Clinical trial results:
Immunogenicity and Safety of Sanofi Pasteur's DTaP-IPV-Hep B-PRP-T Combined Vaccine Given at 6, 10, and 14 Weeks of Age in Infants in India Who Previously Received a Dose of Hepatitis B Vaccine at Birth

Summary

EudraCT number	2016-002089-29
Trial protocol	Outside EU/EEA
Global end of trial date	14 October 2014

Results information

Result version number	v1 (current)
This version publication date	11 June 2016
First version publication date	11 June 2016

Trial information

Trial identification

Sponsor protocol code	A3L33

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01948193
WHO universal trial number (UTN)	U1111-1127-6936
Other trial identifiers	Clinical Trial Registry India: CTRI/2013/09/003997

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon cedex 07, France, F-69367
Public contact	Global Medical Affairs, Sanofi Pasteur SA, 33 (0) 437 65 67 99, Emmanuel.vidor@sanofipasteur.com
Scientific contact	Global Medical Affairs, Sanofi Pasteur SA, 33 (0) 437 65 67 99, Emmanuel.vidor@sanofipasteur.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	23 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the immunogenicity of the study vaccine in terms of seroprotection (diphtheria toxoid, tetanus toxoid, poliovirus types 1, 2, and 3, Haemophilus influenza type b [Hib] polysaccharide [PRP], hepatitis B [Hep B]) and vaccine response for pertussis antigens (pertussis toxoid [PT] and filamentous haemagglutinin [FHA]) one month after the third dose.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

All subjects enrolled in this study received a documented dose of any commercial available oral poliovirus vaccine (OPV) and recombinant Hepatitis B monovalent vaccine at birth according to the National Immunization Program (NIP) in India.

Evidence for comparator:

Not applicable

Actual start date of recruitment	19 February 2014
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	India: 177
Worldwide total number of subjects	177
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)	177

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:

Study subjects were enrolled from 19 February 2014 to 30 June 2014 at 2 clinic sites in India.

Pre-assignment

Screening details:

A total of 177 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and vaccinated.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	All Infants; DTaP-IPV-Hep B-PRP~T

Arm description:

Infants aged 6 to 8 weeks received 3 injections of Sanofi Pasteur's DTaP-IPV-Hep B-PRP~T combined vaccine at 6, 10, and 14 weeks of age following a documented dose of a commercial oral poliovirus vaccine and recombinant Hepatitis B monovalent vaccine at birth.

Arm type	Experimental
Investigational medicinal product name	DTaP-IPV-Hep B-PRP~T combined vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular into the anterolateral aspect of the right thigh, 1 injection each at 6, 10, and 14 weeks

Number of subjects in period 1	All Infants; DTaP-IPV-Hep B-PRP~T
Started	177
Completed	168
Not completed	9
Serious event	2
Lost to follow-up	7

Baseline characteristics

Reporting groups	
Reporting group title	All Infants; DTaP-IPV-Hep B-PRP~T
Reporting group description:	
Infants aged 6 to 8 weeks received 3 injections of Sanofi Pasteur's DTaP-IPV-Hep B-PRP~T combined vaccine at 6, 10, and 14 weeks of age following a documented dose of a commercial oral poliovirus vaccine and recombinant Hepatitis B monovalent vaccine at birth.	

Reporting group values	All Infants; DTaP-IPV-Hep B-PRP~T	Total	
Number of subjects	177	177	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	177	177	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: weeks			
arithmetic mean	6.9		
standard deviation	± 0.6	-	
Gender categorical Units: Subjects			
Female	78	78	
Male	99	99	

End points

End points reporting groups

Reporting group title	All Infants; DTaP-IPV-Hep B-PRP~T

Reporting group description:

Infants aged 6 to 8 weeks received 3 injections of Sanofi Pasteur's DTaP-IPV-Hep B-PRP~T combined vaccine at 6, 10, and 14 weeks of age following a documented dose of a commercial oral poliovirus vaccine and recombinant Hepatitis B monovalent vaccine at birth.

Primary: Percentage of Subjects With Seroprotection After Vaccinations With Sanofi Pasteur’s DTaP-IPV-HB-PRP-T Combined Vaccine Following a Documented Dose of a Commercial Oral Poliovirus Vaccine and Recombinant Hep B Monovalent Vaccine at Birth

End point title	Percentage of Subjects With Seroprotection After Vaccinations With Sanofi Pasteur’s DTaP-IPV-HB-PRP-T Combined Vaccine Following a Documented Dose of a Commercial Oral Poliovirus Vaccine and Recombinant Hep B Monovalent Vaccine at Birth[1]

End point description:

Diphtheria antibodies were measured by a toxin neutralization test, tetanus antibodies by an enzyme-linked immunosorbent assay (ELISA), Haemophilus influenzae type b polysaccharide (PRP) antibodies by Farr type radioimmunoassay, poliovirus 1, 2, and 3 antibodies by a neutralization assay, and Hepatitis B (Hep B) antibodies were measured by VITROS ECi/ECiQ Immunodiagnostic System.

Description of seroprotection: Diphtheria and Tetanus antibody concentrations ≥0.01 International Units (IU)/mL; Poliovirus 1, 2, and 3 titers ≥8 (1/dilution); Hep B concentrations ≥10 mIU/mL, and PRP ≥0.15 µg/mL.

End point type	Primary

End point timeframe:

Pre-dose 1 to one month post-dose 3

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study group and study vaccine administered for this outcome.

End point values	All Infants; DTaP-IPV-Hep B-PRP~T			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Percentage of subjects				
number (not applicable)				
Anti-Diphtheria; Post-dose 3, ≥ 0.01	99.3			
Anti-Tetanus; Post-dose 3, ≥ 0.01	100			
Anti-Polio 1; Post-dose 3	100			
Anti-Polio 2; Post-dose 3	100			
Anti-Polio 3; Post-dose 3	100			
Anti-Hep B; Post-dose 3, ≥ 10	100			
Anti-PRP; Post-dose 3, ≥ 0.15	100			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Vaccine Response After Vaccinations With Sanofi Pasteur's DTaP-IPV-HB-PRP-T Combined Vaccine Following a Documented Dose of a Commercial Oral Poliovirus Vaccine and Recombinant Hep B Monovalent Vaccine at Birth

End point title	Percentage of Subjects With Vaccine Response After Vaccinations With Sanofi Pasteur's DTaP-IPV-HB-PRP-T Combined Vaccine Following a Documented Dose of a Commercial Oral Poliovirus Vaccine and Recombinant Hep B Monovalent Vaccine at Birth[2]

End point description:

Anti-pertussis toxin (PT) and anti-filamentous hemagglutinin (FHA) antibodies were measured with an ELISA. Vaccine response was defined as percentage of participants with post-dose 3 anti-PT and anti-FHA antibody concentrations in ELISA units (EU)/mL ≥ 4 x Lower Limit of Quantification (LLOQ) if pre-vaccination concentration was < 4 x LLOQ or ≥ pre-vaccination concentration if pre-vaccination concentrations ≥ 4 x LLOQ.

End point type	Primary

End point timeframe:

Pre-dose 1 to one month post-dose 3

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study group and study vaccine administered for this outcome.

End point values	All Infants; DTaP-IPV-Hep B-PRP~T			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Percentage of subjects				
number (not applicable)				
Anti-PT; Pre-dose 1	59.9			
Anti-PT; Vaccine response	93.8			
Anti-PT; ≥4-fold increase	88.4			
Anti-FHA; Pre-dose 1	88.7			
Anti-FHA; Vaccine response	99.3			
Anti-FHA; ≥4-fold increase	90.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroprotection Before and After Vaccinations With Sanofi Pasteur's DTaP-IPV-HB-PRP-T Combined Vaccine Following a Documented Dose of a Commercial Oral Poliovirus Vaccine and Recombinant Hep B Monovalent Vaccine at Birth

End point title	Percentage of Subjects With Seroprotection Before and After Vaccinations With Sanofi Pasteur's DTaP-IPV-HB-PRP-T Combined Vaccine Following a Documented Dose of a Commercial Oral Poliovirus Vaccine and Recombinant Hep B Monovalent Vaccine at Birth

End point description:

Diphtheria antibodies were measured by a toxin neutralization test, tetanus antibodies by an enzyme-

linked immunosorbent assay (ELISA), Haemophilus influenzae type b polysaccharide (PRP) antibodies by Farr type radioimmunoassay, poliovirus 1, 2, and 3 antibodies by a neutralization assay, and Hepatitis B (Hep B) antibodies were measured by VITROS ECi/ECiQ Immunodiagnostic System.

Description of seroprotection: Diphtheria and Tetanus antibody concentrations ≥0.01 International Units (IU)/mL; Poliovirus 1, 2, and 3 titers ≥8 (1/dilution); Hep B concentrations ≥10 mIU/mL, and PRP ≥0.15 µg/mL.

End point type	Secondary

End point timeframe:

Pre-dose 1 to one month post-dose 3

End point values	All Infants; DTaP-IPV-Hep B-PRP~T			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Percentage of subjects				
number (not applicable)				
Anti-Diphtheria; Pre-dose 1; ≥0.01	67.1			
Anti-Diphtheria; Pre-dose 1; ≥0.1	15.8			
Anti-Diphtheria; Post-dose 3; ≥0.01	99.3			
Anti-Diphtheria; Post-dose 3; ≥0.1	49.6			
Anti-Diphtheria; Post-dose 3; ≥1.0	5.2			
Anti-Tetanus; Post-dose 3; ≥0.01	100			
Anti-Tetanus; Post-dose 3; ≥0.1	100			
Anti-Tetanus; Post-dose 3; ≥1.0	84.3			
Anti-Polio 1; Post-dose 3	100			
Anti-Polio 2; Post-dose 3	100			
Anti-Polio 3; Post-dose 3	100			
Anti-Hep B; Pre-dose 1, ≥10	13.2			
Anti-Hep B; Post-dose 3, ≥10	100			
Anti-Hep B; Post-dose 3, ≥100	99.3			
Anti-PRP; Post-dose 3, ≥0.15	100			
Anti-PRP; Post-dose 3, ≥1.0	93.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Antibodies Against Vaccine Antigens After Vaccinations With Sanofi Pasteur's DTaP-IPV-HB-PRP-T Combined Vaccine After a Documented Dose of an Oral Poliovirus Vaccine and Recombinant Hep B Monovalent Vaccine at Birth

End point title	Geometric Mean Titers of Antibodies Against Vaccine Antigens After Vaccinations With Sanofi Pasteur's DTaP-IPV-HB-PRP-T Combined Vaccine After a Documented Dose of an Oral Poliovirus Vaccine and Recombinant Hep B Monovalent Vaccine at Birth

End point description:

Diphtheria antibodies were measured by a toxin neutralization test, tetanus, PT, and FHA antibodies by an ELISA, PRP antibodies by a Farr type radioimmunoassay, poliovirus 1, 2, and 3 antibodies by a

neutralization assay, and Hep B antibodies were measured by VITROS ECi/ECiQ Immunodiagnostic System.

End point type	Secondary

End point timeframe:

Pre-dose 1 to one month post-dose 3

End point values	All Infants; DTaP-IPV-Hep B-PRP~T			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Diphtheria; Pre-dose 1	0.019 (0.015 to 0.025)			
Anti-Diphtheria; Post-dose 3	0.12 (0.099 to 0.146)			
Anti-Tetanus; Post-dose 3	1.95 (1.75 to 2.17)			
Anti-PT; Pre-dose 1	3.84 (3 to 4.91)			
Anti-PT; Post-dose 3	191 (173 to 210)			
Anti-FHA; Pre-dose 1	6.17 (5.1 to 7.48)			
Anti-FHA; Post-dose 3	226 (208 to 247)			
Anti-Polio 1; Post-dose 3	1124 (861 to 1468)			
Anti-Polio 2; Post-dose 3	1401 (1108 to 1771)			
Anti-Polio 3; Post-dose 3	2019 (1672 to 2437)			
Anti-Hep B; Pre-dose 1	3.78 (3.23 to 4.43)			
Anti-Hep B; Post-dose 3	2491 (2073 to 2995)			
Anti-PRP; Post-dose 3	7.86 (6.35 to 9.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Ratios of Antibodies Against Vaccine Antigens After Vaccinations With Sanofi Pasteur’s DTaP-IPV-HB-PRP-T Combined Vaccine After a Documented Dose of Oral Poliovirus Vaccine and Recombinant Hep B Monovalent Vaccine at Birth

End point title	Geometric Mean Titer Ratios of Antibodies Against Vaccine Antigens After Vaccinations With Sanofi Pasteur’s DTaP-IPV-HB-PRP-T Combined Vaccine After a Documented Dose of Oral Poliovirus Vaccine and Recombinant Hep B Monovalent Vaccine at Birth

End point description:

Diphtheria antibodies were measured by a toxin neutralization test, PT and FHA antibodies by an ELISA, and Hep B antibodies were measured by VITROS ECi/ECiQ Immunodiagnostic System.

End point type	Secondary

End point timeframe:

Pre-dose 1 to one month post-dose 3

End point values	All Infants; DTaP-IPV-Hep B-PRP~T			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Titer ratios (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Diphtheria	5.85 (3.93 to 8.72)			
Anti-PT	50.7 (37.3 to 69)			
Anti-FHA	36.6 (28.6 to 46.8)			
Anti-Hep B	686 (542 to 870)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Each Vaccination With Sanofi Pasteur's DTaP-IPV-HB-PRP-T Combined Vaccine Following a Documented Dose of Oral Poliovirus and Recombinant Hep B Vaccine at Birth

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Each Vaccination With Sanofi Pasteur's DTaP-IPV-HB-PRP-T Combined Vaccine Following a Documented Dose of Oral Poliovirus and Recombinant Hep B Vaccine at Birth

End point description:

Injection-site reactions: Tenderness, Erythema, and Swelling. Systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3 Injection site reactions: Tenderness, Cries when injected limb is moved, or reduced movement of injected limb; Erythema and Swelling, ≥50 mm. Grade 3 Systemic reactions: Fever, >39.5°C or >103.1°F; Vomiting, ≥6 episodes/24 hours or requires parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time/difficult to wake up; Appetite lost, Refuses ≥3 or most feeds/meals; Irritability, Inconsolable.

End point type	Secondary

End point timeframe:

Within 7 days after each vaccine injection

End point values	All Infants; DTaP-IPV-Hep B-PRP~T			
Subject group type	Reporting group			
Number of subjects analysed	177			
Units: Percentage of subjects				
number (not applicable)				
Any Injection-site Tenderness; Post Inj. 1	19			
Grade 3 Inj. site Tenderness; Post Inj 1	2.3			
Any Injection-site Erythema; Post Inj. 1	4.6			
Grade 3 Inj. site Erythema; Post Inj. 1	0			
Any Injection-site Swelling; Post Inj. 1	10.3			
Grade 3 Inj. site Swelling; Post Inj. 1	0			
Any Injection-site Tenderness; Post Inj. 2	13.8			
Grade 3 Inj.-site Tenderness; Post Inj. 2	1.1			
Any Injection-site Erythema; Post Inj. 2	3.4			
Grade 3 Inj. site Erythema; Post Inj. 2	0			
Any Injection-site Swelling; Post Inj. 2	3.4			
Grade 3 Inj. site Swelling; Post Inj. 2	0			
Any Injection-site Tenderness; Post Inj. 3	11.9			
Grade 3 Inj. site Tenderness; Post Inj. 3	0			
Any Injection-site Erythema; Post Inj. 3	0.6			
Grade 3 Inj. site Erythema; Post Inj. 3	0			
Any Injection-site Swelling; Post Inj. 3	6.5			
Grade 3 Inj. site Swelling; Post Inj. 3	0			
Any Fever; Post-injection 1	7.5			
Grade 3 Fever; Post-injection 1	0			
Any Vomiting; Post-injection 1	9.8			
Grade 3 Vomiting; Post-injection 1	0			
Any Crying abnormal; Post-injection 1	16.1			
Grade 3 Crying abnormal; Post-injection 1	1.1			
Any Drowsiness; Post injection 1	9.8			
Grade 3 Drowsiness; Post Inj. 1	1.1			
Any Appetite lost; Post Inj. 1	6.9			
Grade 3 Appetite lost; Post Inj. 1	0			
Any Irritability; Post Inj. 1	22.4			
Grade 3 Irritability; Post Inj. 1	0.6			
Any Fever; Post Inj. 2	8.6			
Grade 3 Fever; Post Inj. 2	0			
Any Vomiting; Post Inj. 2	3.4			
Grade 3 Vomiting; Post Inj. 2	0			
Any Crying abnormal; Post Inj. 2	9.8			
Grade 3 Crying abnormal; Post Inj. 2	0			
Any Drowsiness; Post Inj. 2	3.4			
Grade 3 Drowsiness; Post Inj. 2	0			
Any Appetite lost; Post Inj. 2	3.4			
Grade 3 Appetite lost; Post Inj. 2	0			
Any Irritability; Post Inj. 2	16.7			
Grade 3 Irritability; Post Inj. 2	0			
Any Fever; Post Inj. 3	7.1			

Grade 3 Fever; Post Inj. 3	0			
Any Vomiting; Post Inj. 3	3			
Grade 3 Vomiting; Post Inj. 3	0			
Any Crying abnormal; Post Inj. 3	7.7			
Grade 3 Crying abnormal; Post Inj. 3	0			
Any Drowsiness; Post Inj. 3	3			
Grade 3 Drowsiness; Post Inj. 3	0			
Any Appetite lost; Post Inj. 3	3			
Grade 3 Appetite lost; Post Inj. 3	0			
Any Irritability; Post Inj. 3	12.5			
Grade 3 Irritability; Post Inj. 3	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected following first vaccination up to Day 30 post-dose 3.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	All Infants; DTaP IPV HB PRP~T

Reporting group description:

Infants aged 6 to 8 weeks received 3 injections of Sanofi Pasteur's DTaP IPV HB PRP~T combined vaccine at 6, 10, and 14 weeks of age following a documented dose of a commercial oral poliovirus vaccine and recombinant Hepatitis B monovalent vaccine at birth.

Serious adverse events	All Infants; DTaP IPV HB PRP~T		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 177 (1.69%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			

subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All Infants; DTaP IPV HB PRP~T		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 177 (22.03%)		
Nervous system disorders			
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed[1]	17 / 174 (9.77%)		
occurrences (all)	17		
General disorders and administration site conditions			
Injection site Tenderness			
alternative assessment type: Systematic			
subjects affected / exposed[2]	33 / 174 (18.97%)		
occurrences (all)	33		
Injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed[3]	8 / 174 (4.60%)		
occurrences (all)	8		
Injection site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed[4]	18 / 174 (10.34%)		
occurrences (all)	18		
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[5]	15 / 174 (8.62%)		
occurrences (all)	15		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 177 (5.08%)		
occurrences (all)	9		

Vomiting alternative assessment type: Systematic subjects affected / exposed[6] occurrences (all)	 17 / 174 (9.77%) 17		
Psychiatric disorders Crying abnormal alternative assessment type: Systematic subjects affected / exposed[7] occurrences (all) Irritability alternative assessment type: Systematic subjects affected / exposed[8] occurrences (all)	 28 / 174 (16.09%) 28 39 / 174 (22.41%) 39		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	 21 / 177 (11.86%) 24		
Metabolism and nutrition disorders Appetite lost alternative assessment type: Systematic subjects affected / exposed[9] occurrences (all)	 12 / 174 (6.90%) 12		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data

were available for the event during the period.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

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