



Clinical trial results:

Revaccination with Pneumococcal Conjugate Vaccine - Characterization of the Immune Response after Polysaccharide (REPLAY)

Summary

EudraCT number	2008-006194-33
Trial protocol	IS
Global end of trial date	16 December 2009

Results information

Result version number	v1 (current)
This version publication date	29 June 2016
First version publication date	17 July 2015

Trial information

Trial identification

Sponsor protocol code	6096A1-3013
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00853749
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: B1851012

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc. , 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc. , 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 November 2010
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the immune response by enzyme-linked immunosorbent assay (ELISA) and opsonophagocytic assay (OPA) at approximately one month after vaccination to a single dose of 13-valent pneumococcal conjugate vaccine (13vPnC) challenge in children vaccinated with a primary series (3 or 2 doses) of pneumococcal conjugate vaccine (PCV) followed by a booster dose of either PCV or 23-valent pneumococcal polysaccharide vaccine (23vPS).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 May 2009
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	Iceland: 89
Worldwide total number of subjects	89
EEA total number of subjects	89

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)	0
Children (2-11 years)	89
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 89 subjects were enrolled in a single site in Iceland. Study was started on 05 May 2009 and completed on 16 Dec 2009.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PCV/23vPS/13vPnC

Arm description:

For this study, subjects received a single dose of 13vPnC. Subject previously must have also received an infant series of 9-valent pneumococcal-conjugate-meningococcal serogroup C conjugate combination vaccine (9V-MnCC) also known as PCV followed by a toddler dose of 23vPS.

Arm type	Experimental
Investigational medicinal product name	13-valent pneumococcal conjugate vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received a single dose 0.5 milliliter (mL) 13vPnC.

Arm title	PCV/PCV/13vPnC
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Arm description:

For this study, subjects received a single dose of 13vPnC. Subjects must have also previously received an infant series of 9V-MnCC followed by a toddler dose of 9V-MnCC (also referred to as PCV).

Arm type	Experimental
Investigational medicinal product name	13-valent pneumococcal conjugate vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received a single dose of 0.5 mL 13vPnC.

Number of subjects in period 1	PCV/23vPS/13vPnC	PCV/PCV/13vPnC
Started	50	39
Vaccinated	50	39
Completed	50	38
Not completed	0	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	PCV/23vPS/13vPnC
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Reporting group description:

For this study, subjects received a single dose of 13vPnC. Subject previously must have also received an infant series of 9-valent pneumococcal-conjugate-meningococcal serogroup C conjugate combination vaccine (9V-MnCC) also known as PCV followed by a toddler dose of 23vPS.

Reporting group title	PCV/PCV/13vPnC
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Reporting group description:

For this study, subjects received a single dose of 13vPnC. Subjects must have also previously received an infant series of 9V-MnCC followed by a toddler dose of 9V-MnCC (also referred to as PCV).

Reporting group values	PCV/23vPS/13vPnC	PCV/PCV/13vPnC	Total
Number of subjects	50	39	89
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	7.6 ± 0.2	7.6 ± 0.2	-
Gender categorical Units: Subjects			
Female	25	20	45
Male	25	19	44

End points

End points reporting groups

Reporting group title	PCV/23vPS/13vPnC
Reporting group description:	
For this study, subjects received a single dose of 13vPnC. Subject previously must have also received an infant series of 9-valent pneumococcal-conjugate-meningococcal serogroup C conjugate combination vaccine (9V-MnCC) also known as PCV followed by a toddler dose of 23vPS.	
Reporting group title	PCV/PCV/13vPnC
Reporting group description:	
For this study, subjects received a single dose of 13vPnC. Subjects must have also previously received an infant series of 9V-MnCC followed by a toddler dose of 9V-MnCC (also referred to as PCV).	

Primary: Percentage of Subjects Achieving a Predefined Serotype-specific Immunoglobulin G (IgG) Antibody Concentration Greater Than or Equal to (\geq) 0.35 Micrograms Per Milliliter (Mcg/mL) Measured 1 Month After Vaccination

End point title	Percentage of Subjects Achieving a Predefined Serotype-specific Immunoglobulin G (IgG) Antibody Concentration Greater Than or Equal to (\geq) 0.35 Micrograms Per Milliliter (Mcg/mL) Measured 1 Month After Vaccination
End point description:	
Percentage of subjects achieving predefined antibody threshold \geq 0.35 mcg/mL along with the corresponding 95 percent (%) Confidence Interval (CI) for the 7 common pneumococcal serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and 6 additional pneumococcal serotypes specific to 13vPnC (serotypes 1, 3, 5, 6A, 7F, and 19A) are presented. Exact 2-sided CI based on the observed proportion of subjects. Evaluable Immunogenicity Population: received 1 dose of 13vPnC at Visit 1, blood drawn within specified timeframes, at least 1 valid and determinate assay result at Visits 1 and 3, no major protocol violations, and no prohibited vaccines.	
End point type	Primary
End point timeframe:	
Day 28	

End point values	PCV/23vPS/13vPnC	PCV/PCV/13vPnC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50 ^[1]	37 ^[2]		
Units: percentage of subjects				
number (confidence interval 95%)				
Common Serotype 4	100 (92.9 to 100)	97.3 (85.8 to 99.9)		
Common Serotype 6B	100 (92.9 to 100)	100 (90.5 to 100)		
Common Serotype 9V	100 (92.9 to 100)	100 (90.5 to 100)		
Common Serotype 14	100 (92.7 to 100)	100 (90.5 to 100)		
Common Serotype18C	100 (92.9 to 100)	97.3 (85.8 to 99.9)		
Common Serotype 19F	100 (92.9 to 100)	100 (90.5 to 100)		

Common Serotype 23F	100 (92.9 to 100)	100 (90.5 to 100)		
Additional Serotype 1	100 (92.9 to 100)	97.3 (85.8 to 99.9)		
Additional Serotype 3	100 (92.9 to 100)	100 (90.5 to 100)		
Additional Serotype 5	100 (92.9 to 100)	100 (90.5 to 100)		
Additional Serotype 6A	100 (92.9 to 100)	100 (90.5 to 100)		
Additional Serotype 7F	100 (92.9 to 100)	100 (90.5 to 100)		
Additional Serotype 19A	100 (92.9 to 100)	100 (90.5 to 100)		

Notes:

[1] - N= Number of subjects with a determinate IgG antibody concentration to the given serotype.

[2] - N= Number of subjects with a determinate IgG antibody concentration to the given serotype.

Statistical analyses

Statistical analysis title	Comparison for Common Serotype 4
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	14.2

Statistical analysis title	Comparison for Common Serotype 6B
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Statistical analysis title	Comparison for Common Serotype 9V
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Statistical analysis title	Comparison for Common Serotype 14
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	9.5

Statistical analysis title	Comparison for Common Serotype 18C
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	14.2

Statistical analysis title	Comparison for Common Serotype 19F
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Statistical analysis title	Comparison for Common Serotype 23F
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Statistical analysis title	Comparison for Additional Serotype 1
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	14.2

Statistical analysis title	Comparison for Additional Serotype 3
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Statistical analysis title	Comparison for Additional Serotype 5
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Statistical analysis title	Comparison for Additional Serotype 6A
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Statistical analysis title	Comparison for Additional Serotype 7F
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Statistical analysis title	Comparison for Additional Serotype 19A
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Primary: Percentage of Subjects Achieving Opsonophagocytic Assay (OPA) Titers ≥ 1:8 Measured 1 Month After Vaccination

End point title	Percentage of Subjects Achieving Opsonophagocytic Assay (OPA) Titers ≥ 1:8 Measured 1 Month After Vaccination
End point description:	Percentage of subjects achieving OPA along with the corresponding 95% CI for the 7 common pneumococcal serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and 6 additional pneumococcal serotypes specific to 13vPnC (serotypes 1, 3, 5, 6A, 7F, and 19A) are presented. Exact 2-sided CI based on the observed proportion of subjects. Evaluable immunogenicity population.
End point type	Primary
End point timeframe:	
Day 28	

End point values	PCV/23vPS/13vPnC	PCV/PCV/13vPnC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50 ^[3]	37 ^[4]		
Units: percentage of subjects				
number (confidence interval 95%)				
Common Serotype 4	98 (89.4 to 99.9)	97.2 (85.5 to 99.9)		

Common Serotype 6B	100 (92.7 to 100)	100 (90.3 to 100)		
Common Serotype 9V	100 (92.7 to 100)	100 (90.3 to 100)		
Common Serotype 14	100 (92.7 to 100)	100 (90.3 to 100)		
Common Serotype 18C	100 (92.9 to 100)	100 (90 to 100)		
Common Serotype 19F	100 (92.7 to 100)	100 (90 to 100)		
Common Serotype 23F	98 (89.4 to 99.9)	100 (89.7 to 100)		
Additional Serotype 1	100 (92.9 to 100)	97.3 (85.8 to 99.9)		
Additional Serotype 3	98 (89.1 to 99.9)	100 (90.3 to 100)		
Additional Serotype 5	98 (89.4 to 99.9)	97.3 (85.8 to 99.9)		
Additional Serotype 6A	100 (92.9 to 100)	100 (90.5 to 100)		
Additional Serotype 7F	98 (89.4 to 99.9)	100 (90.3 to 100)		
Additional Serotype 19A	100 (92.9 to 100)	100 (90.5 to 100)		

Notes:

[3] - N=number of subjects with a determinate OPA antibody titer to the given serotype.

[4] - N=number of subjects with a determinate OPA antibody titer to the given serotype.

Statistical analyses

Statistical analysis title	Comparison for Common Serotype 4
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	12.7

Statistical analysis title	Comparison for Common Serotype 6B
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	9.7

Statistical analysis title	Comparison for Common Serotype 9V
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	9.7

Statistical analysis title	Comparison for Common Serotype 14
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	9.7

Statistical analysis title	Comparison for Common Serotype 18C
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	10

Statistical analysis title	Comparison for Common Serotype 19F
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	10

Statistical analysis title	Comparison for Common Serotype 23F
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	8.1

Statistical analysis title	Comparison for Additional Serotype 1
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	14.2

Statistical analysis title	Comparison for Additional Serotype 3
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Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	7.9

Statistical analysis title	Comparison for Additional Serotype 5
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	12.2

Statistical analysis title	Comparison for Additional Serotype 6A
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Statistical analysis title	Comparison for Additional Serotype 7F
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	7.7

Statistical analysis title	Comparison for Additional Serotype 19A
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in proportions (percentage)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	9.5

Secondary: Antibody Response Measured 1 Month After Vaccination (Avidity Assay)

End point title	Antibody Response Measured 1 Month After Vaccination (Avidity Assay)
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End point description:

Avidity assay had measurable range of 0.117 to 7.5. Results expressed as Avidity Index (AI). Geometric mean avidity presented for 3 common pneumococcal serotypes (serotype 6B, 19F, and 23F) and 2 additional pneumococcal serotypes specific to 13vPnC (Serotypes 1 and 5). Evaluable immunogenicity population; in accordance with the recommendation of the lab completing the assays, values above the upper limit were assigned a value of 8.0 and those below the lower limit were assigned a value of 0.10.

End point type	Secondary
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End point timeframe:

Day 28

End point values	PCV/23vPS/13vPnC	PCV/PCV/13vPnC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50 ^[5]	36 ^[6]		
Units: AI				
geometric mean (confidence interval 95%)				
Additional serotype 1	1.42 (1.15 to 1.76)	4.68 (3.62 to 6.04)		

Additional serotype 5	1.85 (1.46 to 2.36)	5.85 (4.81 to 7.11)		
Common serotype 6B	2.43 (1.77 to 3.35)	5.48 (4.38 to 6.86)		
Common serotype 19F	2.17 (1.69 to 2.79)	2.46 (1.88 to 3.21)		
Common serotype 23F	3.02 (2.36 to 3.85)	6.43 (5.33 to 7.76)		

Notes:

[5] - N=number of subjects with a determinate avidity index for the specified serotype.

[6] - N=number of subjects with a determinate avidity index for the specified serotype.

Statistical analyses

Statistical analysis title	Serotype 1
Statistical analysis description:	
Confidence Intervals (CIs) for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of geometric means
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.42

Statistical analysis title	Serotype 5
Statistical analysis description:	
CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of geometric means
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.44

Statistical analysis title	Serotype 6B
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Statistical analysis description:

CI's for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of geometric means
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.67

Statistical analysis title

Serotype 19F

Statistical analysis description:

CI's for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of geometric means
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.27

Statistical analysis title

Serotype 23F

Statistical analysis description:

CI's for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of geometric means
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.65

Secondary: Antibody Response Measured 1 Month After Vaccination (OPA)

End point title	Antibody Response Measured 1 Month After Vaccination (OPA)
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End point description:

Antibody response as measured by OPA, 1 month after vaccination. Geometric mean titers (GMTs) calculated using all subjects with available data for the specified blood draw. CIs were back transformations of a CI based on the Student t distribution for the mean logarithm of the titers. Evaluable immunogenicity population.

End point type	Secondary
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End point timeframe:

Day 28

End point values	PCV/23vPS/13 vPnC	PCV/PCV/13vP nC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50 ^[7]	37 ^[8]		
Units: GMT				
geometric mean (confidence interval 95%)				
Common Serotype 4	2374 (1656.3 to 3404)	3765 (2339.1 to 6059.8)		
Common Serotype 6B	11156 (9073.5 to 13715.2)	11477 (8418.5 to 15646.8)		
Common Serotype 9V	1651 (1067.8 to 2553.3)	1713 (1087 to 2700)		
Common Serotype 14	3041 (2311.4 to 4001.1)	3048 (2318.3 to 4006.9)		
Common Serotype 18C	3230 (2616.1 to 3987.1)	5684 (3122.2 to 10349.6)		
Common Serotype 19F	1266 (1013.9 to 1582)	1198 (842.3 to 1703.9)		
Common Serotype 23F	1678 (1212.3 to 2322.1)	2714 (1970.1 to 3739.5)		
Additional Serotype 1	217 (162.6 to 290.5)	1087 (717.5 to 1646.3)		
Additional Serotype 3	153 (117.2 to 200.2)	188 (146.6 to 240.8)		
Additional Serotype 5	264 (178.5 to 389.9)	719 (500.9 to 1032.4)		
Additional Serotype 6A	7060 (5352.2 to 9312.6)	5034 (3336.6 to 7594.4)		
Additional Serotype 7F	5835 (4160 to 8184.1)	7887 (6447.9 to 9647)		
Additional Serotype 19A	1256 (990.9 to 1591.9)	1556 (1108.8 to 2182.2)		

Notes:

[7] - N=number of subjects with a determinate antibody titre to the specified serotype.

[8] - N=number of subjects with a determinate antibody titre to the specified serotype.

Statistical analyses

Statistical analysis title	Common Serotype 4
Statistical analysis description: Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.12

Statistical analysis title	Common Serotype 6B
Statistical analysis description: Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/PCV/13vPnC v PCV/23vPS/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.38

Statistical analysis title	Common Serotype 9V
Statistical analysis description: Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.81

Statistical analysis title	Common Serotype 14
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Statistical analysis description:

Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.48

Statistical analysis title	Common Serotype 18C
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Statistical analysis description:

Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.98

Statistical analysis title	Common Serotype 19F
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Statistical analysis description:

Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.56

Statistical analysis title	Common Serotype 23F
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Statistical analysis description:

Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.99

Statistical analysis title	Additional Serotype 1
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Statistical analysis description:

Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.32

Statistical analysis title	Additional Serotype 3
Statistical analysis description: Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.18

Statistical analysis title	Additional Serotype 5
Statistical analysis description: Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.63

Statistical analysis title	Additional Serotype 6A
Statistical analysis description: Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/PCV/13vPnC v PCV/23vPS/13vPnC

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.25

Statistical analysis title	Additional Serotype 7F
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Statistical analysis description:

Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.14

Statistical analysis title	Additional Serotype 19A
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Statistical analysis description:

Ratio of GMTs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMTs
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.2

Other pre-specified: Geometric Mean Concentration (GMC) for Serotype-specific Pneumococcal IgG Antibody 1 Month After Vaccination

End point title	Geometric Mean Concentration (GMC) for Serotype-specific Pneumococcal IgG Antibody 1 Month After Vaccination
End point description: Antibody GMC as measured by mcg/mL for 7 common pneumococcal serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and 6 additional pneumococcal serotypes specific to 13vPnC (Serotypes 1, 3, 5, 6A, 7F, and 19A) are presented. GMC (13vPnC) and corresponding 2-sided 95% CIs were evaluated. CIs were back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations. GMCs were calculated using all subjects with available data for the specified blood draw. Evaluable Immunogenicity Population.	
End point type	Other pre-specified
End point timeframe: Day 28	

End point values	PCV/23vPS/13vPnC	PCV/PCV/13vPnC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50 ^[9]	37 ^[10]		
Units: mcg/mL				
geometric mean (confidence interval 95%)				
Common serotype 4	4.18 (3.38 to 5.16)	11.34 (7.74 to 16.62)		
Common serotype 6B	29.51 (21.32 to 40.83)	41.7 (29.01 to 59.96)		
Common serotype 9V	4.31 (3.68 to 5.04)	7.39 (6.05 to 9.03)		
Common serotype 14	17.47 (12.76 to 23.93)	22.78 (15.75 to 32.96)		
Common serotype 18C	2.76 (2.15 to 3.56)	4.83 (3.48 to 6.71)		
Common serotype 19F	9.78 (7.45 to 12.83)	11.6 (8.46 to 15.92)		
Common serotype 23F	7.89 (6.18 to 10.07)	12.25 (8.92 to 16.81)		
Additional serotype 1	5.28 (4.22 to 6.61)	19.43 (13.77 to 27.41)		
Additional serotype 3	3.28 (2.44 to 4.41)	2.87 (2.19 to 3.76)		
Additional serotype 5	5.75 (4.64 to 7.12)	15.98 (11.99 to 21.3)		
Additional serotype 6A	11.16 (8.8 to 14.16)	14.07 (10.64 to 18.61)		
Additional serotype 7F	7.13 (5.67 to 8.96)	8.05 (5.94 to 10.91)		
Additional serotype 19A	14.62 (11.49 to 18.59)	17.07 (12.92 to 22.55)		

Notes:

[9] - N=number of subjects with a determinate antibody concentration to the specified serotype.

[10] - N=number of subjects with a determinate antibody concentration to the specified serotype.

Statistical analyses

Statistical analysis title	Common Serotype 4
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Statistical analysis description:

Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.55

Statistical analysis title	Common Serotype 6B
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Statistical analysis description:

Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.15

Statistical analysis title	Common Serotype 9V
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Statistical analysis description:

Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.75

Statistical analysis title	Common Serotype 14
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Statistical analysis description:

Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.24

Statistical analysis title	Common Serotype 18C
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Statistical analysis description:

Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.85

Statistical analysis title	Common Serotype 19F
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Statistical analysis description:

Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.27

Statistical analysis title	Common Serotype 23F
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Statistical analysis description:

Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.95

Statistical analysis title	Additional Serotype 1
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Statistical analysis description:

Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.4

Statistical analysis title	Additional Serotype 3
Statistical analysis description: Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/PCV/13vPnC v PCV/23vPS/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.72

Statistical analysis title	Additional Serotype 5
Statistical analysis description: Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.51

Statistical analysis title	Additional Serotype 6A
Statistical analysis description: Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).	
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.14

Statistical analysis title	Additional Serotype 7F
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Statistical analysis description:

Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/PCV/13vPnC v PCV/23vPS/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.28

Statistical analysis title	Additional Serotype 19A
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Statistical analysis description:

Ratio of GMCs (PCV/23vPS/13vPnC, PCV/PCV/13vPnC). CIs for the ratio were back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV/23vPS/13vPnC, PCV/PCV/13vPnC).

Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Ratio of GMCs
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.23

Other pre-specified: Percentage of Subjects Reporting Prespecified Local Reactions Within 4 Days of Vaccination

End point title	Percentage of Subjects Reporting Prespecified Local Reactions Within 4 Days of Vaccination
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End point description:

Local reactions were reported by the parent/legal guardian using a diary card. Tenderness was scaled as Any (tenderness present); Significant (present and interfered with limb movement). Redness and swelling were scaled as Any (redness or swelling present); Mild (0.5 centimeters [cm] to 2.0 cm); Moderate (2.5 to 7.0 cm); Severe (greater than [$>$] 7.0 cm). Subjects may have been represented in more than 1 category. Safety population, included all subjects who received at least 1 dose of the study vaccine; n=number of subjects reporting the specific characteristic.

End point type	Other pre-specified
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End point timeframe:

Day 1 through Day 4

End point values	PCV/23vPS/13vPnC	PCV/PCV/13vPnC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50 ^[11]	39 ^[12]		
Units: percentage of subjects				
number (not applicable)				
Tenderness: Any (n=44, 30)	88	76.9		
Tenderness: Significant (n=6, 8)	12	20.5		
Redness: Any (n=25, 26)	50	66.7		
Redness: Mild (n=5, 6)	10	15.8		
Redness: Moderate (n=20, 20)	40	52.6		
Redness: Severe (n=5, 8)	10	21.1		
Swelling: Any (n=22, 23)	44	59		
Swelling: Mild (n=8, 10)	16.3	26.3		
Swelling: Moderate (n=14, 17)	28.6	44.7		
Swelling: Severe (n=1, 3)	2	7.9		

Notes:

[11] - N=number of subjects reporting yes for at least 1 day or no for all days.

[12] - N=number of subjects reporting yes for at least 1 day or no for all days.

Statistical analyses

Statistical analysis title	Comparing Any Tenderness
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.253
Method	Fisher exact

Statistical analysis title	Comparing Significant Tenderness
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.38
Method	Fisher exact

Statistical analysis title	Comparing Any Redness
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.135
Method	Fisher exact

Statistical analysis title	Comparing Mild Redness
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.52
Method	Fisher exact

Statistical analysis title	Comparing Moderate Redness
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.283
Method	Fisher exact

Statistical analysis title	Comparing Severe Redness
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.225
Method	Fisher exact

Statistical analysis title	Comparing Any Swelling
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.202
Method	Fisher exact

Statistical analysis title	Comparing Mild Swelling
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.294
Method	Fisher exact

Statistical analysis title	Comparing Moderate Swelling
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.175
Method	Fisher exact

Statistical analysis title	Comparing Severe Swelling
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.314
Method	Fisher exact

Other pre-specified: Percentage of Subjects Reporting Prespecified Systemic Reactions Within 4 Days of Vaccination

End point title	Percentage of Subjects Reporting Prespecified Systemic Reactions Within 4 Days of Vaccination
End point description: Pre-specified systemic events (any fever 38 degrees Celsius [C], decreased appetite, irritability, increased sleep, and decreased sleep) were reported using a diary card. Subjects may have been represented in more than 1 category. Safety population; n=number of subjects reporting the specific characteristic	
End point type	Other pre-specified

End point timeframe:

Day 1 through Day 4

End point values	PCV/23vPS/13vPnC	PCV/PCV/13vPnC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50 ^[13]	39 ^[14]		
Units: percentage of subjects				
number (not applicable)				
Fever \geq 38 degrees C but \leq 39 degrees C (n=1, 1)	2	2.8		
Decreased appetite (n=6, 4)	12.2	10.3		
Irritability (n=9, 4)	18.4	11.4		
Increased sleep (n=2, 5)	4	12.8		
Decreased sleep (n=0, 2)	0	5.1		
Rash (n=3, 1)	6	2.6		

Notes:

[13] - N=number of subjects reporting yes for at least 1 day or no for all days.

[14] - N=number of subjects reporting yes for at least 1 day or no for all days.

Statistical analyses

Statistical analysis title	Comparing: Fever \geq 38 Degrees C But \leq 39 Degrees C
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	> 0.99
Method	Fisher exact

Statistical analysis title	Comparing Decreased Appetite
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	> 0.99
Method	Fisher exact

Statistical analysis title	Comparing Irritability
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.543
Method	Fisher exact

Statistical analysis title	Comparing Increased Sleep
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.233
Method	Fisher exact

Statistical analysis title	Comparing Decreased Sleep
Comparison groups	PCV/23vPS/13vPnC v PCV/PCV/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.198
Method	Fisher exact

Statistical analysis title	Comparing Rash
Comparison groups	PCV/PCV/13vPnC v PCV/23vPS/13vPnC
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.628
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline through 1 Month after last study vaccination (28 Days). Local reactions and systemic events assessed within 4 days of dose (Day 1 through Day 4)

Adverse event reporting additional description:

Same event may appear as both an adverse event (AE) and a serious adverse event (SAE). However, what is presented are distinct events. An event may be categorized as serious in one subject, as non-serious in another subject, or one subject may have experienced both the events. Version was not captured, here 0.0 is mentioned for dictionary version.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	0.0
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Reporting groups

Reporting group title	PCV/23vPS/13vPnC
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Reporting group description:

For this study, subjects received a single dose of 13vPnC. Subjects previously must have also received an infant series of 9V-MnCC also known as PCV followed by a toddler dose of 23vPS. Other AEs (non-serious events): the number affected (N) for nonsystematic (unsolicited) Other AEs N=8; systematic (solicited) Local Reactions N=44; systematic (solicited) Systemic Events N=9. Subjects affected and occurrences for Local Reactions (LRs) and Systemic Events (SEs) is same as data collected through e-diaries cannot be used to distinguish one occurrence from another within a subject/vaccination.

Reporting group title	PCV/PCV/13vPnC
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Reporting group description:

For this study, subjects received a single dose of 13vPnC. Subjects must have also previously received 9V-MnCC followed by a toddler dose of 9V-MnCC (also referred to as PCV). Other AEs (non-serious events): the number affected (N) for nonsystematic (unsolicited) Other Adverse Events N=7; systematic (solicited) Local Reactions N=30; systematic (solicited) Systemic Events N=5. Subjects affected and occurrences for LR and SEs is same as data collected through e-diaries cannot be used to distinguish one occurrence from another within a subject/vaccination.

Serious adverse events	PCV/23vPS/13vPnC	PCV/PCV/13vPnC	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	0 / 39 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	PCV/23vPS/13vPnC	PCV/PCV/13vPnC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 50 (88.00%)	30 / 39 (76.92%)	
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	1 / 39 (2.56%) 1	
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 39 (0.00%) 0	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Fever $\geq 38^{\circ}\text{C}$ but $\leq 39^{\circ}\text{C}$ alternative assessment type: Systematic subjects affected / exposed ^[1] occurrences (all) Decreased appetite alternative assessment type: Systematic subjects affected / exposed ^[2] occurrences (all) Irritability alternative assessment type: Systematic subjects affected / exposed ^[3] occurrences (all) Increased sleep alternative assessment type: Systematic subjects affected / exposed occurrences (all) Decreased sleep alternative assessment type: Systematic subjects affected / exposed ^[4] occurrences (all) Rash alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1 1 / 49 (2.04%) 1 6 / 49 (12.24%) 6 9 / 49 (18.37%) 9 2 / 50 (4.00%) 2 0 / 48 (0.00%) 0 3 / 50 (6.00%) 3	0 / 39 (0.00%) 0 1 / 36 (2.78%) 1 4 / 39 (10.26%) 4 4 / 35 (11.43%) 4 5 / 39 (12.82%) 5 2 / 39 (5.13%) 2 1 / 39 (2.56%) 1	

Tenderness (Any)		
alternative assessment type: Systematic		
subjects affected / exposed	44 / 50 (88.00%)	30 / 39 (76.92%)
occurrences (all)	44	30
Tenderness (Significant)		
alternative assessment type: Systematic		
subjects affected / exposed	6 / 50 (12.00%)	8 / 39 (20.51%)
occurrences (all)	6	8
Redness (Any)		
alternative assessment type: Systematic		
subjects affected / exposed	25 / 50 (50.00%)	26 / 39 (66.67%)
occurrences (all)	25	26
Redness (Mild)		
alternative assessment type: Systematic		
subjects affected / exposed ^[5]	5 / 50 (10.00%)	6 / 38 (15.79%)
occurrences (all)	5	6
Redness (Moderate)		
alternative assessment type: Systematic		
subjects affected / exposed ^[6]	20 / 50 (40.00%)	20 / 38 (52.63%)
occurrences (all)	20	20
Redness (Severe)		
alternative assessment type: Systematic		
subjects affected / exposed ^[7]	5 / 50 (10.00%)	8 / 38 (21.05%)
occurrences (all)	5	8
Swelling (Any)		
alternative assessment type: Systematic		
subjects affected / exposed	22 / 50 (44.00%)	23 / 39 (58.97%)
occurrences (all)	22	23
Swelling (Mild)		
alternative assessment type: Systematic		
subjects affected / exposed ^[8]	8 / 49 (16.33%)	10 / 38 (26.32%)
occurrences (all)	8	10
Swelling (Moderate)		
alternative assessment type: Systematic		

subjects affected / exposed ^[9] occurrences (all)	14 / 49 (28.57%) 14	17 / 38 (44.74%) 17	
Swelling (Severe) subjects affected / exposed ^[10] occurrences (all)	1 / 49 (2.04%) 1	3 / 38 (7.89%) 3	
Gastrointestinal disorders			
Vomiting subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2	1 / 39 (2.56%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2	0 / 39 (0.00%) 0	
Abdominal pain subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 39 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	1 / 39 (2.56%) 1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 39 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Urticaria subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 2	0 / 39 (0.00%) 0	
Infections and infestations			
Viral infection subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	3 / 39 (7.69%) 5	
Influenza subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	1 / 39 (2.56%) 1	
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	1 / 39 (2.56%) 1	

Pharyngitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Here number of subjects exposed signifies subjects reporting yes for at least 1 day or no for all days.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Here number of subjects exposed signifies subjects reporting yes for at least 1 day or no for all days.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Here number of subjects exposed signifies subjects reporting yes for at least 1 day or no for all days.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Here number of subjects exposed signifies subjects reporting yes for at least 1 day or no for all days.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Here number of subjects exposed signifies subjects reporting yes for at least 1 day or no for all days.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Here number of subjects exposed signifies subjects reporting yes for at least 1 day or no for all days.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Here number of subjects exposed signifies subjects reporting yes for at least 1 day or no for all days.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Here number of subjects exposed signifies subjects reporting yes for at least 1 day or no for all days.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Here number of subjects exposed signifies subjects reporting yes for at least 1 day or no for all days.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Here number of subjects exposed signifies subjects reporting yes for at least 1 day or no for all days.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2009	Minor clarification was made to temporary delay criterion, as recommended by the Icelandic Medicines Control Agency, to clarify timing of antibiotic therapy and treatment with oral steroid agents.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In protocol, primary analysis was based on all available immunogenicity population and later modified to evaluable immunogenicity population in Statistical Analysis Plan based on subsequent similar studies and suitability for primary objective.

Notes: