

Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as amended

Tetravac

(Purified Diphtheria Toxoid
Purified Tetanus Toxoid
Adsorbed purified pertussis toxoid
Adsorbed purified filamentous
haemagglutinin
Inactivated Poliomyelitis Virus
Inactivated Type 1 poliovirus
Inactivated Type 2 poliovirus
Inactivated Type 3 poliovirus)

IE/W/0005/pdWS/001

Rapporteur:	Ireland
Finalisation procedure (day 120):	01/11/2011
Date of finalisation of PAR	01/02/2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI
INN (or common name) of the active substance(s):	Purified Diphtheria Toxoid Ph. Eur. Purified Tetanus Toxoid Ph. Eur. Adsorbed purified pertussis toxoid Adsorbed purified filamentous haemagglutinin Inactivated Poliomyelitis Virus Ph. Eur Inactivated Type 1 poliovirus Inactivated Type 2 poliovirus Inactivated Type 3 poliovirus
MAH (s):	See section VI
Pharmaco-therapeutic group (ATC Code):	J07CA02
Pharmaceutical form(s) and strength(s):	Suspension for injection

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION¹

This study revealed no additional relevant information regarding the immunogenicity or safety profile not already included in the Company Core Data Sheet and related documents.

No further action required.

III. INTRODUCTION

In April 2010, the MAH submitted a completed paediatric study for TETRAXIM/TETRAVAC, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

TETRAXIM/TETRAVAC is currently authorised for active immunisation against diphtheria, tetanus, pertussis and poliomyelitis;

For primary vaccination in infants,

For booster in children who have previously received a primary vaccination with diphtheria-tetanus-whole-cell or acellular pertussis-poliomyelitis vaccine.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for TETRAXIM/TETRAVAC and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Note: Information on the pharmaceutical formulation used in the study(ies), the existence of a paediatric formulation, or conditions for extemporaneous formulations if applicable, should be mentioned here

The vaccines used in this study were;

Tetraxim/Tetravac (Batch number Z0156-3)

Each 0.5ml dose contains:

Purified diphtheria toxoid	≥30 IU
Purified tetanus toxoid	≥40 IU
Pertussis toxoid	25 □g
Filamentous Haemagglutinin	25 □g
Inactivated type 1 polio virus, D antigen	40 units

Inactivated type 2 polio virus, D antigen	8 units	
Inactivated type 3 polio virus, D antigen	32 units	
Aluminium hydroxide (expressed as Al ⁺⁺)	Formaldehyde	
2-phenoxyethanol	Medium 199 in water for injection	≤0.5 ml

DTaP Monovalent vaccine (CJ purified PDT vaccine):

Each 1.0ml dose contains:

Purified diphtheria toxoid	NMT 30 Lf
Purified tetanus toxoid	NMT 5 Lf
Inactivated purified pertussis antigens	NLT 8 IU

Aluminium hydroxide (expressed as Al ⁺⁺) phosphate dehydrate	Thimerosal	Disodium
Formalin (as formaldehyde)	Sodium phosphate dehydrate	
Sodium chloride	Water for injection	adequate

IPV monovalent vaccine (IMOVAXPOLIO)

Each 0.5ml dose contains:

Inactivated type 1 polio virus, D antigen	40 units
Inactivated type 2 polio virus, D antigen	8 units
Inactivated type 3 polio virus, D antigen	32 units

IV.2 Clinical aspects

1. Introduction

Note: If several studies are submitted, a list of all the clinical studies should be included with a brief description for each study.

The MAH submitted a final report for:

Immunogenicity and safety of Sanofi Pasteurs DTaP-IPV combined vaccine (TETRIXIM/TETRAVAC) given as a three-dose primary vaccination in South Korean healthy infants, as compared to commercially available DTaP and IPV monovalent vaccines.

2. Clinical study(ies)

Note: For each clinical study, the following structure is recommended. Assessors should consider if safety results should be discussed in the context of post-marketing safety data, liaising with pharmacovigilance colleagues if necessary.

➤ **Description**

➤ **Methods**

- Objectives

Primary Objective

The objective of this trial was to demonstrate the non-inferiority in terms of seroprotection rates (diphtheria, tetanus, polio types 1, 2 and 3) and seroconversion/vaccine response rates to pertussis antigens (PT, FHA) of Sanofi Pasteurs DTaP-IPV combined vaccine (Tetravac) versus commercially available Bikens DTaP (CJ purified PDT vaccine) and Sanofi Pasteurs IPV (Imovax Polio) monovalent vaccines, 1 month after the three-dose primary vaccination.

Primary Endpoint

The primary end point was determined one month after the third dose of study vaccine by the following parameters:

Seroprotection rates –
anti-tetanus antibody titres ≥ 0.1 IU/ml (ELISA)
anti-diphtheria antibody titres ≥ 0.01 IU/ml (Seroneutralisation)
anti-polio 1, 2 and 3 antibody titres ≥ 8 (1/dil)

Seroconversion/Vaccines Response rates –
anti-PT and anti-FHA antibody titres (ELISA Unit/ml [EU/ml]) ≥ 4 -fold increase.

Summary of Statistical Methodology for the Primary Objective

Non-inferiority of the study vaccine (Tetraxim/Tetravac) was tested over the control vaccines (Bikens DTaP (CJ purified PDT vaccine) and Sanofi Pasteurs IPV (Imovax Polio) monovalent vaccines) on the primary criteria, 1 month after the three-dose primary vaccination. For each antigen, the non-inferiority was demonstrated if the 95% confidence interval of the difference (study vaccine – reference vaccines) lay entirely above the clonical acceptable limit for non-inferiority (one-sided equivalence test, $\alpha = 2.5\%$).

The primary objective was reached if the non-inferiority was proven for each antigen, allowing the conclusion that the study vaccine was non-inferior to the control vaccines in terms of immunogenicity.

Secondary Objectives

There were a number of secondary objectives associated with this study;

- 1) To assess the non-inferiority in terms of seroprotection rates (diphtheria, tetanus, polio types 1, 2 and 3) and seroconversion/vaccine response rates to pertussis antigens (PT, FHA) of Sanofi Pasteurs DTaP-IPV combined vaccine versus historical reference (Study E2103294 – France and Study IPV07 – South Korea).
- 2) To assess and describe the immunogenicity of the study vaccines in both groups
- 3) To assess and describe the safety of the study vaccines after each dose.

Secondary Endpoints

Immunogenicity:

The secondary endpoints for the immunogenicity parameter were determined one month after the third dose of study vaccine as follows:

Seroprotection rates –
anti-tetanus antibody titres ≥ 0.01 IU/ml (ELISA)
anti-diphtheria antibody titres ≥ 0.1 IU/ml (Seroneutralisation)

Seroconversion/Vaccines Response rates –
anti-PT and anti-FHA antibody titres (ELISA Unit/ml [EU/ml]) ≥ 2 -fold increase.

Percentage of subjects with an anti-PT and anti-FHA antibody titres –
 ≥ 5 EU/ml, ≥ 10 EU/ml and ≥ 25 EU/ml

GMTs for all antibodies and GMTRs

Seroprotection rate: % of subjects with an antibody titre \geq cut-off, regardless of the serological status before vaccination.

Seroconversion/Vaccine response rates: Since there are no known correlates of cut-off values for protection for pertussis antibodies, seroconversion was assessed as a 4-fold increase in antibody titre from pre to post primary vaccination.

GMT ratio (GMTR) = post-primary vaccination/pre-primary vaccination.

According to the MAH, these secondary endpoints were chosen to comply with the requirements of the Korean Food and Drug Administration (KFDA).

Safety:

Occurrence, time to onset, number of days occurrence, severity, and seriousness of solicited (prelisted in the subject diary and Case Report Form), injection site reactions and systemic reactions occurring within 8 days (D0-D7) after each vaccination.

Occurrence, nature (MedDRA preferred term), time to onset, duration, severity, relationship to vaccination and seriousness of unsolicited (spontaneously reported) Adverse Events within 30 days (D0-D30) after each vaccination and of Serious Adverse Events (SAEs) throughout the trial up to last visit.

- Study design

This was a multicenter, randomised, controlled, open, two-arm study on 442 infants. Infants were randomly allocated in one of the two study groups in a 1:1 ratio as follows:

Group A: Tetravac at 2, 4 and 6 months of age.

Group B: Bikens DTaP (CJ purified PDT vaccine) and Sanofi Pasteurs IPV (Imovax Polio) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age.

- Treatments

Three vaccinations were administered: 1 dose of study vaccine(s) at 2, 4 and 6 months of age.

Two blood samples of 5ml were drawn: immediately before dose 1 and 1 month after dose 3.

All infants could also receive commercially available vaccines. The follow-up duration was approximately 5 months per subject.

➤ Results

- Recruitment/ Number analysed

A total of 219 subjects were included in Group A and 223 subjects were included in Group B. Eight subjects had an early termination. Three subjects in Group A and four subjects in Group B were voluntarily withdrawn, these withdrawals did not relate to an AE. One subject in Group B was discontinued for non compliance with the protocol.

Summary of the Studied Populations (All Included Subjects)

	Group A		Group B		Total	
	n	%	n	%	n	%
N planned	221		221		442	
N included	219	100	223	100	442	100
N Per-Protocol Analysis Set	206	94.1	214	96.0	420	95.0
N Full Analysis Set	218	99.5	223	100	441	99.8
N Safety Analysis Set	217	99.1	222	99.6	439	99.3
N Safety Analysis Set post-dose 1	217	99.1	222	99.6	439	99.3
N Safety Analysis Set post-dose 2	217	99.1	222	99.6	439	99.3
N Safety Analysis Set post-dose 3	217	99.1	220	98.7	437	98.9

(Source: Section 9, Table 9.011)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

- Baseline data

The median age was 2.0 months (ranging from 1.8 months to 2.3 months) in Group A and 2.0 months (ranging from 1.8 months to 2.4 months) in Group B.

There were slightly more male than female subjects with 53.0% boys in Group A and 54.3% in Group B.

- Efficacy results

Immunogenicity – Primary Objective

Table 1: Primary Objective – Seroprotection/Vaccine Resp[onse Rates One Month after the Third Dose of Study Vaccine – Per Protocol Analysis Set

	Group A (N=206)			Group B (N=214)			Group A minus Group B (i.e. Test minus Control)		
	n/M	%	(95% CI)	n/M	%	(95% CI)	% observed	(95% CI)*	Clinical delta (%)
Per-Protocol Analysis Set									
Anti-Tetanus ≥0.1 IU/mL	201/203	99.0	[96.5; 99.9]	210/212	99.1	[96.6; 99.9]	-0.04	(-2.67; 2.49)	10
Anti-Diphtheria ≥0.01 IU/mL	202/202	100.0	[98.2; 100.0]	210/210	100.0	[98.3; 100.0]	0.00	(-1.87; 1.80)	10
Anti-Polio 1 ≥8 (1/dil)	203/203	100.0	[98.2; 100.0]	210/211	99.5	[97.4; 100.0]	0.47	(-1.42; 2.64)	10
Anti-Polio 2 ≥8 (1/dil)	205/205	100.0	[98.2; 100.0]	210/212	99.1	[96.6; 99.9]	0.94	(-1.02; 3.37)	10
Anti-Polio 3 ≥8 (1/dil)	205/205	100.0	[98.2; 100.0]	210/212	99.1	[96.6; 99.9]	0.94	(-1.02; 3.37)	10
Anti-PT ≥4-fold increase (EU/mL)	198/205	96.6	[93.1; 98.6]	201/213	94.4	[90.4; 97.1]	2.22	(-1.99; 6.54)	10
Anti-FHA ≥4-fold increase (EU/mL)	189/205	92.2	[87.6; 95.5]	167/213	78.4	[72.3; 83.7]	13.79	(7.07; 20.48)	10

(Source: Section 9, Table 9.014)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

N= number of subjects in the population of analysis

n: number of subjects

M: number of subjects available for the endpoint

Percentages and 95% CI were calculated according to the subjects available for the endpoint

* The 95% CI was calculated based on the Wilson score method without continuity correction as described by Newcombe R.G.

If the lower bound of the 95% CI was greater than -10% then the null hypothesis H0 was rejected and it could be concluded for the non inferiority of valence i.

The seroprotection/seroconversion rates against tetanus, diphtheria, polio (1, 2 and 3) and pertussis (PT and FHA) obtained 1 month after the three-dose primary vaccination are presented in the table 1 above.

Group A (Tetraxim/Tetravac) results shown in Table 1:

Seroprotection rates anti-tetanus (≥ 0.1 IU/ml) were 99.0% in Group A
Seroprotection rate anti-diphtheria (≥ 0.01 IU/ml) was 100% in Group A
Seroprotection rates anti-polio 1, 2 and 3 (> 8 1/dil) were 100% in Group A
Seroconversion rates anti-PT (≥ 4 -fold increase EU/ml) was 96.6%
Seroconversion rates anti-FHA (≥ 4 -fold increase EU/ml) was 92.2%

Group B (DTaP (CJ purified PDT vaccine) and Sanofi Pasteurs IPV (Imovax Polio) monovalent vaccines) results from Table 1:

Seroprotection rates anti-tetanus (≥ 0.1 IU/ml) were 99.1% in Group B
Seroprotection rate anti-diphtheria (≥ 0.01 IU/ml) was 100% in Group B
Seroprotection rates anti-polio 1 (> 8 1/dil) were 99.5% in Group B
Seroprotection rates anti-polio 2 and 3 (> 8 1/dil) were 99.1% in Group B
Seroconversion rates anti-PT (≥ 4 -fold increase EU/ml) was 94.4%
Seroconversion rates anti-FHA (≥ 4 -fold increase EU/ml) was 78.4%

The seroconversion rates for anti-tetanus, anti-diphtheria, anti-polio 1, 2 and 3 and the seroconversion rate for anti-PT were comparable in Group A and B. Seroconversion rate for anti-FHA was higher in Group A than in Group B (92.2% versus 78.4%).

The results suggest that Tetraxim/Tetravac vaccine is statistically non inferior to Bikens DTaP (CJ purified PDT vaccine) and Sanofi Pasteurs IPV (Imovax Polio) monovalent vaccines, in terms of tetanus, diphtheria, polio and pertussis vaccine antigens.

Secondary Objectives

Seroprotection rates against tetanus, diphtheria, polio (1, 2 and 3) and pertussis (PT and FHA) were obtained 1 month after the three-dose primary vaccination and compared with historical references.

Table 2: Secondary Objective – Seroprotection/Vaccine Response Rates One Month after the Third Dose of Study Vaccines

Per-Protocol Analysis Set	Historical references (Studies E2103294 - IPV07)	Group A (N=206)		Group B (N=214)	
		n/M	% Observed with 95% CI	n/M	% Observed with 95% CI
Anti-Tetanus ≥ 0.1 IU/mL	98.9 [93.9; 99.97]	201/203	99.0 [96.5; 99.9]	210/212	99.1 [96.6; 99.9]
Anti-Diphtheria ≥ 0.01 IU/mL	100 [95.8; 100]	202/202	100.0 [98.2; 100.0]	210/210	100.0 [98.3; 100.0]
Anti-Polio 1 ≥ 8 (1/dil)	100 [95.4; 100]	203/203	100.0 [98.2; 100.0]	210/211	99.5 [97.4; 100.0]
Anti-Polio 2 ≥ 8 (1/dil)	100 [95.4; 100]	205/205	100.0 [98.2; 100.0]	210/212	99.1 [96.6; 99.9]
Anti-Polio 3 ≥ 8 (1/dil)	100 [95.4; 100]	205/205	100.0 [98.2; 100.0]	210/212	99.1 [96.6; 99.9]
Anti-PT ≥ 4 -fold increase (EU/mL)	90.8 [83.3; 95.7]	198/205	96.6 [93.1; 98.6]	201/213	94.4 [90.4; 97.1]
Anti-FHA ≥ 4 -fold increase (EU/mL)	92.5 [85.1; 96.9]	189/205	92.2 [87.6; 95.5]	167/213	78.4 [72.3; 83.7]

(Source: Section 9, Table 9.015)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAxIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

n: number of subjects

M: number of subjects available for the endpoint

Percentages and 95% CI were calculated according to the subjects available for the endpoint

* The 95% CI was calculated based on the Wilson score method without continuity correction as described by Newcombe R.G. If the lower bound of the 95% CI of the seroprotection / seroconversion rate was greater than the reference value minus the clinically acceptable limit for non-inferiority (-10%), then the null hypothesis H0 was rejected and it could be concluded for the non inferiority of valence i.

Reference historical control: sanofi pasteur DTaP-IPV//Hib (PENTAXIM™) at 2, 4 and 6 months of age (Study E2103294 - France); and sanofi pasteur's IPV (IMOVAX POLIO™) given at 2, 4 and 6 months of age in South Korean infants.

Comparison of Group A (Tetraxim/Tetravac) to the historical reference:

Seroprotection rates observed in Group A were comparable to those of the historical references (Studies E2103294 [France] and IPV07 [South Korea]):

For historical reference values Study E2103294 were used for anti-tetanus, anti-diphtheria, anti-PT and anti-FHA.

Historical reference values from study IPV07 were used for anti-polio 1, 2 and 3.

Anti-tetanus (≥ 0.1 IU/ml) seroprotection rates were 99.0% and 98.9% in Group A and historical reference group, respectively.

Anti-Diphtheria (≥ 0.01 IU/ml) seroprotection rate was 100% in both groups.

Anti-polio 1, 2 and 3 (≥ 8 1/dil) were 100% in both groups.

Seroprotection rates observed in Group A were comparable to these of the historical references.

Anti-PT (≥ 4 -fold increase EU/ml) seroconversion rates were 96.6% and 90.8% in Group A and historical reference group, respectively.

Anti-FHA (≥ 4 -fold increase EU/ml) seroconversion rates were 92.2% and 92.5% in Group A and historical reference group, respectively.

Seroprotection/seroconversion rates were comparable in the per protocol analysis set between Group A and the historical references (this comparison was not planned in the protocol).

The Group B results in comparison to the historical references are not discussed in this report.

Anti-Diphtheria Antibody Response

Table 3: Anti-Diphtheria (Seroneutralization) – Descriptive Results in the Per-Protocol Analysis Set

	Group A		Group B	
	Pre-Primary	Post-Primary	Pre-Primary	Post-Primary
N Data (=All – Missing)	205 (=206-1)	202 (=206-4)	214 (=214-0)	210 (=214-4)
Distribution {IU/mL}				
GMT	0.005	0.700	0.004	0.700
[95% CI]	[0.004; 0.006]	[0.606; 0.808]	[0.004; 0.005]	[0.615; 0.797]
≥0.01 IU/mL				
% (n)	26.8 (55.0)	100 (202)	21.5 (46.0)	100 (210)
[95% CI]	[20.9; 33.4]	[98.2; 100.0]	[16.2; 27.6]	[98.3; 100.0]
≥0.1 IU/mL				
% (n)	2.9 (6.00)	93.6 (189)	0 (0)	95.7 (201)
[95% CI]	[1.1; 6.3]	[89.2; 96.5]	[0.0; 1.7]	[92.0; 98.0]
INDIVIDUAL RATIO		Post/Pre		Post/Pre
N Data (=All – Missing)		201 (=206-5)		210 (=214-4)
Distribution				
GMTR		139		173
[95% CI]		[109; 177]		[144; 207]

(Source: Section 9, Table 9.016)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

Before the three-dose primary vaccination, GMTs were low and comparable in both groups. The proportion of subjects with a seroprotective anti-diphtheria antibody titre ≥ 0.01 IU/ml was similar in both groups, with values of 26.8% in Group A and 21.5% in Group B. The proportion of subjects with an anti-diphtheria antibody titre ≥ 0.1 IU/ml was low in both groups, with values of 2.9% and 0% in Group A and Group B, respectively.

After the three-dose primary vaccination, GMTs increased in both groups and the increased GMTs were similar in both groups. All subjects (100%) achieved a seroprotective anti-diphtheria antibody titre ≥ 0.01 IU/ml in both Groups A and B. The proportion of subjects with an anti-diphtheria antibody titre ≥ 0.1 IU/ml was high in both groups; 93.6% in Group A and 95.7% in Group B.

Anti-tetanus Antibody Response

Table 4: Anti-Tetanus (ELISA) – Descriptive Results in the Per-Protocol Analysis Set

	Group A		Group B	
	Pre-Primary	Post-Primary	Pre-Primary	Post-Primary
N Data (=All – Missing)	204 (=206-2)	203 (=206-3)	212 (=214-2)	212 (=214-2)
Distribution {IU/mL}				
GMT	0.022 ^I	4.02	0.019	3.67
[95% CI]	[0.018; 0.027]	[3.57; 4.53]	[0.016; 0.023]	[3.29; 4.11]
≥0.01 IU/mL				
% (n)	66.7 (136)	100 (203)	65.1 (138)	100 (212)
[95% CI]	[59.7; 73.1]	[98.2; 100.0]	[58.3; 71.5]	[98.3; 100.0]
≥0.1 IU/mL				
% (n)	16.2 (33.0)	99.0 (201)	12.7 (27.0)	99.1 (210)
[95% CI]	[11.4; 22.0]	[96.5; 99.9]	[8.6; 18.0]	[96.6; 99.9]
INDIVIDUAL RATIO		Post/Pre		Post/Pre
N Data (=All – Missing)		201 (=206-5)		210 (=214-4)
Distribution				
GMTR		185		200
[95% CI]		[144; 237]		[161; 249]

(Source: Section 9, Table 9.017)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

The above table illustrates the immunogenicity results for anti-tetanus GMTs and GMTRs.

Before the three dose primary vaccination, GMTs were low and comparable in both groups; 0.022 IU/ml in Group A and 0.019 IU/ml in Group B. The proportion of subjects with an anti-tetanus antibody titre ≥0.01 IU/ml was 66.7% and 65.1% in Groups A and B, respectively.

In addition, the proportion of subjects with a seroprotective anti-tetanus antibody titre ≥0.1 IU/ml was 16.2% and 12.7% in Groups A and B, respectively.

After the 3 dose primary vaccination, GMT values rose in both groups. GMTs were equal to 4.02 IU/ml in Group A and 3.67 IU/ml in Group B.

All subjects (100%), in both Group A and Group B achieved an anti-tetanus antibody titre of ≥0.01 IU/ml.

The proportion of subjects with a seroprotective anti-tetanus antibody titre ≥0.1 IU/ml was high and similar in both groups, 99.0% in Group A and 99.1% in Group B.

Anti-Polio 1 Antibody Response

Table 5: Anti-Polio 1 (Seroneutralization) – Descriptive Results in the Per-Protocol Analysis Set

	Group A		Group B	
	Pre-Primary	Post-Primary	Pre-Primary	Post-Primary
N Data (=All – Missing)	204 (=206-2)	203 (=206-3)	214 (=214-0)	211 (=214-3)
Distribution {IU/mL}				
GMT	4.20	1353	4.67	491
[95% CI]	[3.63; 4.87]	[1129; 1620]	[4.01; 5.43]	[422; 572]
≥8 (1/dil)				
% (n)	25.5 (52.0)	100 (203)	30.8 (66.0)	99.5 (210)
[95% CI]	[19.7; 32.0]	[98.2; 100.0]	[24.7; 37.5]	[97.4; 100.0]
INDIVIDUAL RATIO		Post/Pre		Post/Pre
N Data (=All – Missing)		201 (=206-5)		211 (=214-3)
Distribution				
GMTR		330		107
[95% CI]		[261; 418]		[84.4; 135]

(Source: Section 9, Table 9.018)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

The above table shows the immunogenicity results for anti-polio 1 in the PP analysis set. Before the three dose primary vaccination, GMTs were 4.20 (1/dil) in Group A and 4.67 (1/dil) in Group B. The proportion of subjects with an anti-polio 1 antibody titre ≥8 (1/dil) was similar in both groups, with values of 25.5% and 30.8% in Group A and Group B, respectively.

After the three dose primary vaccination, GMTs increased in both groups. GMTs were equal to 1353 (1/dil) and 491 (1/dil) in Group A and Group B, respectively. The proportion of subjects with an antibody titre ≥8 (1/dil) was 100.0% in Group A and 99.5% in Group B.

Anti-Polio 2 Antibody Response

Table 6: Anti-Polio 2 (Seroneutralization) – Descriptive Results in the Per-Protocol Analysis Set

	Group A		Group B	
	Pre-Primary	Post-Primary	Pre-Primary	Post-Primary
N Data (=All – Missing)	205 (=206-1)	205 (=206-1)	213 (=214-1)	212 (=214-2)
Distribution {IU/mL}		I		
GMT	6.78	1498	9.27	607
[95% CI]	[5.84; 7.88]	[1240; 1810]	[7.82; 11.0]	[522; 706]
≥8 (1/dil)				
% (n)	45.9 (94.0)	100 (205)	55.4 (118)	99.1 (210)
[95% CI]	[38.9; 52.9]	[98.2; 100.0]	[48.5; 62.2]	[96.6; 99.9]
INDIVIDUAL RATIO		Post/Pre		Post/Pre
N Data (=All – Missing)		204 (=206-2)		211 (=214-3)
Distribution				
GMTR		223		67.2
[95% CI]		[171; 290]		[51.6; 87.5]

(Source: Section 9, Table 9.019)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

Before the three dose primary vaccination, GMTs were low and comparable in both groups, in Group A the GMTs were equal to 6.78 (1/dil) and in Group B the GMTs were equal to 9.27 (1/dil). The proportion of subjects with an anti-polio 2 antibody titre ≥8 (1/dil) was similar in both groups, 45.9% and 55.4% in Groups A and B, respectively.

After the three dose primary vaccination, GMTS were equal to 1498 (1/dil) in Group A and 607 (1/dil) in Group B. The proportion of subjects with an antibody titre ≥8 (1/dil) was 100% in Group A and 99.1 % in Group B.

Anti-Polio 3 Antibody Response

Table 7: Anti-Polio 3 (Seroneutralization) – Descriptive Results in the Per-Protocol Analysis Set

	Group A		Group B	
	Pre-Primary	Post-Primary	Pre-Primary	Post-Primary
N Data (=All – Missing)	205 (=206-1)	205 (=206-1)	214 (=214-0)	212 (=214-2)
Distribution {IU/mL}				
GMT	3.92	1669	4.24	617
[95% CI]	[3.44; 4.46]	[1374; 2028]	[3.74; 4.81]	[520; 732]
≥8 (1/dil)				
% (n)	21.0 (43.0)	100 (205)	26.2 (56.0)	99.1 (210)
[95% CI]	[15.6; 27.2]	[98.2; 100.0]	[20.4; 32.6]	[96.6; 99.9]
INDIVIDUAL RATIO		Post/Pre		Post/Pre
N Data (=All – Missing)		204 (=206-2)		212 (=214-2)
Distribution				
GMTR		427		148
[95% CI]		[340; 536]		[121; 181]

(Source: Section 9, Table 9.020)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

Before the three dose primary vaccination, GMTs were low and comparable in both groups, in Group A the GMTs were equal to 3.92 (1/dil) and in Group B the GMTs were equal to 4.24 (1/dil). The proportion of subjects with an anti-polio 2 antibody titre ≥8 (1/dil) was similar in both groups, 21.0% and 26.2% in Groups A and B, respectively.

After the three dose primary vaccination, GMTS were equal to 1669 (1/dil) in Group A and 617 (1/dil) in Group B. The proportion of subjects with an antibody titre ≥8 (1/dil) was 100% in Group A and 99.1 % in Group B.

Anti-PT Antibody Response

Table 8: Anti-PT (ELISA) – Descriptive Results Per-Protocol Analysis Set.

	Group A		Group B	
	Pre-Primary	Post-Primary	Pre-Primary	Post-Primary
N Data (=All – Missing)	205 (-206-1)	205 (-206-1)	214 (-214-0)	213 (-214-1)
Distribution {EU/mL}				
GMT	2.27	203	2.88	201
[95% CI]	[1.99; 2.59]	[178; 233]	[2.46; 3.38]	[174; 231]
≥ 5 EU/mL				
% (n)	27.8 (57.0)	99.5 (204)	35.0 (75.0)	98.1 (209)
[95% CI]	[21.8; 34.5]	[97.3; 100.0]	[28.7; 41.8]	[95.3; 99.5]
≥ 10 EU/mL				
% (n)	5.9 (12.0)	96.6 (198)	13.6 (29.0)	96.2 (205)
[95% CI]	[3.1; 10.0]	[93.1; 98.6]	[9.3; 18.9]	[92.7; 98.4]
≥ 25 EU/mL				
% (n)	2.0 (4.00)	95.6 (196)	5.6 (12.0)	95.8 (204)
[95% CI]	[0.5; 4.9]	[91.8; 98.0]	[2.9; 9.6]	[92.1; 98.0]
INDIVIDUAL RATIO		Post/Pre		Post/Pre
N Data (=All – Missing)		204 (=206-2)		213 (=214-1)
Distribution				
GMTR		89.0		69.3
[95% CI]		[72.8; 109]		[55.5; 86.5]
≥ 2 -fold increase				
% (n)		97.1 (199)		94.8 (202)
[95% CI]		[93.7; 98.9]		[90.9; 97.4]
≥ 4 -fold increase				
% (n)		96.6 (198)		94.4 (201)
[95% CI]		[93.1; 98.6]		[90.4; 97.1]

(Source: Section 9, Table 9.021)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

From the table above it can be seen that before the three dose primary vaccination, GMTs were equal to 2.27 EU/ml in Group A and 2.88 EU/ml in Group B. The proportion of subjects with an anti-PT antibody titre ≥ 5 EU/ml was 27.8% and 35.0% in Group A and B, respectively. The proportion of subjects with an anti-PT antibody titre ≥ 10 EU/ml and ≥ 25 EU/ml was 5.9% and 2.0% in Group A and 13.6% and 5.6% in Group B.

After the three dose primary vaccination GMTs were equal to 203 EU/ml and 201 EU/ml in Group A and B respectively.

The proportion of subjects with an anti-PT antibody titre ≥ 5 EU/ml was 99.5% and 98.1% in Group A and B, respectively. The proportion of subjects with an anti-PT antibody titre ≥ 10 EU/ml and ≥ 25 EU/ml was 96.6% and 95.6% in Group A and 96.2% and 95.8% in Group B.

Anti-FHA Antibody Response

Table 9: Anti-FHA (ELISA) – Descriptive Results in the Per Protocol Analysis Set

	Group A		Group B	
	Pre-Primary	Post-Primary	Pre-Primary	Post-Primary
N Data (=All – Missing)	204 (=206-2)	205 (=206-1)	213 (=214-1)	213 (=214-1)
Distribution {IU/mL}				
GMT	4.09	132	4.19	44.5
[95% CI]	[3.61; 4.64]	[120; 146]	[3.65; 4.80]	[40.8; 48.5]
≥5 EU/mL				
% (n)	49.5 (101)	100 (205)	44.6 (95.0)	100 (213)
[95% CI]	[42.5; 56.6]	[98.2; 100.0]	[37.8; 51.5]	[98.3; 100.0]
≥10 EU/mL				
% (n)	14.7 (30.0)	100 (205)	21.6 (46.0)	99.1 (211)
[95% CI]	[10.1; 20.3]	[98.2; 100.0]	[16.3; 27.7]	[96.6; 99.9]
≥25 EU/mL				
% (n)	2.0 (4.00)	96.6 (198)	4.7 (10.0)	86.4 (184)
[95% CI]	[0.5; 4.9]	[93.1; 98.6]	[2.3; 8.5]	[81.0; 90.7]
INDIVIDUAL RATIO		Post/Pre		Post/Pre
N Data (=All – Missing)		203 (=206-3)		212 (=214-2)
Distribution				
GMTR		32.0		10.8
[95% CI]		[27.0; 38.0]		[9.07; 12.9]
≥2-fold increase				
% (n)		97.1 (199)		89.7 (191)
[95% CI]		[93.7; 98.9]		[84.8; 93.4]
≥4-fold increase				
% (n)		92.2 (189)		78.4 (167)
[95% CI]		[87.6; 95.5]		[72.3; 83.7]

(Source: Section 9, Table 9.022)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

Before the three dose primary vaccination GMTs were equal to 4.09 EU/ml in Group A and 4.19 EU/ml in Group B. The proportion of subjects with an anti-FHA antibody titre ≥ 5 EU/ml and ≥ 10 EU/ml was 49.5% and 14.7% in Group A and 44.6% and 21.6% in Group B, respectively. The proportion of subjects with an anti-FHA antibody titre ≥ 25 EU/ml was low in both groups with values of 2.0% and 4.7% in Group A and Group B, respectively.

After the three dose primary vaccination, as shown in the table above, GMTs increased on both groups. GMTs were higher in Group A where a value of 132 EU/ml was obtained than in Group B where a value of 44.5 EU/ml was obtained. In Group A the proportion of subjects achieving an anti-FHA antibody titre ≥ 5 EU/ml was 100.0%, ≥ 10 EU/ml was 100.0% and ≥ 25 EU/ml was 96.6%. In Group B the proportion of subjects achieving an anti-FHA antibody titre ≥ 5 EU/ml was 100.0%, ≥ 10 EU/ml was 99.1% and ≥ 25 EU/ml was 86.4%.

- Safety results

The following table presents the safety overview for Group A and Group B of solicited and unsolicited events/reactions:

Table 10: Safety Overview after and Vaccine Injection by Vaccine Group (Safety Analysis Set)

	Group A (N=217)			Group B (N=222)		
	n/N	%	[95% CI]	n/N	%	[95% CI]
Subjects with at least one:						
- Solicited reaction	194/217	89.4	[84.5 ; 93.2]	188/222	84.7	[79.3 ; 89.2]
- Solicited injection site reaction	157/217	72.4	[65.9 ; 78.2]	128/222	57.7	[50.9 ; 64.2]
- Solicited systemic reaction	169/217	77.9	[71.8 ; 83.2]	165/222	74.3	[68.1 ; 79.9]
- Unsolicited event	158/217	72.8	[66.4 ; 78.6]	164/222	73.9	[67.6 ; 79.5]
- Unsolicited reaction	5/217	2.3	[0.8 ; 5.3]	3/222	1.4	[0.3 ; 3.9]
- Unsolicited injection site reaction	4/217	1.8	[0.5 ; 4.7]	3/222	1.4	[0.3 ; 3.9]
- Unsolicited systemic reaction	1/217	0.5	[0.0 ; 2.5]	0/222	0.0	[0.0 ; 1.6]
- Adverse event leading to study discontinuation	0/217	0.0	[0.0 ; 1.7]	0/222	0.0	[0.0 ; 1.6]
- Serious adverse event	14/217	6.5	[3.6 ; 10.6]	12/222	5.4	[2.8 ; 9.3]
- Death	0/217	0.0	[0.0 ; 1.7]	0/222	0.0	[0.0 ; 1.6]

A total of 194 subjects (89.4%) in Group A and 188 subjects (84.7%) in Group B experienced at least one solicited reaction. The proportion of subjects with at least one solicited systemic reaction was 77.9% in Group A and 74.3% in Group B.

Solicited injection site reactions were slightly more frequent in Group A (72.4% of subjects) compared to Group B (57.7% of subjects).

Unsolicited events were reported in 158 subjects (72.8%) in Group A and in 164 subjects (73.9%) in Group B,

Eight subjects experienced unsolicited AEs assessed by the Investigator as related to vaccination, 5 subjects in Group A (2.3%) and 3 subjects in Group B (1.4%) – all these were injection site reactions.

With regard to the 1 subject in Group A who is reported to have experienced an unsolicited systemic reaction it should be noted that according to company documentation this was in fact an unsolicited injection site reaction and was recorded by mistake as an unsolicited systemic reaction by the Investigator.

Fourteen subjects in Group A (6.5%) and 12 subjects in Group B (5.4%) experienced at least one SAE.

No AE led to study discontinuation and no death occurred during the trial.

Table 11: Solicited Injection Site Reactions occurring between D0 and D7 after any and each Vaccine Injection per Vaccine Group - Safety Analysis Set.

	Group A (N=217)				Group B (N=222)											
	DTaP-IPV				DTaP				IPV				Total			
	Any		Severe		Any		Severe		Any		Severe		Any		Severe	
Subjects with	n/M	%	n/M	%	n/M	%	n/M	%	n/M	%	n/M	%	n/M	%	n/M	%
Injection site reactions																
Post any injection	157/217	72.4	3/217	1.4	126/222	56.8	5/222	2.3	86/222	38.7	3/222	1.4	128/222	57.7	6/222	2.7
Injection site tenderness																
Per subject*																
Post any injection	109/217	50.2	2/217	0.9	86/222	38.7	2/222	0.9	77/222	34.7	2/222	0.9	90/222	40.5	3/222	1.4
Post 1 st injection	82/217	37.8	0/217	0.0	58/222	26.1	1/222	0.5	59/222	26.6	1/222	0.5	64/222	28.8	1/222	0.5
Post 2 nd injection	68/217	31.3	2/217	0.9	52/222	23.4	0/222	0.0	38/222	17.1	0/222	0.0	58/222	26.1	0/222	0.0
Post 3 rd injection	65/217	30.0	0/217	0.0	49/220	22.3	1/220	0.5	37/220	16.8	1/220	0.5	54/220	24.5	2/220	0.9
Per Injected dose**	215/651	33.0	2/651	0.3	159/664	23.9	2/664	0.3	134/664	20.2	2/664	0.3	293/1328	22.1	4/1328	0.3
Injection site erythema																
Per subject*																
Post any injection	131/217	60.4	1/217	0.5	91/222	41.0	3/222	1.4	38/222	17.1	1/222	0.5	94/222	42.3	3/222	1.4
Post 1 st injection	68/217	31.3	1/217	0.5	16/222	7.2	0/222	0.0	21/222	9.5	0/222	0.0	23/222	10.4	0/222	0.0
Post 2 nd injection	91/217	41.9	0/217	0.0	73/222	32.9	3/222	1.4	22/222	9.9	1/222	0.5	75/222	33.8	3/222	1.4
Post 3 rd injection	81/217	37.3	0/217	0.0	49/220	22.3	1/220	0.5	26/220	11.8	0/220	0.0	51/220	23.2	1/220	0.5
Per Injected dose**	240/651	36.9	1/651	0.2	138/664	20.8	4/664	0.6	69/664	10.4	1/664	0.2	207/1328	15.6	5/1328	0.4

I	Group A (N=217)				Group B (N=222)											
	DTaP-IPV				DTaP				IPV				Total			
	Any		Severe		Any		Severe		Any		Severe		Any		Severe	
Subjects with	n/M	%	n/M	%	n/M	%	n/M	%	n/M	%	n/M	%	n/M	%	n/M	%
Injection site swelling																
Per subject*																
Post any injection	99/217	45.6	1/217	0.5	59/222	26.6	1/222	0.5	26/222	11.7	1/222	0.5	65/222	29.3	1/222	0.5
Post 1st injection	48/217	22.1	1/217	0.5	9/222	4.1	0/222	0.0	12/222	5.4	0/222	0.0	13/222	5.9	0/222	0.0
Post 2nd injection	65/217	30.0	0/217	0.0	41/222	18.5	1/222	0.5	13/222	5.9	1/222	0.5	43/222	19.4	1/222	0.5
Post 3rd injection	63/217	29.0	0/217	0.0	27/220	12.3	0/220	0.0	15/220	6.8	0/220	0.0	32/220	14.5	0/220	0.0
Per Injected dose**	176/651	27.0	1/651	0.2	77/664	11.6	1/664	0.2	40/664	6.0	1/664	0.2	117/1328	8.8	2/1328	0.2

(Source: Section 9, Tables 9.033, 9.034, 9.035, 9.055, 9.056, 9.057, 9.058, 9.071 and 9.102)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRIXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

*Number and percentage of subjects presenting with at least one specific solicited injection site reaction.

**Number and percentage of doses followed by a specific solicited injection site reaction after any dose given.

N = number of injected subjects with available safety data

n/% = number of subjects presenting with or doses followed by a solicited systemic adverse reaction

Any = number of subjects with at least one particular symptom regardless of the intensity/severity:

Severe: number of subjects with at least one particular symptom recorded as severe

Tenderness "severe" = cries when injected limb is moved or the movement of the injected limb is reduced. Erythema/Swelling "severe" = longest diameter was ≥ 5 cm

Note: Reactions are solicited events or events identified by the Investigator in the CRF as related to the study vaccine

Note: For each individual solicited reactions, the denominator for percentages is the number of vaccinated subjects with at least one safety record for this solicited reaction available

The table above shows the incidence of solicited injection site reactions in Group A and Group B within 8 days after each dose and any doses injected.

The Birkens DTaP vaccine and Sanofi Pasteur IPV vaccine were injected at separate sites, therefore the results of the injection site reactions of these two vaccines are also presented for Group B.

After any Vaccine Injection:

More subjects experienced at least one injection site reaction in Group A (72.4%) than in Group B after administration of DTaP (56.8%) and IPV vaccines (38.7%).

Severe injection site reactions were reported in the same proportion of subjects in each vaccine group; Group A 1.4%, Group B DTaP 2.3% and Group B IPV 1.4%.

In Group A, erythema and tenderness, were the most frequent solicited injection site reactions, 60.4% and 50.2% of subjects, respectively. Swelling was reported in 45.6% of subjects.

In Group B, after administration of DTaP vaccine, erythema and tenderness were the most frequently reported solicited injection site reactions, 41.0% and 38.7% of subjects, respectively. Swelling was reported in 26.6% of subjects.

In Group B, after administration of IPV vaccine, the most frequent solicited injection site reaction was tenderness (34.7%), followed by erythema (17.1%) and then swelling (11.7%).

After Each Vaccine Injection:

The incidence of tenderness reactions did not increase with the subsequent doses but decreased slightly in both groups for all vaccines given.

The incidence of erythema and swelling reactions tended to increase in both groups after the 2nd injection, with significant increases with the subsequent DTaP vaccine doses in Group B.

Overall, during the three-dose primary vaccination period, the proportion of vaccine injections followed by tenderness, erythema and swelling was higher in Group A (33.0%, 36.9% and 27.0%, respectively) than in Group B DTaP vaccine (23.9%, 20.8% and 11.6%, respectively) and Group B IPV vaccine (20.2%, 10.4% and 6.0%, respectively).

Tenderness

Most of the tenderness episodes were of mild severity. Severe tenderness was reported in two subjects in each study group. All of these episodes were self limiting and resolved within 3 days except for one of the two cases in Group A where tenderness was reported for 'less than seven days'.

Erythema

All episodes of erythema occurred between D0 and D3. Most episodes of erythema were of mild severity. Severe erythema was reported in one subject in Group A, three subjects in Group B following DTaP vaccine and one subject in Group B following IPV vaccine.

The episodes of severe erythema were self limiting and resolved within 3 days.

Swelling

All swelling episodes occurred between D0 and D3 and most of the swelling episodes were of mild severity.

Severe swelling was reported in one subject in each study group; this swelling was self limiting and persisted for less than 3 days.

Table 12: Solicited Systemic Adverse Reactions Occurred between D0 and D7 after any and each Vaccine Injection per Vaccine Group (Safety Analysis Set)

	Group A (N=217)				Group B (N=222)			
	Any		Severe		Any		Severe	
Subjects with	n/M	%	n/M	%	n/M	%	n/M	%
Solicited systemic reactions								
Post any injection	169/217	77.9	10/217	4.6	165/222	74.3	4/222	1.8
Fever								
Per subject*								
Post any injection	51/217	23.5	2/217	0.9	38/222	17.1	1/222	0.5
Post 1st injection	21/217	9.7	0/217	0.0	14/222	6.3	0/222	0.0
Post 2nd injection	20/217	9.2	1/217	0.5	14/222	6.3	0/222	0.0
Post 3rd injection	21/217	9.7	1/217	0.5	19/220	8.6	1/220	0.5
Per Injected dose**	62/651	9.5	2/651	0.3	47/664	7.1	1/664	0.2
Vomiting								
Per subject*								
Post any injection	89/217	41.0	1/217	0.5	88/222	39.6	0/222	0.0
Post 1st injection	67/217	30.9	1/217	0.5	61/222	27.5	0/222	0.0
Post 2nd injection	38/217	17.5	0/217	0.0	38/221	17.2	0/221	0.0
Post 3rd injection	29/217	13.4	0/217	0.0	28/220	12.7	0/220	0.0
Per Injected dose**	134/651	20.6	1/651	0.2	127/664	19.1	0/664	0.0
Crying abnormal								
Per subject*								
Post any injection	100/217	46.1	2/217	0.9	92/222	41.4	1/222	0.5
Post 1st injection	73/217	33.6	2/217	0.9	63/222	28.4	1/222	0.5
Post 2nd injection	53/217	24.4	0/217	0.0	53/221	24.0	0/221	0.0
Post 3rd injection	41/217	18.9	0/217	0.0	41/220	18.6	0/220	0.0
Per Injected dose**	167/651	25.7	2/651	0.3	157/664	23.6	1/664	0.2
Drowsiness								
Per subject*								
Post any injection	93/217	42.9	1/217	0.5	86/222	38.7	0/222	0.0
Post 1st injection	71/217	32.7	1/217	0.5	65/222	29.3	0/222	0.0
Post 2nd injection	42/217	19.4	0/217	0.0	41/221	18.6	0/221	0.0
Post 3rd injection	33/217	15.2	0/217	0.0	34/220	15.5	0/220	0.0
Per Injected dose**	146/651	22.4	1/651	0.2	140/664	21.1	0/664	0.0

Table 12 cont.: Solicited Systemic Adverse Reactions Occurred between D0 and D7 after any and each Vaccine Injection per Vaccine Group (Safety Analysis Set)

Subjects with	Group A (N=217)				Group B (N=222)			
	Any		Severe		Any		Severe	
	n/M	%	n/M	%	n/M	%	n/M	%
Appetite lost								
Per subject*								
Post any injection	111/217	51.2	3/217	1.4	106/222	47.7	1/222	0.5
Post 1st injection	71/217	32.7	2/217	0.9	72/222	32.4	0/222	0.0
Post 2nd injection	56/217	25.8	1/217	0.5	50/221	22.6	1/221	0.5
Post 3rd injection	49/217	22.6	0/217	0.0	41/220	18.6	0/220	0.0
Per Injected dose**	176/651	27.0	3/651	0.5	163/664	24.5	1/664	0.2
Irritability								
Per subject*								
Post any injection	99/217	45.6	4/217	1.8	103/222	46.4	1/222	0.5
Post 1st injection	74/217	34.1	1/217	0.5	72/222	32.4	0/222	0.0
Post 2nd injection	54/217	24.9	3/217	1.4	50/221	22.6	1/221	0.5
Post 3rd injection	39/217	18.0	0/217	0.0	41/220	18.6	0/220	0.0
Per Injected dose**	167/651	25.7	4/651	0.6	163/664	24.5	1/664	0.2

(Source: Section 9, Tables 9.040, 9.041, 9.042, 9.072 to 9.075, 9.088 and 9.103)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAVAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

All solicited adverse events (AE) are considered as reactions (or related to the vaccination), as per protocol.

*Number and percentage of subjects presenting with a specific solicited systemic adverse reaction after any dose given.

**Number and percentage of doses followed by a specific solicited systemic reaction after any dose given.

N = number of injected subjects with available safety data

n/% = number/percentage of subjects presenting with or doses followed by a solicited systemic adverse reaction

Any = number of subjects with at least one particular symptom regardless of the intensity/severity:

Any fever – axillary temperature $\geq 37.4^{\circ}\text{C}$

Severe: number of subjects with at least one particular symptom recorded as severe

Fever $\geq 39.0^{\circ}\text{C}$ (axillary temperature); vomiting ≥ 6 episodes per 24 hours or requiring parenteral hydration;

Crying abnormal >3 hours; drowsiness sleeping most of the time or difficult to wake up;

Appetite lost: Refuses ≥ 3 feeds or refuses most feeds; irritability: Inconsolable.

After any vaccine injection:

The proportion of subjects with at least one solicited systemic reaction was similar in Group A (77.9%) and in Group B (74.3%). Severe solicited systemic reactions were reported in 10 subjects in Group A (4.6%) and 4 subjects in Group B (1.8%).

In Group A, appetite lost was the most frequent solicited systemic reaction (51.2%), followed by abnormal crying (46.1%), irritability (45.6%), drowsiness (42.9%), vomiting (41.0%) and fever (23.5%).

In Group B, appetite lost and irritability were the most frequent solicited systemic reactions (47.7% and 46.4% of the subjects, respectively), followed by abnormal crying (41.4%), vomiting (39.6%) and drowsiness (38.7%). Fever was less common (17.1%).

After each vaccine injection:

The incidence of vomiting, abnormal crying, drowsiness, loss of appetite and irritability decreased in both groups from the 1st to the 3rd vaccine injection.

The incidence of fever remained stable in both groups after each vaccine injection.

Overall, during the three-dose primary vaccination period, the proportion of vaccine injections followed by fever, vomiting, abnormal crying, drowsiness, appetite lost and irritability was similar in Group A (9.5%, 20.6%, 25.7%, 22.4%, 27.0% and 25.7%, respectively) and in Group B (7.1%, 19.1%, 23.6%, 21.1%, 24.5% and 24.5%, respectively).

Fever

Most episodes of fever occurred between D0 and D3 and most were considered of mild severity. Severe fever (>39°C) was reported in two subjects in Group A (1.8%) and one subject in Group B (0.9%).

Vomiting

Most vomiting episodes occurred between D0 and D3; most of the episodes were of mild severity and lasted less than 3 days. After any given dose, vomiting lasted more than 8 days in five subjects (2.3%) in Group A and four subjects (1.8%) in Group B.

Severe vomiting was reported in one subject in Group A (0.5%), the episode lasted less than 3 days and resolved spontaneously.

Abnormal crying

Most of the crying episodes were of mild severity and lasted less than 3 days. After any given dose, abnormal crying lasted more than 8 days in ten subjects (4.6%) in Group A and two subjects (0.9%) in Group B.

Severe abnormal crying was reported in two subjects in Group A (0.9%) and one subject in Group B (0.5%). These severe episodes lasted less than 3 days.

Drowsiness

Most of the drowsiness episodes were reported as mild in nature and lasted for less than 3 days. After any given dose, drowsiness lasted more than 8 days in one subject (0.5%) in Group A.

Severe drowsiness was reported in one subject in Group A (0.5%). This case reported severe self limited drowsiness within 4 days after the first injection, lasting less than 3 days. In this case drowsiness was also associated with severe appetite loss.

Appetite loss

Most episodes of appetite loss were of mild severity and lasted less than 3 days. After any given dose, appetite loss lasted more than 8 days in six subjects (2.8%) in Group A and four subjects (1.8%) in Group B.

Severe appetite loss was reported in three subjects in Group A (1.4%) and one subject in Group B (0.5%).

Irritability

Most of the irritability episodes were of mild severity and lasted less than 3 days. However, after any given dose, irritability lasted more than 8 days in 11 subjects in Group A (5/1%) and one subject in Group B (0.5%).

Severe irritability was reported in four subjects in Group A (1.8%) and one subject in Group B (0.5%); each episode lasted less than 3 days.

Unsolicited Adverse Events Between Day 0 and Day 30

Table 13: Summary of Unsolicited Adverse Events which Occurred within 30 Days after each Injection (Safety Analysis Set)

	Group A (N=217)			Group B (N=222)		
	n/N	%	[95% CI]	n/N	%	[95% CI]
Subjects with at least one:						
-Unsolicited event	158/217	72.8	[66.4 ; 78.6]	164/222	73.9	[67.6 ; 79.5]
-Severe unsolicited event	6/217	2.8	[1.0 ; 5.9]	6/222	2.7	[1.0 ; 5.8]
-Unsolicited systemic event	157/217	72.4	[65.9 ; 78.2]	163/222	73.4	[67.1 ; 79.1]
-Severe unsolicited systemic event	6/217	2.8	[1.0 ; 5.9]	5/222	2.3	[0.7 ; 5.2]
-Unsolicited reaction	5/217	2.3	[0.8 ; 5.3]	3/222	1.4	[0.3 ; 3.9]
-Severe unsolicited reaction	0/217	0.0	[0.0 ; 1.7]	1/222	0.5	[0.0 ; 2.5]
-Unsolicited injection site reaction	4/217	1.8	[0.5 ; 4.7]	3/222	1.4	[0.3 ; 3.9]
-Severe unsolicited injection site reaction	0/217	0.0	[0.0 ; 1.7]	1/222	0.5	[0.0 ; 2.5]
-Unsolicited systemic reaction	1/217*	0.5	[0.0 ; 2.5]	0/222	0.0	[0.0 ; 1.6]
-Severe unsolicited systemic reaction	0/217	0.0	[0.0 ; 1.7]	0/222	0.0	[0.0 ; 1.6]

(Source: Section 9, Table 9.059)

*: inflammation at the injection site which was classified by mistake as systemic reaction by the Investigator

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

Note: Reactions are solicited events or events identified by the Investigator in the CRF as related to the study vaccine

Note: The denominator for percentages is the number of vaccinated subjects (Safety Analysis Set) with at least one safety data available

Unsolicited events were reported in 158 subjects (72.8%) in Group A and 164 subjects (73.9%) in Group B within 30 days after any vaccine injection. The results from Table 13, above indicates that most of the unsolicited events were systemic. The proportion of subjects with at least one unsolicited event tended to increase from the first to the third injection in both groups, the increase was from 34.6% to 44.7% in Group A and from 36.5% to 50.0% in Group B.

Unsolicited events were assessed as related to vaccination by the investigator in five subjects in Group A (2.3%) and three subjects in Group B (1.4%). All unsolicited reactions were injection site reactions except for one subject in Group A (this was in fact an unsolicited injection site reaction and was recorded by mistake as an unsolicited systemic reaction by the Investigator).

Severe unsolicited events were reported in six subjects in Group A (2.8%) and six subjects in Group B (2.7%). None was assessed as related to vaccination, except for one subject in Group B.

Table 14: Unsolicited Adverse Reactions Occurred within 30 Days after any Vaccine Injection, by System Organ Class and Preferred Term – Safety Analysis Set

	Group A (N=217)			Group B (N=222)		
	n/N	%	[95% CI]	n/N	%	[95% CI]
Subjects with at least one unsolicited reaction	5/217	2.3	[0.8 ; 5.3]	3/222	1.4	[0.3 ; 3.9]
General disorders and administration site conditions	5/217	2.3	[0.8 ; 5.3]	3/222	1.4	[0.3 ; 3.9]
Injection site bruising	0/217	0.0	[0.0 ; 1.7]	1/222	0.5	[0.0 ; 2.5]
Injection site erythema	0/217	0.0	[0.0 ; 1.7]	1/222	0.5	[0.0 ; 2.5]
Injection site induration	2/217	0.9	[0.1 ; 3.3]	0/222	0.0	[0.0 ; 1.6]
Injection site inflammation	3/217	1.4	[0.3 ; 4.0]	0/222	0.0	[0.0 ; 1.6]
Swelling	0/217	0.0	[0.0 ; 1.7]	1/222	0.5	[0.0 ; 2.5]
Tenderness	0/217	0.0	[0.0 ; 1.7]	1/222	0.5	[0.0 ; 2.5]
Injury, poisoning and procedural complications	1/217	0.5	[0.0 ; 2.5]	0/222	0.0	[0.0 ; 1.6]
Contusion	1/217	0.5	[0.0 ; 2.5]	0/222	0.0	[0.0 ; 1.6]
Skin and subcutaneous tissue disorders	0/217	0.0	[0.0 ; 1.7]	1/222	0.5	[0.0 ; 2.5]
Erythema	0/217	0.0	[0.0 ; 1.7]	1/222	0.5	[0.0 ; 2.5]

(Source: Section 9, Table 9.049)

Group A: sanofi pasteur's DTaP-IPV vaccine (TETRAXIM™) at 2, 4 and 6 months of age

Group B: Biken's DTaP (CJ purified PDT vaccine™) and sanofi pasteur's IPV (IMOVAX POLIO™) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age

Note: The denominator for percentages is the number of vaccinated subjects (Safety Analysis Set) with at least one safety data available

Note: Reactions are solicited events or events identified by the Investigator in the CRF as related to the study vaccine

Most of the unsolicited reactions were injection site reactions (induration and inflammation in Group A and bruising, erythema, swelling and tenderness in Group B). Erythema was reported in one subject in Group B and contusion at the administration site in one subject in Group A.

Table 15: Serious Adverse Events Occurring Throughout the Trial per Subject – Safety Analysis Set

Subject number	Description of event	Onset - Delay after the last dose	Relationship to vaccination	Outcome
Group A				
002-00028	Bronchiolitis	11 days post-dose 3	Not related	Recovered
002-00039	Bronchiopneumonia	22 days post-dose 1	Not related	Recovered
002-00041	Acute pyelonephritis	30 days post-dose 3	Not related	Recovered
003-00009	Abcess axilla left after BCG vaccination	2 days post-dose 3	Not related	Recovered
004-00013	Urinary tract infection	41 days post-dose 1	Not related	Recovered
004-00037	Bronchiolitis	40 days post-dose 1	Not related	Recovered
005-00036	Bronchiolitis	7 days post-dose 1	Not related	Recovered
006-00004	Urinary tract infection	2 days post-dose 2	Not related	Recovered
006-00009	Suspected gastroenteritis	3 days post-dose 1	Not related	Recovered
006-00019	Suspected sepsis	9 days post-dose 1	Not related	Recovered
006-00030	Acute bronchiolitis	35 days post-dose 1	Not related	Recovered
	Bronchiolitis	6 days post-dose 2	Not related	Recovered
006-00043	Bronchiolitis	20 days post-dose 3	Not related	Recovered
006-00045	Bronchiolitis	2 days post-dose 2	Not related	Recovered
008-00020	Sinusitis	12 days post-dose 1	Not related	Recovered
	Sinusitis	46 days post-dose 1	Not related	Recovered
	Pneumonia	11 days post-dose 3	Not related	Recovered
Group B				
001-00024	Bronchiolitis	37 days post-dose 1	Not related	Recovered
	Acute gastroenteritis	2 days post-dose 2	Not related	Recovered
	Bronchiolitis	41 days post-dose 2	Not related	Recovered
002-00025	Acute bronchiolitis	56 days post-dose 1	Not related	Recovered
004-00005	Bronchiolitis	35 days post-dose 2	Not related	Recovered
004-00055	Bronchiolitis	3 days post-dose 1	Not related	Recovered
004-00057	Urinary tract infection	24 days post-dose 1	Not related	Recovered
005-00005	Pharyngitis	2 days post-dose 2	Not related	Recovered
005-00015	Pharyngitis	6 days post-dose 3	Not related	Recovered
006-00003	Bronchiolitis	1 day post-dose 1	Not related	Recovered
006-00036	Urinary tract infection	10 days post-dose 2	Not related	Recovered
007-00011	Acute bronchiolitis	4 days post-dose 2	Not related	Recovered
007-00037	Suspected sepsis	23 days post-dose 1	Not related	Recovered
009-00009	Suspected sepsis	9 days post-dose 1	Not related	Recovered

(Source: Appendix 15, Listing 15.4)

The table above indicates that from a total of 442 subjects included in the study, a total of 31 SAEs were reported in 26 subjects. Fourteen subjects in Group A (6.5%) experienced 17 SAEs, and 12 subjects in Group B (5.4%) experienced 14 SAEs.

Bronchiolitis was the most frequent SAE (seven SAEs in each group), followed by urinary tract infection/pyelonephritis (three SAEs in Group A and two SAEs in Group B), sepsis (one SAE in Group A and two SAEs in Group B), gastroenteritis (one SAE in each group), pneumonia or bronchopneumonia

(two SAEs in Group A), sinusitis (two SAEs in Group A) and pharyngitis (two SAEs in Group B). These are all common childhood illness and the rate of occurrence is not unexpected in this population.

No SAEs were assessed as related to vaccination by the Investigator and the Sponsor.

3. Discussion on clinical aspects

This study, E2128, was a randomised, open, multicenter, clinical study to assess the immunogenicity and safety of the Sanofi Pasteur DTaP-IPV combination vaccine (Tetraxim/Tetravac) administered as a three-dose primary vaccination at 2, 4 and 6 months of age, compared with the commercially available vaccines: Birkens DTaP (Cheil Jedang (CJ) purified PDT vaccine) and Sanofi Pasteurs IPV (IMOVAX POLIO) vaccine.

Subjects were assigned as follows:

Group A: Tetraxim/Tetravac at 2, 4 and 6 months of age.

Group B: Birkens DTaP (CJ purified PDT vaccine) and Sanofi Pasteurs IPV (Imovax Polio) monovalent vaccines at separate injection sites at 2, 4 and 6 months of age.

Adherence to the study vaccination schedule was satisfactory for both groups.

The study was carried out to meet the requirements for registration of the Tetraxim/Tetravac vaccine in the Republic of Korea [authorisation for Tetraxim/Tetravac was granted by the KFDA in August 2009].

The primary objective of this study was to demonstrate the non-inferiority of Tetraxim/Tetravac versus Birkens DTaP (Cheil Jedang (CJ) purified PDT) vaccine and Sanofi Pasteurs IPV (IMOVAX POLIO) vaccine, in terms of seroprotection rates (diphtheria, tetanus, polio types 1, 2 and 3) and seroconversion/vaccine response rates to pertussis antigens (PT, FHA), 1 month after the three-dose primary vaccination.

The primary objective was considered to be demonstrated since the study showed the non-inferiority of Tetraxim/Tetravac over Birkens DTaP vaccine and Sanofi Pasteurs IPV vaccine in terms of seroprotection or seroconversion rates.

The immunogenicity, in terms of seroprotection and seroconversion rates was high and similar in both groups for each vaccine antigen, with the exception of anti-FHA in Group B. After the third dose, the seroprotection rate for polio types 1, 2 and 3 (≥ 8 1/dil) and diphtheria (≥ 0.01 IU/ml, neutralisation assay) was 100% and the seroprotection rate for tetanus (≥ 0.1 IU/ml) was 99.0% in Group A. The seroconversion rate to pertussis antigens (4-fold increase in antibody titres from pre- to post-vaccination) was 96.6% and 92.2% for PT and FHA respectively in Group A and 94.4% and 78.4% respectively in Group B.

The non-inferiority of Tetraxim/Tetravac was also demonstrated for all vaccine antigens to the historical control. The historical controls were from Study E2103 France and Study IPV07 South Korea (same vaccine antigens in DTaP-IPFV based combination at 2, 4 and 6 months of age).

After the third vaccine dose, GMTs increased significantly from pre-dose 1 to post-dose 3 for each vaccine antigen in the Tetraxim/Tetravac vaccinated group. These results are in line with several other studies which have demonstrated the immunogenicity of the Tetraxim/Tetravac vaccine.

The safety profile in terms of solicited adverse reactions or events suggested that Tetraxim/Tetravac was associated with low reactogenicity when given at 2, 4 and 6 months of age.

After any dose given, tenderness, erythema and swelling reactions at the injection site were observed in 33.0%, 36.9% and 27.0%, respectively of doses given in Group A.

In Group B observations were made after DTaP vaccination in 23.9%, 20.8%, and 11.6% of subjects respectively and after IPV vaccination in 20.2%, 10.4% and 6.0% of subjects respectively.

Most of the solicited injection site reactions occurred within 4 days after vaccination and lasted less than 3 days. In most cases they were considered to be of mild severity.

The incidence of solicited systemic adverse events was low in both study groups. Any fever ($\geq 37.4^{\circ}\text{C}$, axillary) was observed in 9.5% and 7.1% of doses given in Group A and B, respectively.

All other solicited systemic adverse events, vomiting, abnormal crying, drowsiness, appetite lost and irritability were recorded between 20.6% to 27.0% of doses given in Group A and between 19.1% and 24.5% in Group B. Most of the solicited systemic reactions occurred within 4 days after vaccination, lasted less than 3 days and were considered to be of mild severity.

The incidence of solicited adverse reactions (either at the injection site or systemic) which were recorded as severe in intensity/severity was low, less than 0.9% of doses given, after vaccination regardless of the study group.

Within 30 days after any vaccine injection 158 out of 217 subjects in Group A and 164 out of 222 subjects in Group B reported at least one unsolicited adverse event

Overall, 14 subjects in Group A and 12 subjects in Group B experienced at least one serious adverse event. No serious adverse events were reported to be related to vaccination and none as assessed as related to vaccination by either the Investigator or the Sponsor. All serious adverse events resolved.

No case of hypotonic hyporesponsive episodes or seizures was reported during the safety follow-up period defined in the protocol. No dropouts were reported due to adverse events.

Note: If relevant any relevant Pharmacovigilance information related to the active substance should be mentioned and discussed in this section.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

*Note: Please ensure that the **final** conclusion does not contain references to individual Member States. "If a type II variation is recommended, please specify the texts proposed for inclusion in the relevant SPC sections.*

➤ Overall conclusion

This study would appear to confirm the immunogenicity and safety profile for Tetraxim/Tetravac which has been generated in other clinical studies for this vaccine.

This study revealed no additional, relevant information regarding the immunogenicity or safety profile not already included in the Company's Core Data Sheet and related documents.

➤ **Recommendation**

No further action required

**VI. LIST OF MEDICINAL PRODUCTS AND MARKETING
AUTHORISATION HOLDERS INVOLVED**

The list can be taken from the spreadsheet compiled from the EMA.