SANOFI PASTEUR

These results are supplied for informational purposes only. *Prescribing decisions should be made based on the approved package insert.*			
Name of Sponsor/ Company:	Sanofi Pasteur	**Study Code:** **Study Identifier:**	A5I19 NCT00355654
Proprietary Vaccine Name: PEDIACEL®	**Generic Vaccine Name:** Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and Haemophilus type b conjugate vaccine (adsorbed).	**Therapeutic Area and Approved Indications (Germany):** Primary and booster vaccination against diphtheria, tetanus, pertussis, poliomyelitis and invasive *Haemophilus influenzae* type b disease in infants and children from the age of 6 weeks up to the fourth birthday	
Submission Dossier:	Decentralized Procedure (UK/H/2388/01/DC)	**Dossier Location:** **Submission Date:**	Section 5.3.5.1 21 October 2009
Title of the Study:	Safety and Immunogenicity of Booster Vaccination with PEDIACEL®, a Combined Diphtheria, Tetanus, Five Component Acellular Pertussis, Inactivated Poliomyelitis and Haemophilus Influenzae Type b Conjugate Vaccine (Adsorbed), Compared to Booster Vaccination with INFANRIX® hexa when Both Vaccines Are Co-Administered with Prevenar® to Toddlers 11-18 Months of Age.		
Trial centres:	53 Clinical sites in Germany		
Publications:	None		
Study period:	Date of First enrollment: 29 September 2006 Date of Last visit: 17 September 2007		
Development phase:	Phase 3		
Primary objective:	To evaluate the safety of PEDIACEL® booster dose by comparing the fever rates between PEDIACEL® and INFANRIX® hexa vaccines when both are co-administered with Prevenar® to toddlers at 11 to 18 months of age.		
Primary Endpoint:	The primary endpoint for analysis of safety was the fever rate reported within 4 days (Day 0 to Day 3) of booster vaccination for both groups.		
Statistical methods for the primary objective	The difference in the proportion of toddlers reporting fever (defined as temperature ≥ 38.0°C) within 4 days (Day 0 to Day 3) of booster vaccination between Group A (PEDIACEL® and Prevenar®) and Group B (INFANRIX® hexa and Prevenar®), ($P_A - P_B$) and the associated two-sided 95% confidence intervals (CIs) were computed. If the upper limit of the 95% CIs for the difference in the proportion of toddlers reporting fever (defined as temperature ≥ 38.0°C) within 4 days (Day 0 to Day 3) of booster vaccination between Group A and Group B ($P_A - P_B$) was < 0.1, then PEDIACEL® was considered non-inferior to INFANRIX® hexa.		

Secondary objectives:	**Safety:** • To show whether the incidence rate of fever (defined as temperature ≥ 38.0°C) reported within 4 days of booster vaccination is lower with PEDIACEL®. • To describe the incidence rate of severe fever (defined as temperature ≥ 39.6°C) within 4 days post-vaccination. **Immunogenicity:** • To describe the antibody responses to all antigens in PEDIACEL®, INFANRIX® hexa, Prevenar® and ENGERIX®-B Kinder vaccines in a subgroup of subjects at baseline and post-vaccination.
Secondary endpoint:	**Safety Assessment:** • If non-inferiority of PEDIACEL® to INFANRIX® hexa was achieved and the upper limit of the 95% CI of the difference in the proportion of toddlers reporting fever (defined as temperature ≥ 38.0°C) within 4 days of booster vaccination between Group A and Group B ($P_A - P_B$) was < 0, then PEDIACEL® was considered superior to INFANRIX® hexa. • The incidence rate of severe fever (defined as temperature ≥ 39.6°C) reported within 4 days post-vaccination for both groups. **Immunogenicity Assessment:** • The parameters for the secondary immunogenicity endpoints were: (i). Proportion of subjects achieving seroprotective titres at 1 month (28 to 42 days) post-vaccination to the following antigens: • Polyribosylribitol phosphate (PRP) (at the level of ≥ 1.0 μg/mL) • Diphtheria toxoid (at the level of ≥ 0.1 IU/mL) • Tetanus toxoid (at the level of ≥ 0.1 IU/mL) • Poliovirus types 1, 2 and 3 (at a titre of ≥ 1:8 dilution [dil])* • Hepatitis B (at the level of ≥ 10 mIU/mL) • Pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (at a level ≥ 0.15 μg/mL). *Referred to in tables as ≥ 1:8 1/dil. (ii). Geometric mean titres (GMTs) for antibodies against all antigens (PRP, diphtheria toxoid, tetanus toxoid, poliovirus types 1, 2 and 3, hepatitis B, pneumococcal serotypes [4, 6B, 9V, 14, 18C, 19F and 23F], PT, FHA, PRN and FIM) at baseline and 1 month (28 to 42 days) post-vaccination. (iii). Proportion of subjects achieving a booster response to pertussis antigens PT, FHA, PRN and FIM from baseline to 1 month (28 to 42 days) post-vaccination.
Observational objective:	To describe the safety profile of booster vaccination with PEDIACEL® or INFANRIX® hexa vaccine when co-administered with Prevenar® at Visit 1, and the safety profile of ENGERIX®-B Kinder administered at Visit 2.

<table>
<tr><td>Observational endpoints:</td><td>The number and percentage of subjects in both groups with any of the following:
Solicited injection site reactions (tenderness, erythema and swelling) reported from Day 0 to Day 7 following each vaccination
Extensive limb swelling solicited and reported from Day 0 to Day 7 following each booster (PEDIACEL® or INFANRIX® hexa) vaccination
Solicited systemic reactions (fever, vomiting, abnormal crying, drowsiness, loss of appetite and irritability) reported from Day 0 to Day 7 following each vaccination; for subjects in Group B, solicited systemic reactions were collected for 7 days after Visit 2
Unsolicited Adverse Events (AEs) reported within 28 days following each vaccination; for subjects in Group B, unsolicited AEs were collected for 28 days after Visit 2
Serious Adverse Events (SAEs) reported from the time the consent form was signed and throughout the course of the study.
A diary card was used to record solicited reactions (from Day 0 to 7) and unsolicited AEs (for 28 days after each vaccination).</td></tr>
<tr><td>Methodology / Trial Design:</td><td>Randomised, double-blind (maintained up to 1 month post-immunisation [Visit 2]), controlled, multi-centre and 2-armed Phase III study in Germany in which toddlers previously primed with a hexavalent vaccine at 2, 3 and 4 months of age, received a booster dose of PEDIACEL® or INFANRIX® hexa vaccine co-administered with Prevenar® at 11 to 18 months of age. Eligible toddlers were randomly assigned to 1 of the 2 study groups:

Study Groups<table><tr><td>Group A</td><td>PEDIACEL® (0.5 mL) as a booster dose (following a primary series with a hexavalent vaccine) administered concomitantly with the first dose of Prevenar® (0.5 mL) at 11 to 18 months followed by ENGERIX®-B Kinder (0.5 mL) 1 month later, at 12 to 19 months.</td></tr><tr><td>Group B</td><td>INFANRIX® hexa (0.5 mL) as a booster dose (following a primary series with a hexavalent vaccine) administered concomitantly with the first dose of Prevenar® (0.5 mL) at 11 to 18 months.</td></tr></table>Subjects in both groups were followed-up for approximately 2 months. All subjects received a second dose of Prevenar® at the end of the follow-up period, approximately 2 months after the first dose. The second dose was provided by the Sponsor outside of the study scope.

The term “booster vaccine” referenced herein is defined as the investigational vaccine PEDIACEL® or the control vaccine INFANRIX® hexa and does not include Prevenar® or ENGERIX®-B Kinder.</td></tr>
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Sample size:	Originally, the study was planned to enroll 1200 subjects (600 per group). Of the 600 subjects per group, a subgroup of 170 subjects per group was to be evaluated for immunogenicity endpoints. Owing to slow enrolment, several alternative sample size calculations were examined to ensure a minimum power of 80% (discussed in the Statistical Methods section below). The final number of randomised subjects was 847 of which 190 were in the immunogenicity subset
Schedules of Vaccination and Specimen Collection and Duration of Participation in the Trial	Subjects were randomised to receive either PEDIACEL® with Prevenar® at Visit 1 and ENGERIX®-B Kinder at Visit 2 (Group A) or INFANRIX® hexa with Prevenar® at Visit 1 (Group B). Total duration of the follow-up period was 2 months (Visit 1 to Visit 3) for all subjects. All subjects received a second dose of Prevenar® at the end of the follow-up period, approximately 2 months after the first dose.
Inclusion criteria:	• Toddlers 11 to 18 months of age (from the 11th month birthday to 1 day prior to the 19th month birthday) who previously received the primary immunisation series with a hexavalent vaccine (consisting of three doses of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and *H. influenzae* type b combined vaccine administered within the first 9 months of life). The interval period between the 3rd dose of the primary series and the booster dose was at least 6 months. • Informed consent form (ICF) signed by both parents or by the legal guardian. • Parents or a legal guardian were able to read and write the German language. • Parents or a legal guardian were able to attend all scheduled visits and to comply with the study procedures.
Exclusion criteria:	• Presence of fever (defined as rectal body temperature ≥ 38.0°C) reported within the last 72 hours. • Moderate or severe acute illness with or without fever. • Participation in another clinical trial in the 30 days preceding study vaccination. • Planned participation in another clinical trial during the present study period. • Immunisation with a pneumococcal vaccine prior to study vaccination or planned during the participation in the study • Received more than 3 doses of a hexavalent vaccine prior to study vaccination. • Received any vaccination in the 30 days preceding the trial. • History of serological/microbiologically-confirmed diagnosis of infection due to pertussis, tetanus, diphtheria, poliomyelitis, hepatitis B, H. influenzae type b and/or Streptococcus pneumoniae. • Congenital or acquired humoral/cellular immunodeficiency or immunosuppressive therapy such as long-term systemic corticosteroids therapy (≥ 2 mg/kg/day prednisone equivalent for ≥ 14 days in the 30 days prior to study vaccination).

Exclusion criteria (Continued):	• Systemic or local hypersensitivity to any of the study vaccine components (including neomycin, streptomycin, polymyxin B and formaldehyde). • History of a life-threatening reaction (such as encephalopathy, Hypotonic-Hyporesponsive Episode (HHE), rectal body temperature ≥ 40.0°C, convulsions with or without fever) to any vaccine containing the same components as the study vaccines. • Blood or blood-derived products (immunoglobulins) received during 3 months prior to study vaccination. • Known human immunodeficiency virus seropositivity. • Known thrombocytopenia or a bleeding disorder contraindicating IM vaccination. • History of encephalopathy, seizures or progressive, evolving or unstable neurological condition. • Clinically significant findings on review of systems that might interfere with study vaccination or which, in the opinion of the Investigator, would interfere with the evaluation of the study vaccine/objectives or pose a health risk to the subject.
Product Under Investigation:	**PEDIACEL®:** Diphtheria, tetanus, five component acellular pertussis, inactivated poliomyelitis and *H. influenzae* type b conjugate vaccine, adsorbed.
Form/Dose/Route:	Liquid / 0.5 mL / Intramuscular (IM)
Batch number:	C2415AA
Manufacturer	Sanofi Pasteur (formerly Aventis Pasteur)
Control Product:	**INFANRIX® hexa:** Diphtheria, tetanus, acellular pertussis, hepatitis B recombinant (adsorbed), inactivated poliomyelitis and adsorbed conjugated *H. influenzae* type b vaccine.
Form/Dose/Route:	Liquid / 0.5 mL / Intramuscular (IM)
Batch number:	A21CA191A; A21CA192A; A21CA193A, A21CA175A, A21CA202A, A21CA254E, and A21CA267C.
Manufacturer:	GlaxoSmithKline
Other Product 1:	**Prevenar®:** Pneumococcal saccharide conjugated vaccine, adsorbed.
Form/Dose/Route:	Liquid / 0.5 mL / Intramuscular (IM)
Batch number:	20587
Manufacturer:	Wyeth Pharmaceuticals
Other Product 2:	**Engerix®-B Kinder:** Hepatitis B recombinant vaccine, adsorbed.
Form/Dose/Route:	Liquid / 0.5 mL / Subcutaneous (SC)
Batch number:	AHBVB105AK
Manufacturer	GlaxoSmithKline

Statistical methods:	**Primary Objective and Hypothesis:** The difference in the proportion of toddlers reporting fever (temperature ≥ 38.0°C) within 4 days (Day 0 to Day 3) of booster vaccination between groups A and B ($P_A - P_B$) and the associated two-sided 95% CIs were computed. • If the upper limit of the 95% CI was < 0.1, then PEDIACEL® was considered non-inferior to INFANRIX® hexa. **Secondary Objectives: - Safety** • If non-inferiority of PEDIACEL® to INFANRIX® hexa was achieved and the upper limit of the 95% CI of the difference in the proportion of toddlers reporting fever (defined as temperature ≥ 38.0°C) within 4 days (Day 0 to Day 3) of booster vaccination between Groups A and B ($P_A - P_B$) was < 0, then PEDIACEL® was considered superior to INFANRIX® hexa. • The proportion of toddlers reporting severe fever (temperature ≥ 39.6°C) within 4 days post-vaccination and the 95% CI was calculated. **Secondary Objectives: - Immunogenicity** • Proportion of subjects achieving seroprotective titres at 1 month (28 to 42 days) post-vaccination and the 95% CIs for the following antigens: • PRP (at the level of ≥ 1.0 μg/mL) • Diphtheria toxoid (at the level of ≥ 0.1 IU/mL) • Tetanus toxoid (at the level of ≥ 0.1 IU/mL) • Poliovirus types 1, 2 and 3 (at a titre of ≥ 1:8 dil) • Hepatitis B (at the level of ≥ 10 mIU/mL) • Pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (at a level ≥ 0.15 μg/mL). • GMTs and the 95% CIs were calculated for antibodies against all antigens - (PRP-T, diphtheria toxoid, tetanus toxoid, poliovirus types 1, 2 and 3, and pneumococcal serotypes [4, 6B, 9V, 14, 18C, 19F and 23F] PT, FHA, PRN and FIM) and hepatitis B (where applicable) in the study groups at baseline and at 1 month (28 to 42 days) post-vaccination. The GMTs for hepatitis B for Group A were calculated at Visit 2 and 1 month (28 to 42 days) post-vaccination against hepatitis B • Proportion of subjects achieving a booster response (defined as ≥ 4-fold rise from baseline if baseline antibody response was < 4xlower limit of quantitation (LLOQ), and ≥ 2-fold rise from baseline if baseline antibody response was ≥ 4xLLOQ to pertussis antigens PT, FHA, PRN and FIM and the 95% CI was calculated from baseline to 1 month (28 to 42 days) post-vaccination. **Observational Objective:** The number and percentage of subjects reporting solicited injection site reactions (tenderness, erythema and swelling), extensive limb swelling, and solicited systemic reactions (fever, vomiting, abnormal crying, drowsiness, loss of appetite and irritability) were presented by group.

Unsolicited AEs and SAEs were summarised as:

- number of events
- number and percentage of subjects reporting the events
- their relationship to the study vaccines (for unsolicited events only) by group.

Sample Size and Power Estimation:

Owing to slow enrolment due to the introduction of reimbursement for the concomitantly administered vaccine (Prevenar®), and loss of the cohort of eligible subjects for inclusion in the trial, the planned sample size was not achieved and a recalculation of power was performed based on different sample sizes:

Table 1: Sample Size and Power

Total Sample Size	Sample Size Per Group	Power
788	394	80%
800	400	81%
1044	522	90%
1200	600	93%

Thus, for the primary hypothesis, a sample size of 394 evaluable subjects per group was sufficient to show non-inferiority, assuming an expected fever rate of 38%, delta=10% and power=80%. With an attrition rate of 5%, at least 830 subjects (415 per group) needed to be enrolled.

For the immunogenicity subset, no minimum sample size was established given the descriptive nature of the endpoint.

Results:

Disposition of subjects

Table 2 presents a summary of subject disposition.

Immunogenicity Subset:

Of the 190 subjects that were randomised to the immunogenicity subset, 94 subjects were in the PEDIACEL® group and 96 subjects were in the INFANRIX® hexa group. Among these, 182 were included in the full analysis set (FAS) (92 subjects in the PEDIACEL® group and 90 subjects in the INFANRIX® hexa group). The subjects included in each of the analysis sets (SAS, FAS and PP) are presented in Table 2.

Demographic and Baseline Characteristics

There were 247 (58.5%) males in the PEDIACEL® group and 216 (51.3%) males in the INFANRIX® hexa group. The mean age at booster vaccination was similar between the 2 groups (14.0 and 14.1 months at Visit 1 in the PEDIACEL® and INFANRIX® hexa groups respectively) and confirmed an 11 to 18 month vaccination schedule.

Table 2: Summary of Subject Disposition and Data Sets Analysed

	PEDIACEL® [1]	INFANRIX® hexa [1]	Total
	n (%)	n (%)	n (%)
Enrolled			855
Randomised Subjects	423	424	847
Completed the Study [2]	420 (99.3)*	417 (98.3)	837 (98.8)
Did Not Complete the Study [2,3]	3 (0.7)	7 (1.7)	10 (1.2)
Serious Adverse Event [2]	0 (0.0)	0 (0.0)	0 (0.0)
Other Adverse Event [2]	0 (0.0)	0 (0.0)	0 (0.0)
Non-Compliance With the Protocol [2]	1 (0.2)	2 (0.5)	3 (0.4)
Lost to Follow-Up [2]	1 (0.2)	3 (0.7)	4 (0.5)
Voluntary Withdrawal Not Due to Adverse Event [2]	1 (0.2)	2 (0.5)	3 (0.4)
Received Booster Vaccines as Randomised	423	422	845
Safety Analysis Set [4]	422	421	843
Subject Disposition for Immunogenicity			
Randomised for Immunogenicity	94	96	190
Full Analysis Set [5,7]	92 (97.9)	90 (93.8)	182 (95.8)
Per-Protocol (PP) Analysis Set for All Antigens Excluding Hepatitis B [6,7]	79 (84.0)	80 (83.3)	159 (83.7)
Per-Protocol (PP) Analysis Set for Hepatitis B [6,7]	76 (80.9)	80 (83.3)	156 (82.1)

[1] Both vaccines were to be administered concomitantly with Prevenar®. PEDIACEL® subjects received PEDIACEL® and Prevenar® at 11 to 18 months of age (Visit 1) and ENGERIX®-B Kinder 1 month after (12 to 19 months) (Visit 2). INFANRIX® hexa subjects received INFANRIX® hexa and Prevenar® at 11 to 18 months of age (Visit 1).
[2] Percentages are based on the number of randomised subjects.
[3] Each subject is counted only once according to the primary reason for termination.
[4] Safety Analysis Set: randomised subjects who received the booster vaccination (PEDIACEL® or INFANRIX® hexa) and had at least 1 safety assessment. Subjects are classified according to the vaccine they actually received.
[5] Full Analysis Set (FAS): randomised subjects who received the booster vaccination (PEDIACEL® or INFANRIX® hexa) and had post-booster vaccination blood sample drawn. Subjects are classified by the vaccine group they were randomised to.
[6] Per-Protocol (PP) Analysis Set for All Antigens / Hepatitis B: subjects who were valid for the FAS and did not have a protocol violation that affects the immunogenicity evaluation of results.
[7] Percentages are based on the number of randomised subjects selected for immunogenicity.
Notes: All antigens include PRP, diphtheria, tetanus, polio, pertussis and pneumococcal serotype antigens.
*Includes a Subject who did not receive ENGERIX®-B Kinder vaccination but did attend all visits (i.e., completed the study).

Immunogenicity

Seroprotection Rates for PRP, Diphtheria, Tetanus, Polio and Pneumococcal Serotype Antigens:

Following booster vaccination, the seroprotection rates for PRP (≥ 1.00 µg/mL), diphtheria (≥ 0.1 IU/mL), tetanus (≥ 0.1 IU /mL) and polio (≥ 1:8 dil) were all 100.0% in both groups (Table 3).

Following co-administration with Prevenar®, the seroprotection rates (≥ 0.15 µg/mL) against the 7 pneumococcal serotypes were similar in both groups and ranged from 75.0% to 100.0% depending on the serotype (Table 3). The analysis using the FAS confirmed the above results.

Table 3: Seroprotection Rates Post-Booster Vaccination of PRP, Diphtheria, Tetanus, Polio and Pneumococcal Serotype Antigens– Per-Protocol Analysis Set for All Antigens Excluding Hepatitis B

	PEDIACEL® [1] (N=79)			INFANRIX® hexa [1] (N=80)		
	n/M	%	95% CI	n/M	%	95% CI
PRP (≥ 1.00 µg/mL)	78/78	100.0	(95.4; 100.0)	80/80	100.0	(95.5; 100.0)
Diphtheria Toxoid (≥ 0.1 IU/mL)	78/78	100.0	(95.4; 100.0)	80/80	100.0	(95.5; 100.0)
Tetanus Toxoid (≥ 0.1 IU/mL)	78/78	100.0	(95.4; 100.0)	80/80	100.0	(95.5; 100.0)
Polio 1 (≥ 1:8 1/dil)	75/75	100.0	(95.2; 100.0)	79/79	100.0	(95.4; 100.0)
Polio 2 (≥ 1:8 1/dil)	76/76	100.0	(95.3; 100.0)	80/80	100.0	(95.5; 100.0)
Polio 3 (≥ 1:8 1/dil)	73/73	100.0	(95.1; 100.0)	76/76	100.0	(95.3; 100.0)
Pneumo 4 (≥ 0.15 µg/mL)	76/76	100.0	(95.3; 100.0)	78/78	100.0	(95.4; 100.0)
Pneumo 6B (≥ 0.15 µg/mL)	59/72	81.9	(71.1; 90.0)	61/74	82.4	(71.8; 90.3)
Pneumo 9V (≥ 0.15 µg/mL)	74/76	97.4	(90.8; 99.7)	77/78	98.7	(93.1; 100.0)
Pneumo 14 (≥ 0.15 µg/mL)	75/75	100.0	(95.2; 100.0)	78/78	100.0	(95.4; 100.0)
Pneumo 18C (≥ 0.15 µg/mL)	75/76	98.7	(92.9; 100.0)	78/78	100.0	(95.4; 100.0)
Pneumo 19F (≥ 0.15 µg/mL)	75/75	100.0	(95.2; 100.0)	77/77	100.0	(95.3; 100.0)
Pneumo 23F (≥ 0.15 µg/mL)	56/74	75.7	(64.3; 84.9)	57/76	75.0	(63.7; 84.2)

[1] Both vaccines were to be administered concomitantly with Prevenar®. PEDIACEL® subjects received PEDIACEL® and Prevenar® at 11 to 18 months of age (Visit 1) and ENGERIX®-B Kinder 1 month after (12 to 19 months) (Visit 2). INFANRIX® hexa subjects received INFANRIX® hexa and Prevenar® at 11 to 18 months of age (Visit 1).
Notes: For each antigen, n=number of subjects who met the criteria of the test indicated.
M=number of subjects with at least 1 available PP record.
N=number of subjects in the PP Analysis Set for All Antigens.
PP Analysis Set for All Antigens: subjects who were valid for the FAS and did not have a protocol violation that affects the immunogenicity evaluation of results.
All antigens include PRP, diphtheria, tetanus, polio, pertussis and pneumococcal serotype antigens.

GMTs Pre- and Post-Booster Vaccination for PRP, Diphtheria, Tetanus, Polio, Pneumococcal and Pertussis Antigens:

The pre-booster GMTs were similar in both groups for all antigens although the pre-booster GMTs for poliovirus types 1, 2 and 3 were numerically higher in the INFANRIX® hexa group.

Following booster vaccination with PEDIACEL® or INFANRIX® hexa, both co-administered with Prevenar®, the GMTs for PRP, diphtheria, tetanus, polio and the pneumococcal serotypes were similar between the 2 groups (Table 4). Notably, the PEDIACEL® post-booster GMTs for Polio 1, 2 and 3 showed fold increases that were as high or higher than observed for INFANRIX® hexa, indicating a robust booster response (22.9, 49.9 and 23.8 fold increase for Polio 1, 2 and 3 respectively in the PEDIACEL® group and 22.0, 28.0 and 23.2 fold increase for Polio 1, 2 and 3 respectively for the INFANRIX® hexa group).

It is noted that FIM was not present in the hexavalent vaccines used for the primary series (INFANRIX® hexa or HEXAVAC®) and this would have been the first dose of FIM antigens received by subjects in the PEDIACEL® group. For all pertussis antigens, given that there is no established serological correlate of protection for pertussis, the clinical significance of the numerical differences in GMTs is not known. The analysis using the FAS confirmed the above results.

Table 4: Geometric Mean Titres (GMTs) at Pre- and Post-Booster Vaccination of PRP, Diphtheria, Tetanus, Polio, Pertussis and Pneumococcal Antigens - Per-Protocol Analysis Set for All Antigens Excluding Hepatitis B

		PEDIACEL® [1] (N=79)			INFANRIX® hexa [1] (N=80)		
Antigen	**Visit**	**M**	**GMT**	**95% CI**	**M**	**GMT**	**95% CI**
PRP (µg/mL)	Pre-Booster Vaccination	77	0.44	(0.31; 0.63)	80	0.56	(0.40; 0.78)
	Post-Booster Vaccination	78	37.16	(27.80; 49.67)	80	30.27	(24.23; 37.82)
Diphtheria Toxoid (IU/mL)	Pre-Booster Vaccination	77	0.06	(0.04; 0.09)	80	0.06	(0.04; 0.08)
	Post-Booster Vaccination	78	2.72	(2.04; 3.64)	80	2.23	(1.71; 2.90)
Tetanus Toxoid (IU/mL)	Pre-Booster Vaccination	77	0.39	(0.31; 0.49)	80	0.41	(0.33; 0.50)
	Post-Booster Vaccination	78	6.47	(5.25; 7.97)	80	4.67	(3.99; 5.47)
Polio 1 (1/dil)	Pre-Booster Vaccination	77	230.86	(148.41; 359.10)	79	311.93	(209.67; 464.05)
	Post-Booster Vaccination	75	5281.24	(3722.08; 7493.52)	79	6873.53	(5302.40; 8910.19)
Polio 2 (1/dil)	Pre-Booster Vaccination	77	156.07	(98.80; 246.55)	78	235.26	(160.52; 344.79)
	Post-Booster Vaccination	76	7791.20	(5634.91; 10772.63)	80	6596.57	(5110.91; 8514.09)
Polio 3 (1/dil)	Pre-Booster Vaccination	77	339.96	(216.74; 533.25)	78	464.31	(326.34; 660.61)
	Post-Booster Vaccination	73	8076.24	(5380.26; 12123.16)	76	10770.02	(8274.75; 14017.75)
PT (EU/mL)	Pre-Booster Vaccination	76	19.50	(15.70; 24.22)	79	17.99	(14.85; 21.80)
	Post-Booster Vaccination	74	128.94	(105.70; 157.28)	77	126.80	(109.89; 146.31)
FHA (EU/mL)	Pre-Booster Vaccination	76	23.13	(18.31; 29.23)	79	24.65	(19.73; 30.80)
	Post-Booster Vaccination	76	125.53	(105.21; 149.79)	77	190.58	(166.15; 218.59)
PRN (EU/mL)	Pre-Booster Vaccination	76	20.02	(15.38; 26.07)	79	18.30	(13.79; 24.28)
	Post-Booster Vaccination	75	257.46	(205.63; 322.35)	77	324.30	(253.96; 414.10)
FIM (EU/mL)	Pre-Booster Vaccination	75	2.11	(1.98; 2.26)	79	2.18	(2.01; 2.35)
	Post-Booster Vaccination	74	6.61	(4.79; 9.12)	76	2.64	(2.22; 3.13)
Pneumo 4 (µg/mL)	Pre-Booster Vaccination	75	0.03	(0.02; 0.04)	77	0.04	(0.03; 0.06)
	Post-Booster Vaccination	76	5.04	(4.01; 6.34)	78	4.41	(3.51; 5.55)
Pneumo 6B (µg/mL)	Pre-Booster Vaccination	71	0.10	(0.08; 0.13)	78	0.11	(0.08; 0.14)
	Post-Booster Vaccination	72	0.66	(0.46; 0.95)	74	0.56	(0.41; 0.77)
Pneumo 9V (µg/mL)	Pre-Booster Vaccination	76	0.04	(0.03; 0.05)	78	0.04	(0.03; 0.05)
	Post-Booster Vaccination	76	3.48	(2.62; 4.62)	78	3.27	(2.65; 4.03)
Pneumo 14 (µg/mL)	Pre-Booster Vaccination	73	0.08	(0.06; 0.12)	79	0.10	(0.07; 0.15)
	Post-Booster Vaccination	75	4.35	(3.50; 5.40)	78	4.85	(3.87; 6.07)
Pneumo 18C (µg/mL)	Pre-Booster Vaccination	76	0.02	(0.01; 0.03)	78	0.02	(0.01; 0.03)
	Post-Booster Vaccination	76	3.57	(2.92; 4.37)	78	3.89	(3.26; 4.63)
Pneumo 19F (µg/mL)	Pre-Booster Vaccination	75	0.52	(0.41; 0.65)	78	0.63	(0.49; 0.81)
	Post-Booster Vaccination	75	1.72	(1.40; 2.11)	77	1.86	(1.54; 2.25)
Pneumo 23F (µg/mL)	Pre-Booster Vaccination	73	0.04	(0.03; 0.06)	77	0.04	(0.03; 0.06)
	Post-Booster Vaccination	74	0.51	(0.36; 0.73)	76	0.46	(0.33; 0.65)

[1] Both vaccines were to be administered concomitantly with Prevenar®. PEDIACEL® subjects received PEDIACEL® and Prevenar® at 11-18 months of age (Visit 1) and ENGERIX®-B Kinder 1 month after (12-19 months) (Visit 2). INFANRIX® hexa subjects received INFANRIX® hexa and Prevenar® at 11-18 months of age (Visit 1).

Notes: For each antigen, 'M' is the number of subjects with at least 1 available PP record and 'N' is the number of subjects in the PP Analysis Set for all Antigens.

PP Analysis Set for All Antigens: subjects who were valid for FAS and did not have a protocol violation that affects the immunogenicity evaluation of results.

All antigens include PRP, diphtheria, tetanus, polio, pertussis and pneumococcal serotype antigens.

Post-Booster Response Rates for Pertussis Antigens

Table 5 shows the the post-booster seroresponse rates for PT, FHA, PRN and FIM. Again, it is noted that FIM was not present in hexavalent vaccines used for primary immunisation (INFANRIX® hexa or HEXAVAC®), and this would be the first dose of FIM in the PEDIACEL® group. The analysis using the FAS confirmed the results.

Table 5: Booster Response Rates for Pertussis Antigens – Per-Protocol Analysis Set for all Antigens, Excluding Hepatitis B

	PEDIACEL® [1] (N=79)			INFANRIX® hexa [1] (N=80)		
Booster Response to Antigen (EU/mL) [2]	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
PT	66/73	90.4	(81.2; 96.1)	70/76	92.1	(83.6; 97.0)
FHA	65/75	86.7	(76.8; 93.4)	72/76	94.7	(87.1; 98.5)
PRN	71/74	95.9	(88.6; 99.2)	73/76	96.1	(88.9; 99.2)
FIM*	19/72	26.4	(16.7; 38.1)	4/75	5.3	(1.5; 13.1)

[1] Both vaccines were to be administered concomitantly with Prevenar®. PEDIACEL® subjects received PEDIACEL® and Prevenar® at 11 to 18 months of age (Visit 1) and ENGERIX®-B Kinder 1 month after (12 to 19 months) (Visit 2). INFANRIX® hexa subjects received INFANRIX® hexa and Prevenar® at 11 to 18 months of age (Visit 1).

[2] ≥ 4-fold rise from baseline if baseline antibody response is < 4x lower limit of quantification (LLOQ) or ≥ 2-fold rise from baseline if baseline antibody response is ≥ 4xLLOQ.

Notes: n=number of subjects who met the criteria of the test indicated, 'M' is the number of subjects with at least 1 available PP record and 'N' is the number of subjects in the PP Analysis Set for All Antigens.

PP Analysis Set for All Antigens: subjects who were valid for FAS and did not have a protocol violation that affects the immunogenicity evaluation of results.

All antigens include PRP, diphtheria, tetanus, polio, pertussis and pneumococcal serotype antigens.

The LLOQ values for pertussis antigens are 4 EU/mL for PT, PRN and FIM, and 3 EU/mL for FHA.

*This was the first dose of FIM in the PEDIACEL® group.

Seroprotection Rates Post-Hepatitis B Vaccination

The seroprotection rates (≥10 mIU/mL) pre- and post-vaccination against hepatitis B were similar and high in both groups (Table 6). The analysis using the FAS confirmed the results.

Table 6: Seroprotection Rates Post-Hepatitis B Vaccination– Per-Protocol Analysis Set for Hepatitis B Antigen

		PEDIACEL® [1] (N=76)			INFANRIX® hexa [1] (N=80)		
Antigen/Criteria	**Visit**	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
Hepatitis B (mIU/mL)							
≥ 10	Visit 1[2]	--	--	--	74/79	93.7	(85.8; 97.9)
	Visit 2[3]	68/73	93.2	(84.7; 97.7)	76/77	98.7	(93.0; 100.0)
	Visit 3[4]	76/76	100.0	(95.3; 100.0)	--	--	--

[1] Both vaccines were to be administered concomitantly with Prevenar®. PEDIACEL® subjects received PEDIACEL® and Prevenar® at 11 to 18 months of age (Visit 1) and ENGERIX®-B Kinder 1 month after (12 to 19 months) (Visit 2). INFANRIX® hexa subjects received INFANRIX® hexa and Prevenar® at 11 to 18 months of age (Visit 1).

[2] Pre-booster vaccination (PEDIACEL® or INFANRIX® hexa).

[3] Post-booster vaccination (PEDIACEL® or INFANRIX® hexa) and pre-ENGERIX®-B Kinder vaccination.

[4] Post-ENGERIX®-B Kinder vaccination.

Notes: n=number of subjects who met the hepatitis B antigen criteria of ≥ 10 mIU/mL. M=number of subjects with at least 1 available PP record. N=number of subjects in the PP Analysis Set for Hepatitis B.

PP Analysis Set for Hepatitis B: subjects who were valid for FAS and did not have a protocol violation that affects the hepatitis B immunogenicity evaluation of results.

GMTs Pre- and Post-Hepatitis B Vaccination

The pre-vaccination hepatitis B GMTs for the PEDIACEL® and INFANRIX® hexa groups were similar (Table 7). The analysis using the FAS confirmed the above results.

Table 7: Geometric Mean Titres (GMTs) Pre- and Post-Hepatitis B Vaccination – Per-Protocol Analysis Set for Hepatitis B Antigen

		PEDIACEL® [1] (N=76)			INFANRIX® hexa [1] (N=80)		
Antigen	**Visit**	**M**	**GMT**	**95% CI**	**M**	**GMT**	**95% CI**
Hepatitis B mIU/mL)	**Visit 1 [2]**	--	--	--	79	196.00	(131.91; 291.25)
	Visit 2 [3]	73	194.48	(132.62; 285.21)	77	2866.13	(1872.12; 4387.91)
	Visit 3 [4]	76	9066.36	(6029.63; 13632.49)	--	--	--

[1] Both vaccines were to be administered concomitantly with Prevenar®. PEDIACEL® subjects received PEDIACEL® and Prevenar® at 11 to 18 months of age (Visit 1) and ENGERIX®-B Kinder 1 month after (12 to 19 months) (Visit 2). INFANRIX® hexa subjects received INFANRIX® hexa and Prevenar® at 11 to 18 months of age (Visit 1).
[2] Pre-booster vaccination (PEDIACEL® or INFANRIX® hexa).
[3] Post-booster vaccination (PEDIACEL® or INFANRIX® hexa) and pre-ENGERIX®-B Kinder vaccination.
[4] Post-ENGERIX®-B Kinder vaccination.
Notes: n=number of subjects who met the hepatitis B antigen criteria of ≥ 10 mIU/mL. M=number of subjects with at least 1 available PP record. N=number of subjects in the PP Analysis Set for Hepatitis B.
PP Analysis Set for Hepatitis B: subjects who were valid for FAS and did not have a protocol violation that affects the immunogenicity evaluation of results.

Safety:

Overall, the safety profiles of PEDIACEL® and INFANRIX® hexa when co-administered with Prevenar® were similar following booster vaccination at 11 to 18 months of age. There were no new or unexpected safety issues identified and no deaths were reported during the study.

Primary Safety Objective: Non-Inferiority of PEDIACEL® to INFANRIX® hexa (Both Co-Administered with Prevenar®) With Respect to Fever Rates (≥ 38.0°C) Within 4 Days Post-Booster Vaccination

For the primary objective, PEDIACEL® was non-inferior to INFANRIX® hexa, both co-administered with Prevenar®; when comparing fever rates (≥ 38.0°C) within 4 days (Day 0 to Day 3) following booster vaccination. Since the upper limit (3.4%) of the two-sided 95% CI on the difference was less than 10% (i.e., the non-inferiority margin), it was concluded that PEDIACEL® was non-inferior to INFANRIX® hexa with regards to fever rates within 4 days post-booster vaccination when both were co-administered with Prevenar®. The percentages of antipyretics, analgesics and non-steroidal anti-inflammatory drugs recorded within 3 days of booster vaccination at Visit 1 were similar in both groups.

Secondary Safety Objective #1: Incidence Rate of Fever (≥ 38.0°C) Within 4 Days of PEDIACEL® to INFANRIX® hexa Post-Vaccination (Both Co-Administered with Prevenar®)

Given that the upper limit of the two-sided 95% CI on the difference (PEDIACEL® group – INFANRIX® hexa group) in fever rates within 4 days was 3.4% (i.e., greater than 0%), the data did not demonstrate that PEDIACEL® induced less fever compared to INFANRIX® hexa when both were co-administered with Prevenar® (Table 8).

Table 8: Differences in Rates for Fever (≥ 38.0°C) Within 4 Days (Day 0- Day 3) of Booster Vaccination Between PEDIACEL® and INFANRIX® hexa (Primary Analysis Method) – Safety Analysis Set

	PEDIACEL® [1] (N=422)			INFANRIX® hexa [1] (N=421)			Difference with 95% CI [2]	Non-Inferiority [3] (Yes/No)	Superiority [4] (Yes/No)
	n/M	%	95% CI	n/M	%	95% CI			
Fever (≥ 38.0°C) [5]	250/421	59.4	(54.5; 64.1)	262/419	62.5	(57.7; 67.2)	-3.1 (-9.7; 3.4)	Yes	No

[1] Both vaccines were to be administered concomitantly with Prevenar®. PEDIACEL® subjects received PEDIACEL® and Prevenar® at 11 to 18 months of age (Visit 1) and ENGERIX®-B Kinder 1 month after (12 to 19 months) (Visit 2). INFANRIX® hexa subjects received INFANRIX® hexa and Prevenar® at 11 to 18 months of age (Visit 1).
[2] Difference= PEDIACEL® fever rate - INFANRIX® hexa fever rate. The CIs were computed using the normal approximation to the binomial distribution without continuity correction.
[3] Non-inferiority is achieved if the upper limit of the two-sided 95% CI of PEDIACEL® - INFANRIX® hexa is < 10% (primary objective).
[4] Superiority is achieved if the upper limit of the two-sided 95% CI of PEDIACEL® - INFANRIX® hexa is < 0% (secondary objective).
[5] Primary analysis method: no replacement of missing values.
Notes: n=number of subjects with fever after booster vaccination. Each subject is counted once for fever. M=number of vaccinated subjects in the SAS with presence of fever recorded or at least 1 temperature measurement taken.

Secondary Safety Objective #2: Incidence Rate of Severe Fever (≥ 39.6°C) Post-Vaccination

This secondary safety objective was to describe the incidence rate of severe fever (≥ 39.6°C) within 4 days (Day 0 to Day 3) post-booster vaccination, co-administered with Prevenar®. The rates of severe fever in both groups were similar: 6.7% (28/421) in the PEDIACEL® group and 4.1% (17/419) in the INFANRIX® hexa group.

The rate of severe fever after ENGERIX®-B Kinder vaccination (administered to the PEDIACEL® group only and after unblinding at Visit 2,) was 2.4% (10/418) whereas the rate of any fever (≥ 38.0°C) was 20.6% (86/418) within 4 days of Visit 2. In the INFANRIX® hexa group (no vaccination at Visit 2) the rate of severe fever was 1.0% (4/403) and the rate of any fever (≥ 38.0°C) was 10.9% (44/403) within 4 days of Visit 2.

Observational Objective - Safety

A summary of the safety data after the booster vaccine co-administered with Prevenar® (Visit 1) is presented in Table 9. Following Visit 1, the safety profiles of the PEDIACEL® and INFANRIX® hexa groups were similar. There were no new or unexpected safety issues identified. There were no immediate unsolicited events reported during the study. No subjects withdrew from the study due to an SAE. No deaths occurred in the study.

Table 9: Safety Overview After Booster Vaccination (Visit 1 up to Visit 2) – Safety Analysis Set

	PEDIACEL® [1] (N=422)			INFANRIX® hexa [1] (N=421)		
	n/M	%	95% CI	n/M	%	95% CI
Subjects With at Least One:						
Immediate Unsolicited Event	0/422	0.0	(0.0; 0.9)	0/421	0.0	(0.0; 0.9)
Immediate Unsolicited Reaction	0/422	0.0	(0.0; 0.9)	0/421	0.0	(0.0; 0.9)
Solicited Reaction	388/422	91.9	(88.9; 94.4)	399/421	94.8	(92.2; 96.7)
Solicited Injection Site Reaction*	332/422	78.7	(74.5; 82.5)	343/421	81.5	(77.4; 85.1)
Solicited Systemic Reaction	347/422	82.2	(78.2; 85.8)	360/421	85.5	(81.8; 88.7)
Severe Solicited Reaction	121/422	28.7	(24.4; 33.2)	118/421	28.0	(23.8; 32.6)
Severe Solicited Injection Site Reaction	82/422	19.4	(15.8; 23.5)	76/421	18.1	(14.5; 22.1)
Severe Solicited Systemic Reaction	56/422	13.3	(10.2; 16.9)	57/421	13.5	(10.4; 17.2)
Unsolicited Event [2]	203/422	48.1	(43.2; 53.0)	204/421	48.5	(43.6; 53.3)
Unsolicited Reaction	24/422	5.7	(3.7; 8.3)	24/421	5.7	(3.7; 8.4)
Unsolicited Injection Site Reaction	20/422	4.7	(2.9; 7.2)	20/421	4.8	(2.9; 7.2)
Unsolicited Systemic Reaction	5/422	1.2	(0.4; 2.7)	5/421	1.2	(0.4; 2.7)
Severe Unsolicited Event	32/422	7.6	(5.2; 10.5)	20/421	4.8	(2.9; 7.2)
Severe Unsolicited Reaction	1/422	0.2	(0.0; 1.3)	0/421	0.0	(0.0; 0.9)
Severe Unsolicited Injection Site Reaction	0/422	0.0	(0.0; 0.9)	0/421	0.0	(0.0; 0.9)
Severe Unsolicited Systemic Reaction	1/422	0.2	(0.0; 1.3)	0/421	0.0	(0.0; 0.9)
AE Leading to Study Discontinuation	0/422	0.0	(0.0; 0.9)	0/421	0.0	(0.0; 0.9)
SAE	7/422	1.7	(0.7; 3.4)	4/421	1.0	(0.3; 2.4)
Death	0/422	0.0	(0.0; 0.9)	0/421	0.0	(0.0; 0.9)

[1] Both vaccines were to be administered concomitantly with Prevenar®. PEDIACEL® subjects received PEDIACEL® and Prevenar® at 11 to 18 months of age (Visit 1) and ENGERIX®-B Kinder 1 month after (12 to 19 months) (Visit 2). INFANRIX® hexa subjects received INFANRIX® hexa and Prevenar® at 11 to 18 months of age (Visit 1).

[2] Includes 1 subject in the INFANRIX® hexa group who had genital candidiasis that started 30 days after booster vaccination.

Notes: n=number of subjects who reported at least 1 event/reaction after booster vaccination. For solicited reactions, M=number of vaccinated subjects from the SAS with at least 1 safety record for a solicited reaction at Visit 1. For unsolicited AEs, 'M'='N', where 'N' is the number of subjects in SAS.

*Three subjects with injection site erythema > 10 cm and 5 subjects with injection site swelling > 10 cm that started within 0-7 days of vaccination reported these reactions twice as solicited reactions and unsolicited reactions; these subjects were counted once with subjects reporting solicited injection site reactions.

Safety Analysis Set (SAS): randomised subjects who received the booster vaccination (PEDIACEL® or INFANRIX® hexa) and had at least 1 safety assessment. Subjects are classified according to the vaccine they actually received.

Solicited Reactions Between Day 0 and 7: - Solicited Injection Site Reactions

Post-Booster Vaccination (Visit 1):

Following the booster vaccine co-administered with Prevenar, the rates of all solicited injection site reactions (tenderness, erythema, and swelling) were similar in both groups [Table 9]) and most were mild in intensity.

Severe solicited injection site reactions were reported by 19.4% (82/422) of subjects in the PEDIACEL group and 18.1% (76/421) of subjects in the Infanrix hexa group; all severe solicited injection site reactions occurred (i.e., total number of days of severe intensity) for no more than 3 days with the exception of 4 subjects in each group who reported severe erythema that occurred 4 to 7 days; and 7 subjects in the PEDIACEL group and 8 subjects in the Infanrix hexa group who reported severe swelling for greater than 4 days. There were no unexpected safety findings with respect to solicited injection site reactions in either group following booster vaccination.

Post-ENGERIX®-B Kinder Vaccination (Visit 2)

ENGERIX®-B Kinder vaccination was only administered in the PEDIACEL® group at Visit 2 when subjects were unblinded. No vaccination was administered to the INFANRIX® hexa group at Visit 2. Therefore, solicited injection site reaction data were not collected for the INFANRIX® hexa group. There were no unexpected safety findings with respect to solicited injection site reactions following ENGERIX®-B Kinder vaccination.

Extensive Limb Swelling (ELS)

ELS was defined in this study as a swelling extending from the injection site beyond 1 or both adjacent joints (i.e., elbow and/or shoulder). The protocol required the Investigator to confirm the ELS at an evaluation visit.

From Day 0 to Day 7 post-booster vaccination, the number of subjects where the Investigator reported ELS was similar in both groups (0.5% [2/422] in the PEDIACEL® group and 1.2% [5/421] in the Infanrix-hexa group). No subjects discontinued the study as a result of ELS (confirmed or not).

This is the first clinical study of PEDIACEL® to prospectively define and collect information on ELS as a solicited reaction. While some reports were not consistent with the protocol definition for ELS, the data demonstrate that subjects that receive a booster dose of PEDIACEL® do not have a higher risk of developing ELS as compared to those receiving the licensed standard of care vaccine.

Solicited Systemic Reactions - Post-Booster Vaccination (Visit 1)

Following the booster vaccine co-administered with Prevenar®, the rates of all solicited systemic site reactions (fever, vomiting, crying abnormal, drowsiness, and appetite loss) were similar in both groups in the INFANRIX® hexa group [Table 9]) and most were mild in intensity.

To assess fever, the preferred route for recording temperature was the rectal route. Over 95.6% of temperature recording measurements following Visit 1 were performed by the rectal route.

Following the booster vaccination with PEDIACEL® or INFANRIX® hexa co-administered with Prevenar®, the incidence rates of fever (≥ 38.0°C) from Day 0 to Day 7 were similar in both groups. The rate of fever for PEDIACEL® was 63.7% (269/422) and for INFANRIX® hexa was 65.0% (273/420). Most fevers were reported to be of mild to moderate intensity in both groups. The rates of severe fever (≥ 39.6°C) were similar in both groups with 7.8% (33/422) in the PEDIACEL® group and 6.0% (25/420) in the INFANRIX® hexa group.

For the PEDIACEL® group, 31/422 [7.3%] subjects reported severe fever occurring for 1 to 3 days and 2 subjects (2/422 [0.5%]) reported occurrence for 4 to 6 days. Of the subjects with severe fever occurring for 4 to 6 days in the PEDIACEL® group, a subject had severe fever with onset on Day 2 that occurred for 6 days and the action taken was hospitalisation where bronchitis secondary to RSV infection was diagnosed. A subject had severe fever with onset on Day 0 that occurred for 4 days and the action taken was health care contact.

For the INFANRIX® hexa group, 22/420 (5.2%) subjects reported severe fever occurring for 1 to 3 days, 2 subjects (2/420 [0.5%]) reported occurrence for 4 days, and 1 subject reported occurrence of > 7 days. Of the subjects with severe fever occurring for 4 days in the INFANRIX® hexa group, one had an onset of moderate fever on Day 7 and a maximum intensity of severe fever following Day 7 that resolved within 4 days and the action taken being health care contact. A subject had severe fever starting on Day 6 that was on-going after Day 7 and resolved within 4 days, and included actions taken of health care contact and prescription of a new medication. One subject (1/420 [0.2%]) reported occurrence of severe fever for 23 days. A subject developed a mild fever that started on Day 4 and was on-going at Day 7. Given that a maximum intensity of severe fever was recorded after Day 7, the maximum number of days of occurrence is calculated from Day 8 to the stop date which is 23 days. No action was taken for this subject.

The rates of all solicited systemic reactions (fever, vomiting, crying abnormal, drowsiness, and appetite loss) were similar in both groups after the booster dose, co-administered with Prevenar®. For each solicited systemic reaction, no more than 7.8% of subjects reported a severe solicited systemic reaction in both groups after Visit 1. Most other severe solicited systemic reactions (other than fever) occurred for 1 to 3 days.

In summary, after Visit 1 booster vaccination, with either PEDIACEL® or INFANRIX® hexa co-administered with Prevenar®, the rates of solicited systemic reactions were similar. In the PEDIACEL® group, there were 2 subjects with severe fever that occurred for more than 3 days in which the actions of

hospitalisation (diagnosed with bronchitis as a non-related SAE) and health care contact were taken. In the INFANRIX® hexa group, there were 3 subjects with severe fever that occurred for more than 3 days in which the actions taken were health care contact and health care contact with a prescription for new medication and one subject had no action taken. There were no new safety findings with respect to solicited systemic reactions following booster vaccination.

Post-ENGERIX®-B Kinder Vaccination (Visit 2)

Unblinding occurred at Visit 2 for all subjects in order to administer hepatitis B vaccine to subjects who received PEDIACEL® (subjects in the INFANRIX® hexa group received no vaccination). Therefore, safety data following Visit 2 were collected from subjects who were no longer blinded to vaccine group and describe the relative safety of ENGERIX®-B Kinder vaccination in the PEDIACEL® group compared to no vaccination in the INFANRIX® hexa group. Solicited systemic reaction data were collected for the PEDIACEL® and INFANRIX® hexa groups.

The rate of solicited systemic reactions following ENGERIX®-B Kinder was 53.0% (222/419). After Visit 2, the rate of solicited systemic reactions in the INFANRIX® hexa group (no vaccination at Visit 2) was 32.3% (134/415). Over 96.8% of temperature recording measurements following Visit 2 were performed by the rectal route as recommended by the protocol.

Following the ENGERIX®-B Kinder vaccination at Visit 2, the rate of fever was 28.9% (121/418). Severe fever was reported by 21/418 (5.0%) subjects of which severe fever occurred in 18/418 [4.3%] subjects for 1 to 3 days and 3/418 (0.7%) subjects for 4 to 7 days. Three subjects had severe fever that occurred for 4, 5 and 7 days respectively and the action taken was for all 3 subjects was health care contact and prescription of a new medication.

Following the ENGERIX®-B Kinder vaccination at Visit 2, the rates of solicited systemic reactions (fever, vomiting, crying abnormal, drowsiness and appetite loss) show no more than 5.0% of subjects reporting severe solicited systemic reaction after Visit 2.

In the INFANRIX® hexa group, following no vaccination at Visit 2, the rate of fever was 19.4% (78/403) and the rate of severe fever was 3.7% (15/403). Most of the occurrences of severe fever (14/403 [3.5%] occurred for 1 to 3 days with the exception of 1 subject (1/403 [0.2%]; A subject who reported a mild fever starting on Day 6, had a maximum intensity of severe fever after Day 7; the fever occurred for 10 days and the action taken was health care contact and prescription of a new medication.

Following no vaccination in the INFANRIX® hexa group at Visit 2 the rates of solicited systemic reactions (fever, vomiting, crying abnormal, drowsiness and appetite loss) with severe intensity was reported by no more than 3.7% of subjects.

There were no unexpected safety findings with respect to solicited systemic reactions following ENGERIX®-B Kinder vaccination.

Unsolicited Adverse Events Between Day 0 and Day 28: - Immediate Adverse Events

There were no immediate unsolicited events reported in the study after any vaccination.

Unsolicited Adverse Events Between Day 0 and Day 28

Unsolicited AEs were collected from Day 0 to Day 28 following each vaccination.

Post-Booster Vaccination (Visit 1)

Overall, 48.1% (203/422) of subjects in the PEDIACEL® group and 48.2% (203/421) of those in the INFANRIX® hexa group reported at least 1 unsolicited AE (includes SAEs from 0-28 days) following the booster vaccination.

The most frequently reported unsolicited AEs within 0-28 days post-booster vaccination in both groups were in the Infections and Infestations System Organ Class (SOC), (with 32.2% [136/422] and 32.3% [136/421] of subjects reporting in the PEDIACEL® and INFANRIX® hexa group respectively), General Disorders and Adminstitration Administration Sites Conditions (with 15.2% [64/422] and 17.6% [74/421] of subjects reporting in the PEDIACEL® and INFANRIX® hexa group respectively), and Respiratory, Thoracic and Mediastinal Disorders in the PEDIACEL® group (9.5% [40/422]) and Gastrointestinal Disorders in the INFANRIX® hexa group (11.4% [48/421]).

The proportion of subjects with unsolicited adverse reactions (ARs) within 28 days of Visit 1 by SOC were similar in both groups. The most frequently reported unsolicited ARs in both groups were in the General Disorders and Administration Site Conditions SOC, with 4.7% [20/422] and 5.0% [21/421] of subjects reporting in the PEDIACEL® and INFANRIX® hexa group respectively.

Overall, therefore, the safety of PEDIACEL® and INFANRIX® hexa, with respect to unsolicited AEs (including unsolicited ARs) was similar.

Post-ENGERIX®-B Kinder Vaccination (Visit 2)

Overall, 42.1% (177/420) subjects vaccinated with ENGERIX®-B Kinder in the PEDIACEL® group and 42.4% (177/417) of those with no vaccination in the INFANRIX® hexa group reported at least 1 AE within 28 days of Visit 2 (includes SAEs from Day 0 to 28).

Following the ENGERIX®-B Kinder vaccination in the PEDIACEL® group at Visit 2, the most frequently reported unsolicited AEs were Infections and Infestations (29.0% [122/420]), Gastrointestinal Disorders (11.7% [49/420]) and General Disorders and Administration Site Conditions (10.0% [42/420]). Following no vaccination in the INFANRIX® hexa group at Visit 2 the most frequently reported unsolicited AEs were Infections and Infestations (27.6% [115/417]), General Disorders and Administration Site Conditions (12.0% [50/417]) and Respiratory, Thoracic and Mediastinal Disorders (8.6% [36/417]).

Overall, 1.4% (6/420) of subjects in the PEDIACEL® group reported at least 1 unsolicited AR within 28 days following the ENGERIX®-B Kinder vaccination at Visit 2. Since there was no vaccination administered in the INFANRIX® hexa group, there were no unsolicited ARs.

Following the ENGERIX®-B Kinder vaccination in the PEDIACEL® group at Visit 2 the most frequently reported unsolicited ARs were in the General Disorders and Administration Site Conditions SOC (1.2% [5/420]) followed by Infections and Infestations (0.2% [1/420]).

There were no new safety findings with respect to unsolicited AEs or ARs following ENGERIX®-B Kinder vaccination. Therefore, the safety of PEDIACEL® and INFANRIX® hexa with respect to unsolicited AEs (including unsolicited ARs) was similar.

Deaths, Other SAEs and Other Significant AEs:

No deaths occurred during the study. Overall, the proportion of subjects reporting SAEs in each group was similar during the study and within 30 days of each visit.

All subjects with SAEs recovered in both groups. There were no SAEs that led to withdrawal from the study.

In assessing the safety profile of PEDIACEL®, hypotonic-hyporesponsive episodes (HHE), extensive limb swelling (ELS), and generalised convulsive seizures were events that were considered significant for on-going safety monitoring. There were no cases of HHE reported in the study.

As discussed above, a total of 2/422 (0.5%) subjects in the PEDIACEL® group and 1/421 (0.2%) subject in the INFANRIX® hexa group had complete information to confirm ELS as per the protocol definition. In addition, there were 4/421 (1.0%) subjects in the INFANRIX® hexa group for which ELS was reported by the Investigator but could not be confirmed as per the protocol definition. No reports of ELS led to withdrawal from the study.

There was 1 subject with febrile convulsion that was considered related to vaccination with PEDIACEL® and Prevenar®. In addition, there were 2 subjects in the INFANRIX® hexa group with febrile convulsions attributed to other diagnoses: A subject reported an unrelated SAE of salmonellosis 30 days after vaccination that resulted in a febrile convulsion and a subject reported an unrelated SAE of viral infection 29 days after vaccination that resulted in a febrile convulsion.

Overall, the safety of PEDIACEL® and INFANRIX® hexa with respect to SAEs, HHE, ELS and seizures after each vaccination and during the study were similar.

Conclusions:

The primary objective of this study was achieved and demonstrated that PEDIACEL® was non-inferior to INFANRIX® hexa, (both co-administered with Prevenar®), when comparing fever rates (≥ 38.0°C) within 4 days (Day 0 to Day 3) following booster vaccination at 11 to 18 months of age in subjects previously primed with a hexavalent vaccine at 2, 3 and 4 months of age.

In addition, secondary and observational objectives were addressed as follows:

- The data did not demonstrate that PEDIACEL® induces less fever compared to INFANRIX® hexa when both were co-administered with Prevenar®
- The rates of severe fever (defined as ≥ 39.6°C) reported within 4 days were similar following PEDIACEL® or INFANRIX® hexa booster vaccination
- The safety profile of PEDIACEL® was similar to INFANRIX® hexa when co-administered with Prevenar® as a booster vaccination
- Post-booster GMTs and seroprotection rates for PRP, diphtheria, tetanus, polio and pneumococcal antigens and post-booster seroresponse rates for pertussis antigens (PT, FHA and PRN) were similar in both groups
- Pre-vaccination seroprotection rates against hepatitis B were > 93% in both groups while post-vaccination seroprotection rates were > 98% following INFANRIX® hexa or ENGERIX®-B Kinder (PEDIACEL® group) vaccination. Post-booster vaccination GMTs for Hepatitis B were higher in the PEDIACEL® group after administration of the monovalent hepatitis B vaccine (ENGERIX®-B Kinder) compared to the INFANRIX® hexa group.

Thus, this study supports the use of the PEDIACEL® vaccine as a booster dose in subjects primed with 3 doses of a hexavalent vaccine. In addition, for schedules requiring a 4th dose of hepatitis B vaccine, a monovalent hepatitis B vaccine can be given 1 month after PEDIACEL® to complete the hepatitis B vaccination schedule.

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