Clinical trial results:
A Phase III Randomized, Open-Label, Active-Comparator Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V419 in Infants When Given at 2, 4, and 6 Months Concomitantly with Prevnar 13™ and RotaTeq™

Summary

EudraCT number	2011-004095-10
Trial protocol	Outside EU/EEA
Global end of trial date	09 May 2013

Results information

Result version number	v1 (current)
This version publication date	03 February 2016
First version publication date	24 July 2015

Trial information

Trial identification

Sponsor protocol code	V419-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01337167
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp and Dohme Corp., A Subsidiary of Merck & Co. Inc.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, United States, 07033
Public contact	VP, Late Stage Development, Merck Sharp and Dohme Corp., A Subsidiary of Merck & Co., Inc., 1 800 672 6372, ClinicalTrialsDisclosure@merck.com
Scientific contact	VP, Late Stage Development, Merck Sharp and Dohme Corp., A Subsidiary of Merck & Co., Inc., 1 800 672 6372, ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000394-PIP01-08
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	09 May 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

(1) To compare the immunogenicity of V419 with the component vaccine control(s).

(2) To compare the immunogenicity of pertussis responses at one month after the Toddler dose of DAPTACEL after receiving an infant series of either 3 doses of V419 or PENTACEL

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and 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:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	20 April 2011
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	United States: 1473
Worldwide total number of subjects	1473
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)	1473
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 20 April 2011 to 09 May 2013 at 39 clinical sites in the United States.

Pre-assignment

Screening details:

A total of 1473 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and randomized; however, only 1465 subjects received study vaccinations.

Period 1

Period 1 title	Infant Series
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	V419

Arm description:

V419 0.5 mL intramuscular (IM) at 2, 4, and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; PedvaxHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.

Arm type	Experimental
Investigational medicinal product name	PR5I
Investigational medicinal product code	V419
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection each at 2, 4, and 6 months.

Investigational medicinal product name	DAPTACEL™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection at 15 months.

Investigational medicinal product name	Prevnar13™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection each at 2, 4, 6, and 15 months.

Investigational medicinal product name	PedvaxHIB™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:	
0.5 mL, intramuscular, 1 injection at 15 months.	
Investigational medicinal product name	RotaTeq™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details:	
2 mL, oral, 1 dose each at 2, 4, and 6 months.	
Arm title	Control
Arm description:	
PENTACEL™ 0.5 mL IM at 2, 4, and 6 months of age; Modified Process Hepatitis B vaccine 0.5 mL IM at 2 and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; ActHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.	
Arm type	Active comparator
Investigational medicinal product name	PENTACEL™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL, intramuscular, 1 injection each at 2, 4, and 6 months.	
Investigational medicinal product name	RECOMBIVAX HB™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL, intramuscular, 1 injection each at 2 and 6 months.	
Investigational medicinal product name	DAPTACEL™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL, intramuscular, 1 injection at 15 months.	
Investigational medicinal product name	ActHIB™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL, intramuscular, 1 injection at 15 months.	
Investigational medicinal product name	Prevnar13™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL, intramuscular, 1 injection each at 2, 4, 6, and 15 months.	

Investigational medicinal product name	RotaTeq™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

2 mL, oral, 1 dose each at 2, 4, and 6 months.

Number of subjects in period 1	V419	Control
Started	986	487
Completed	924	460
Not completed	62	27
Consent withdrawn by subject	15	4
Physician decision	3	1
Adverse event, non-fatal	1	1
Death	1	1
Non-compliance with study drug	2	1
Not vaccinated	5	3
Lost to follow-up	13	7
Protocol deviation	22	9

Period 2

Period 2 title	Interim Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	V419

Arm description:

V419 0.5 mL intramuscular (IM) at 2, 4, and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; PedvaxHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.

Arm type	Experimental
Investigational medicinal product name	PR5I
Investigational medicinal product code	V419
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:	
0.5 mL, intramuscular, 1 injection each at 2, 4, and 6 months.	
Investigational medicinal product name	Prevnar13™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL, intramuscular, 1 injection each at 2, 4, 6, and 15 months.	
Investigational medicinal product name	DAPTACEL™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL, intramuscular, 1 injection at 15 months.	
Investigational medicinal product name	PedvaxHIB™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL, intramuscular, 1 injection at 15 months.	
Investigational medicinal product name	RotaTeq™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details:	
2 mL, oral, 1 dose each at 2, 4, and 6 months.	
Arm title	Control

Arm description:

PENTACEL™ 0.5 mL IM at 2, 4, and 6 months of age; Modified Process Hepatitis B vaccine 0.5 mL IM at 2 and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; ActHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.

Arm type	Active comparator
Investigational medicinal product name	PENTACEL™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL, intramuscular, 1 injection each at 2, 4, and 6 months.	
Investigational medicinal product name	RECOMBIVAX HB™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL, intramuscular, 1 injection each at 2 and 6 months.	

Investigational medicinal product name	DAPTACEL™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection at 15 months.

Investigational medicinal product name	ActHIB™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection at 15 months.

Investigational medicinal product name	Prevnar13™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection each at 2, 4, 6, and 15 months.

Investigational medicinal product name	RotaTeq™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

2 mL, oral, 1 dose each at 2, 4, and 6 months.

Number of subjects in period 2	V419	Control
Started	924	460
Completed	843	420
Not completed	81	40
Consent withdrawn by subject	18	10
Physician decision	6	3
Non-compliance with study drug	1	-
Lost to follow-up	51	23
Protocol deviation	5	3
Other protocol criterion not met	-	1

Period 3

Period 3 title	Toddler Dose Vaccinations
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	V419

Arm description:

V419 0.5 mL intramuscular (IM) at 2, 4, and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; PedvaxHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.

Arm type	Experimental
Investigational medicinal product name	PR5I
Investigational medicinal product code	V419
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection each at 2, 4, and 6 months.

Investigational medicinal product name	DAPTACEL™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection at 15 months.

Investigational medicinal product name	Prevnar13™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection each at 2, 4, 6, and 15 months.

Investigational medicinal product name	PedvaxHIB™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection at 15 months.

Investigational medicinal product name	RotaTeq™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

2 mL, oral, 1 dose each at 2, 4, and 6 months.

Arm title	Control

Arm description:

PENTACEL™ 0.5 mL IM at 2, 4, and 6 months of age; Modified Process Hepatitis B vaccine 0.5 mL IM at 2 and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; ActHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.

Arm type	Active comparator
Investigational medicinal product name	PENTACEL™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection each at 2, 4, and 6 months.

Investigational medicinal product name	RECOMBIVAX HB™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection each at 2 and 6 months.

Investigational medicinal product name	DAPTACEL™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection at 15 months.

Investigational medicinal product name	ActHIB™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection at 15 months.

Investigational medicinal product name	Prevnar13™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection each at 2, 4, 6, and 15 months.

Investigational medicinal product name	RotaTeq™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

2 mL, oral, 1 dose each at 2, 4, and 6 months.

Number of subjects in period 3	V419	Control
Started	843	420
Completed	829	407
Not completed	14	13
Consent withdrawn by subject	3	-
Lost to follow-up	11	12
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	V419
Reporting group description:	
V419 0.5 mL intramuscular (IM) at 2, 4, and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; PedvaxHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.	
Reporting group title	Control
Reporting group description:	
PENTACEL™ 0.5 mL IM at 2, 4, and 6 months of age; Modified Process Hepatitis B vaccine 0.5 mL IM at 2 and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; ActHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.	

Reporting group values	V419	Control	Total
Number of subjects	986	487	1473
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	986	487	1473
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: days			
arithmetic mean	65.6	65	
standard deviation	± 7.5	± 6.9	-
Gender categorical Units: Subjects			
Female	479	214	693
Male	507	273	780

End points

End points reporting groups

Reporting group title	V419
Reporting group description:	
V419 0.5 mL intramuscular (IM) at 2, 4, and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; PedvaxHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.	
Reporting group title	Control
Reporting group description:	
PENTACEL™ 0.5 mL IM at 2, 4, and 6 months of age; Modified Process Hepatitis B vaccine 0.5 mL IM at 2 and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; ActHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.	
Reporting group title	V419
Reporting group description:	
V419 0.5 mL intramuscular (IM) at 2, 4, and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; PedvaxHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.	
Reporting group title	Control
Reporting group description:	
PENTACEL™ 0.5 mL IM at 2, 4, and 6 months of age; Modified Process Hepatitis B vaccine 0.5 mL IM at 2 and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; ActHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.	
Reporting group title	V419
Reporting group description:	
V419 0.5 mL intramuscular (IM) at 2, 4, and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; PedvaxHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.	
Reporting group title	Control
Reporting group description:	
PENTACEL™ 0.5 mL IM at 2, 4, and 6 months of age; Modified Process Hepatitis B vaccine 0.5 mL IM at 2 and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; ActHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.	

Primary: Percentage of Subjects Responding to Polyribosylribitol Phosphate (PRP) Antigen

End point title	Percentage of Subjects Responding to Polyribosylribitol Phosphate (PRP) Antigen
End point description:	
Subject serum samples were collected for testing with a radioimmunoassay for antibodies to Haemophilus influenza type b capsular polysaccharide polyribosylribitol phosphate (PRP). Sera response or endpoint was defined as a titer ≥0.15 µg/mL and ≥1.0 µg/mL. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.	
End point type	Primary
End point timeframe:	
Postdose 3 (Month 7)	

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765	382		
Units: Percentage of subjects				
number (confidence interval 95%)				
PRP ≥1.0 µg/mL	84.97 (82.24 to 87.43)	75.39 (70.76 to 79.63)		
PRP ≥0.15 µg/mL	97.25 (95.83 to 98.29)	92.41 (89.28 to 94.86)		

Statistical analyses

Statistical analysis title	Non-inferiority (PRP; ≥1.0 µg/mL)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001 [2]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	9.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.83
upper limit	14.83

Notes:

[1] - For PRP (≥1.0 µg/mL), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.

[2] - One-side p-value

Statistical analysis title	Non-inferiority (PRP; ≥0.15 µg/mL)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.001 [4]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	4.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.23
upper limit	8.14

Notes:

[3] - For PRP (≥0.15 µg/mL), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-5%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[4] - One-sided p-value

Statistical analysis title	Secondary; Non-inferiority (PRP; ≥0.15 µg/mL)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	< 0.001 [6]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	4.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.23
upper limit	8.14

Notes:

[5] - For PRP (≥0.15 µg/mL), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[6] - One-sided p-value

Primary: Percentage of Subjects Responding to Hepatitis B Surface Antigen

End point title	Percentage of Subjects Responding to Hepatitis B Surface Antigen

End point description:

Subject serum samples were collected for testing with an enhanced chemiluminescence assay for antibodies to Hepatitis B Surface Antigen (HBsAg). Sera response or endpoint was defined as a titer ≥10 milli International units (mIU)/mL. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	688	353		
Units: Percentage of subjects				
number (confidence interval 95%)				
HBsAg; ≥10 mIU/mL	99.42 (98.52 to 99.84)	98.58 (96.73 to 99.54)		

Statistical analyses

Statistical analysis title	Non-inferiority (HBsAg; ≥10 mIU/mL)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1041
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	< 0.001 [8]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	2.74

Notes:

[7] - For HBsAg (≥10 mIU/mL), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[8] - One-sided p-value

Primary: Percentage of Subjects Responding to Diphtheria Toxin

End point title	Percentage of Subjects Responding to Diphtheria Toxin

End point description:

Subject serum samples were collected for testing with a micrometabolic inhibition test for neutralizing antibodies to diphtheria toxin. Sera response or endpoint was defined as a titer ≥0.1 International unit (IU)/mL. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	786	393		
Units: Percentage of subjects				
number (confidence interval 95%)				
Diphtheria Toxin ≥ 0.1 IU/mL	82.44 (79.6 to 85.04)	86.26 (82.45 to 89.51)		

Statistical analyses

Statistical analysis title	Non-inferiority (Diphtheria; ≥0.1 IU/mL)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1179
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
P-value	= 0.002 [10]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	-3.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.02
upper limit	0.66

Notes:

[9] - For Diphtheria (≥0.1 IU/mL), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[10] - One-sided p-value

Primary: Percentage of Subjects Responding to Tetanus Toxin

End point title	Percentage of Subjects Responding to Tetanus Toxin

End point description:

Subject serum samples were collected for testing with an enzyme-linked immunosorbent assay for anti-tetanus antibodies. Sera response or endpoint was defined as a titer ≥0.1 IU/mL. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	787	390		
Units: Percentage of subjects				
number (confidence interval 95%)				
Tetanus Toxin ≥ 0.1 IU/mL	99.87 (99.29 to 100)	99.49 (98.16 to 99.94)		

Statistical analyses

Statistical analysis title	Non-inferiority (Tetanus; ≥0.1 IU/mL)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1177
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	< 0.001 [12]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	1.74

Notes:

[11] - For Tetanus (≥0.1 IU/mL), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-5%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[12] - One-sided p-value

Primary: Percentage of Subjects Responding to Pertussis Toxin

End point title	Percentage of Subjects Responding to Pertussis Toxin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis toxin. Sera response or endpoint was defined as follows: 1) if the predose titer was < 4 times the lower limit of quantitation (4X LLOQ) then the post-dose titer was ≥4X LLOQ; 2) if the pre-dose titer was ≥4X LLOQ then the post-dose titer was ≥ the pre-dose titer. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	796	391		
Units: Percentage of subjects				
number (confidence interval 95%)				
Pertussis toxin	98.12 (96.91 to 98.94)	98.47 (96.69 to 99.43)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis toxin)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	Control v V419
Number of subjects included in analysis	1187
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	< 0.001 [14]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.6

Notes:

[13] - For Pertussis toxin, if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[14] - One-sided p-value

Primary: Percentage of Subjects Responding to Pertussis Filamentous Hemagglutinin

End point title	Percentage of Subjects Responding to Pertussis Filamentous Hemagglutinin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to Pertussis filamentous hemagglutinin (FHA). Sera response or endpoint was defined as follows: 1) if the pre-dose titer was <4X LLOQ then the post-dose titer was ≥4X LLOQ; 2) if the pre-dose titer was ≥4X LLOQ then the post-dose titer was ≥ the pre-dose titer. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	796	391		
Units: Percentage of subjects				
number (confidence interval 95%)				
Pertussis FHA	87.31 (84.8 to 89.55)	92.07 (88.93 to 94.55)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis FHA)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1187
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	= 0.001 [16]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.14
upper limit	-0.97

Notes:

[15] - For Pertussis FHA, if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[16] - One-sided p-value

Primary: Percentage of Subjects Responding to Pertussis Pertactin

End point title	Percentage of Subjects Responding to Pertussis Pertactin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to Pertussis pertactin. Sera response or endpoint was defined as follows: 1) if the pre-dose titer was <4X LLOQ then the post-dose titer was ≥4X LLOQ; 2) if the pre-dose titer was ≥4X LLOQ then the post-dose titer was ≥ the pre-dose titer. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	794	390		
Units: Percentage of subjects				
number (confidence interval 95%)				
Pertussis Pertactin	79.35 (76.36 to 82.11)	82.05 (77.88 to 85.73)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis Pertactin)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1184
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
P-value	< 0.001 [18]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	-2.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.27
upper limit	2.23

Notes:

[17] - For Pertussis Pertactin, if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[18] - One-sided p-value

Primary: Percentage of Subjects Responding to Pertussis Fimbriae

End point title	Percentage of Subjects Responding to Pertussis Fimbriae

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis fimbriae. Sera response or endpoint was defined as follows: 1) if the pre-dose titer was <4X LLOQ then the post-dose titer was ≥4X LLOQ; 2) if the pre-dose titer was ≥4X LLOQ then the post-dose titer was ≥ the pre-dose titer. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	796	391		
Units: Percentage of subjects				
number (confidence interval 95%)				
Pertussis Fimbriae	90.2 (87.92 to 92.18)	86.19 (82.37 to 89.45)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis Fimbriae)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1187
Analysis specification	Pre-specified
Analysis type	non-inferiority[19]
P-value	< 0.001 [20]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	4.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	8.28

Notes:

[19] - For Pertussis Fimbriae, if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[20] - One-sided p-value

Primary: Percentage of Subjects Responding to Poliovirus Type 1

End point title	Percentage of Subjects Responding to Poliovirus Type 1

End point description:

Subject serum samples were collected for testing with a micrometabolic inhibition test for neutralizing antibodies to Poliovirus Type 1. Sera response or endpoint was defined as a titer ≥8. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	806	398		
Units: Percentage of subjects				
number (confidence interval 95%)				
Poliovirus Type 1	100 (99.54 to 100)	98.24 (96.41 to 99.29)		

Statistical analyses

Statistical analysis title	Non-inferiority (Poliovirus Type 1; ≥1:8 dilution)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1204
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
P-value	< 0.001 [22]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	3.59

Notes:

[21] - For Poliovirus Type 1 (1:8 dilution), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-5%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[22] - One-sided p-value

Statistical analysis title	Acceptability (Poliovirus Type 1; ≥1:8 dilution)

Statistical analysis description:

Acceptability of Poliovirus Type 1

Comparison groups	V419 v Control
Number of subjects included in analysis	1204
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	< 0.001 [24]
Method	Clopper and Pearson
Parameter estimate	Response rate
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	99.54
upper limit	100

Notes:

[23] - Acceptability requires that the lower bound of the 2-sided 95% confidence interval of the response rate is ≥90.
[24] - One-sided P-value

Primary: Percentage of Subjects Responding to Poliovirus Type 2

End point title	Percentage of Subjects Responding to Poliovirus Type 2

End point description:

Subject serum samples were collected for testing with a micrometabolic inhibition test for neutralizing antibodies to Poliovirus Type 2. Sera response or endpoint was defined as a titer ≥8. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	801	399		
Units: Percentage of subjects				
number (confidence interval 95%)				
Poliovirus Type 2	100 (99.54 to 100)	99.75 (98.61 to 99.99)		

Statistical analyses

Statistical analysis title	Non-inferiority (Poliovirus Type 2; ≥1:8 dilution)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1200
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
P-value	< 0.001 [26]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	1.42

Notes:

[25] - For Poliovirus Type 2 (≥1:8 dilution), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-5%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.

[26] - One-sided p-value

Statistical analysis title	Acceptability (Poliovirus Type 2; ≥1:8 dilution)
Statistical analysis description:	
Acceptability of Poliovirus Type 2	
Comparison groups	V419 v Control
Number of subjects included in analysis	1200
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	< 0.001 [28]
Method	Clopper and Pearson
Parameter estimate	Response rate
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	99.54
upper limit	100

Notes:

[27] - Acceptability requires that the lower bound of the 2-sided 95% confidence interval of the response rate is ≥90.
[28] - One-sided P-value

Primary: Percentage of Subjects Responding to Poliovirus Type 3	
End point title	Percentage of Subjects Responding to Poliovirus Type 3
End point description:	
Subject serum samples were collected for testing with a micrometabolic inhibition test for neutralizing Poliovirus Type 3. Sera response or endpoint was defined as a titer ≥8. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.	
End point type	Primary
End point timeframe:	
Postdose 3 (Month 7)	

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	790	396		
Units: Percentage of subjects				
number (confidence interval 95%)				
Poliovirus Type 3	100 (99.53 to 100)	99.75 (98.6 to 99.99)		

Statistical analyses

Statistical analysis title	Non-inferiority (Poliovirus Type 3; ≥1:8 dilution)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1186
Analysis specification	Pre-specified
Analysis type	non-inferiority[29]
P-value	< 0.001 [30]
Method	Miettinen and Nurminen
Parameter estimate	Estimated difference
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	1.41

Notes:

[29] - For Poliovirus Type 3 (≥1:8 dilution), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-5%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[30] - One-sided P-value

Statistical analysis title	Acceptability (Poliovirus Type 3; ≥1:8 dilution)

Statistical analysis description:

Acceptability of Poliovirus Type 3

Comparison groups	V419 v Control
Number of subjects included in analysis	1186
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	< 0.001 [32]
Method	Clopper and Pearson
Parameter estimate	Response rate
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	99.53
upper limit	100

Notes:

[31] - Acceptability requires that the lower bound of the 2-sided 95% confidence interval of the response rate is ≥90.
[32] - One-sided P-value

Primary: Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Toxin

End point title	Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Toxin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis toxin. The unit of measure is ELISA units/mL (EU/mL). The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	810	400		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Pertussis Toxin GMC	110.4 (105.78 to 115.21)	86.54 (81.87 to 91.48)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis toxin; GMC)

Statistical analysis description:

Estimates of GMC, GMC ratio (V419/control), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as response variable, and vaccination group, natural log-transformed prevaccination titer, brand of birth dose of Hepatitis B vaccine as explanatory variables.

Comparison groups	V419 v Control
Number of subjects included in analysis	1210
Analysis specification	Pre-specified
Analysis type	non-inferiority[33]
P-value	< 0.001 [34]
Method	ANCOVA
Parameter estimate	GMC Ratio
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1.38

Notes:

[33] - For Pertussis toxin (GMC), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥0.67) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.

[34] - One-sided P-value

Primary: Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Filamentous Hemagglutinin

End point title	Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Filamentous Hemagglutinin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis filamentous hemagglutinin (FHA). The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:
Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	810	400		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Pertussis FHA GMC	48.17 (45.68 to 50.8)	74.44 (68.99 to 80.33)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis FHA; GMC)

Statistical analysis description:

Estimates of GMC, GMC ratio (V419/control), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as response variable, and vaccination group, natural log-transformed prevaccination titer, brand of birth dose of Hepatitis B vaccine as explanatory variables.

Comparison groups	V419 v Control
Number of subjects included in analysis	1210
Analysis specification	Pre-specified
Analysis type	non-inferiority[35]
P-value	= 0.786 [36]
Method	ANCOVA
Parameter estimate	GMC Ratio
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.7

Notes:

[35] - For Pertussis FHA (GMC), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥0.67) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was not achieved in this analysis.
[36] - One-sided P-value

Primary: Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Pertactin

End point title	Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Pertactin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis pertactin. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	808	400		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Pertussis Pertactin GMC	56.22 (51.93 to 60.85)	66.16 (59.5 to 73.57)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis Pertactin; GMC)

Statistical analysis description:

Estimates of GMC, GMC ratio (V419/control), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as response variable, and vaccination group, natural log-transformed prevaccination titer, brand of birth dose of Hepatitis B vaccine as explanatory variables.

Comparison groups	V419 v Control
Number of subjects included in analysis	1208
Analysis specification	Pre-specified
Analysis type	non-inferiority[37]
P-value	< 0.001 [38]
Method	ANCOVA
Parameter estimate	GMC Ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	0.95

Notes:

[37] - For Pertussis Pertactin (GMC), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥0.67) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.

[38] - One-sided p-value

Primary: Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Fimbriae

End point title	Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Fimbriae

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis fimbriae.The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Primary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	809	400		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Pertussis Fimbriae GMC	235.62 (221.43 to 250.73)	185.54 (169.33 to 203.31)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis Fimbriae; GMC)

Statistical analysis description:

Estimates of GMC, GMC ratio (V419/control), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as response variable, and vaccination group, natural log-transformed prevaccination titer, brand of birth dose of Hepatitis B vaccine as explanatory variables.

Comparison groups	V419 v Control
Number of subjects included in analysis	1209
Analysis specification	Pre-specified
Analysis type	non-inferiority[39]
P-value	< 0.001 [40]
Method	ANCOVA
Parameter estimate	GMC Ratio
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	1.42

Notes:

[39] - For Pertussis Fimbriae (GMC), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥0.67) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.

[40] - One-sided p-value

Primary: Percentage of Subjects Responding to Pertussis Toxin

End point title	Percentage of Subjects Responding to Pertussis Toxin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis toxin. Sera response or endpoint was defined as follows: 1) if the pre-dose titer was <4X LLOQ then the post-dose titer was ≥4X LLOQ; 2) if the pre-dose titer was ≥4X LLOQ then the post-dose titer was ≥ the predose titer. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 4.

End point type	Primary

End point timeframe:

Postdose 4 (Month 16)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	701	349		
Units: Percentage of subjects				
number (confidence interval 95%)				
Pertussis Toxin	99.29 (98.34 to 99.77)	97.42 (95.16 to 98.81)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis toxin)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1050
Analysis specification	Pre-specified
Analysis type	non-inferiority[41]
P-value	< 0.001 [42]
Method	Miettinen and Nurminen
Parameter estimate	Mean difference (final values)
Point estimate	1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	4.18

Notes:

[41] - For Pertussis Toxin, if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[42] - One-sided p-value

Primary: Percentage of Subjects Responding to Pertussis Filamentous Hemagglutinin

End point title	Percentage of Subjects Responding to Pertussis Filamentous Hemagglutinin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis filamentous hemagglutinin (FHA). Sera response or endpoint was defined as follows: 1) if the predose titer was <4X LLOQ then the postdose titer was ≥4X LLOQ; 2) if the predose titer was ≥4X LLOQ then the postdose titer was ≥ the predose titer. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 4.

End point type	Primary

End point timeframe:

Postdose 4 (Month 16)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	699	350		
Units: Percentage of subjects				
number (confidence interval 95%)				
Pertussis FHA	94.42 (92.45 to 96)	93.14 (89.97 to 95.56)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis FHA)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1049
Analysis specification	Pre-specified
Analysis type	non-inferiority[43]
P-value	< 0.001 [44]
Method	Miettinen and Nurminen
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	4.78

Notes:

[43] - For Pertussis FHA, if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[44] - One-sided p-value

Primary: Percentage of Subjects Responding to Pertussis Pertactin

End point title	Percentage of Subjects Responding to Pertussis Pertactin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis pertactin. Sera response or endpoint was defined as follows: 1) if the pre-dose titer was <4X LLOQ then the post-dose titer was ≥4X LLOQ; 2) if the pre-dose titer was ≥4X LLOQ then the post-dose titer was ≥ the pre-dose titer. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 4.

End point type	Primary

End point timeframe:

Postdose 4 (Month 16)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	701	351		
Units: Percentage of subjects				
number (confidence interval 95%)				
Pertussis Pertactin	93.01 (90.86 to 94.78)	93.45 (90.33 to 95.8)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis Pertactin)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1052
Analysis specification	Pre-specified
Analysis type	non-inferiority[45]
P-value	< 0.001 [46]
Method	Miettinen and Nurminen
Parameter estimate	Mean difference (final values)
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.46
upper limit	3.1

Notes:

[45] - For Pertussis Pertactin, if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[46] - One-sided p-value

Primary: Percentage of Subjects Responding to Pertussis Fimbriae

End point title	Percentage of Subjects Responding to Pertussis Fimbriae

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis fimbriae. Sera response or endpoint was defined as follows: 1) if the pre-dose titer was <4X LLOQ then the post-dose titer was ≥4X LLOQ; 2) if the pre-dose titer was ≥4X LLOQ then the post-dose titer was ≥ the predose titer. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 4.

End point type	Primary

End point timeframe:

Postdose 4 (Month 16)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	700	351		
Units: Percentage of subjects				
number (confidence interval 95%)				
Pertussis Fimbriae	97.29 (95.79 to 98.36)	91.17 (87.7 to 93.92)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis Fimbriae)

Statistical analysis description:

Estimates for response rate, rate difference (V419-Control), and p-value were based on the Miettinen and Nurminen method stratified by brand of birth dose of hepatitis B vaccine (RECOMBIVAX™ or other).

Comparison groups	V419 v Control
Number of subjects included in analysis	1051
Analysis specification	Pre-specified
Analysis type	non-inferiority[47]
P-value	< 0.001 [48]
Method	Miettinen and Nurminen
Parameter estimate	Mean difference (final values)
Point estimate	6.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.26
upper limit	9.78

Notes:

[47] - For Pertussis Fimbriae, if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥-10%) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[48] - One-sided p-value

Primary: Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Toxin

End point title	Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Toxin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis toxin.

End point type	Primary

End point timeframe:

Postdose 4 (Month 16)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	356		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Pertussis Toxin GMC	127.22 (121.17 to 133.57)	91.31 (85.09 to 97.98)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis toxin; GMC)

Statistical analysis description:

Estimates of GMC, GMC ratio (V419/control), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as response variable, and vaccination group, natural log-transformed prevaccination titer, brand of birth dose of Hepatitis B vaccine as explanatory variables.

Comparison groups	V419 v Control
Number of subjects included in analysis	1069
Analysis specification	Pre-specified
Analysis type	non-inferiority[49]
P-value	< 0.001 [50]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	1.52

Notes:

[49] - For Pertussis Toxin (GMC), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥0.67) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.

[50] - One-sided p-value

Primary: Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Filamentous Hemagglutinin

End point title	Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Filamentous Hemagglutinin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis filamentous hemagglutinin (FHA). The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 4.

End point type	Primary

End point timeframe:

Postdose 4 (Month 16)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	357		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Pertussis FHA GMC	88.92 (84.06 to 94.05)	89.18 (82.54 to 96.35)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis FHA; GMC)

Statistical analysis description:

Estimates of GMC, GMC ratio (V19/control), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as response variable, and vaccination group, natural log-transformed prevaccination titer, brand of birth dose of Hepatitis B vaccine as explanatory variables.

Comparison groups	V419 v Control
Number of subjects included in analysis	1067
Analysis specification	Pre-specified
Analysis type	non-inferiority[51]
P-value	< 0.001 [52]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.1

Notes:

[51] - For Pertussis FHA (GMC), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥0.67) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[52] - One-sided p-value

Primary: Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Pertactin

End point title	Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Pertactin

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis pertactin. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 4.

End point type	Primary

End point timeframe:

Postdose 4 (Month 16)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	358		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Pertussis Pertactin GMC	108.05 (99.88 to 116.9)	139.35 (124.81 to 155.58)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis Pertactin; GMC)

Statistical analysis description:

Estimates of GMC, GMC ratio (V419/control), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as response variable, and vaccination group, natural log-transformed prevaccination titer, brand of birth dose of Hepatitis B vaccine as explanatory variables.

Comparison groups	V419 v Control
Number of subjects included in analysis	1071
Analysis specification	Pre-specified
Analysis type	non-inferiority[53]
P-value	= 0.014 [54]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.89

Notes:

[53] - For Pertussis Pertactin (GMC), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥0.67) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.

[54] - One-sided p-value

Primary: Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Fimbriae

End point title	Geometric Mean Concentrations (GMC) for Antibodies to Pertussis Fimbriae

End point description:

Subject serum samples were collected for testing with an ELISA for antibodies to pertussis fimbriae. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 4.

End point type	Primary

End point timeframe:

Postdose 4 (Month 16)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	713	358		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Pertussis Fimbriae GMC	658.5 (617.53 to 702.2)	414.66 (371.41 to 462.94)		

Statistical analyses

Statistical analysis title	Non-inferiority (Pertussis Fimbriae; GMC)

Statistical analysis description:

Estimates of GMC, GMC ratio (V419/control), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as response variable, and vaccination group, natural log-transformed prevaccination titer, brand of birth dose of Hepatitis B vaccine as explanatory variables.

Comparison groups	V419 v Control
Number of subjects included in analysis	1071
Analysis specification	Pre-specified
Analysis type	non-inferiority[55]
P-value	< 0.001 [56]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.41
upper limit	1.78

Notes:

[55] - For Pertussis Fimbriae (GMC), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥0.67) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.

[56] - One-sided p-value

Secondary: Geometric Mean Concentrations (GMC) for Antibodies to Polyribosylribitol Phosphate (PRP) Antigen

End point title	Geometric Mean Concentrations (GMC) for Antibodies to Polyribosylribitol Phosphate (PRP) Antigen

End point description:

Subject serum samples were collected for testing with a radioimmunoassay for antibodies to Haemophilus influenza type b capsular polysaccharide polyribosylribitol phosphate (PRP). The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Secondary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765	382		
Units: µg/mL				
geometric mean (confidence interval 95%)				
PRP GMC	5.11 (4.55 to 5.73)	3.18 (2.66 to 3.81)		

Statistical analyses

Statistical analysis title	Non-inferiority (PRP; GMC)

Statistical analysis description:

Estimates of GMC, GMC ratio (V419/control), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as response variable, and vaccination group, natural log-transformed prevaccination titer, brand of birth dose of Hepatitis B vaccine as explanatory variables.

Comparison groups	V419 v Control
Number of subjects included in analysis	1147
Analysis specification	Pre-specified
Analysis type	non-inferiority[57]
P-value	< 0.001 [58]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.32
upper limit	1.98

Notes:

[57] - For PRP (GMC), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥0.67) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.
[58] - One-sided p-value

Secondary: Geometric Mean Concentrations (GMC) for Antibodies for Immunoglobulin A (IgA) Antibodies to Rotavirus

End point title	Geometric Mean Concentrations (GMC) for Antibodies for Immunoglobulin A (IgA) Antibodies to Rotavirus

End point description:

Subject serum samples were collected for testing with an ELISA for IgA antibodies to rotavirus. The analysis population included subjects who met the inclusion criteria, were not protocol violators, had a vaccination window of 42 to 84 days after the previous dose, and a blood draw sample window for the endpoint of 28 to 51 days after dose 3.

End point type	Secondary

End point timeframe:

Postdose 3 (Month 7)

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	522	274		
Units: units/mL				
geometric mean (confidence interval 95%)				
IgA Antibodies to Rotavirus GMC	278.19 (246.99 to 313.32)	274.46 (232.83 to 323.52)		

Statistical analyses

Statistical analysis title	Non-inferiority (Rotavirus IgA; GMC)

Statistical analysis description:

Estimates of GMC, GMC ratio (V419/control), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as response variable, and vaccination group, natural log-transformed prevaccination titer, brand of birth dose of Hepatitis B vaccine as explanatory variables.

Comparison groups	V419 v Control
Number of subjects included in analysis	796
Analysis specification	Pre-specified
Analysis type	non-inferiority[59]
P-value	< 0.001 [60]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.24

Notes:

[59] - For Rotavirus IgA (GMC), if the lower bound of the 2-sided 95% confidence interval for the group difference was above the prespecified non-inferiority margin (≥0.67) then the non-inferiority was achieved and indicated that V419 group immunogenicity was non-inferior to the Control group. Non-inferiority was achieved in this analysis.

[60] - One-sided p-value

Secondary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Within Five Days Following Any Infant Dose Vaccination in the V419 and Control Groups

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Within Five Days Following Any Infant Dose Vaccination in the V419 and Control Groups

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Pyrexia, Vomiting, Crying abnormal, Somnolence, Decreased appetite, and Irritability. Grade 3 Solicited injection site reaction: Pain, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, >5 cm. Grade 3 Solicited systemic reactions: Pyrexia, ≥39.5°C (≥103.1°F) rectal; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Somnolence, Sleeping most of the time or difficult to wake up; Decreased appetite, Refuses ≥3

feeds or refuses most feeds; Irritability, Inconsolable. Subjects included in these analyses were All Subjects as Treated population and were defined as all vaccinated subjects with safety follow up.

End point type	Secondary

End point timeframe:

Day 0 up to Day 5 post-any Infant dose

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	981	484		
Units: Percentage of subjects				
number (not applicable)				
Any Injection site Pain	73.4	71.8		
Grade 3 Injection site Pain	5.9	4.6		
Any Injection site Erythema	48.8	42.2		
Grade 3 Injection site Erythema	0.2	0.6		
Any Injection site Swelling	40.1	34.8		
Grade 3 Injection site Swelling	0.3	0.4		
Any Pyrexia	47.4	34.4		
Grade 3 Pyrexia	1.5	1.2		
Any Vomiting	25.7	21.5		
Grade 3 Vomiting	0.4	0.6		
Any Crying abnormal	74.8	72.3		
Grade 3 Crying abnormal	7.9	8.3		
Any Somnolence	74.1	71.6		
Grade 3 Somnolence	3.5	2.9		
Any Decreased Appetite	48.9	43.3		
Grade 3 Decreased Appetite	1.3	0.4		
Any Irritability	83.1	81.8		
Grade 3 Irritability	7.7	5.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Adverse Events Related to V419 or Control Within Five Days Following Any Infant Dose Vaccination

End point title	Percentage of Subjects Reporting Solicited Adverse Events Related to V419 or Control Within Five Days Following Any Infant Dose Vaccination

End point description:

Solicited systemic reactions: Pyrexia, Vomiting, Crying abnormal, Somnolence, Decreased appetite, and Irritability. Subjects included in this analyses were All Subjects as Treated population and were defined as all vaccinated subjects with safety follow up.

End point type	Secondary

End point timeframe:

Day 0 up to Day 5 post-any Infant dose

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	981	484		
Units: Percentage of subjects				
number (not applicable)				
Any Pyrexia	45.1	32.1		
Any Vomiting	20.8	16.4		
Any Crying abnormal	71.4	68.5		
Any Somnolence	68.5	66.7		
Any Decreased appetite	45.7	40.2		
Any Irritability	79.6	77.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Adverse Events Related to V419 or Control Within Five Days By Vaccination Visit Following Each Infant Dose Vaccination

End point title	Percentage of Subjects Reporting Solicited Adverse Events Related to V419 or Control Within Five Days By Vaccination Visit Following Each Infant Dose Vaccination

End point description:

Solicited systemic reactions: Pyrexia, Vomiting, Crying abnormal, Somnolence, Decreased appetite, and Irritability.

End point type	Secondary

End point timeframe:

Day 0 up to Day 5 post-each Infant dose

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	981	484		
Units: Percentage of subjects				
number (not applicable)				
Any Pyrexia, Visit 1	16.1	12.6		
Any Pyrexia, Visit 2	26.6	16.4		
Any Pyrexia, Visit 3	26.6	16.2		
Any Vomiting, Visit 1	11.2	7.9		
Any Vomiting, Visit 2	10.2	8.5		
Any Vomiting, Visit 3	8	4.6		
Any Crying abnormal, Visit 1	50.9	48.7		
Any Crying abnormal, Visit 2	48.4	42.9		
Any Crying abnormal, Visit 3	42	36.1		

Any Somnolence, Visit 1	54.6	54		
Any Somnolence, Visit 2	42.9	41.4		
Any Somnolence, Visit 3	38.3	35		
Any Decreased appetite, Visit 1	27.4	24		
Any Decreased appetite, Visit 2	24.1	19.8		
Any Decreased appetite, Visit 3	20.9	17.3		
Any Irritability, Visit 1	63.2	60.5		
Any Irritability, Visit 2	56.6	52.7		
Any Irritability, Visit 3	52.7	48.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Elevated Temperature By Severity Within Five Days Following Any Infant Dose Vaccination in the V419 and Control Groups

End point title	Percentage of Subjects With Elevated Temperature By Severity Within Five Days Following Any Infant Dose Vaccination in the V419 and Control Groups

End point description:

Maximum temperature (all routes) was based on actual temperatures recorded with no adjustments to the measurement route. Maximum temperature (rectal) was required of all subjects if the reading by another method was ≥38.0°C. Percentages were based on the number of subjects in the population with safety follow-up and temperature data.

End point type	Secondary

End point timeframe:

Day 0 up to Day 5 post-any Infant dose

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	981	484		
Units: Percentage of subjects				
number (not applicable)				
Maximum temperature (all routes); <38.0°C	51.1	64.3		
Max. temp. (all routes); ≥38°C and <38.5°C	24.2	19.1		
Max. temp. (all routes); ≥38.5°C and <39.5°C	22.7	15.5		
Max. temp. (all routes); ≥39.5°C	2	1.1		
Maximum temperature (rectal); <38°C	44.5	57.7		
Maximum temperature (rectal); ≥38°C and <38.5°C	24.3	17.9		
Maximum temperature (rectal); ≥38.5°C and <39.5°C	21.6	14.9		
Maximum temperature (rectal); ≥39.5°C	2	0.9		

Statistical analyses

Statistical analysis title	Estimated Difference; All routes, <38°C
Statistical analysis description:	
The estimated difference was calculated for the V419 group minus the Control group.	
Comparison groups	V419 v Control
Number of subjects included in analysis	1465
Analysis specification	Pre-specified
Analysis type	other[61]
Parameter estimate	Mean difference (final values)
Point estimate	-13.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.4
upper limit	-7.7

Notes:

[61] - The 95% confidence intervals were based on the unstratified Miettinen and Nurminen method.

Statistical analysis title	Est. Difference; All routes, ≥38°C and <38.5°C
Statistical analysis description:	
The estimated difference was calculated for the V419 group minus the Control group.	
Comparison groups	V419 v Control
Number of subjects included in analysis	1465
Analysis specification	Pre-specified
Analysis type	other[62]
Parameter estimate	Mean difference (final values)
Point estimate	5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	9.5

Notes:

[62] - The 95% confidence intervals were based on the unstratified Miettinen and Nurminen method.

Statistical analysis title	Est. Difference; All routes, ≥38.5°C and <39.5°C
Statistical analysis description:	
The estimated difference was calculated for the V419 group minus the Control group.	
Comparison groups	V419 v Control

Number of subjects included in analysis	1465
Analysis specification	Pre-specified
Analysis type	other[63]
Parameter estimate	Mean difference (final values)
Point estimate	7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	11.2

Notes:

[63] - The 95% confidence intervals were based on the unstratified Miettinen and Nurminen method.

Statistical analysis title	Est. Difference; All routes, ≥39.5°C

Statistical analysis description:

The estimated difference was calculated for the V419 group minus the Control group.

Comparison groups	V419 v Control
Number of subjects included in analysis	1465
Analysis specification	Pre-specified
Analysis type	other[64]
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	2.2

Notes:

[64] - The 95% confidence intervals were based on the unstratified Miettinen and Nurminen method.

Statistical analysis title	Estimated Difference; Rectal, <38°C

Statistical analysis description:

The estimated difference was calculated for the V419 group minus the Control group.

Comparison groups	V419 v Control
Number of subjects included in analysis	1465
Analysis specification	Pre-specified
Analysis type	other[65]
Parameter estimate	Mean difference (final values)
Point estimate	-13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.6
upper limit	-7.7

Notes:

[65] - The 95% confidence intervals were based on the unstratified Miettinen and Nurminen method.

Statistical analysis title	Estimated Difference; Rectal, ≥38°C and <38.5°C

Statistical analysis description:

The estimated difference was calculated for the V419 group minus the Control group.

Comparison groups	V419 v Control
Number of subjects included in analysis	1465
Analysis specification	Pre-specified
Analysis type	other[66]
Parameter estimate	Mean difference (final values)
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	10.8

Notes:

[66] - The 95% confidence intervals were based on the unstratified Miettinen and Nurminen method.

Statistical analysis title	Estimated Difference; Rectal, ≥38.5°C and <39.5°C

Statistical analysis description:

The estimated difference was calculated for the V419 group minus the Control group.

Comparison groups	V419 v Control
Number of subjects included in analysis	1465
Analysis specification	Pre-specified
Analysis type	other[67]
Parameter estimate	Mean difference (final values)
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.4
upper limit	10.7

Notes:

[67] - The 95% confidence intervals were based on the unstratified Miettinen and Nurminen method.

Statistical analysis title	Estimated Difference; Rectal, ≥39.5°C

Statistical analysis description:

The estimated difference was calculated for the V419 group minus the Control group.

Comparison groups	V419 v Control
Number of subjects included in analysis	1465
Analysis specification	Pre-specified
Analysis type	other[68]
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	2.4

Notes:

[68] - The 95% confidence intervals were based on the unstratified Miettinen and Nurminen method.

Secondary: Percentage of Subjects With Pyrexia, Febrile Convulsion and Convulsion Following Any Infant Dose Vaccination in the V419 and Control Groups

End point title	Percentage of Subjects With Pyrexia, Febrile Convulsion and Convulsion Following Any Infant Dose Vaccination in the V419 and Control Groups

End point description:

The percentage of subjects with adverse events (AE), serious adverse events (SAE), and vaccine-related SAE (pyrexia, febrile convulsion, and convulsion) with an incidence >0% in 1 or more vaccination groups is reported.

End point type	Secondary

End point timeframe:

Day 1 up to Day 181 post-any Infant dose

End point values	V419	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	981	484		
Units: Percentage of subjects				
number (not applicable)				
Pyrexia (AE, Days 1-15)	49.3	35.6		
Febrile convulsion (AE, Days 1-15)	0	0		
Convulsion (AE, Days 1-15)	0	0		
Pyrexia (SAE, Days 1-15)	0	0		
Febrile convulsion (SAE, Days 1-15)	0	0		
Convulsion (SAE, Days 1-15)	0	0		
Pyrexia (SAE, Days 1-181)	0	0.2		
Febrile convulsion (SAE, Days 1-181)	0.2	0		
Convulsion (SAE, Days 1-181)	0.1	0.4		
Pyrexia (Vaccine-related SAE, Days 1-181)	0	0		
Febrile convulsion (Related SAE, Days 1-181)	0	0		
Convulsion (Vaccine-related SAE, Days 1-181)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: up to 6 months after vaccination 3 (the last infant vaccination) and up to 15 days after vaccination 4 (the toddler vaccination); Vaccine-related SAEs and deaths: up to Month 16 (duration of the study); Other AEs: up to 15 days after any vaccination

Adverse event reporting additional description:

The All Subjects as Treated population included all randomized subjects who received at least one dose of study vaccine and had safety follow up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	V419 group

Reporting group description:

V419 0.5 mL intramuscular (IM) at 2, 4, and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; PedvaxHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.

Reporting group title	Control group

Reporting group description:

PENTACEL™ 0.5 mL IM at 2, 4, and 6 months of age; Modified Process Hepatitis B vaccine 0.5 mL IM at 2 and 6 months of age; Daptacel™ 0.5 mL IM at 15 months of age; ActHIB™ 0.5 mL IM at 15 months of age; Prevnar13™ 0.5 mL IM at 2, 4, 6, and 15 months of age; and RotaTeq™ 2 mL oral dose at 2, 4, and 6 months of age.

Serious adverse events	V419 group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 980 (5.92%)	32 / 483 (6.63%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
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			
Device expulsion			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apparent life threatening event			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asphyxia			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	2 / 980 (0.20%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 980 (0.10%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infantile apnoeic attack			

subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 980 (0.00%)	2 / 483 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 980 (0.10%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Urine output decreased			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (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			
Foreign body			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (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	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post concussion syndrome			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (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 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (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 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 980 (0.10%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			

subjects affected / exposed	1 / 980 (0.10%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dystonia			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	2 / 980 (0.20%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Movement disorder			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonic convulsion			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 980 (0.00%)	2 / 483 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Anal fistula			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 980 (0.41%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (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 / 980 (0.10%)	0 / 483 (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			
Abscess			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	6 / 980 (0.61%)	5 / 483 (1.04%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	4 / 980 (0.41%)	3 / 483 (0.62%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastritis viral			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	5 / 980 (0.51%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (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	2 / 980 (0.20%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human herpesvirus 6 infection			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (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	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis enteroviral			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (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	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			

subjects affected / exposed	1 / 980 (0.10%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 980 (0.51%)	2 / 483 (0.41%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	6 / 980 (0.61%)	4 / 483 (0.83%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Roseola			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	2 / 980 (0.20%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (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	2 / 980 (0.20%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Abnormal weight gain			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	12 / 980 (1.22%)	2 / 483 (0.41%)	
occurrences causally related to treatment / all	0 / 12	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 980 (0.00%)	1 / 483 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 980 (0.10%)	0 / 483 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	V419 group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	939 / 980 (95.82%)	458 / 483 (94.82%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	755 / 980 (77.04%)	369 / 483 (76.40%)	
occurrences (all)	1863	887	
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	853 / 980 (87.04%)	415 / 483 (85.92%)	
occurrences (all)	2390	1109	
Pyrexia			
subjects affected / exposed	560 / 980 (57.14%)	216 / 483 (44.72%)	
occurrences (all)	1015	356	
Crying			
subjects affected / exposed	788 / 980 (80.41%)	370 / 483 (76.60%)	
occurrences (all)	1934	857	
Injection site bruising			
subjects affected / exposed	62 / 980 (6.33%)	36 / 483 (7.45%)	
occurrences (all)	103	61	
Injection site erythema			
subjects affected / exposed	597 / 980 (60.92%)	277 / 483 (57.35%)	
occurrences (all)	2665	1365	
Injection site pain			
subjects affected / exposed	826 / 980 (84.29%)	391 / 483 (80.95%)	
occurrences (all)	4276	2234	
Injection site swelling			
subjects affected / exposed	513 / 980 (52.35%)	219 / 483 (45.34%)	
occurrences (all)	1974	989	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	61 / 980 (6.22%)	22 / 483 (4.55%)	
occurrences (all)	68	25	
Vomiting			

subjects affected / exposed	282 / 980 (28.78%)	125 / 483 (25.88%)	
occurrences (all)	432	186	
Infections and infestations			
Otitis media			
subjects affected / exposed	69 / 980 (7.04%)	26 / 483 (5.38%)	
occurrences (all)	76	28	
Upper respiratory tract infection			
subjects affected / exposed	100 / 980 (10.20%)	40 / 483 (8.28%)	
occurrences (all)	108	41	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	577 / 980 (58.88%)	271 / 483 (56.11%)	
occurrences (all)	1087	469	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2010	The analysis of the pertussis responses at one month post-Toddler dose of DAPTACEL™ was moved to a primary objective and hypothesis, an additional statistical criterion for the non-inferiority analysis of the anti-PRP response at one month post-third dose of PR5I or Control was added, an acceptability criterion of 90% (lower bound of the 2-sided 95% CI >90%) for the observed seroprotection rate in the PR5I group was added as a primary endpoint for Inactivated Poliovirus (Types 1, 2, and 3), name of the company was changed to Merck Sharp & Dohme Corp. throughout the document and protocol, pneumococcal conjugate vaccine was changed to Prevnar13™, sample size increased to 1440 subjects, PR5I group sample size increased to 960 subjects, and changes were made throughout the protocol, including all references to Interactive Voice Response System being changed to Interactive Response Technology.
03 March 2011	Revised statistical criteria for the non-inferiority analysis of the anti-PRP response at one month post-third dose of PR5I or Control, analysis of anti-PRP GMTs was moved to a secondary endpoint, and other changes to the text regarding change in the primary and secondary endpoints and analysis methods and revisions for the purpose of clarity.
08 March 2012	Revised the primary objective and hypothesis as well as statistical criteria for the acceptability of Inactivated Poliovirus response, approved the modified manufacturing process for RECOMBIVAX HB™ by the FDA and information related to the new vaccine supply shippers.
24 January 2013	Added a new primary statistical analysis method for all GMT analyses to account for missing baseline titers, added a second Per Protocol Population (Per Protocol-Revised Window) in addition to the existing Per Protocol Original Window to account for subjects who received study vaccinations and/or blood draws outside of narrow protocol-defined visit windows, added 2 sensitivity analyses (analysis of GMT endpoints with no baseline adjustment and analysis of GMT endpoints based on data from subjects with both baseline and postvaccination titers to support the ANCOVA with missing imputation for missing baseline titers primary analysis for GMT endpoints), and added revised systemic corticosteroid use criteria to the description of protocol violations for which a subject was excluded from the Per Protocol Population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported