Clinical trial results:
A phase IIIA, randomized, single-blind, multi-centric study to evaluate the immunogenicity, reactogenicity and safety of three doses of Pediarix, Hiberix and Prevenar 13 when co-administered with two doses of the PCV-free liquid formulation of GSK Biologicals' oral live attenuated HRV vaccine as compared to the currently licensed lyophilized formulation of the HRV vaccine in healthy infants 6-12 weeks of age.

Summary

EudraCT number	2016-003210-27
Trial protocol	Outside EU/EEA
Global end of trial date	06 June 2019

Results information

Result version number	v1 (current)
This version publication date	24 October 2019
First version publication date	24 October 2019

Trial information

Trial identification

Sponsor protocol code	201663

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03207750
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	06 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 October 2018
Global end of trial reached?	Yes
Global end of trial date	06 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of the immune responses to three doses of Pediarix, Hiberix and Prevenar 13 when co-administered with two doses of the PCV-free liquid HRV vaccine, as compared to when coadministered with the currently licensed lyophilized HRV vaccine, 1 month after Dose 3 of routine infant vaccines.

Protection of trial subjects:

The subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 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: 1272
Worldwide total number of subjects	1272
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)	1272
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:

The study was conducted at 48 centers in the United States (US).

Pre-assignment

Screening details:

Out of 1280 subjects enrolled in the study, 7 subjects did not receive any study treatment and 1 subject was eliminated from all analyses as there was a deviation in informed consent.
1272 subjects were vaccinated and included in the Exposed Set, 1148 subjects completed the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	HRV Porcine circovirus (PCV)-free Liquid Group

Arm description:

Healthy female or male subjects, between and including 6 and 12 weeks (42-90 days) of age at the time of the first study vaccination who received two doses of oral live-attenuated human rotavirus (HRV) vaccine in PCV-free liquid formulation, according to a 0, 2-month schedule, co-administrated with one dose of each Pediarix, Hiberix and Prevnar-13 at three timepoints (day 1, month 2 and month 4). PCV-free implies no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.

Arm type	Active comparator
Investigational medicinal product name	Oral live-attenuated HRV vaccine in PCV-free liquid formulation
Investigational medicinal product code	
Other name	SB444563
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Two doses administered according to a 0, 2-month schedule

Arm title	HRV Lyophilized Group

Arm description:

Healthy female or male subjects, between and including 6 and 12 weeks (42-90 days) of age at the time of the first study vaccination who received two doses of oral live-attenuated human rotavirus (HRV) vaccine in lyophilized formulation, according to a 0, 2-month schedule, co-administrated with one dose of each Pediarix, Hiberix and Prevnar-13 at three timepoints (day 1, month 2 and month 4).

Arm type	Active comparator
Investigational medicinal product name	Oral live-attenuated HRV vaccine in lyophilized formulation
Investigational medicinal product code	
Other name	SB444563
Pharmaceutical forms	Oral liquid, Oral lyophilisate
Routes of administration	Oral use

Dosage and administration details:

Two doses administered according to a 0, 2-month schedule

Number of subjects in period 1	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group
Started	632	640
Completed	574	574
Not completed	58	66
CONSENT WITHDRAWAL, NOT DUE TO AN AE	11	13
NOT WILLING / NOT ABLE TO BE CONTACTED	1	2
OTHER, NOT SPECIFIED	5	4
NOT WILLING TO PARTICIPATE THIS VISIT	10	5
Adverse event, non-fatal	3	2
MIGRATED / MOVED FROM THE STUDY AREA	7	10
Lost to follow-up	21	29
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	HRV Porcine circovirus (PCV)-free Liquid Group
Reporting group description:	
Healthy female or male subjects, between and including 6 and 12 weeks (42-90 days) of age at the time of the first study vaccination who received two doses of oral live-attenuated human rotavirus (HRV) vaccine in PCV-free liquid formulation, according to a 0, 2-month schedule, co-administrated with one dose of each Pediarix, Hiberix and Prevnar-13 at three timepoints (day 1, month 2 and month 4). PCV-free implies no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.	
Reporting group title	HRV Lyophilized Group
Reporting group description:	
Healthy female or male subjects, between and including 6 and 12 weeks (42-90 days) of age at the time of the first study vaccination who received two doses of oral live-attenuated human rotavirus (HRV) vaccine in lyophilized formulation, according to a 0, 2-month schedule, co-administrated with one dose of each Pediarix, Hiberix and Prevnar-13 at three timepoints (day 1, month 2 and month 4).	

Reporting group values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group	Total
Number of subjects	632	640	1272
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)	632	640	1272
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Sex: Female, Male Units: Subjects			
Female	308	309	617
Male	324	331	655
Race/Ethnicity, Customized Units: Subjects			
American Indian Or Alaska Native	8	7	15
Asian	20	22	42
Black Or African American	74	78	152
Native Hawaiian Or Other Pacific Islander	2	2	4
White	468	471	939
Other, not specified	60	60	120
Age, Continuous Units: Weeks			
arithmetic mean	8.7	8.7	
standard deviation	± 1.1	± 1.1	-

End points

End points reporting groups

Reporting group title	HRV Porcine circovirus (PCV)-free Liquid Group

Reporting group description:

Healthy female or male subjects, between and including 6 and 12 weeks (42-90 days) of age at the time of the first study vaccination who received two doses of oral live-attenuated human rotavirus (HRV) vaccine in PCV-free liquid formulation, according to a 0, 2-month schedule, co-administrated with one dose of each Pediarix, Hiberix and Prevnar-13 at three timepoints (day 1, month 2 and month 4). PCV-free implies no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.

Reporting group title	HRV Lyophilized Group

Reporting group description:

Healthy female or male subjects, between and including 6 and 12 weeks (42-90 days) of age at the time of the first study vaccination who received two doses of oral live-attenuated human rotavirus (HRV) vaccine in lyophilized formulation, according to a 0, 2-month schedule, co-administrated with one dose of each Pediarix, Hiberix and Prevnar-13 at three timepoints (day 1, month 2 and month 4).

Primary: Number of seroprotected subjects with anti-diphtheria (anti-D) and anti-tetanus (anti-T) antibody concentrations above or equal to cut-off value.

End point title	Number of seroprotected subjects with anti-diphtheria (anti-D) and anti-tetanus (anti-T) antibody concentrations above or equal to cut-off value.

End point description:

Immunogenicity was assessed using Enzyme Linked Immunosorbent Assay (ELISA) in terms of seroprotection rates against diphtheria toxoid. A seroprotected subject is a subject whose antibody concentration is ≥ the level defining clinical protection. The following seroprotection thresholds were applicable:anti-D antibody concentrations ≥ 0.1 International Units/milliliter (IU/mL), anti-T antibody concentrations ≥ 0.1 IU/mL.

End point type	Primary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	486	495		
Units: Participants				
Anti-D	478	486		
Anti-T	486	495		

Statistical analyses

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered

with lyophilized HRV vaccine in terms of group difference in percentage of subjects with seroprotective concentrations (≥ 0.1 IU/mL) of anti-D antibodies.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in concentration
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.79

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group difference in percentage of subjects with seroprotective concentrations (≥ 0.1 IU/mL) of anti-T antibodies.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in concentration
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	0.77

Primary: Number of seroprotected subjects with anti-hepatitis B (anti-HBs) antibody concentrations above or equal to cut-off value.

End point title	Number of seroprotected subjects with anti-hepatitis B (anti-HBs) antibody concentrations above or equal to cut-off value.

End point description:

Immunogenicity was assessed using ChemiLuminescence ImmunoAssay (CLIA) in terms of seroprotection rates against Hepatitis B. A seroprotected subject is a subject whose antibody concentration is ≥ the level defining clinical protection. The following seroprotection thresholds were applicable:anti-HB antibody concentrations ≥ 10 milli International Units/milliliter (mIU/mL).

End point type	Primary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	460	471		
Units: Participants	457	471		

Statistical analyses

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group difference in percentage of subjects with seroprotective concentrations (≥ 10 mIU/mL) of anti-HB antibodies.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	931
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in concentration
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.16

Primary: Number of seroprotected subjects with anti-polio virus types 1, 2 and 3 antibody titers above or equal to cut-off value.

End point title	Number of seroprotected subjects with anti-polio virus types 1, 2 and 3 antibody titers above or equal to cut-off value.

End point description:

Immunogenicity was assessed using virus micro-neutralization test in terms of seroprotection rates against polio virus types 1, 2 and 3. A seroprotected subject is a subject whose antibody concentration is ≥ the level defining clinical protection. The following seroprotection thresholds were applicable:anti-polio virus types 1, 2 and 3 types antibody titers ≥ 8 Estimated Dose 50% (ED50).

End point type	Primary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	487		
Units: Participants				
Anti-Polio 1	477	486		
Anti-Polio 2	463	478		
Anti-Polio 3	439	454		

Statistical analyses

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group difference in percentage of subjects with seroprotective titers (≥ 8 ED50) of anti-poliovirus type 1 antibodies.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	964
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in concentration
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.15

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group difference in percentage of subjects with seroprotective titers (≥ 8 ED50) of anti-poliovirus type 3 antibodies.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	964
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in concentration
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	0.84

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized
Statistical analysis description:	
Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group difference in percentage of subjects with seroprotective titers (≥ 8 ED50) of anti-poliovirus type 2 antibodies.	
Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	964
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in concentration
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	0.98

Primary: Immunogenicity in terms of anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations.

End point title	Immunogenicity in terms of anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations.
End point description:	
Antibody concentrations against PT, FHA and PRN were determined and expressed as Geometric Mean Concentrations (GMCs).The GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations.	
End point type	Primary
End point timeframe:	
At Month 5 (One month after Dose 3 of co-administered vaccines)	

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	486	495		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-PT	51 (47.8 to 54.5)	54.2 (51.3 to 57.4)		
Anti-FHA	107.3 (101.4 to 113.5)	107.7 (101.6 to 114.1)		

Anti-PRN	55 (50.1 to 60.4)	56.6 (51.9 to 61.7)		

Statistical analyses

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized
Statistical analysis description:	
Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for anti-PT antibodies.	
Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.03

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized
Statistical analysis description:	
Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for anti-FHA antibodies.	
Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.08

Statistical analysis title	Non-inferiority of liquid PCV-free to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for anti-PRN antibodies.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.1

Primary: Immunogenicity in terms of anti-pneumococcal serotypes (anti-PnPS) antibody concentrations.

End point title	Immunogenicity in terms of anti-pneumococcal serotypes (anti-PnPS) antibody concentrations.

End point description:

Antibody concentrations against pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) were determined and expressed as GMCs in micrograms per milliliter (µg/mL).The GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations.

End point type	Primary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	448	466		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PnPS 1	1.95 (1.81 to 2.10)	1.89 (1.76 to 2.03)		
Anti-PnPS 3	0.53 (0.49 to 0.57)	0.53 (0.49 to 0.57)		
Anti-PnPS 4	1.24 (1.16 to 1.34)	1.25 (1.18 to 1.34)		
Anti-PnPS 5	1.28 (1.17 to 1.39)	1.22 (1.13 to 1.31)		
Anti-PnPS 6A	2.84 (2.64 to 3.05)	2.8 (2.61 to 3.00)		
Anti-PnPS 6B	1.93 (1.72 to 2.15)	2 (1.80 to 2.22)		

Anti-PnPS 7F	3.01 (2.83 to 3.21)	3.04 (2.86 to 3.22)		
Anti-PnPS 9V	1.68 (1.56 to 1.81)	1.63 (1.52 to 1.75)		
Anti-PnPS 14	6.27 (5.74 to 6.84)	6.26 (5.75 to 6.82)		
Anti-PnPS 18C	1.81 (1.68 to 1.95)	1.76 (1.64 to 1.89)		
Anti-PnPS 19A	1.87 (1.73 to 2.02)	1.8 (1.68 to 1.93)		
Anti-PnPS 19F	2.94 (2.76 to 3.12)	2.85 (2.69 to 3.03)		
Anti-PnPS 23F	1.14 (1.04 to 1.24)	1.16 (1.07 to 1.26)		

Statistical analyses

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 1.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.14

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 3.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group

Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.11

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 4.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.09

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 5.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.17

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 6A.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.12

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 6B.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.12

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 7F.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.08

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 9V.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.14

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 14.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group

Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.13

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 18C.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.14

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 19A.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.15

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 19F.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.12

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of GMC ratios for Streptococcus pneumoniae (S. pneumoniae) serotype 23F.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.1

Primary: Number of seroprotected subjects with anti-polyribosyl ribitol phosphate (anti-PRP) antibody concentrations above or equal to cut-off value of 0.15 µg/mL.

End point title	Number of seroprotected subjects with anti-polyribosyl ribitol phosphate (anti-PRP) antibody concentrations above or equal to cut-off value of 0.15 µg/mL.

End point description:

Immunogenicity was assessed in terms of seroprotection rates against PRP antibodies. A seroprotected subject is a subject whose antibody concentration is ≥ the level defining clinical protection. The following seroprotection thresholds were applicable:anti-PRP antibody concentrations ≥ 0.15 µg/mL.

End point type	Primary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	492		
Units: Participants	473	479		

Statistical analyses

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group difference in percentage of subjects with concentrations (≥ 0.15 µg/mL) of anti-PRP antibodies.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	977
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in concentration
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	2.28

Primary: Number of seroprotected subjects with anti-polyribosyl ribitol phosphate (anti-PRP) antibody concentrations above or equal to cut-off value of 1.0 µg/mL.

End point title	Number of seroprotected subjects with anti-polyribosyl ribitol phosphate (anti-PRP) antibody concentrations above or equal to cut-off value of 1.0 µg/mL.

End point description:

Immunogenicity was assessed in terms of seroprotection rates against PRP antibodies. A seroprotected subject is a subject whose antibody concentration is ≥ the level defining clinical protection. The following seroprotection thresholds were applicable:anti-PRP antibody concentrations ≥ 1.0 µg/mL.

End point type	Primary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	492		
Units: Participants	394	404		

Statistical analyses

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

Non-inferiority of the immune responses to 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group difference in percentage of subjects with concentrations (≥ 1.0 µg/mL) of anti-PRP antibodies.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	977
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in concentration
Point estimate	-0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.75
upper limit	3.99

Primary: Number of Subjects With Seroresponse to anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibodies.

End point title	Number of Subjects With Seroresponse to anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibodies.

End point description:

Seroresponse is defined as the percentage of subjects showing an antibody concentration above a threshold that leads to 95% seroresponse in the HRV lyophilized Group. The cut-offs used were as follows: anti-PT (18.566 IU/mL), anti-FHA (35.711 IU/mL) and anti-PRN (11.034 IU/mL).

End point type	Primary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	486	495		
Units: Participants				
Anti-PT	440	470		
Anti-FHA	466	470		
Anti-PRN	455	470		

Statistical analyses

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

To rule out 10% decrease in seroresponse to PT antigen in subjects who received Pediarix co-administered with PCV-free-Liquid-HRV vaccine compared to subjects who received Pediarix co-administered with currently licensed lyophilized HRV vaccine where seroresponse was defined as percentage of subjects who showed a concentration above a threshold that led to 95% seroresponse in HRV lyophilized group.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 1-sided

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

To rule out 10% decrease in seroresponse to FHA antigen in subjects who received Pediarix co-administered with PCV-free-Liquid-HRV vaccine compared to subjects who received Pediarix co-administered with currently licensed lyophilized HRV vaccine where seroresponse was defined as percentage of subjects who showed a concentration above a threshold that led to 95% seroresponse in HRV lyophilized group.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 1-sided

Statistical analysis title	Non-inferiority of PCV-free liquid to lyophilized

Statistical analysis description:

To rule out 10% decrease in seroresponse to PRN antigen in subjects who received Pediarix co-administered with PCV-free-Liquid-HRV vaccine compared to subjects who received Pediarix co-administered with currently licensed lyophilized HRV vaccine where seroresponse was defined as percentage of subjects who showed a concentration above a threshold that led to 95% seroresponse in HRV lyophilized group.

Comparison groups	HRV Porcine circovirus (PCV)-free Liquid Group v HRV Lyophilized Group
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 1-sided

Secondary: Number of seropositive subjects with anti-Rota virus Immunoglobulin A (anti-RV IgA) antibody concentrations above or equal to cut-off value of 20 Units/milliliter (U/mL).

End point title	Number of seropositive subjects with anti-Rota virus Immunoglobulin A (anti-RV IgA) antibody concentrations above or equal to cut-off value of 20 Units/milliliter (U/mL).

End point description:

Immunogenicity was assessed in terms of seropositivity against Rota virus IgA antibodies. The cut off used was ≥ 20 U/mL.

End point type	Secondary

End point timeframe:

At Month 5 (Three months after Dose 2 of HRV vaccine)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	417	426		
Units: Participants	318	336		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects with anti-RV IgA antibody concentrations above or equal to cut-off value of 90 U/mL.

End point title	Number of seropositive subjects with anti-RV IgA antibody concentrations above or equal to cut-off value of 90 U/mL.

End point description:

Immunogenicity was assessed in terms of seropositivity against Rota virus IgA antibodies. The cut off used was ≥ 90 U/mL.

End point type	Secondary

End point timeframe:

At Month 5 (Three months after Dose 2 of HRV vaccine)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	417	426		
Units: Participants	219	238		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations above or equal to cut-off value.

End point title	Number of seropositive subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations above or equal to cut-off value.

End point description:

Immunogenicity was assessed using ELISA technique in terms of seropositivity against PT, FHA and PRN antibodies. The cut-offs for antibodies were the Lower Limit Of Quantification (LLOQ) of the assays which were ≥ 2.693 IU/mL (anti-PT), ≥ 2.046 IU/mL (anti-FHA) and ≥ 2.187 IU/mL (anti-PRN).
The Limit of Quantification is the lowest analyte concentration that can be quantitatively detected with a stated accuracy and precision, and LLOQ is the lowest standard curve point obtained by extrapolation, that can still be used for quantification.

End point type	Secondary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	486	495		
Units: Participants				
Anti-PT	485	495		
Anti-FHA	486	495		
Anti-PRN	486	495		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects with anti-PnPS antibody concentrations above or equal to cut-off value.

End point title	Number of seropositive subjects with anti-PnPS antibody concentrations above or equal to cut-off value.

End point description:

Immunogenicity was assessed using ELISA technique in terms of seropositivity against Pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibodies. The cut-off used was ≥ 0.35 µg/mL.

End point type	Secondary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	448	466		
Units: Participants				
Anti-PnPS 1	442	463		
Anti-PnPS 3	317	322		
Anti-PnPS 4	434	453		
Anti-PnPS 5	409	424		
Anti-PnPS 6A	441	461		
Anti-PnPS 6B	407	434		
Anti-PnPS 7F	448	466		
Anti-PnPS 9V	431	454		
Anti-PnPS 14	441	454		
Anti-PnPS 18C	436	451		
Anti-PnPS 19A	438	458		
Anti-PnPS 19F	448	465		
Anti-PnPS 23F	409	425		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity in terms of anti-D and anti-T antibody concentrations.

End point title	Immunogenicity in terms of anti-D and anti-T antibody concentrations.

End point description:

Antibody concentrations against diphtheria and tetanus were determined and expressed as GMCs. The GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations.

End point type	Secondary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	486	495		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-D	1.85 (1.72 to 1.98)	1.88 (1.75 to 2.02)		
Anti-T	1.88 (1.75 to 2.02)	1.86 (1.74 to 1.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity in terms of anti-PRP antibody concentrations.

End point title	Immunogenicity in terms of anti-PRP antibody concentrations.

End point description:

Antibody concentrations against PRP were determined and expressed as GMCs. The GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations.

End point type	Secondary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	492		
Units: µg/mL				
geometric mean (confidence interval 95%)	4.41 (3.82 to 5.09)	4.28 (3.71 to 4.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity in terms of anti-HBs antibody concentrations.

End point title	Immunogenicity in terms of anti-HBs antibody concentrations.

End point description:

Antibody concentrations against Hepatitis B were determined and expressed as GMCs. The GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations.

End point type	Secondary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	460	471		
Units: mIU/mL				
geometric mean (confidence interval 95%)	2031.3 (1834.6 to 2249.0)	2168.9 (1977.5 to 2378.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity in terms of anti-poliovirus types 1, 2 and 3 antibody titers

End point title	Immunogenicity in terms of anti-poliovirus types 1, 2 and 3 antibody titers

End point description:

Antibody concentrations against Poliovirus types 1, 2 and 3 were determined and expressed as Geometric Mean Titers (GMTs).

End point type	Secondary

End point timeframe:

At Month 5 (One month after Dose 3 of co-administered vaccines)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	487		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-Polio 1	747.2 (673.5 to 828.8)	728.2 (656.3 to 808.0)		
Anti-Polio 2	659.6 (587.9 to 740.0)	699.3 (627.7 to 779.0)		
Anti-Polio 3	1228.7 (1100.3 to 1372.1)	1291.6 (1159.1 to 1439.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any solicited general adverse events (AEs).

End point title	Number of subjects with any solicited general adverse events (AEs).

End point description:

Assessed solicited general AEs were cough/runny nose, diarrhoea, fever measured by 3 routes which were oral, axillary and rectal (defined as temperature ≥ 38.0°C), irritability, loss of appetite and vomiting. Any = any solicited general AE irrespective of its intensity grade and relationship to vaccination

End point type	Secondary

End point timeframe:

During the 8-day (Days 1-8) follow-up period after each HRV vaccination.

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	632	640		
Units: Participants				
Cough / Runny Nose (Dose 1), Any	172	180		
Cough / Runny Nose (Dose 2), Any	224	222		
Cough / Runny Nose (Across doses), Any	305	313		
Diarrhea (Dose 1), Any	39	36		
Diarrhea (Dose 2), Any	34	26		
Diarrhea (Across doses), Any	69	55		
Fever (Dose 1), ≥ 38.0°C	36	32		
Fever (Dose 2), ≥ 38.0°C	64	75		
Fever (Across doses), ≥ 38.0°C	89	95		
Irritability / Fussiness (Dose 1), Any	448	458		

Irritability / Fussiness (Dose 2), Any	440	427		
Irritability / Fussiness (Across doses), Any	523	522		
Loss of appetite (Dose 1), Any	204	214		
Loss of appetite (Dose 2), Any	179	178		
Loss of appetite (Across doses), Any	292	293		
Vomiting (Dose 1), Any	110	105		
Vomiting (Dose 2), Any	83	78		
Vomiting (Across doses), Any	147	148		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any unsolicited AEs.

End point title	Number of subjects with any unsolicited AEs.

End point description:

Unsolicited AEs assessed include any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms were reported as an unsolicited AE. Any= Any unsolicited AE irrespective of its intensity grade and relationship to vaccination.

End point type	Secondary

End point timeframe:

During the 31-day (Days 1-31) follow-up period after each HRV vaccination.

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	632	640		
Units: Participants	294	327		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

SAEs assessed include any untoward medical occurrence that resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization or resulted in disability/incapacity.

End point type	Secondary

End point timeframe:

During the entire study period (Day 1 to Month 10)

End point values	HRV Porcine circovirus (PCV)-free Liquid Group	HRV Lyophilized Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	632	640		
Units: Participants	20	19		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited AEs: During the 8-day (Day 1 to Day 8) follow-up period after each HRV vaccination.
Unsolicited AEs: During the 31-day (Day 1 to Day 31) follow-up period after each HRV vaccination.
SAEs: Throughout the study period (Day 1 to Month 10).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	HRV Lyophilized Group

Reporting group description:

Healthy female or male subjects, between and including 6 and 12 weeks (42-90 days) of age at the time of the first study vaccination who received two doses of oral live-attenuated human rotavirus (HRV) vaccine in liquid formulation, according to a 0, 2-month schedule, co-administrated with one dose of each Pediarix, Hiberix and Prevnar-13 at three timepoints (day 1, month 2 and month 4).

Reporting group title	HRV Liquid Group

Reporting group description:

Healthy female or male subjects, between and including 6 and 12 weeks (42-90 days) of age at the time of the first study vaccination who received two doses of oral live-attenuated human rotavirus (HRV) vaccine in liquid formulation, according to a 0, 2-month schedule, co-administrated with one dose of each Pediarix, Hiberix and Prevnar-13 at three timepoints (day 1, month 2 and month 4).

Serious adverse events	HRV Lyophilized Group	HRV Liquid Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 640 (2.97%)	20 / 632 (3.16%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden infant death syndrome			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute respiratory failure			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose abnormal			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Pharyngeal perforation			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			

subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Laryngomalacia			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Seizure			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure like phenomena			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	2 / 640 (0.31%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Botulism			

subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	4 / 640 (0.63%)	5 / 632 (0.79%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus infection			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			

subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	4 / 640 (0.63%)	3 / 632 (0.47%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchitis			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid intake reduced			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	HRV Lyophilized Group	HRV Liquid Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	589 / 640 (92.03%)	571 / 632 (90.35%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	0 / 640 (0.00%)	3 / 632 (0.47%)	
occurrences (all)	0	3	
Discomfort			

subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Influenza like illness			
subjects affected / exposed	2 / 640 (0.31%)	1 / 632 (0.16%)	
occurrences (all)	2	1	
Fatigue			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Injection site erythema			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences (all)	1	2	
Injection site discomfort			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Injection site inflammation			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Injection site nodule			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences (all)	0	2	
Injection site mass			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Injection site pain			
subjects affected / exposed	9 / 640 (1.41%)	13 / 632 (2.06%)	
occurrences (all)	11	16	
Injection site swelling			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Nodule			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			

subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	116 / 640 (18.13%)	102 / 632 (16.14%)	
occurrences (all)	133	116	
Swelling			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences (all)	0	2	
Vaccination site pain			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Milk allergy			
subjects affected / exposed	2 / 640 (0.31%)	1 / 632 (0.16%)	
occurrences (all)	2	1	
Reproductive system and breast disorders			
Breast cyst			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Breast mass			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Genital labial adhesions			
subjects affected / exposed	2 / 640 (0.31%)	3 / 632 (0.47%)	
occurrences (all)	2	3	
Penile adhesion			
subjects affected / exposed	2 / 640 (0.31%)	3 / 632 (0.47%)	
occurrences (all)	2	3	
Testicular retraction			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences (all)	1	2	
Choking			

subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	330 / 640 (51.56%)	320 / 632 (50.63%)	
occurrences (all)	446	423	
Dysphonia			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Lower respiratory tract congestion			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	40 / 640 (6.25%)	28 / 632 (4.43%)	
occurrences (all)	47	31	
Productive cough			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Respiratory disorder			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Respiratory tract congestion			
subjects affected / exposed	0 / 640 (0.00%)	3 / 632 (0.47%)	
occurrences (all)	0	3	
Rhinorrhoea			
subjects affected / exposed	21 / 640 (3.28%)	9 / 632 (1.42%)	
occurrences (all)	21	9	
Wheezing			
subjects affected / exposed	6 / 640 (0.94%)	3 / 632 (0.47%)	
occurrences (all)	6	3	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	

Irritability			
subjects affected / exposed	522 / 640 (81.56%)	523 / 632 (82.75%)	
occurrences (all)	896	896	
Restlessness			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Cardiac murmur			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Urine output decreased			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Viral test positive			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences (all)	0	2	
Craniocerebral injury			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Exposure to communicable disease			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Exposure to toxic agent			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Eyelid injury			

subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	2 / 640 (0.31%)	1 / 632 (0.16%)	
occurrences (all)	2	1	
Mouth injury			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Respiratory fume inhalation disorder			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Vaccination complication			
subjects affected / exposed	2 / 640 (0.31%)	1 / 632 (0.16%)	
occurrences (all)	2	2	
Congenital, familial and genetic disorders			
Ankyloglossia congenital			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Atrial septal defect			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Birth mark			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Congenital musculoskeletal anomaly			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Congenital torticollis			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Dacryostenosis congenital			

subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Macrocephaly			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Plagiocephaly			
subjects affected / exposed	9 / 640 (1.41%)	7 / 632 (1.11%)	
occurrences (all)	9	7	
Nervous system disorders			
Drooling			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Febrile convulsion			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Hypersomnia			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Lethargy			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Poor quality sleep			
subjects affected / exposed	1 / 640 (0.16%)	3 / 632 (0.47%)	
occurrences (all)	1	3	
Seizure			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	5 / 640 (0.78%)	7 / 632 (1.11%)	
occurrences (all)	5	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			

Cerumen impaction			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences (all)	1	2	
Ear pain			
subjects affected / exposed	2 / 640 (0.31%)	8 / 632 (1.27%)	
occurrences (all)	2	9	
Otorrhoea			
subjects affected / exposed	2 / 640 (0.31%)	3 / 632 (0.47%)	
occurrences (all)	2	3	
Tympanic membrane perforation			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Dacryostenosis acquired			
subjects affected / exposed	1 / 640 (0.16%)	5 / 632 (0.79%)	
occurrences (all)	1	5	
Eye discharge			
subjects affected / exposed	6 / 640 (0.94%)	6 / 632 (0.95%)	
occurrences (all)	6	8	
Eye swelling			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Eyelid irritation			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	2 / 640 (0.31%)	3 / 632 (0.47%)	
occurrences (all)	2	3	
Abdominal pain upper			

subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Abnormal faeces			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	12 / 640 (1.88%)	10 / 632 (1.58%)	
occurrences (all)	12	10	
Diarrhoea			
subjects affected / exposed	113 / 640 (17.66%)	126 / 632 (19.94%)	
occurrences (all)	164	185	
Dysphagia			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Faeces discoloured			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences (all)	0	2	
Flatulence			
subjects affected / exposed	13 / 640 (2.03%)	12 / 632 (1.90%)	
occurrences (all)	15	17	
Gastric haemorrhage			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	13 / 640 (2.03%)	13 / 632 (2.06%)	
occurrences (all)	13	13	
Haematochezia			
subjects affected / exposed	3 / 640 (0.47%)	2 / 632 (0.32%)	
occurrences (all)	3	2	
Impaired gastric emptying			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Infantile colic			

subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Infantile vomiting			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Infrequent bowel movements			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Mucous stools			
subjects affected / exposed	2 / 640 (0.31%)	1 / 632 (0.16%)	
occurrences (all)	2	1	
Post-tussive vomiting			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Pylorospasm			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Rectal fissure			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Salivary hypersecretion			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Teething			
subjects affected / exposed	10 / 640 (1.56%)	12 / 632 (1.90%)	
occurrences (all)	11	12	
Vomiting			
subjects affected / exposed	156 / 640 (24.38%)	155 / 632 (24.53%)	
occurrences (all)	197	208	
Skin and subcutaneous tissue disorders			
Acne infantile			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	

Cafe au lait spots			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences (all)	0	2	
Dermatitis atopic			
subjects affected / exposed	10 / 640 (1.56%)	5 / 632 (0.79%)	
occurrences (all)	10	5	
Dermatitis contact			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Dermatitis diaper			
subjects affected / exposed	17 / 640 (2.66%)	14 / 632 (2.22%)	
occurrences (all)	17	15	
Dry skin			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences (all)	1	2	
Eczema			
subjects affected / exposed	3 / 640 (0.47%)	8 / 632 (1.27%)	
occurrences (all)	3	9	
Eczema infantile			
subjects affected / exposed	1 / 640 (0.16%)	5 / 632 (0.79%)	
occurrences (all)	1	5	
Erythema			
subjects affected / exposed	4 / 640 (0.63%)	0 / 632 (0.00%)	
occurrences (all)	4	0	
Erythema toxicum neonatorum			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Miliaria			
subjects affected / exposed	2 / 640 (0.31%)	2 / 632 (0.32%)	
occurrences (all)	2	2	
Perioral dermatitis			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences (all)	1	2	

Rash			
subjects affected / exposed	12 / 640 (1.88%)	7 / 632 (1.11%)	
occurrences (all)	15	7	
Rash erythematous			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences (all)	0	2	
Rash generalised			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Rash macular			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences (all)	0	2	
Seborrhoea			
subjects affected / exposed	3 / 640 (0.47%)	1 / 632 (0.16%)	
occurrences (all)	3	1	
Seborrhoeic dermatitis			
subjects affected / exposed	5 / 640 (0.78%)	5 / 632 (0.79%)	
occurrences (all)	5	5	
Skin discolouration			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Skin fissures			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Skin hypopigmentation			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Skin induration			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences (all)	1	2	
Swelling face			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	

Umbilical haemorrhage			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	2 / 640 (0.31%)	0 / 632 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Urethral discharge			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Urine odour abnormal			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Acquired plagiocephaly			
subjects affected / exposed	2 / 640 (0.31%)	3 / 632 (0.47%)	
occurrences (all)	2	3	
Joint noise			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 640 (0.31%)	1 / 632 (0.16%)	
occurrences (all)	2	1	
Torticollis			
subjects affected / exposed	5 / 640 (0.78%)	4 / 632 (0.63%)	
occurrences (all)	5	4	

Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Bronchiolitis			
subjects affected / exposed	16 / 640 (2.50%)	16 / 632 (2.53%)	
occurrences (all)	16	16	
Bronchitis			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Candida infection			
subjects affected / exposed	5 / 640 (0.78%)	1 / 632 (0.16%)	
occurrences (all)	5	1	
Candida nappy rash			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Cellulitis			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Clostridium difficile infection			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	11 / 640 (1.72%)	14 / 632 (2.22%)	
occurrences (all)	11	14	
Conjunctivitis bacterial			
subjects affected / exposed	2 / 640 (0.31%)	0 / 632 (0.00%)	
occurrences (all)	2	0	
Corona virus infection			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Croup infectious			
subjects affected / exposed	4 / 640 (0.63%)	6 / 632 (0.95%)	
occurrences (all)	4	6	
Ear infection			

subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Ear infection bacterial			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Enterovirus infection			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Eye infection			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences (all)	0	2	
Fungal skin infection			
subjects affected / exposed	4 / 640 (0.63%)	1 / 632 (0.16%)	
occurrences (all)	4	1	
Gastroenteritis			
subjects affected / exposed	2 / 640 (0.31%)	7 / 632 (1.11%)	
occurrences (all)	3	7	
Gastroenteritis viral			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Impetigo			
subjects affected / exposed	2 / 640 (0.31%)	0 / 632 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	9 / 640 (1.41%)	3 / 632 (0.47%)	
occurrences (all)	9	3	
Laryngitis			
subjects affected / exposed	2 / 640 (0.31%)	0 / 632 (0.00%)	
occurrences (all)	2	0	
Laryngotracheitis obstructive			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	10 / 640 (1.56%)	6 / 632 (0.95%)	
occurrences (all)	10	7	
Neonatal candida infection			

subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	7 / 640 (1.09%)	6 / 632 (0.95%)	
occurrences (all)	8	6	
Otitis media			
subjects affected / exposed	23 / 640 (3.59%)	26 / 632 (4.11%)	
occurrences (all)	26	28	
Otitis media acute			
subjects affected / exposed	23 / 640 (3.59%)	14 / 632 (2.22%)	
occurrences (all)	25	14	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	2 / 640 (0.31%)	0 / 632 (0.00%)	
occurrences (all)	2	0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences (all)	1	2	
Pyelonephritis			
subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	3 / 640 (0.47%)	2 / 632 (0.32%)	
occurrences (all)	3	2	
Respiratory syncytial virus infection			
subjects affected / exposed	10 / 640 (1.56%)	2 / 632 (0.32%)	
occurrences (all)	10	2	

Respiratory tract infection			
subjects affected / exposed	2 / 640 (0.31%)	2 / 632 (0.32%)	
occurrences (all)	2	2	
Respiratory tract infection viral			
subjects affected / exposed	2 / 640 (0.31%)	1 / 632 (0.16%)	
occurrences (all)	2	1	
Rhinitis			
subjects affected / exposed	4 / 640 (0.63%)	1 / 632 (0.16%)	
occurrences (all)	5	1	
Rhinovirus infection			
subjects affected / exposed	2 / 640 (0.31%)	1 / 632 (0.16%)	
occurrences (all)	2	1	
Sinusitis			
subjects affected / exposed	3 / 640 (0.47%)	2 / 632 (0.32%)	
occurrences (all)	3	2	
Skin bacterial infection			
subjects affected / exposed	0 / 640 (0.00%)	2 / 632 (0.32%)	
occurrences (all)	0	2	
Skin candida			
subjects affected / exposed	2 / 640 (0.31%)	3 / 632 (0.47%)	
occurrences (all)	2	3	
Skin infection			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Streptococcal infection			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Subcutaneous abscess			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Subglottic laryngitis			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	

Upper respiratory tract infection			
subjects affected / exposed	69 / 640 (10.78%)	63 / 632 (9.97%)	
occurrences (all)	77	72	
Urinary tract infection			
subjects affected / exposed	3 / 640 (0.47%)	1 / 632 (0.16%)	
occurrences (all)	3	1	
Urogenital infection fungal			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	8 / 640 (1.25%)	8 / 632 (1.27%)	
occurrences (all)	8	9	
Viral pharyngitis			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Viral rash			
subjects affected / exposed	2 / 640 (0.31%)	0 / 632 (0.00%)	
occurrences (all)	2	0	
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 640 (0.63%)	5 / 632 (0.79%)	
occurrences (all)	4	5	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Breast milk substitute intolerance			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Cow's milk intolerance			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	293 / 640 (45.78%)	293 / 632 (46.36%)	
occurrences (all)	392	384	
Dehydration			

subjects affected / exposed	1 / 640 (0.16%)	1 / 632 (0.16%)	
occurrences (all)	1	1	
Failure to thrive			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences (all)	1	2	
Feeding disorder			
subjects affected / exposed	1 / 640 (0.16%)	2 / 632 (0.32%)	
occurrences (all)	1	2	
Increased appetite			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Milk soy protein intolerance			
subjects affected / exposed	0 / 640 (0.00%)	1 / 632 (0.16%)	
occurrences (all)	0	1	
Underweight			
subjects affected / exposed	3 / 640 (0.47%)	2 / 632 (0.32%)	
occurrences (all)	4	2	
Weight gain poor			
subjects affected / exposed	1 / 640 (0.16%)	0 / 632 (0.00%)	
occurrences (all)	1	0	

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