Clinical trial results:
A phase 3 open-label study to evaluate the immunogenicity and safety of a mixed (HEXA/PENTA/HEXA) primary series schedule that includes V419 (PR5I) at 2 and 6 months of age and Pediacel® at 4 months of age.

Summary

EudraCT number	2012-004221-25
Trial protocol	ES
Global end of trial date	27 October 2014

Results information

Result version number	v1
This version publication date	27 April 2016
First version publication date	27 May 2015

Trial information

Trial identification

Sponsor protocol code	PRI02C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01839188
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur MSD S.N.C.
Sponsor organisation address	162 avenue Jean Jaurès - CS 50712, Lyon Cedex 07, France, 69367
Public contact	Clinical Trials Disclosure, Sanofi Pasteur MSD S.N.C., ClinicalTrialsDisclosure@spmsd.com
Scientific contact	Clinical Trials Disclosure, Sanofi Pasteur MSD S.N.C., ClinicalTrialsDisclosure@spmsd.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	27 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the mixed schedule induced acceptable responses for Hepatitis B (% of subjects with an anti-HBs titre ≥10 mIU/mL) 1 month after the third dose of the mixed schedule (i.e. at Month 7).
To demonstrate that the mixed schedule induced acceptable responses for Haemophilus influenzae b (Hib) (% of subjects with an anti-polyribosylribitol phosphate [PRP] titre ≥0.15 µg/mL) 1 month after the third dose of the mixed schedule (i.e. at Month 7).

Protection of trial subjects:

Subjects in the study received the study vaccines (PR5I and Pediacel®) in line with the recommended infant immunisation schedule in Spain, and the immunisation schedule was consistent with other paediatric vaccines routinely given at the same age. NeisVac-C®, Prevenar 13®, and RotaTeq® were administered in accordance with their respective Summary of Product Characteristics.
Subjects with allergy to any of the vaccine components or history of a life-threatening reaction to a vaccine containing the same substances as the study vaccines (including concomitants) were not vaccinated.
Vaccines were administered by qualified study personnel.
After each vaccination, subjects were kept under observation for 30 minutes to ensure their safety.
Adequate treatment provisions, including epinephrine, were available for immediate use, should an anaphylactic or anaphylactoid reaction occurred.

Background therapy:

Infants were previously vaccinated with only 1 dose of monovalent Hepatitis B vaccine, within the 3 days after birth, outside of the study context.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	01 May 2013
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	Spain: 385
Worldwide total number of subjects	385
EEA total number of subjects	385

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)	385
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 in 12 active sites in Spain. Enrolment started on 01 May 2013.

Pre-assignment

Screening details:

Overall, 16 investigational sites were evaluated and considered eligible to screen subjects for study participation. Of these 16 sites, 12 screened 385 subjects in total. Of the 385 screened subjects, 100% were enrolled and vaccinated.

Period 1

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

Arms

Arm title	All subjects

Arm description:

Subjects received:
At 2 months of age, 1 dose of PR5I (DTaP-HB-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) + 1 dose of NeisVac-C (MCC = Meningococcal group C polysaccharide Conjugate vaccine adsorbed) + 1 dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by intramuscular route (IM) + 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) by oral route.
At 4 months of age, 1 dose of Pediacel (DTaP-IPV-Hib) + 1 dose of NeisVac-C (MCC) + 1 dose of Prevenar 13 (PCV-13) by IM route + 1 dose of RotaTeq by oral route.
At 6 months of age, 1 dose of PR5I (DTaP-HB-IPV-Hib) by IM route + 1 dose of RotaTeq by oral route.

Arm type	Experimental
Investigational medicinal product name	PR5I vaccine
Investigational medicinal product code	DTaP-HB-IPV-Hib
Other name	V419
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (left upper thigh), one dose at 2 and 6 months of age.

Investigational medicinal product name	Pediacel®
Investigational medicinal product code	DTaP-IPV-Hib
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (left upper thigh), one dose at 4 months of age.

Investigational medicinal product name	NeisVac-C®
Investigational medicinal product code	MCC
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (right upper thigh), one dose at 2 and 4 months of age.
NeisVac-C and Prevenar 13 were both administered in the right upper thigh, provided that the injections were separated by at least 5 cm.

Investigational medicinal product name	Prevenar 13®
Investigational medicinal product code	PCV-13
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (right upper thigh), one dose at 4 months of age.
NeisVac-C and Prevenar 13 were both administered in the right upper thigh, provided that the injections were separated by at least 5 cm.

Investigational medicinal product name	RotaTeq®
Investigational medicinal product code	RotaTeq
Other name	
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

2 mL, oral route, one dose at 2 and 6 months of age.
RotaTeq was administered orally, prior to any other vaccine administration to avoid the subject to spit up RotaTeq when crying.

Number of subjects in period 1	All subjects
Started	385
Completed	384
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description:

Subjects received:
At 2 months of age, 1 dose of PR5I (DTaP-HB-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) + 1 dose of NeisVac-C (MCC = Meningococcal group C polysaccharide Conjugate vaccine adsorbed) + 1 dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by intramuscular route (IM) + 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) by oral route.
At 4 months of age, 1 dose of Pediacel (DTaP-IPV-Hib) + 1 dose of NeisVac-C (MCC) + 1 dose of Prevenar 13 (PCV-13) by IM route + 1 dose of RotaTeq by oral route.
At 6 months of age, 1 dose of PR5I (DTaP-HB-IPV-Hib) by IM route + 1 dose of RotaTeq by oral route.

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	385	385	
Age categorical			
Vaccinated set, N=385			
Units: Subjects			
Infants and toddlers (28 days-23 months)	385	385	
Age continuous			
Vaccinated set, N=385			
Units: days			
arithmetic mean	60.72		
standard deviation	± 7.75	-	
Gender categorical			
Vaccinated set, N=385			
Units: Subjects			
Female	199	199	
Male	186	186	
Weight continuous			
Weight in kg at vaccination Vaccinated set, N=385			
Units: kg			
arithmetic mean	5.14		
standard deviation	± 0.59	-	

End points

End points reporting groups

Reporting group title	All subjects

Reporting group description:

Subjects received:
At 2 months of age, 1 dose of PR5I (DTaP-HB-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) + 1 dose of NeisVac-C (MCC = Meningococcal group C polysaccharide Conjugate vaccine adsorbed) + 1 dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by intramuscular route (IM) + 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) by oral route.
At 4 months of age, 1 dose of Pediacel (DTaP-IPV-Hib) + 1 dose of NeisVac-C (MCC) + 1 dose of Prevenar 13 (PCV-13) by IM route + 1 dose of RotaTeq by oral route.
At 6 months of age, 1 dose of PR5I (DTaP-HB-IPV-Hib) by IM route + 1 dose of RotaTeq by oral route.

Primary: Proportion of subjects with anti-HBs titre ≥10 mIU/mL one month after the third dose of the mixed schedule (i.e. at Month 7)

End point title	Proportion of subjects with anti-HBs titre ≥10 mIU/mL one month after the third dose of the mixed schedule (i.e. at Month 7)[1]

End point description:

Percentage of subjects with an anti-Hepatitis B (HBs) titre ≥10 mIU/mL (measured by Hepatitis B enhanced chemiluminescence assay), one month after the third dose of the mixed schedule.
Analysis was done on the PR5I-Per Protocol set (PR5I-PPS).
The immune response to PR5I vaccine was considered as acceptable if the lower bound of the two-sided 95% CI of the percentage of subjects with anti-HBs titre ≥10 mIU/mL one month after the third dose of the mixed schedule was greater than 90%.
The success of the study required that the primary objective was achieved for both Hepatitis B and PRP.
Note: (N= ***) represents the number of assessed subjects.

End point type	Primary

End point timeframe:

One month after the third dose of the mixed schedule (i.e. at Month 7).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm study, subjects were all enrolled in the same treatment group.
The success of the study required that the primary objective was achieved for both Hepatitis B and PRP.
For Hepatitis B, the immune response to PR5I vaccine was considered as acceptable if the lower bound of the 2-sided 95% CI of the % of subjects with anti-HBs titre ≥10 mIU/mL one month after the third dose of the mixed schedule was greater than 90%. The lower bound was 97.2%.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	370[2]			
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-HBs titre≥10 mIU/mL (N=369)	98.9 (97.2 to 99.7)			

Notes:

[2] - PR5I-PPS

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of subjects with anti-Hib titre ≥0.15 µg/mL one month after the third dose of the mixed schedule (i.e. at Month 7)

End point title	Proportion of subjects with anti-Hib titre ≥0.15 µg/mL one month after the third dose of the mixed schedule (i.e. at Month 7)[3]

End point description:

Percentage of subjects with an anti-polyribosylribitol phosphate (PRP) titre ≥0.15 µg/mL for Haemophilus influenzae type b (Hib), one month after the third dose of the mixed schedule. Anti-PRP titres were measured by radioimmunoassay (RIA).
Analysis was done on the PR5I-Per Protocol set (PR5I-PPS).
The immune response to PR5I vaccine was considered as acceptable if the lower bound of the two-sided 95% CI of the percentage of subjects with anti-PRP titre ≥0.15 µg/mL one month after the third dose of the mixed schedule was greater than 80%.
The success of the study required that the primary objective was achieved for both Hepatitis B and PRP.
Note: (N= ***) represents the number of assessed subjects.

End point type	Primary

End point timeframe:

One month after the third dose of the mixed schedule (i.e. at Month 7).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm study, subjects were all enrolled in the same treatment group.
The success of the study required that the primary objective was achieved for both Hepatitis B and PRP. For Hib (PRP), the immune response to PR5I vaccine was considered as acceptable if the lower bound of the 2-sided 95% CI of the % of subjects with anti-PRP titre ≥0.15 µg/mL one month after the third dose of the mixed schedule was greater than 80%. The lower bound was 99%.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	370[4]			
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PRP titre ≥0.15 µg/mL (N= 365)	100 (99 to 100)			

Notes:

[4] - PR5I-PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titres or Concentrations of all PR5I vaccine antigens one month after the third dose of the mixed schedule (i.e. at Month 7)

End point title	Geometric Mean Titres or Concentrations of all PR5I vaccine antigens one month after the third dose of the mixed schedule (i.e. at Month 7)

End point description:

Antibody titres or concentrations were measured for Hepatitis B (HBs) by enhanced chemiluminescence assay (mIU/mL), for Haemophilus influenzae type b (Hib, anti-PRP antibodies) by radioimmunoassay (RIA) (µg/mL), for diphtheria (D) by Metabolic Inhibition Test (MIT) (IU/mL), for tetanus (T) by Enzyme-Linked Immunosorbent Assay (ELISA) (IU/mL), for inactivated poliovirus types 1, 2 & 3 (IPV1, IPV2 & IPV3) by MIT (1/dil), and for pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN) and fimbriae types (FIM) 2&3 by ELISA (EU/mL).
Analysis was done on the PR5I-Per Protocol set (PR5I-PPS).
Note: (N=***) represents the number of assessed subjects.

End point type	Secondary

End point timeframe:

One month after the third dose of the mixed schedule (i.e. at Month 7): one dose of PR5I at Month 2, one dose of Pediacel at Month 4, and one dose of PR5I at Month 6.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Titres or Concentrations				
geometric mean (confidence interval 95%)				
Anti-HBs (N=369)	1054.97 (911.49 to 1221.03)			
Anti-PRP (N=365)	8 (7.17 to 8.93)			
Anti-D (N=359)	0.47 (0.42 to 0.52)			
Anti-T (N=350)	2.44 (2.31 to 2.59)			
Anti-IPV1 (N=356)	663.97 (588.1 to 749.62)			
Anti-IPV2 (N=356)	1198.93 (1051.9 to 1366.51)			
Anti-IPV3 (N=356)	764.64 (664.7 to 879.61)			
Anti-PT (N=349)	107.46 (101.55 to 113.71)			
Anti-FHA (N=349)	67.09 (62.38 to 72.15)			
Anti-PRN (N=349)	56.46 (51.6 to 61.78)			
Anti-FIM 2&3 (N=349)	360.99 (332.58 to 391.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rates for Haemophilus influenzae type b, diphtheria, tetanus, pertussis, and inactivated poliovirus types 1, 2 & 3 one month after the third dose of the mixed schedule (i.e. at Month 7)

End point title	Response rates for Haemophilus influenzae type b, diphtheria, tetanus, pertussis, and inactivated poliovirus types 1, 2 & 3 one month after the third dose of the mixed schedule (i.e. at Month 7)

End point description:

Percentages of subjects with anti-PRP titre ≥1 µg/mL (measured by radioimmunoassay (RIA)) for Hib, anti-D concentration ≥0.01 IU/mL and anti-D concentration ≥0.10 IU/mL (measured by Metabolic Inhibition Test (MIT)) for diphtheria, anti-T concentration ≥0.01 IU/mL and anti-T concentration ≥0.10

IU/mL (measured by Enzyme-Linked Immunosorbent Assay (ELISA)) for tetanus, anti-IPV titre ≥8 (1/dil) (measured by MIT) for inactivated poliovirus types 1, 2 & 3 (IPV1, IPV2 & IPV3), one month after the third dose of the mixed schedule.
Analysis was done on the PR5I-Per Protocol set (PR5I-PPS).
Note: (N=***) represents the number of assessed subjects.

End point type	Secondary

End point timeframe:

One month after the third dose of the mixed schedule (i.e. at Month 7): one dose of PR5I at Month 2, one dose of Pediacel at Month 4, and one dose of PR5I at Month 6.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	370			
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PRP ≥1 µg/mL (N=365)	95.3 (92.6 to 97.3)			
Anti-D ≥0.01 IU/mL (N=359)	100 (99 to 100)			
Anti-D ≥0.10 IU/mL (N=359)	92.2 (88.9 to 94.8)			
Anti-T ≥0.01 IU/mL (N=350)	100 (99 to 100)			
Anti-T ≥0.10 IU/mL (N=350)	100 (99 to 100)			
Anti-IPV1 ≥8 (1/dil) (N=356)	100 (99 to 100)			
Anti-IPV2 ≥8 (1/dil) (N=356)	100 (99 to 100)			
Anti-IPV3 ≥8 (1/dil) (N=356)	100 (99 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate for Meningococcal group C polysaccharide Conjugate (MCC) one month after the second dose of MCC vaccine (i.e. at Month 5)

End point title	Response rate for Meningococcal group C polysaccharide Conjugate (MCC) one month after the second dose of MCC vaccine (i.e. at Month 5)

End point description:

Percentages of subjects with anti-MCC titre ≥8 (1/dil) measured by Serum Bactericidal Antibody with rabbit complement Assay (rBSA) for Meningococcal serogroup C Conjugate (MCC), one month after the second dose of MCC vaccine (i.e. at Month 5), when used concomitantly with the mixed schedule.
Analysis was done on the MCC-Per Protocol set (MCC-PPS).
Note: (N=***) represents the number of assessed subjects.

End point type	Secondary

End point timeframe:

One month after the second dose of MCC vaccine (i.e. at Month 5) when used concomitantly with the mixed schedule: one dose of MCC at Month 2 and one dose of MCC at Month 4.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	375			
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-MCC ≥8 (1/dil) (N=375)	99.2 (97.7 to 99.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titre of MCC one month after the second dose of MCC vaccine (i.e. at Month 5)

End point title	Geometric Mean Titre of MCC one month after the second dose of MCC vaccine (i.e. at Month 5)

End point description:

Antibody titres were measured for Meningococcal group C polysaccharide Conjugate (MCC) by Serum Bactericidal Antibody with rabbit complement Assay (rBSA) (1/dil).
Analysis was done on the MCC-Per Protocol set (MCC-PPS).
Note: (N=***) represents the number of assessed subjects.

End point type	Secondary

End point timeframe:

One month after the second dose of MCC vaccine (i.e. at Month 5) when used concomitantly with the mixed schedule: one dose of MCC at Month 2 and one dose of MCC at Month 4.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	375			
Units: Titre				
geometric mean (confidence interval 95%)				
Anti-MCC (N=375)	739.63 (659.94 to 828.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with at least one body temperature ≥38.0°C from

Day 1 to Day 5 after each vaccination

End point title	Proportion of subjects with at least one body temperature ≥38.0°C from Day 1 to Day 5 after each vaccination

End point description:

The subject's parent(s)/legal representative recorded all adverse events (AEs). As per protocol instructions, axillary route was used for daily temperature measurement, in the evening, in most of the subjects (rectal route was used in 3 subjects, and oral route in 1 subject).
Temperatures were based on actual temperatures recorded with no adjustements to the route of assessment. The % of subjects with at least one body temperature ≥38.0°C from Day 1 to Day 5 after each vaccination was calculated.
Four Safety sets (SS) were defined in this study: SS1 after vaccination 1 (Month 2), SS2 after vaccination 2 (Month 4), SS3 after vaccination 3 (Month 6) and overall (all subjects who received at least 1 dose of 1 study vaccine, with any safety follow-up).
% are based on the number of subjects with available temperature data within the 5 days following each vaccination.
Note: (N=***) represents the number of subjects with available temperature.

End point type	Secondary

End point timeframe:

Day 1 to Day 5 after each vaccination (V): V1 (PR5I + MCC + Prevenar 13 + RotaTeq), V2 (Pediacel + MCC + Prevenar 13 + RotaTeq) & V3 (PR5I + RotaTeq), respectively administered at 2, 4 and 6 months of age, and after any vaccination.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	385[5]			
Units: Percentage of subjects				
number (not applicable)				
Vaccination 1 (N=384)	4.9			
Vaccination 2 (N=383)	6.3			
Vaccination 3 (N=383)	4.7			

Notes:

[5] - Subjects with at least 1 dose of 1 study vaccine

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of solicited Injection-Site Reactions related to PR5I or Pediacel from Day 1 to Day 5 after any vaccination and after each vaccination

End point title	Incidence of solicited Injection-Site Reactions related to PR5I or Pediacel from Day 1 to Day 5 after any vaccination and after each vaccination

End point description:

The subject's parent(s)/legal representative recorded all adverse events (AEs) on the vaccine report card (VRC).
AEs at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Solicited ISRs (erythema, pain and swelling that occurred from Day 1 to Day 5 following PRI5 or Pediacel vaccination) were presented after each vaccination and after any vaccination.
Four Safety sets (SS) were defined in this study: SS1 after vaccination 1 (at Month 2), SS2 after vaccination 2 (at Month 4), SS3 after vaccination 3 (at Month 6) and Global SS (all subjects who received at least 1 dose of 1 study vaccine, with any safety data).
Analysis was done on the Safety sets.

End point type	Secondary

End point timeframe:

Day 1 to Day 5 after each vaccination (V): V1 (PR5I + MCC + Prevenar 13 + RotaTeq), V2 (Pediacel + MCC + Prevenar 13 + RotaTeq) & V3 (PR5I + RotaTeq), respectively administered at 2, 4 and 6 months of age, and after any vaccination.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	385[6]			
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 ISR (vaccination 1) (N=385)	50.6 (45.5 to 55.8)			
Injection-site erythema (vaccination 1) (N=385)	21 (17.1 to 25.5)			
Injection-site pain (vaccination 1) (N=385)	39.5 (34.6 to 44.6)			
Injection-site swelling (vaccination 1) (N=385)	17.7 (14 to 21.8)			
At least 1 ISR (vaccination 2) (N=385)	36.6 (31.8 to 41.7)			
Injection-site erythema (vaccination 2) (N=385)	16.9 (13.3 to 21)			
Injection-site pain (vaccination 2) (N=385)	25.2 (20.9 to 29.8)			
Injection-site swelling (vaccination 2) (N=385)	13.5 (10.3 to 17.3)			
At least 1 ISR (vaccination 3) (N=384)	39.1 (34.2 to 44.1)			
Injection-site erythema (vaccination 3) (N=384)	18 (14.3 to 22.2)			
Injection-site pain (vaccination 3) (N=384)	24.2 (20 to 28.8)			
Injection-site swelling (vaccination 3) (N=384)	16.9 (13.3 to 21.1)			
At least 1 ISR (any vaccination) (N=385)	68.6 (63.7 to 73.2)			
Injection-site erythema (any vaccination) (N=385)	35.3 (30.5 to 40.3)			
Injection-site pain (any vaccination) (N=385)	51.9 (46.8 to 57)			
Injection-site swelling (any vaccination) (N=385)	31.4 (26.8 to 36.3)			

Notes:

[6] - All subjects who received at least 1 dose of 1 study vaccine

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of solicited Injection-Site Reactions related to MCC from Day 1 to Day 5 after any vaccination and after each vaccination

End point title	Incidence of solicited Injection-Site Reactions related to MCC from Day 1 to Day 5 after any vaccination and after each vaccination

End point description:

The subject's parent(s)/legal representative recorded all adverse events (AEs) on the vaccine report card (VRC).
Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Solicited Injection-Site Reactions (ISRs) (erythema, pain and swelling that were collected from Day 1 to Day 5 following each vaccination with MCC) are presented after each vaccination and following any vaccination.
Four Safety sets (SS) were defined in this study: SS1 after vaccination 1 (at Month 2), SS2 after vaccination 2 (at Month 4), SS3 after vaccination 3 (at Month 6) and Global SS (all subjects who received at least 1 dose of 1 study vaccine, with any safety follow-up).
Analysis was done on the Safety sets.

End point type	Secondary

End point timeframe:

Day 1 to Day 5 after vaccination 1 (PR5I +, MCC + Prevenar 13 + RotaTeq) & vaccination 2 (Pediacel+ MCC + Prevenar 13 + RotaTeq), respectively administered at 2 and 4 months of age, and after any vaccination.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	385[7]			
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 ISR (vaccination 1) (N=385)	35.1 (30.3 to 40.1)			
Injection-site erythema (vaccination 1) (N=385)	10.6 (7.8 to 14.2)			
Injection-site pain (vaccination 1) (N=385)	29.4 (24.8 to 34.2)			
Injection-site swelling (vaccination 1) (N=385)	8.8 (6.2 to 12.1)			
At least 1 ISR (vaccination 2) (N=385)	34.3 (29.6 to 39.3)			
Injection-site erythema (vaccination 2) (N=385)	15.3 (11.9 to 19.3)			
Injection-site pain (vaccination 2) (N=385)	23.1 (19 to 27.7)			
Injection-site swelling (vaccination 2) (N=385)	10.9 (8 to 14.5)			
At least 1 ISR (any vaccination) (N=385)	50.6 (45.5 to 55.8)			
Injection-site erythema (any vaccination) (N=385)	22.1 (18 to 26.6)			
Injection-site pain (any vaccination) (N=385)	39.2 (34.3 to 44.3)			
Injection-site swelling (any vaccination) (N=385)	17.1 (13.5 to 21.3)			

Notes:

[7] - All subjects who received at least 1 dose of 1 study vaccine

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of solicited systemic AEs (crying, decreased appetite,

irritability, somnolence and vomiting) from Day 1 to Day 5 after each vaccination and after any vaccination

End point title	Incidence of solicited systemic AEs (crying, decreased appetite, irritability, somnolence and vomiting) from Day 1 to Day 5 after each vaccination and after any vaccination

End point description:

The subject's parent(s)/legal representative recorded all adverse events (AEs) on the vaccine report card (VRC).
Solicited systemic AEs (crying, decreased appetite, irritability, somnolence, pyrexia, and vomiting that occurred from Day 1 to Day 5) were collected daily. The investigator had to assess whether these systemic AEs were related or not to the vaccine. All (related and unrelated) are displayed here.
Temperature ≥38°C (fever or pyrexia) are presented in a specific endpoint.
Four Safety sets (SS) were defined in this study: SS1 after vaccination 1 (at Month 2), SS2 after vaccination 2 (at Month 4), SS3 after vaccination 3 (at Month 6) and Global SS (all subjects who received at least 1 dose of 1 study vaccine, with any safety follow-up).
Analysis was done on the Safety sets.

End point type	Secondary

End point timeframe:

Day 1 to Day 5 after each vaccination (V): V1 (PR5I + MCC + Prevenar 13 + RotaTeq), V2 (Pediacel + MCC + Prevenar 13 + RotaTeq) & V3 (PR5I + RotaTeq), respectively administered at 2, 4 and 6 months of age, and after any vaccination.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	385[8]			
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 solicited syst. AE (vacc. 1) (N=385)	75.1 (70.4 to 79.3)			
Crying (vaccination 1) (N=385)	48.8 (43.7 to 53.9)			
Decreased appetite (vaccination 1) (N=385)	36.6 (31.8 to 41.7)			
Irritability (vaccination 1) (N=385)	50.9 (45.8 to 56)			
Somnolence (vaccination 1) (N=385)	47.8 (42.7 to 52.9)			
Vomiting (vaccination 1) (N=385)	14.5 (11.2 to 18.5)			
At least 1 solicited syst. AE (vacc. 2) (N=385)	60.5 (55.4 to 65.4)			
Crying (vaccination 2) (N=385)	34 (29.3 to 39)			
Decreased appetite (vaccination 2) (N=385)	22.9 (18.8 to 27.4)			
Irritability (vaccination 2) (N=385)	40 (35.1 to 45.1)			
Somnolence (vaccination 2) (N=385)	32.7 (28.1 to 37.7)			
Vomiting (vaccination 2) (N=385)	9.1 (6.4 to 12.4)			
At least 1 solicited syst. AE (vacc. 3) (N=384)	45.8 (40.8 to 51)			
Crying (vaccination 3) (N=384)	26.6 (22.2 to 31.3)			
Decreased appetite (vaccination 3) (N=384)	19.8 (15.9 to 24.1)			

Irritability (vaccination 3) (N=384)	31 (26.4 to 35.9)			
Somnolence (vaccination 3) (N=384)	21.9 (17.8 to 26.3)			
Vomiting (vaccination 3) (N=384)	7 (4.7 to 10.1)			
At least 1 solicited syst. AE (any vacc.) (N=385)	86.8 (83 to 90)			
Crying (any vaccination) (N=385)	66.2 (61.3 to 70.9)			
Decreased appetite (any vaccination) (N=385)	50.6 (45.5 to 55.8)			
Irritability (any vaccination) (N=385)	69.6 (64.7 to 74.2)			
Somnolence (any vaccination) (N=385)	59.5 (54.4 to 64.4)			
Vomiting (any vaccination) (N=385)	22.9 (18.8 to 27.4)			

Notes:

[8] - All subjects who received at least 1 dose of 1 study vaccine

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unsolicited adverse events (AEs) were recorded daily from Day 1 to Day 15 following each vaccination. Unsolicited serious AEs (SAEs) were collected from the first vaccination to the last visit.

Adverse event reporting additional description:

Every subject was counted a single time for each applicable specific adverse event (AE).
A subject with multiple AEs within a system organ class (SOC) was counted a single time for that SOC.
For each AE, the number of occurrences from Day 1 to Day 15 was by convention equal to the number of subjects reporting the AE.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	All subjects

Reporting group description:

Subjects received # At 2 months of age, 1 dose of PR5I + 1 dose of MCC + 1 dose of PCV-13 by IM route + 1 dose of RotaTeq by oral route; # at 4 months of age, 1 dose of Pediacel + 1 dose of MCC + 1 dose of PCV-13 by IM route + 1 dose of RotaTeq by oral route; # at 6 months of age, 1 dose of PR5I by IM route + 1 dose of RotaTeq by oral route.
Numbers and % of subjects reporting at least 1 SAE and at least 1 unsolicited non-serious ISR or AE with incidence ≥2% are presented below.
12 subjects reported at least 1 SAE. If each unsolicited ISR or AE with incidence ≥2% was reported by a different subject, 128 subjects would have reported at least 1 unsolicited ISR or AE with incidence ≥2%.
Overall, 21 (5.5%) subjects reported at least 1 unsolicited ISR at PR5I or Pediacel site, and 7 (1.8%) at MCC site; 163 (42.3%) subjects reported at least 1 unsolicited non-serious systemic AE, and 15 (3.9%) at least 1 vaccine-related unsolicited non-serious systemic AE.

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 385 (3.12%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
D1-D15, Head injury	Additional description: 1 subject experienced head injury of mild intensity 3 days after vaccination 1. This serious adverse event lasted 7 days. It was assessed as not related to vaccine.		
subjects affected / exposed	1 / 385 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
D1-D15, Overdose	Additional description: 1 subject experienced overdose (administration of more than 1 dose of any individual study vaccine in any 24 hour period) on the day of vaccination 1. This serious adverse event was assessed as not related to vaccine.		

subjects affected / exposed	1 / 385 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
D1-D15, Bronchospasm	Additional description: 1 subject experienced bronchospasm of moderate intensity 9 days after vaccination 1. This serious adverse event lasted 19 days. It was assessed as not related to vaccine.		
subjects affected / exposed	1 / 385 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
D1-D15, Choking episode	Additional description: 1 subject experienced a choking episode of severe intensity 4 days after vaccination 1. This serious adverse event lasted 3 days. It was assessed as not related to vaccine.		
subjects affected / exposed	1 / 385 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Outside D1-D15 period, Sepsis	Additional description: 1 subject experienced suspected clinical sepsis without bacteriological confirmation of severe intensity 16 days after vaccination 1. This serious adverse event lasted 12 days. It was assessed as not related to vaccine.		
subjects affected / exposed	1 / 385 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Outside D1-D15 period, Bronchiolitis	Additional description: 5 subjects experienced bronchiolitis of moderate intensity, 16 to 50 days after vaccination 2 (3 subjects) or 3 (2 subjects). These serious adverse events lasted between 11 and 25 days. They were assessed as not related to vaccine.		
subjects affected / exposed	5 / 385 (1.30%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Outside D1-D15 period, Periorbital cellulitis	Additional description: 1 subject experienced preseptal cellulitis left eye of moderate intensity 19 days after vaccination 3. This serious adverse event lasted 5 days. It was assessed as not related to vaccine.		
subjects affected / exposed	1 / 385 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Outside D1-D15 period, Urinary tract infection	Additional description: 1 subject experienced urinary tract infection with fever of mild intensity 23 days after vaccination 1. This serious adverse event lasted 6 days. It was assessed as not related to vaccine.		

subjects affected / exposed	1 / 385 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	128 / 385 (33.25%)		
General disorders and administration site conditions			
Injection site induration			
subjects affected / exposed	16 / 385 (4.16%)		
occurrences (all)	16		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 385 (2.86%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	15 / 385 (3.90%)		
occurrences (all)	15		
Vomiting			
subjects affected / exposed	9 / 385 (2.34%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	9 / 385 (2.34%)		
occurrences (all)	9		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	16 / 385 (4.16%)		
occurrences (all)	16		
Conjunctivitis			
subjects affected / exposed	11 / 385 (2.86%)		
occurrences (all)	11		
Nasopharyngitis			

subjects affected / exposed	21 / 385 (5.45%)		
occurrences (all)	21		
Respiratory tract infection			
subjects affected / exposed	12 / 385 (3.12%)		
occurrences (all)	12		
Upper respiratory tract infection			
subjects affected / exposed	8 / 385 (2.08%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported