Anti-polio 1, PI(M1) [N=113]	1288.8 (1029.1 to 1614)			
Anti-polio 2, PRE [N=109]	11.8 (9.2 to 15)			
Anti-polio 2, PI(M1) [N=113]	1231 (961 to 1576.9)			
Anti-polio 3, PRE [N=109]	21.3 (16.4 to 27.7)			
Anti-polio 3, PI(M1) [N=113]	1794.8 (1426.8 to 2257.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-PRP antibody concentrations

End point title	Anti-PRP antibody concentrations[31]

End point description:

End point type	Secondary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[31] - 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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PRP, PRE [N=111]	0.487 (0.383 to 0.62)			
Anti-PRP, PRE [N=119]	77.087 (60.224 to 98.672)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a vaccine response to PT, FHA and PR

End point title	Number of subjects with a vaccine response to PT, FHA and

End point description:

Vaccine response was defined as appearance of antibodies in subjects who were initially seronegative (i.e. with concentrations < cut-off value) or at least doubling of pre-vaccination antibody concentrations in subjects who were initially seropositive (i.e. with concentrations > cut-off value).

End point type	Secondary

End point timeframe:

One month after the booster dose

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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: Subjects				
Anti-PT, S- [N=17]	17			
Anti-PT, S+ [N=93]	93			
Anti-PT, Total [N=110]	110			
Anti-FHA, S- [N=0]	0			
Anti-FHA, S+ [N=109]	105			
Anti-FHA, Total [N=109]	105			
Anti-PRN, S- [N=12]	12			
Anti-PRN, S+ [N=99]	98			
Anti-PRN, Total [N=111]	110			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL

End point title	Number of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL[33]

End point description:

End point type	Secondary

End point timeframe:

Before (PRE) and one month after the booster vaccination [PI(M1)]

Notes:

[33] - 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 results in this study were tabulated by treatment group. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

End point values	Control Group			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: Subjects				
Anti-PRP ≥ 0.15µg/mL, PRE [N=111]	92			
Anti-PRP ≥ 0.15µg/mL, PI(M1) [N=119]	119			
Anti-PRP ≥ 1.0µg/mL, PRE [N=111]	32			
Anti-PRP ≥ 1.0µg/mL, PI(M1) [N=119]	118			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: during the 4-day (Day 0–Day 3) period after the booster vaccination.
Unsolicited AEs: during the 31-day (Day 0–Day 30) period after the booster vaccination.
SAEs: during the entire study period

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Preservative-free Group

Reporting group description:

Subjects received the preservative-free (PF) formulation of DSSITGDPa-HBV-IPV/Hib in the primary phase and a booster dose of DTPa-HBV-IPV/Hib in the booster phase.

Reporting group title	Preservative-containing Group

Reporting group description:

Subjects received the preservative-containing (PC) formulation of DSSITGDPa-HBV-IPV/Hib in the primary phase and a booster dose of DTPa-HBV-IPV/Hib in the booster phase.

Reporting group title	Control Group

Reporting group description:

Subjects received the licensed formulation of DTPa-HBV-IPV/Hib in the primary phase and a booster dose in the booster phase.

Serious adverse events	Preservative-free Group	Preservative-containing Group	Control Group
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 127 (0.79%)	2 / 137 (1.46%)	1 / 139 (0.72%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 127 (0.79%)	1 / 137 (0.73%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 137 (0.73%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia adenoviral			

subjects affected / exposed	0 / 127 (0.00%)	0 / 137 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Preservative-free Group	Preservative-containing Group	Control Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 127 (58.27%)	86 / 137 (62.77%)	94 / 139 (67.63%)
General disorders and administration site conditions			
Pain			
subjects affected / exposed[1]	74 / 126 (58.73%)	76 / 136 (55.88%)	82 / 138 (59.42%)
occurrences (all)	74	76	82
Redness			
subjects affected / exposed[2]	66 / 126 (52.38%)	79 / 136 (58.09%)	94 / 138 (68.12%)
occurrences (all)	66	79	94
Swelling			
subjects affected / exposed[3]	44 / 126 (34.92%)	53 / 136 (38.97%)	60 / 138 (43.48%)
occurrences (all)	44	53	60
Drowsiness			
subjects affected / exposed[4]	50 / 126 (39.68%)	48 / 136 (35.29%)	58 / 138 (42.03%)
occurrences (all)	50	48	58
Fever/(Rectal)			
subjects affected / exposed[5]	22 / 126 (17.46%)	34 / 136 (25.00%)	31 / 138 (22.46%)
occurrences (all)	22	34	31
Irritability			
subjects affected / exposed[6]	68 / 126 (53.97%)	86 / 136 (63.24%)	78 / 138 (56.52%)
occurrences (all)	68	86	78
Loss of appetite			
subjects affected / exposed[7]	37 / 126 (29.37%)	46 / 136 (33.82%)	45 / 138 (32.61%)
occurrences (all)	37	46	45
Pyrexia			
subjects affected / exposed	6 / 127 (4.72%)	5 / 137 (3.65%)	8 / 139 (5.76%)
occurrences (all)	6	5	8
Injection site induration			

subjects affected / exposed	5 / 127 (3.94%)	2 / 137 (1.46%)	10 / 139 (7.19%)
occurrences (all)	5	2	10
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 127 (5.51%)	4 / 137 (2.92%)	5 / 139 (3.60%)
occurrences (all)	7	4	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 127 (1.57%)	9 / 137 (6.57%)	0 / 139 (0.00%)
occurrences (all)	2	9	0
Infections and infestations			
Otitis media			
subjects affected / exposed	4 / 127 (3.15%)	7 / 137 (5.11%)	14 / 139 (10.07%)
occurrences (all)	4	7	14
Upper respiratory tract infection			
subjects affected / exposed	9 / 127 (7.09%)	8 / 137 (5.84%)	6 / 139 (4.32%)
occurrences (all)	9	8	6
Rhinitis			
subjects affected / exposed	3 / 127 (2.36%)	8 / 137 (5.84%)	9 / 139 (6.47%)
occurrences (all)	3	8	9

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported