



Clinical trial results:

A phase IV, randomised, open-label, controlled study to assess the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine Squarekids when co-administered with GSK Biologicals' oral live attenuated human rotavirus (HRV) liquid vaccine Rotarix in healthy Japanese infants aged 6 - 12 weeks at the time of the first dose of HRV vaccination.

Summary

EudraCT number	2014-005282-78
Trial protocol	Outside EU/EEA
Global end of trial date	29 May 2017

Results information

Result version number	v1 (current)
This version publication date	31 May 2018
First version publication date	31 May 2018

Trial information

Trial identification

Sponsor protocol code	114720
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02907216
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, 1330
Public contact	Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, (44)2089 904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, (44)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	22 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2017
Global end of trial reached?	Yes
Global end of trial date	29 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the immunogenicity to the antigens contained in DPT-IPV vaccine is not impaired by the co-administration with GSK Biologicals' liquid HRV vaccine.

Protection of trial subjects:

All vaccinated subjects were 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	16 September 2016
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	Japan: 292
Worldwide total number of subjects	292
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)	292
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:

146 subjects i.e., the first 73 subjects enrolled into each of the 2 study groups were allocated to the HRV immunogenicity sub-cohort to evaluate immunogenicity of the liquid HRV vaccine.

Pre-assignment period milestones

Number of subjects started	292
Number of subjects completed	292

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Co-administration Group

Arm description:

Subjects aged 6 to 12 weeks who received the Squarekids vaccine (diphtheria, tetanus, pertussis and inactivated poliovirus [DPT-IPV] vaccine) according to a 3, 4, 6 month schedule and the liquid Rotarix vaccine (oral live attenuated human rotavirus [HRV] vaccine) according to a 2, 3 month schedule. The HRV vaccine was administered orally while the DTP-IPV vaccine was administered subcutaneously in the upper arm or upper thigh.

Arm type	Experimental
Investigational medicinal product name	Rotarix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Two doses administered orally

Investigational medicinal product name	Squarekids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Three doses administered subcutaneously in the upper arm or thigh

Arm title	Staggered Group
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Arm description:

Subjects aged 6 to 12 weeks who received the Squarekids vaccine (diphtheria, tetanus, pertussis and inactivated poliovirus [DPT-IPV] vaccine) according to a 3, 4.5, 6 month schedule and the liquid Rotarix vaccine (oral live attenuated human rotavirus [HRV] vaccine) according to a 2, 3.5 month schedule. The HRV vaccine was administered orally while the DTP-IPV vaccine was administered subcutaneously in the upper arm or upper thigh.

Arm type	Active comparator
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Investigational medicinal product name	Squarekids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Three doses administered subcutaneously in the upper arm or thigh	
Investigational medicinal product name	Rotarix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use
Dosage and administration details:	
Two doses administered orally	

Number of subjects in period 1	Co-administration Group	Staggered Group
Started	147	145
Completed	146	144
Not completed	1	1
Consent withdrawn by subject	1	-
No benefit to be obtained by continuing	-	1

Baseline characteristics

Reporting groups

Reporting group title	Co-administration Group
Reporting group description:	
Subjects aged 6 to 12 weeks who received the Squarekids vaccine (diphtheria, tetanus, pertussis and inactivated poliovirus [DPT-IPV] vaccine) according to a 3, 4, 6 month schedule and the liquid Rotarix vaccine (oral live attenuated human rotavirus [HRV] vaccine) according to a 2, 3 month schedule. The HRV vaccine was administered orally while the DPT-IPV vaccine was administered subcutaneously in the upper arm or upper thigh.	
Reporting group title	Staggered Group
Reporting group description:	
Subjects aged 6 to 12 weeks who received the Squarekids vaccine (diphtheria, tetanus, pertussis and inactivated poliovirus [DPT-IPV] vaccine) according to a 3, 4.5, 6 month schedule and the liquid Rotarix vaccine (oral live attenuated human rotavirus [HRV] vaccine) according to a 2, 3.5 month schedule. The HRV vaccine was administered orally while the DPT-IPV vaccine was administered subcutaneously in the upper arm or upper thigh.	

Reporting group values	Co-administration Group	Staggered Group	Total
Number of subjects	147	145	292
Age categorical			
Units: Subjects			

Age continuous			
Units: weeks			
arithmetic mean	9.5	9.4	
standard deviation	± 1.1	± 1.1	-
Gender categorical			
Units: Subjects			
Female	72	65	137
Male	75	80	155
Race/Ethnicity, Customized			
Units: Subjects			
Asian - Japanese Heritage	147	145	292
Age Continuous - Weeks of age at Dose 2 of HRV			
Units: Weeks			
arithmetic mean	14	15.5	
standard deviation	± 1.1	± 1.3	-
Age Continuous - Weeks of age at Dose 1 of DPT-IPV			
Units: Weeks			
arithmetic mean	14	13.9	
standard deviation	± 1.1	± 1	-
Age Continuous - Weeks of age at Dose 2 of DPT-IPV			
Units: Weeks			
arithmetic mean	18.5	20	
standard deviation	± 1.2	± 1.4	-
Age Continuous - Weeks of age at Dose 3 of DPT-IPV			

Units: Weeks			
arithmetic mean	23.7	25	
standard deviation	± 1.8	± 1.9	-

End points

End points reporting groups

Reporting group title	Co-administration Group
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Reporting group description:

Subjects aged 6 to 12 weeks who received the Squarekids vaccine (diphtheria, tetanus, pertussis and inactivated poliovirus [DPT-IPV] vaccine) according to a 3, 4, 6 month schedule and the liquid Rotarix vaccine (oral live attenuated human rotavirus [HRV] vaccine) according to a 2, 3 month schedule. The HRV vaccine was administered orally while the DTP-IPV vaccine was administered subcutaneously in the upper arm or upper thigh.

Reporting group title	Staggered Group
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Reporting group description:

Subjects aged 6 to 12 weeks who received the Squarekids vaccine (diphtheria, tetanus, pertussis and inactivated poliovirus [DPT-IPV] vaccine) according to a 3, 4.5, 6 month schedule and the liquid Rotarix vaccine (oral live attenuated human rotavirus [HRV] vaccine) according to a 2, 3.5 month schedule. The HRV vaccine was administered orally while the DTP-IPV vaccine was administered subcutaneously in the upper arm or upper thigh.

Primary: Percentage of subjects with anti-diphtheria (anti-D) and anti-tetanus (anti-T) antibody concentrations greater than or equal to ($\geq$) the cut-off value

End point title	Percentage of subjects with anti-diphtheria (anti-D) and anti-tetanus (anti-T) antibody concentrations greater than or equal to ($\geq$) the cut-off value
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End point description:

Percentage of subjects with anti-D and anti-T antibody concentrations $\geq$ 0.1 international units per milliliter (IU/mL).

End point type	Primary
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End point timeframe:

One month post third dose of DTP-IPV vaccine (At Month 5)

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	138		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-D antibody $\geq$ 0.1 IU/mL (N=141; 137)	100 (97.4 to 100)	100 (97.3 to 100)		
Anti-T antibody $\geq$ 0.1 IU/mL (N=141; 138)	98.6 (95 to 99.8)	99.3 (96 to 100)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

Difference between Co-administration Group minus Staggered Group in terms of percentage of subjects with anti-D antibody concentration $\geq$ 0.1 IU/mL.

Comparison groups	Staggered Group v Co-administration Group
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Difference-Seroprotective concentration
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.66
upper limit	2.74

Notes:

[1] - Criteria for non-inferiority: The Lower Limit (LL) of the standardised asymptotic 95% Confidence Interval (CI) on the difference (Co-administration Group minus Staggered Group) in the percentage of subjects with seroprotective concentrations ≥ 0.1 IU/mL for anti-D antibodies should be $\geq -10\%$.

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Difference between Co-administration Group minus Staggered Group in terms of percentage of subjects with anti-T antibody concentration ≥ 0.1 IU/mL.	
Comparison groups	Co-administration Group v Staggered Group
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Difference-Seroprotective concentration
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.39
upper limit	2.71

Notes:

[2] - Criteria for non-inferiority: The LL of the standardised asymptotic 95% CI on the difference (Co-administration Group minus Staggered Group) in the percentage of subjects with seroprotective concentrations ≥ 0.1 IU/mL for anti-T antibodies should be $\geq -10\%$.

Primary: Percentage of subjects with anti-pertussis toxoid (anti-PT) and anti-filamentous haemagglutinin (anti-FHA) antibody concentrations $\geq$ the cut-off value

End point title	Percentage of subjects with anti-pertussis toxoid (anti-PT) and anti-filamentous haemagglutinin (anti-FHA) antibody concentrations $\geq$ the cut-off value
End point description:	
Percentage of subjects with anti-PT and anti-FHA antibody concentrations ≥ 10 IU/mL.	
End point type	Primary
End point timeframe:	
One month post third dose of DTP-IPV vaccine (At Month 5)	

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	138		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PT antibody ≥ 10 IU/mL	95.7 (91 to 98.4)	92.8 (87.1 to 96.5)		
Anti-FHA antibody ≥ 10 IU/mL	100 (97.4 to 100)	100 (97.4 to 100)		

Statistical analyses

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Difference between Co-administration Group minus Staggered Group in terms of percentage of subjects with anti-FHA antibody concentration ≥ 10 IU/mL.	
Comparison groups	Staggered Group v Co-administration Group
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Parameter estimate	Difference-Seroprotective concentration
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.66
upper limit	2.72

Notes:

[3] - Criteria for non-inferiority: The LL of the standardised asymptotic 95% CI on the difference (Co-administration Group minus Staggered Group) in the percentage of subjects with seroprotective concentrations ≥ 10 IU/mL for anti-FHA antibodies should be $\geq -10\%$.

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Difference between Co-administration Group minus Staggered Group in terms of percentage of subjects with anti-PT antibody concentration ≥ 10 IU/mL.	
Comparison groups	Staggered Group v Co-administration Group
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
Parameter estimate	Difference-Seroprotective concentration
Point estimate	2.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	9.12

Notes:

[4] - Criteria for non-inferiority: The LL of the standardised asymptotic 95% CI on the difference (Co-administration Group minus Staggered Group) in the percentage of subjects with seroprotective concentrations ≥ 10 IU/mL for anti-PT antibodies should be $\geq -10\%$.

Primary: Percentage of subjects with anti-poliovirus serotypes 1, 2 and 3 (anti-polio 1, 2 and 3) antibody titers ≥ the cut-off value

End point title	Percentage of subjects with anti-poliovirus serotypes 1, 2 and 3 (anti-polio 1, 2 and 3) antibody titers ≥ the cut-off value
End point description: Percentage of subjects with anti-polio 1, 2 and 3 antibody titers ≥ 8 estimated doses 50% (ED50).	
End point type	Primary
End point timeframe: One month post third dose of DTP-IPV vaccine (At Month 5)	

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	137		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-Polio 1 antibody ≥ 8 ED50 (N=140; 137)	100 (97.4 to 100)	100 (97.3 to 100)		
Anti-Polio 2 antibody ≥ 8 ED50 (N=128; 127)	100 (97.2 to 100)	100 (97.1 to 100)		
Anti-Polio 3 antibody ≥ 8 ED50 (N=132; 123)	100 (97.2 to 100)	99.2 (95.6 to 100)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Difference between Co-administration Group minus Staggered Group in terms of percentage of subjects with anti-polio 1 seroprotective titres ≥ 8 ED50.	
Comparison groups	Staggered Group v Co-administration Group
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
Parameter estimate	Difference in seroprotective titer
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.68
upper limit	2.74

Notes:

[5] - Criteria for non-inferiority: The LL of the standardised asymptotic 95% CI on the difference (Co-administration Group minus Staggered Group) in the percentage of subjects with seroprotective titers ≥ 8 ED50 for anti-polio 1 antibodies should be ≥ -10%.

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Difference between Co-administration Group minus Staggered Group in terms of percentage of subjects with anti-polio 2 seroprotective titres $\geq$ 8 ED50.	
Comparison groups	Staggered Group v Co-administration Group
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[6]
Parameter estimate	Difference in seroprotective titer
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.92
upper limit	2.95

Notes:

[6] - Criteria for non-inferiority: The LL of the standardised asymptotic 95% CI on the difference (Co-administration Group minus Staggered Group) in the percentage of subjects with seroprotective titers $\geq$ 8 ED50 for anti-polio 2 antibodies should be $\geq$ -10%.

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Difference between Co-administration Group minus Staggered Group in terms of percentage of subjects with anti-polio 3 seroprotective titres $\geq$ 8 ED50.	
Comparison groups	Staggered Group v Co-administration Group
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[7]
Parameter estimate	Difference in seroprotective titer
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	4.47

Notes:

[7] - Criteria for non-inferiority: The LL of the standardised asymptotic 95% CI on the difference (Co-administration Group minus Staggered Group) in the percentage of subjects with seroprotective titers $\geq$ 8 ED50 for anti-polio 3 antibodies should be $\geq$ -10%.

Secondary: Percentage of seropositive subjects for serum anti-rotavirus (anti-RV) immunoglobulin A (IgA) antibodies

End point title	Percentage of seropositive subjects for serum anti-rotavirus (anti-RV) immunoglobulin A (IgA) antibodies
End point description:	
A seropositive subject for serum anti-RV IgA antibodies was defined as a subject with anti-RV IgA antibody concentration $\geq$ the seropositivity cut-off value of 20 units per milliliter (U/mL).	
End point type	Secondary
End point timeframe:	
One month post second dose of liquid HRV vaccine (At Month 2 for the Co-administration Group and at Month 2.5 for the Staggered Group)	

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	67		
Units: Percentage of subjects				
number (confidence interval 95%)				
Percentage of subjects	92.8 (83.9 to 97.6)	92.5 (83.4 to 97.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum anti-RV IgA antibody concentration to evaluate immunogenicity

End point title	Serum anti-RV IgA antibody concentration to evaluate immunogenicity
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End point description:

Concentration of serum anti-RV IgA antibody was assessed by Enzyme Linked Immunosorbent Assay (ELISA) and expressed as geometric mean concentration (GMC) in U/mL. The assay cut-off was 20 U/mL.

End point type	Secondary
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End point timeframe:

One month post second dose of liquid HRV vaccine (At Month 2 for the Co-administration Group and at Month 2.5 for the Staggered Group)

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	67		
Units: U/mL				
geometric mean (confidence interval 95%)				
U/mL	350.1 (223.3 to 548.8)	362.5 (251 to 523.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-D and anti-T antibody concentrations to evaluate immunogenicity

End point title	Anti-D and anti-T antibody concentrations to evaluate immunogenicity
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End point description:

Concentrations of anti-D and anti-T antibodies were assessed by ELISA, presented as GMCs and expressed in IU/mL. The assay cut-off for anti-D and anti-T antibody concentrations was 0.1 IU/mL.

End point type	Secondary
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End point timeframe:

One month post third dose of DTP-IPV vaccine (At Month 5)

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	138		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-D antibody (N=141; 137)	5.4 (4.9 to 6)	6 (5.5 to 6.6)		
Anti-T antibody (N=141; 138)	1.6 (1.3 to 2)	2 (1.7 to 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-polio 1, 2 and 3 antibodies titers to evaluate immunogenicity

End point title	Anti-polio 1, 2 and 3 antibodies titers to evaluate immunogenicity
End point description: Titers of anti-polio 1, 2 and 3 were assessed by Neutralisation Assay (NEU) and presented as Geometric Mean Titers (GMTs). The assay cut-off was 8 ED50.	
End point type	Secondary
End point timeframe: One month post third dose of DTP-IPV vaccine (At Month 5)	

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	137		
Units: Titer				
geometric mean (confidence interval 95%)				
Anti-Polio 1 antibody (N=140; 137)	404.7 (341.4 to 479.8)	427.9 (359.3 to 509.6)		
Anti-Polio 2 antibody (N=128; 127)	371 (307 to 448.5)	470.6 (388.3 to 570.3)		
Anti-Polio 3 antibody (N=132; 123)	436.3 (365.6 to 520.7)	409.8 (330.8 to 507.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-PT and anti-FHA antibody concentrations to evaluate immunogenicity

End point title	Anti-PT and anti-FHA antibody concentrations to evaluate immunogenicity
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End point description:

Concentrations of anti-PT and anti-FHA antibodies were assessed by ELISA, presented as GMCs and expressed in IU/mL. The assay cut-offs for anti-PT and anti-FHA antibody concentrations were 2.693 IU/mL and 2.046 IU/mL respectively.

End point type	Secondary
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End point timeframe:

One month post third dose of DTP-IPV vaccine (At Month 5)

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	138		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-PT antibody	31.5 (28.4 to 34.9)	31.5 (27.9 to 35.6)		
Anti-FHA antibody	83.7 (74.8 to 93.6)	97.2 (86.7 to 109)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any solicited general adverse events (AEs) after each dose of liquid HRV vaccine

End point title	Number of subjects with any solicited general adverse events (AEs) after each dose of liquid HRV vaccine
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End point description:

Assessed solicited general AEs were fever (defined as axillary temperature ≥ 37.5 degrees Celsius [$^{\circ}\text{C}$]), irritability/fussiness, diarrhoea (defined as passage of three or more looser than normal stools within a day), vomiting (defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day), loss of appetite and cough/runny nose. Any = occurrence of the symptom regardless of intensity grade or relation to vaccination.

End point type	Secondary
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End point timeframe:

During the 8-day (Days 0-7) follow-up period after each dose of liquid HRV vaccine

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	145		
Units: Participants				
Any Fever, Dose 1	31	32		
Any Irritability / Fussiness, Dose 1	66	62		
Any Diarrhoea, Dose 1	30	32		
Any Vomiting, Dose 1	19	19		
Any Loss of Appetite, Dose 1	18	10		
Any Cough, Dose 1	41	40		
Any Fever, Dose 2	31	15		
Any Irritability / Fussiness, Dose 2	61	41		
Any Diarrhoea, Dose 2	22	26		
Any Vomiting, Dose 2	14	18		
Any Loss of Appetite, Dose 2	17	9		
Any Cough, Dose 2	53	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any solicited local AEs after first dose of DTP-IPV vaccine

End point title	Number of subjects with any solicited local AEs after first dose of DTP-IPV vaccine
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End point description:

Assessed solicited local AEs were pain, redness and swelling at injection site. Any = occurrence of the symptom regardless of intensity grade or relation to vaccination.

End point type	Secondary
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End point timeframe:

During the 8-day (Days 0-7) follow-up period after first dose of DTP-IPV vaccine

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	144		
Units: Participants				
Any Pain	32	24		
Any Redness (mm)	85	84		
Any Swelling (mm)	50	44		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any solicited general AEs after first dose of DTP-IPV vaccine

End point title	Number of subjects with any solicited general AEs after first dose of DTP-IPV vaccine
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End point description:

Assessed solicited general AEs were drowsiness, fever (defined as axillary temperature ≥ 37.5 °C), irritability/fussiness and loss of appetite. Any = occurrence of the symptom regardless of intensity grade or relation to vaccination.

End point type	Secondary
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End point timeframe:

During the 8-day (Days 0-7) follow-up period after first dose of DTP-IPV vaccine

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	144		
Units: Participants				
Any Drowsiness	37	39		
Any Fever	31	32		
Any Irritability / Fussiness	61	59		
Any Loss of Appetite	17	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any unsolicited AEs after each dose of liquid HRV vaccine

End point title	Number of subjects with any unsolicited AEs after each dose of liquid HRV vaccine
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End point description:

Unsolicited AEs were defined as any AE reported in addition to those solicited during the clinical study and any solicited AE with onset outside the specified period of follow-up for solicited AEs. Any = occurrence of the symptom regardless of intensity grade or relation to vaccination.

End point type	Secondary
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End point timeframe:

During the 31-day (Days 0-30) follow-up period after each dose of liquid HRV vaccine

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	145		
Units: Participants				
Participants	88	81		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any unsolicited AE after first dose of DTP-IPV vaccine

End point title	Number of subjects with any unsolicited AE after first dose of DTP-IPV vaccine
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End point description:

Unsolicited AEs were defined as any AE reported in addition to those solicited during the clinical study and any solicited AE with onset outside the specified period of follow-up for solicited AEs. Any = occurrence of the symptom regardless of intensity grade or relation to vaccination.

End point type	Secondary
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End point timeframe:

During the 31-day (Days 0-30) follow-up period after first dose of DTP-IPV vaccine

End point values	Co-administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	144		
Units: Participants				
Participants	65	59		

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)
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End point description:

Assessed SAEs included any untoward medical occurrence that resulted in death, was life threatening, required hospitalization or prolongation of existing hospitalization or resulted in disability/incapacity. Any = occurrence of the symptom regardless of intensity grade or relation to vaccination.

End point type	Secondary
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End point timeframe:

During the entire study period (from Day 0 to Month 5)

End point values	Co- administration Group	Staggered Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	145		
Units: Participants				
Participants	4	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited local & general AE: 8-day post-vaccination after DTP-IPV 1st dose; solicited general AE: 8-day post-vaccination after HRV each dose. Unsolicited AE: 31-day post-vaccination after DTP-IPV 1st dose & HRV each dose. SAE: entire study period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Co-administration Group
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Reporting group description:

Subjects aged 6 to 12 weeks who received the DPT-IPV vaccine according to a 3, 4, 6 month schedule and the liquid HRV vaccine according to a 2, 3 month schedule. The HRV vaccine was administered orally while the DTP-IPV vaccine was administered subcutaneously in the upper arm or upper thigh.

Reporting group title	Staggered Group
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Reporting group description:

Subjects aged 6 to 12 weeks who received the DPT-IPV vaccine according to a 3, 4.5, 6 month schedule and the liquid HRV vaccine according to a 2, 3.5 month schedule. The HRV vaccine was administered orally while the DTP-IPV vaccine was administered subcutaneously in the upper arm or upper thigh.

Serious adverse events	Co-administration Group	Staggered Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 147 (2.72%)	5 / 145 (3.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Fibrinous bronchitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Hand-foot-and-mouth disease			

subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
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	2 / 147 (1.36%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
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	Co-administration Group	Staggered Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 147 (95.92%)	143 / 145 (98.62%)	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	85 / 147 (57.82%)	84 / 145 (57.93%)	
occurrences (all)	85	84	

Injection site induration subjects affected / exposed occurrences (all)	1 / 147 (0.68%) 1	0 / 145 (0.00%) 0	
Injection site pain subjects affected / exposed occurrences (all)	32 / 147 (21.77%) 32	24 / 145 (16.55%) 24	
Injection site swelling subjects affected / exposed occurrences (all)	50 / 147 (34.01%) 50	44 / 145 (30.34%) 44	
Irritability postvaccinal subjects affected / exposed occurrences (all)	93 / 147 (63.27%) 127	99 / 145 (68.28%) 162	
Peripheral swelling subjects affected / exposed occurrences (all)	2 / 147 (1.36%) 2	0 / 145 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	54 / 147 (36.73%) 62	56 / 145 (38.62%) 80	
Swelling subjects affected / exposed occurrences (all)	1 / 147 (0.68%) 1	0 / 145 (0.00%) 0	
Vaccination site induration subjects affected / exposed occurrences (all)	2 / 147 (1.36%) 2	4 / 145 (2.76%) 4	
Vaccination site swelling subjects affected / exposed occurrences (all)	1 / 147 (0.68%) 1	0 / 145 (0.00%) 0	
Reproductive system and breast disorders Balanoposthitis subjects affected / exposed occurrences (all)	1 / 147 (0.68%) 1	0 / 145 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	69 / 147 (46.94%) 95	72 / 145 (49.66%) 85	
Nasal congestion			

subjects affected / exposed occurrences (all)	0 / 147 (0.00%) 0	1 / 145 (0.69%) 1	
Rhinorrhoea subjects affected / exposed occurrences (all)	7 / 147 (4.76%) 7	6 / 145 (4.14%) 6	
Upper respiratory tract inflammation subjects affected / exposed occurrences (all)	18 / 147 (12.24%) 21	20 / 145 (13.79%) 24	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 147 (0.68%) 1	0 / 145 (0.00%) 0	
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all)	1 / 147 (0.68%) 1	0 / 145 (0.00%) 0	
Contusion subjects affected / exposed occurrences (all)	1 / 147 (0.68%) 1	0 / 145 (0.00%) 0	
Excoriation subjects affected / exposed occurrences (all)	1 / 147 (0.68%) 1	0 / 145 (0.00%) 0	
Superficial injury of eye subjects affected / exposed occurrences (all)	0 / 147 (0.00%) 0	1 / 145 (0.69%) 1	
Nervous system disorders Somnolence subjects affected / exposed occurrences (all)	37 / 147 (25.17%) 37	39 / 145 (26.90%) 39	
Ear and labyrinth disorders Excessive cerumen production subjects affected / exposed occurrences (all)	0 / 147 (0.00%) 0	1 / 145 (0.69%) 1	
Otorrhoea subjects affected / exposed occurrences (all)	1 / 147 (0.68%) 1	0 / 145 (0.00%) 0	

Eye disorders			
Eczema eyelids			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Eye discharge			
subjects affected / exposed	3 / 147 (2.04%)	1 / 145 (0.69%)	
occurrences (all)	3	1	
Ocular hyperaemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 147 (1.36%)	3 / 145 (2.07%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	41 / 147 (27.89%)	50 / 145 (34.48%)	
occurrences (all)	52	61	
Haematochezia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Mucous stools			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	24 / 147 (16.33%)	30 / 145 (20.69%)	
occurrences (all)	33	38	
Skin and subcutaneous tissue disorders			
Asteatosis			
subjects affected / exposed	0 / 147 (0.00%)	2 / 145 (1.38%)	
occurrences (all)	0	2	
Dermatitis contact			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Dermatitis diaper			

subjects affected / exposed	2 / 147 (1.36%)	1 / 145 (0.69%)	
occurrences (all)	2	1	
Dry skin			
subjects affected / exposed	2 / 147 (1.36%)	0 / 145 (0.00%)	
occurrences (all)	2	0	
Eczema			
subjects affected / exposed	9 / 147 (6.12%)	10 / 145 (6.90%)	
occurrences (all)	9	10	
Eczema asteatotic			
subjects affected / exposed	2 / 147 (1.36%)	0 / 145 (0.00%)	
occurrences (all)	2	0	
Eczema infantile			
subjects affected / exposed	13 / 147 (8.84%)	11 / 145 (7.59%)	
occurrences (all)	14	11	
Erythema			
subjects affected / exposed	3 / 147 (2.04%)	1 / 145 (0.69%)	
occurrences (all)	4	1	
Erythema multiforme			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Leukoderma			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Miliaria			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	2 / 147 (1.36%)	0 / 145 (0.00%)	
occurrences (all)	2	0	
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 147 (0.68%)	2 / 145 (1.38%)	
occurrences (all)	1	2	
Skin induration			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue			

disorders			
Pain in extremity			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Bronchiolitis			
subjects affected / exposed	1 / 147 (0.68%)	2 / 145 (1.38%)	
occurrences (all)	1	2	
Bronchitis			
subjects affected / exposed	2 / 147 (1.36%)	1 / 145 (0.69%)	
occurrences (all)	2	1	
Candida infection			
subjects affected / exposed	0 / 147 (0.00%)	2 / 145 (1.38%)	
occurrences (all)	0	2	
Conjunctivitis			
subjects affected / exposed	3 / 147 (2.04%)	4 / 145 (2.76%)	
occurrences (all)	3	4	
Exanthema subitum			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	2 / 147 (1.36%)	1 / 145 (0.69%)	
occurrences (all)	2	1	
Influenza			
subjects affected / exposed	0 / 147 (0.00%)	2 / 145 (1.38%)	
occurrences (all)	0	2	
Metapneumovirus infection			

subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	22 / 147 (14.97%)	33 / 145 (22.76%)	
occurrences (all)	26	37	
Otitis media			
subjects affected / exposed	1 / 147 (0.68%)	1 / 145 (0.69%)	
occurrences (all)	1	1	
Pharyngitis			
subjects affected / exposed	2 / 147 (1.36%)	1 / 145 (0.69%)	
occurrences (all)	2	2	
Respiratory syncytial virus bronchitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Respiratory syncytial virus infection			
subjects affected / exposed	6 / 147 (4.08%)	5 / 145 (3.45%)	
occurrences (all)	6	5	
Rhinitis			
subjects affected / exposed	1 / 147 (0.68%)	1 / 145 (0.69%)	
occurrences (all)	1	1	
Skin infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Streptococcal infection			
subjects affected / exposed	0 / 147 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	4 / 147 (2.72%)	2 / 145 (1.38%)	
occurrences (all)	6	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	27 / 147 (18.37%)	31 / 145 (21.38%)	
occurrences (all)	35	37	
Lactose intolerance			
subjects affected / exposed	1 / 147 (0.68%)	0 / 145 (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