



Clinical trial results:

A Phase 3b, Open-Label, Randomized, Parallel-Group, Multi-Center Study to Evaluate the Safety of Novartis MenACWY Conjugate Vaccine when Administered with Routine Infant Vaccinations to Healthy Infants

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

Summary

EudraCT number	2014-004537-95
Trial protocol	Outside EU/EEA
Global end of trial date	10 November 2011

Results information

Result version number	v2 (current)
This version publication date	04 June 2016
First version publication date	12 February 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	V59P23
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00806195
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics Inc.
Sponsor organisation address	350 Massachusetts Avenue, Cambridge, United States, 02139-4182
Public contact	Posting Director, Novartis Vaccines and Diagnostics Inc., RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines and Diagnostics Inc., RegistryContactVaccinesUS@novartis.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 December 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 November 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of 4 doses of MenACWY through 6 months post-final dose when given concomitantly with routine infant vaccines.

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations, including the European Directive 2001/20/EC, the US CFR Title 21, and the Japanese Ministry of Health, Labor, and Welfare, Novartis codes on the protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 3854
Country: Number of subjects enrolled	Peru: 396
Country: Number of subjects enrolled	Guatemala: 1096
Country: Number of subjects enrolled	Taiwan: 795
Country: Number of subjects enrolled	Costa Rica: 1301
Country: Number of subjects enrolled	Panama: 302
Worldwide total number of subjects	7744
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)	7744
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 centers were located in the US, Taiwan, Costa Rica, Guatemala, Peru and Panama.

Pre-assignment

Screening details:

All subjects enrolled were included in the trial.

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
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Arm title	MenACWY-CRM197 + Routine Vaccines (Non-detailed)
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Arm description:

Infants received one vaccination of MenACWY-CRM197 vaccine at 2, 4, 6 and 12 months of age and one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6, months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR: 12 months. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Non-Detailed - subjects who only provided Serious Adverse Events (SAEs) and medically attended Adverse Events (AEs).

Additional vaccines could be included if required according to local guidelines for ex-US subjects, with the exception of all meningococcal vaccines.

Arm type	Experimental
Investigational medicinal product name	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

After reconstitution, one dose (0.5 ml) of MenACWY injectable solution was administered by IM at 2, 4, 6 and 12 months of age.

Investigational medicinal product name	DTaP (Diphtheria, Tetanus, Pertussis) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccines was used according to site practice.

Investigational medicinal product name	Hib (Haemophilus influenza b) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine was used according to site practice.

Investigational medicinal product name	IPV (Inactivated Polio Vaccine) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Vaccine was used according to site practice.	
Investigational medicinal product name	Pneumococcal conjugate Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Vaccine was used according to site practice.	
Investigational medicinal product name	MMR (Measles, Mumps, and Rubella) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Vaccine was used according to site practice.	
Arm title	Routine Vaccines (Non-detailed)
Arm description:	
<p>Infants received one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6 months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR: 12 months. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Non-Detailed - subjects who only provided SAEs and medically attended AEs. Additional vaccines could be included if required according to local guidelines for ex-US subjects, with the exception of all meningococcal vaccines.</p>	
Arm type	Active comparator
Investigational medicinal product name	DTaP (Diphtheria, Tetanus, Pertussis) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Vaccines was used according to site practice.	
Investigational medicinal product name	Hib (Haemophilus influenza b) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Vaccine was used according to site practice.	
Investigational medicinal product name	IPV (Inactivated Polio Vaccine) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Vaccine was used according to site practice.	

Investigational medicinal product name	Pneumococcal conjugate Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine was used according to site practice.

Investigational medicinal product name	MMR (Measles, Mumps, and Rubella) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Vaccine was used according to site practice.

Arm title	MenACWY-CRM197 + Routine Vaccines (Detailed)
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Arm description:

Infants received one vaccination of MenACWY-CRM197 vaccine at 2, 4, 6 and 12 months of age and one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6, months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR, Varicella, Hepatitis A: 12 months. HBV and rotavirus vaccines should be administered according to ACIP guidelines during the first year of life. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Detailed - subjects who provided Reactogenicity and all AEs for 7 days, SAEs and medically attended AEs.

Arm type	Experimental
Investigational medicinal product name	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

After reconstitution, one dose (0.5 ml) of MenACWY injectable solution was administered by IM at 2, 4, 6 and 12 months of age.

Investigational medicinal product name	DTaP (Diphtheria, Tetanus, Pertussis) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccines was used according to site practice.

Investigational medicinal product name	Hib (Haemophilus influenza b) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine was used according to site practice.

Investigational medicinal product name	IPV (Inactivated Polio Vaccine) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine was used according to site practice.

Investigational medicinal product name	Pneumococcal conjugate Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine was used according to site practice.

Investigational medicinal product name	MMR (Measles, Mumps, and Rubella) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Vaccine was used according to site practice.

Investigational medicinal product name	Varicella Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine was used according to site practice.

Investigational medicinal product name	Hepatitis A Virus Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine was used according to site practice.

Arm title	Routine Vaccines (Detailed)
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Arm description:

Infants received one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6 months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR, Varicella, and Hepatitis A: 12 months. HBV and rotavirus vaccines should be administered according to ACIP guidelines during the first year of life. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Detailed - subjects who provided Reactogenicity, all AEs for 7 days, SAEs and medically attended AEs.

Arm type	Active comparator
Investigational medicinal product name	DTaP (Diphtheria, Tetanus, Pertussis) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccines was used according to site practice.

Investigational medicinal product name	Hib (Haemophilus influenza b) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine was used according to site practice.

Investigational medicinal product name	IPV (Inactivated Polio Vaccine) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Vaccine was used according to site practice.	
Investigational medicinal product name	Pneumococcal conjugate Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Vaccine was used according to site practice.	
Investigational medicinal product name	MMR (Measles, Mumps, and Rubella) Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Vaccine was used according to site practice.	
Investigational medicinal product name	Varicella Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Vaccine was used according to site practice.	
Investigational medicinal product name	Hepatitis A Virus Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Vaccine was used according to site practice.	

Number of subjects in period 1	MenACWY-CRM197 + Routine Vaccines (Non-detailed)	Routine Vaccines (Non-detailed)	MenACWY-CRM197 + Routine Vaccines (Detailed)
Started	4363	1483	1409
Completed	3849	1321	1139
Not completed	514	162	270
Consent withdrawn by subject	119	31	76
Death	6	-	1
Inappropriate enrollment	-	1	-
Adverse event	25	5	11
Lost to follow-up	217	66	90

Protocol deviation	34	24	26
Administrative reason	113	35	66

Number of subjects in period 1	Routine Vaccines (Detailed)
Started	489
Completed	383
Not completed	106
Consent withdrawn by subject	35
Death	-
Inappropriate enrollment	-
Adverse event	2
Lost to follow-up	34
Protocol deviation	9
Administrative reason	26

Baseline characteristics

Reporting groups

Reporting group title	MenACWY-CRM197 + Routine Vaccines (Non-detailed)
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Reporting group description:

Infants received one vaccination of MenACWY-CRM197 vaccine at 2, 4, 6 and 12 months of age and one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6, months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR: 12 months. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Non-Detailed - subjects who only provided Serious Adverse Events (SAEs) and medically attended Adverse Events (AEs).

Additional vaccines could be included if required according to local guidelines for ex-US subjects, with the exception of all meningococcal vaccines.

Reporting group title	Routine Vaccines (Non-detailed)
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Reporting group description:

Infants received one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6 months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR: 12 months. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Non-Detailed - subjects who only provided SAEs and medically attended AEs. Additional vaccines could be included if required according to local guidelines for ex-US subjects, with the exception of all meningococcal vaccines.

Reporting group title	MenACWY-CRM197 + Routine Vaccines (Detailed)
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Reporting group description:

Infants received one vaccination of MenACWY-CRM197 vaccine at 2, 4, 6 and 12 months of age and one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6, months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR, Varicella, Hepatitis A: 12 months. HBV and rotavirus vaccines should be administered according to ACIP guidelines during the first year of life. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Detailed - subjects who provided Reactogenicity and all AEs for 7 days, SAEs and medically attended AEs.

Reporting group title	Routine Vaccines (Detailed)
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Reporting group description:

Infants received one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6 months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR, Varicella, and Hepatitis A: 12 months. HBV and rotavirus vaccines should be administered according to ACIP guidelines during the first year of life. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Detailed - subjects who provided Reactogenicity, all AEs for 7 days, SAEs and medically attended AEs.

Reporting group values	MenACWY-CRM197 + Routine Vaccines (Non-detailed)	Routine Vaccines (Non-detailed)	MenACWY-CRM197 + Routine Vaccines (Detailed)
Number of subjects	4363	1483	1409
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			

Age continuous Units: days arithmetic mean standard deviation	64.9 ± 7.4	64.7 ± 7.1	65.5 ± 6.5
Gender categorical Units: Subjects			
Female	2135	703	716
Male	2228	780	693

Reporting group values	Routine Vaccines (Detailed)	Total	
Number of subjects	489	7744	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: days arithmetic mean standard deviation	65.2 ± 6.3	-	
Gender categorical Units: Subjects			
Female	232	3786	
Male	257	3958	

End points

End points reporting groups

Reporting group title	MenACWY-CRM197 + Routine Vaccines (Non-detailed)
Reporting group description: Infants received one vaccination of MenACWY-CRM197 vaccine at 2, 4, 6 and 12 months of age and one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6, months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR: 12 months. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Non-Detailed - subjects who only provided Serious Adverse Events (SAEs) and medically attended Adverse Events (AEs). Additional vaccines could be included if required according to local guidelines for ex-US subjects, with the exception of all meningococcal vaccines.	
Reporting group title	Routine Vaccines (Non-detailed)
Reporting group description: Infants received one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6 months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR: 12 months. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Non-Detailed - subjects who only provided SAEs and medically attended AEs. Additional vaccines could be included if required according to local guidelines for ex-US subjects, with the exception of all meningococcal vaccines.	
Reporting group title	MenACWY-CRM197 + Routine Vaccines (Detailed)
Reporting group description: Infants received one vaccination of MenACWY-CRM197 vaccine at 2, 4, 6 and 12 months of age and one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6, months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR, Varicella, Hepatitis A: 12 months. HBV and rotavirus vaccines should be administered according to ACIP guidelines during the first year of life. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Detailed - subjects who provided Reactogenicity and all AEs for 7 days, SAEs and medically attended AEs.	
Reporting group title	Routine Vaccines (Detailed)
Reporting group description: Infants received one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6 months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR, Varicella, and Hepatitis A: 12 months. HBV and rotavirus vaccines should be administered according to ACIP guidelines during the first year of life. Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. Detailed - subjects who provided Reactogenicity, all AEs for 7 days, SAEs and medically attended AEs.	
Subject analysis set title	All enrolled population (ACWY-All)
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who: - whose parents have signed an informed consent, - had undergone screening procedure and were randomized.	
Subject analysis set title	Exposed population (ACWY-All)
Subject analysis set type	Intention-to-treat
Subject analysis set description: All enrolled subjects who actually received a study vaccination (MenACWY-CRM197 vaccine and routine vaccination).	
Subject analysis set title	Safety population (ACWY-All)
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects enrolled who received MenACWY-CRM197 vaccine and routine vaccination; - had postbaseline safety data reported	
Subject analysis set title	Per Protocol safety population (ACWY-All)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects enrolled who received MenACWY-CRM197 vaccine as specified in the protocol and received all routine vaccinations concomitantly, as per-protocol.

Subject analysis set title	All enrolled population (RVAX-All)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects:

- whose parents have signed an informed consent,
- had undergone screening procedure and were randomized.

Subject analysis set title	Exposed population (RVAX-All)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All enrolled subjects who actually received the routine vaccination.

Subject analysis set title	Safety population (RVAX-All)
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects enrolled who:

- had received the routine vaccination
- had postbaseline safety data reported

Subject analysis set title	Per Protocol safety population (RVAX-All)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects enrolled who received all routine vaccinations concomitantly, as per-protocol.

Primary: 1. Percentages of Subjects With At Least One Severe Systemic Reaction After Any Vaccination

End point title	1. Percentages of Subjects With At Least One Severe Systemic Reaction After Any Vaccination ^[1]
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End point description:

To compare the percentages of subjects who reported at least one severe systemic reaction after any vaccination of MenACWY-CRM197 plus routine vaccines (detailed) group to that observed in the routine vaccines alone (detailed) group administered at 2, 4, 6, and 12 months of age.

Detailed - infants who provided reactogenicity and all Adverse Events (AEs) for 7 days, Serious Adverse Events (SAEs) and medically attended AEs.

End point type	Primary
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End point timeframe:

15 minutes to Day 7 after any vaccination administered at 2, 4, 6 and 12 months of age

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis is associated to this endpoint.

End point values	MenACWY-CRM197 + Routine Vaccines (Detailed)	Routine Vaccines (Detailed)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1349	461		
Units: Percentages of subjects				
Subjects With At Least One Severe Systemic Reaction	16	13		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

MenACWY-CRM 197 administered concomitantly with routine vaccines was considered noninferior to routine vaccines alone with respect to severe systemic reactions if the upper limit of the 2-sided 95% CI of the difference (MenACWY-CRM197 vaccine plus routine vaccines group minus routine vaccines only group) in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (days 1-7) after any vaccination was <6%.

Comparison groups	Routine Vaccines (Detailed) v MenACWY-CRM197 + Routine Vaccines (Detailed)
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Method	Miettinen and Nurminen
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	6.4

Notes:

[2] - The null hypothesis associated with the safety objective was that the upper limit of the two-sided 95% CI for this difference in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after any vaccination (PMenACWY+Routine Vaccines–PRoutine Vaccines) was $\geq 6\%$.

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

MenACWY-CRM 197 administered concomitantly with routine vaccines was considered noninferior to routine vaccines alone with respect to severe systemic reactions if the upper limit of the 2-sided 95% CI of the difference (MenACWY-CRM197 vaccine plus routine vaccines group minus routine vaccines only group) in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (days 1-7) after any vaccination was <6%.

Comparison groups	MenACWY-CRM197 + Routine Vaccines (Detailed) v Routine Vaccines (Detailed)
Number of subjects included in analysis	1810
Analysis specification	Post-hoc
Analysis type	non-inferiority ^[3]
Method	Grizzle, Starmer, and Koch Model
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	4.7

Notes:

[3] - The null hypothesis associated with the safety objective was that the upper limit of the two-sided 95% CI for this difference in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after any vaccination (PMenACWY+Routine Vaccines-PRoutine Vaccines) was $\geq 6\%$.

Secondary: 2. Percentages of Subjects With At Least One Serious Adverse Event During the Entire Study Period

End point title	2. Percentages of Subjects With At Least One Serious Adverse Event During the Entire Study Period
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End point description:

To compare the percentages of subjects presenting at least one serious adverse event (SAE) through 6 months postfinal dose in subjects who received MenACWY-CRM197 vaccine concomitantly with routine vaccinations to the percentages of subjects who received routine vaccinations alone.

End point type	Secondary
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End point timeframe:

Day 1 (2 months of age) to 18 months of age

End point values	Safety population (ACWY-All)	Safety population (RVAX-All)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5760	1968		
Units: Percentages of subjects				
Subjects With At Least One Serious Adverse Event	6	6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

MenACWY-CRM 197 administered concomitantly with routine vaccines was considered non inferior to routine vaccines alone with respect to serious adverse events if the upper limit of the 2-sided 95% CI of the difference (MenACWY vaccine plus routine vaccines group minus routine vaccines only group) of the proportion of subjects experiencing at least one serious adverse event was $<5\%$.

Comparison groups	Safety population (ACWY-All) v Safety population (RVAX-All)
Number of subjects included in analysis	7728
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
Method	Miettinen and Nurminen
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.5

Notes:

[4] - The null hypothesis associated with the SAE safety objective was that the upper limit of the two-sided 95% confidence interval for the difference between the MenACWY and routine vaccine groups in the proportion of subjects experiencing at least one SAE (PMenACWY + Routine Vaccines - PRoutine

Vaccines) was $\geq 5\%$.

Secondary: 3. Percentages of Subjects Reporting Solicited Adverse Events, After Each Vaccination

End point title	3. Percentages of Subjects Reporting Solicited Adverse Events, After Each Vaccination ^[5]
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End point description:

To compare the percentage of subjects who reported local and systemic solicited adverse events from day 1 to day 7 after each vaccination with MenACWY-CRM197 given concomitantly with routine vaccinations to the routine vaccinations alone group.

End point type	Secondary
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End point timeframe:

15 minutes to Day 7

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis is associated to this endpoint.

End point values	MenACWY-CRM197 + Routine Vaccines (Detailed)	Routine Vaccines (Detailed)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1313	451		
Units: Percentages of subjects				
Any Local (2 month vaccination) (N=1313, 451)	53	56		
Injection Site Tenderness (N=1301, 446)	46	49		
Injection Site Erythema (N=1297, 445)	17	21		
Injection Site Induration (N=1297, 446)	8	16		
Any Local (4 month vaccination) (N=1262, 420)	46	54		
Injection Site Tenderness (N=1255, 418)	37	42		
Injection Site Erythema (N=1257, 417)	19	29		
Injection Site Induration (N=1257, 417)	9	17		
Any Local (6 month vaccination) (N=1120, 374)	41	50		
Injection Site Tenderness (N=1106, 372)	30	37		
Injection Site Erythema (N=1104, 370)	22	29		
Injection Site Induration (N=1107, 370)	9	19		
Any Local (12 month vaccination) (N=1102, 355)	47	57		
Injection Site Tenderness (N=1098, 353)	39	50		
Injection Site Erythema (N=1095, 349)	21	30		
Injection Site Induration (N=1095, 351)	10	23		
Any Systemic (2 month vaccination) (N=1313, 451)	77	73		
Rash (N=1296, 446)	3	3		
Change in Eating Habits (N=1289, 446)	23	24		
Sleepiness (N=1297, 447)	52	52		
Persistent crying (N=1299,46)	42	40		

Irritability (N=1300, 446)	59	59		
Vomiting (N=1298, 446)	10	9		
Diarrhea (N=1299, 446)	16	11		
Fever (≥ 38°C) (N=1297, 446)	3	2		
Analges.Antipyr.Meds (N=1302, 448)	66	60		
Any Systemic (4 month vaccination) (N=1262, 420)	65	63		
Rash (N=1253, 416)	3	4		
Change in Eating Habits (N=1245, 414)	18	17		
Sleepiness (N=1253, 416)	38	37		
Persistent Crying (N=1254, 417)	31	28		
Irritability (N=1254, 416)	50	48		
Vomiting (N=1254, 416)	8	6		
Diarrhea (N=1255, 416)	11	8		
Fever (≥ 38°C) (N=1251, 416)	4	6		
Analges.Antipyr.Meds (N=1254, 416)	58	55		
Any Systemic (6 month vaccination) (N=1120, 374)	58	54		
Rash (N=1101, 367)	3	3		
Change in Eating Habits (N=1094, 367)	17	14		
Sleepiness (N=1104, 367)	31	29		
Persistent Crying (N=1103, 368)	26	20		
Irritability (N=1104, 369)	46	41		
Vomiting (N=1106, 369)	6	4		
Diarrhea (N=1102, 369)	8	6		
Fever (≥ 38°C) (N=1101, 368)	7	6		
Analges.Antipyr.Meds (N=1103, 370)	53	49		
Any Systemic (12 month vaccination) (N=1102, 355)	63	62		
Rash (N=1093, 353)	4	5		
Change in Eating Habits (N=1089, 348)	18	16		
Sleepiness (N=1096, 353)	30	29		
Persistent Crying (N=1094, 353)	28	24		
Irritability (N=1094, 354)	50	49		
Vomiting (N=1094, 353)	5	4		
Diarrhea (N=1094, 353)	12	9		
Fever (≥ 38°C) (N=1092, 353)	9	8		
Analges.Antipyr.Meds (N=1095, 354)	49	50		

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Number of Subjects Who Reported Unsolicited Adverse Events After Any Vaccination

End point title	4. Number of Subjects Who Reported Unsolicited Adverse Events After Any Vaccination
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End point description:

Safety data with medically attended events were collected throughout the study in all safety groups and all unsolicited AEs were collected from Day 1 to Day 7 after each vaccination in the detailed safety groups.

Possibly or Probably Related AEs were only assessed in the MenACWY-CRM197 + Routine Vaccines (All) arm.

End point type	Secondary
End point timeframe:	
Day 1 (2 months of age) to 18 months of age	

End point values	Safety population (ACWY-All)	Safety population (RVAX-All)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5760	1968		
Units: Subjects				
Any AE	4848	1659		
Any SAE-Total	354	114		
Possibly or Probably Related AEs	520	2		
AEs Leading to Premature Withdrawals	44	8		
Deaths	7	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

2 months to 18 months of age

Adverse event reporting additional description:

Post-injection solicited Adverse Events (AEs) and all unsolicited AEs were collected from Days 1-7 after each vaccination in the detailed groups.

Medically attended AEs and Serious AEs were collected throughout the study period. Subjects who terminated early were followed for 6 months post final dose for safety.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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Reporting groups

Reporting group title	MenACWY-CRM197 + Routine Vaccines (All)
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Reporting group description:

Infants received one vaccination of MenACWY-CRM197 vaccine at 2, 4, 6 and 12 months of age and one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6, months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR, Varicella, Hepatitis A: 12 months. HBV and rotavirus vaccines should be administered according to ACIP guidelines during the first year of life.

Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. All (Detailed and Non-Detailed subjects): Detailed - subjects who provided Reactogenicity and all AEs for 7 days, SAEs and medically attended AEs; Non-Detailed - subjects who only provided SAEs and medically attended AEs.

Reporting group title	Routine Vaccines (All)
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Reporting group description:

Infants received one vaccination of routine vaccines (according to the local vaccination schedule) - DTaP: 2, 4, 6, 15 months, IPV: 2, 4, 6, months, Hib: 2, 4, 6, 15 months, Pneumococcal conjugate: 2, 4, 6, 12 months, MMR, Varicella, and Hepatitis A: 12 months. HBV and rotavirus vaccines should be administered according to ACIP guidelines during the first year of life.

Routine vaccines given to subjects in these arms will be consistent with the US ACIP recommended vaccines. All (Detailed and Non-Detailed subjects): Detailed - subjects who provided Reactogenicity and all AEs for 7 days, SAEs and medically attended AEs; Non-Detailed - subjects who only provided SAEs and medically attended AEs.

Serious adverse events	MenACWY-CRM197 + Routine Vaccines (All)	Routine Vaccines (All)	
Total subjects affected by serious adverse events			
subjects affected / exposed	354 / 5760 (6.15%)	114 / 1968 (5.79%)	
number of deaths (all causes)	7	1	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Angiopathy			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kawasaki's disease			

subjects affected / exposed	4 / 5760 (0.07%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia repair			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
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			
Brain death			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hernia			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 5760 (0.12%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Balanoposthitis			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal mass			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (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			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnoea			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	6 / 5760 (0.10%)	2 / 1968 (0.10%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	6 / 5760 (0.10%)	6 / 1968 (0.30%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchomalacia			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			

subjects affected / exposed	2 / 5760 (0.03%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoxia			
subjects affected / exposed	3 / 5760 (0.05%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	12 / 5760 (0.21%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	0 / 15	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Status asthmaticus			
subjects affected / exposed	1 / 5760 (0.02%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Breath holding			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram Qt prolonged			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental poisoning			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Contusion			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	5 / 5760 (0.09%)	2 / 1968 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrical burn			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Head injury			
subjects affected / exposed	1 / 5760 (0.02%)	2 / 1968 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			

subjects affected / exposed	1 / 5760 (0.02%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
subdural haemorrhage			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (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 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (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			
Anomalous pulmonary venous connection			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital absence of bile ducts			

subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital aplastic anaemia			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniosynostosis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryptorchism			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hamartoma			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitochondrial enzyme deficiency			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteogenesis imperfecta			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patent ductus arteriosus			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phimosis			

subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyloric stenosis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitello-intestinal duct remnant			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital cardiovascular anomaly			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cyanosis			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 5760 (0.02%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (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			

Acute disseminated encephalomyelitis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	5 / 5760 (0.09%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	9 / 5760 (0.16%)	6 / 1968 (0.30%)	
occurrences causally related to treatment / all	1 / 10	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonic epilepsy			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tremor			

subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Imune Thrombocytopenic Purpura			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			

subjects affected / exposed	4 / 5760 (0.07%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (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 pain			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 5760 (0.09%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	3 / 5760 (0.05%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroesophageal reflux disease			
subjects affected / exposed	3 / 5760 (0.05%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 5760 (0.02%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	4 / 5760 (0.07%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 5760 (0.05%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Jaundice			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis atopic			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (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			
Renal failure acute			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal mass			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicoureteric reflux			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (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 Acute tonsillitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 5760 (0.02%) 0 / 1 0 / 0	1 / 1968 (0.05%) 0 / 1 0 / 0	
Adenovirus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 5760 (0.02%) 0 / 1 0 / 0	0 / 1968 (0.00%) 0 / 0 0 / 0	
Arthritis bacterial subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 5760 (0.00%) 0 / 0 0 / 0	1 / 1968 (0.05%) 0 / 1 0 / 0	
Ascariasis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 5760 (0.02%) 0 / 1 0 / 0	0 / 1968 (0.00%) 0 / 0 0 / 0	
Bacteraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 5760 (0.02%) 0 / 1 0 / 0	0 / 1968 (0.00%) 0 / 0 0 / 0	
Bacterial diarrhoea subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 5760 (0.02%) 0 / 1 0 / 0	0 / 1968 (0.00%) 0 / 0 0 / 0	
Bacterial tracheitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 5760 (0.02%) 0 / 1 0 / 0	0 / 1968 (0.00%) 0 / 0 0 / 0	
Bronchiolitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	64 / 5760 (1.11%) 0 / 67 0 / 0	15 / 1968 (0.76%) 0 / 17 0 / 0	
Bronchopneumonia			

subjects affected / exposed	19 / 5760 (0.33%)	5 / 1968 (0.25%)	
occurrences causally related to treatment / all	0 / 19	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 5760 (0.02%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	5 / 5760 (0.09%)	4 / 1968 (0.20%)	
occurrences causally related to treatment / all	1 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis streptococcal			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall abscess			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	10 / 5760 (0.17%)	5 / 1968 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysentery			

subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus infection			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 5760 (0.02%)	2 / 1968 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exanthema subitum			
subjects affected / exposed	0 / 5760 (0.00%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	20 / 5760 (0.35%)	7 / 1968 (0.36%)	
occurrences causally related to treatment / all	0 / 20	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	7 / 5760 (0.12%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital abscess			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus bacteraemia			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand-foot-and-mouth disease			
subjects affected / exposed	10 / 5760 (0.17%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpangina			
subjects affected / exposed	4 / 5760 (0.07%)	2 / 1968 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site cellulitis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected cyst			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	3 / 5760 (0.05%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node abscess			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningitis enteroviral			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (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	2 / 5760 (0.03%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 5760 (0.02%)	3 / 1968 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	3 / 5760 (0.05%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	31 / 5760 (0.54%)	10 / 1968 (0.51%)	
occurrences causally related to treatment / all	0 / 35	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia adenoviral			

subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	3 / 5760 (0.05%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 5760 (0.02%)	2 / 1968 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	4 / 5760 (0.07%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	20 / 5760 (0.35%)	7 / 1968 (0.36%)	
occurrences causally related to treatment / all	0 / 20	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	4 / 5760 (0.07%)	2 / 1968 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotavirus infection			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	3 / 5760 (0.05%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal abscess			
subjects affected / exposed	1 / 5760 (0.02%)	2 / 1968 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	4 / 5760 (0.07%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urachal abscess			

subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	28 / 5760 (0.49%)	10 / 1968 (0.51%)	
occurrences causally related to treatment / all	0 / 28	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral diarrhoea			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	4 / 5760 (0.07%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
meningitis viral			

subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute focal bacterial nephritis			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 5760 (0.00%)	1 / 1968 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	18 / 5760 (0.31%)	9 / 1968 (0.46%)	
occurrences causally related to treatment / all	0 / 19	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding disorder			

subjects affected / exposed	1 / 5760 (0.02%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	2 / 5760 (0.03%)	0 / 1968 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	MenACWY-CRM197 + Routine Vaccines (All)	Routine Vaccines (All)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4662 / 5760 (80.94%)	1587 / 1968 (80.64%)	
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	929 / 5760 (16.13%)	307 / 1968 (15.60%)	
occurrences (all)	2025	659	
General disorders and administration site conditions			
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	519 / 5760 (9.01%)	241 / 1968 (12.25%)	
occurrences (all)	948	444	
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	284 / 5760 (4.93%)	181 / 1968 (9.20%)	
occurrences (all)	448	311	
Injection site pain			
alternative assessment type: Systematic			

subjects affected / exposed	916 / 5760 (15.90%)	338 / 1968 (17.17%)	
occurrences (all)	1890	720	
Pyrexia alternative assessment type: Systematic			
subjects affected / exposed	1239 / 5760 (21.51%)	373 / 1968 (18.95%)	
occurrences (all)	1734	520	
Crying alternative assessment type: Systematic			
subjects affected / exposed	859 / 5760 (14.91%)	277 / 1968 (14.08%)	
occurrences (all)	1767	517	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	732 / 5760 (12.71%)	234 / 1968 (11.89%)	
occurrences (all)	889	301	
Gastrointestinal disorders			
Teething			
subjects affected / exposed	294 / 5760 (5.10%)	106 / 1968 (5.39%)	
occurrences (all)	336	122	
Diarrhoea alternative assessment type: Systematic			
subjects affected / exposed	1181 / 5760 (20.50%)	356 / 1968 (18.09%)	
occurrences (all)	1750	500	
Vomiting alternative assessment type: Systematic			
subjects affected / exposed	500 / 5760 (8.68%)	155 / 1968 (7.88%)	
occurrences (all)	674	195	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	504 / 5760 (8.75%)	171 / 1968 (8.69%)	
occurrences (all)	630	203	
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	628 / 5760 (10.90%)	201 / 1968 (10.21%)	
occurrences (all)	738	244	

<p>Eczema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>399 / 5760 (6.93%)</p> <p>440</p> <p>307 / 5760 (5.33%)</p> <p>373</p>	<p>145 / 1968 (7.37%)</p> <p>158</p> <p>109 / 1968 (5.54%)</p> <p>127</p>	
<p>Psychiatric disorders</p> <p>Irritability</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1148 / 5760 (19.93%)</p> <p>3051</p>	<p>405 / 1968 (20.58%)</p> <p>955</p>	
<p>Eating disorder</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>593 / 5760 (10.30%)</p> <p>1029</p>	<p>187 / 1968 (9.50%)</p> <p>313</p>	
<p>Infections and infestations</p> <p>Bronchiolitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>826 / 5760 (14.34%)</p> <p>1094</p>	<p>299 / 1968 (15.19%)</p> <p>390</p>	
<p>Croup infectious</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>284 / 5760 (4.93%)</p> <p>339</p>	<p>98 / 1968 (4.98%)</p> <p>116</p>	
<p>Bronchitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>446 / 5760 (7.74%)</p> <p>666</p>	<p>153 / 1968 (7.77%)</p> <p>218</p>	
<p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>524 / 5760 (9.10%)</p> <p>640</p>	<p>179 / 1968 (9.10%)</p> <p>209</p>	
<p>Influenza</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>415 / 5760 (7.20%)</p> <p>568</p>	<p>124 / 1968 (6.30%)</p> <p>167</p>	
<p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>751 / 5760 (13.04%)</p> <p>1358</p>	<p>239 / 1968 (12.14%)</p> <p>409</p>	

Otitis media			
subjects affected / exposed	1579 / 5760 (27.41%)	551 / 1968 (28.00%)	
occurrences (all)	3472	1107	
Otitis media acute			
subjects affected / exposed	412 / 5760 (7.15%)	154 / 1968 (7.83%)	
occurrences (all)	736	263	
Pharyngitis			
subjects affected / exposed	609 / 5760 (10.57%)	208 / 1968 (10.57%)	
occurrences (all)	796	258	
Sinusitis			
subjects affected / exposed	296 / 5760 (5.14%)	93 / 1968 (4.73%)	
occurrences (all)	370	111	
Upper respiratory tract infection			
subjects affected / exposed	2358 / 5760 (40.94%)	842 / 1968 (42.78%)	
occurrences (all)	5140	1751	
Viral infection			
subjects affected / exposed	591 / 5760 (10.26%)	175 / 1968 (8.89%)	
occurrences (all)	748	210	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2009	Amendment 1. Addition of detailed safety arm; addition of 1000 control subjects; primary objective changed from descriptive to comparison with statistical testing; standard core routine vaccines defined; DTaP and Hib at 15 months of age.
14 May 2009	Amendment 2. The major changes incorporated into this version of the protocol were related to AE collection as follows: <ul style="list-style-type: none">- Instead of only collecting serious and medically significant AEs, the protocol was modified to include collection of medically attended AEs from postvaccination day 8 through end of study for groups 3 and 4 subjects and for the duration of the trial for group 1 and 2 subjects. All AEs were collected from Day 1 to Day 7 postvaccination for Groups 3 and 4 (unchanged).- The definitions of relatedness of AEs were modified so that an AE would now be considered related to the study vaccine unless there was clear evidence of an alternative cause.- Review of the trial data by an independent Data Monitoring Committee was added to trial procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24397906>