These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

Sponsor/ Company:	Sanofi Pasteur	**Study Code:** E2I41 **Study Identifier:** NCT00259337
Proprietary Vaccine Name:	DTacP-IPV//PRP~T (PENTAXIM™)	

Title of the Study: Immunogenicity and Safety of the sanofi pasteur DTacP-IPV//PRP~T Combined Vaccine (PENTAXIM™) Given as a Three-Dose Primary Vaccination at 6, 10, and 14 Weeks of Age and Followed by a Booster Dose at 18-19 Months of Age in Healthy Infants in India

Study centres: 2 sites in India

Publications: None at the time of report writing.

Study period: 15 February 2006 to 10 January 2007 for primary series
Expected end of study: January 2009, after the booster dose

Development phase: Phase III

Methodology / Trial Design: Multicenter, open, phase III clinical study.

226 infants were sequentially enrolled and received the sanofi pasteur's DTacP- IPV//PRP~T combined vaccine (PENTAXIM™) at 6, 10 and 14 weeks of age. All subjects will receive a booster dose at 18-19 months of age.
According to the National Immunization program and the clinical practice in each study center, hepatitis B vaccination could be given either at 0, 6 and 14 weeks of age or at 6,10 and 14 weeks of age.

Objectives:

Primary Objective:

Immunogenicity:
To assess the seroprotection rates (Diphtheria, Tetanus, polio types 1, 2 and 3, and Polyribosyl Ribitol Phosphate [PRP]) and seroconversion rates to Pertussis antigens (PT, FHA) of sanofi pasteur's DTacP-IPV//PRP~T combined vaccine, one month after the three-dose primary vaccination.

Safety:

To describe the safety after each of the three doses of combined vaccine (PENTAXIM™) administered as primary vaccination series.

Secondary Objective: (not presented in this report)

Immunogenicity:
To describe the immunogenicity of the study combined vaccine (PENTAXIM™), prior to the booster dose and one month after the booster dose.

Safety:

To describe the safety after the booster dose of the study combined vaccine (PENTAXIM™).

Endpoints:

Immunogenicity:

One month after the third dose of study combined vaccine (Visit 4)

- individual antibodies titers : all antibodies;
- anti-Diphtheria antibody titers ≥ 0.01 IU/mL and ≥ 0.1 IU/mL (seroneutralization)
- anti-Tetanus antibody titers ≥ 0.01 IU/mL and ≥ 0.1 IU/mL (ELISA)
- anti-Polio 1, 2 and 3 antibody titers ≥ 8 (1/dil) (seroneutralization)
- anti-PRP antibody titer ≥ 0.15 µg/mL and ≥ 1.0 µg/mL (Farr type RIA)
- anti-PT and anti-FHA antibody titers (EU/mL) ≥ 4-fold increase and ≥ 2-fold increase (ELISA)
- anti-PT and anti-FHA antibody titers ≥ 5 EU/mL, ≥ 10 EU/mL and ≥ 25 EU/mL (ELISA)
- individual antibody titer ratios* of all antibodies.

Before (Visit 5) and after (Visit 6) the booster dose of the study combined vaccine

- individual antibodies titers : all antibodies;
- anti-Diphtheria antibody titers ≥ 0.01 IU/mL and ≥ 0.1 IU/mL (seroneutralization)
- anti-Tetanus antibody titers ≥ 0.01 IU/mL and ≥ 0.1 IU/mL (ELISA)
- anti-Polio 1, 2 and 3 antibody titers ≥ 8 (1/dil) (seroneutralization)
- anti-PT and anti-FHA antibody titers ≥ 5 EU/mL, ≥ 10 EU/mL and ≥ 25 EU/mL (ELISA)

One month after the booster dose of the study combined vaccine (Visit 6)

- anti-PT and anti-FHA antibody titers (EU/mL) ≥ 4-fold increase and ≥ 2-fold increase (ELISA)
- individual titers ratios* of all antibodies

**Individual titer ratio: post-primary vaccination / pre-primary vaccination and post-booster dose /pre-booster dose*

Safety:

- Occurrence, time to onset, duration, severity and seriousness of any solicited local reaction (tenderness, erythema, swelling) / systemic (Fever, vomiting, abnormal crying, drowsiness, appetite lost, irritability) adverse event (AE), within 8 days (D0-D7) after each vaccine injection
- Occurrence, nature (MedDRA preferred term), time to onset, duration, severity, relationship to vaccination, and seriousness of any unsolicited systemic and injection site AE between D0 and the next study visit after each vaccine injection,
- Occurrence, nature, time to onset, duration, severity, and relationship to vaccination of any serious AE (SAE) throughout the trial

Safety of Sanofi Pasteur's DTacP-IPV//PRP~T combined vaccine will be evaluated for each subject after the booster injection using the same criteria.

Sample size (Number of Subjects):

226 eligible subjects were to be enrolled to ensure a total of 180 evaluable subjects

	Total	
	n	%N
Planned	226	100%
N included	226	100%
N completed	216	95.6%
Immunogenicity Analysis Set Post-dose 3	213	94.2%
N Full Analysis Set	226	100%
N Safety Analysis Set	226	100%

Schedules of Vaccination and Specimen Collection:

A total of four visits and 2 blood samples (BL) were performed in all infants for the three-dose primary vaccination followed by two visits and 2 BL for the booster vaccination.

Subjects received sanofi pasteur's DTacP-IPV// PRP~T combined vaccine (PENTAXIM™) at 6, 10 and 14 weeks of age.

Subjects will receive the booster dose of sanofi pasteur's DTacP-IPV// PRP~T combined vaccine (PENTAXIM™) at 18-19 months of age (Visit 5) even if oral poliovirus (OPV) is previously given as part of the National Immunization Days campaign between Visit 4 and Visit 5.

According to the National Immunization program and the clinical practice in each study center, hepatitis B (HB) vaccination could be given either at 0, 6 and 14 weeks of age or at 6, 10 and 14 weeks of age.

A maximum volume of 4 mL of blood was taken:

- Just before the first dose (BL01-Visit 1)
- One month after the third dose (BL02-Visit 4)

A maximum volume of 4 ml of blood remains to be taken:

- Just before the booster dose (BL03-Visit 5), and
- One month after the booster dose (BL04-Visit 6) of combined vaccine.

Duration of Participation in the Trial:

The expected total duration of follow-up (first visit to last visit) for a subject is of approximately 19 months.

Product Under Investigation:

DTacP-IPV//PRP~T combined vaccine (PENTAXIM™) manufactured by sanofi pasteur

Form/Dose/Route:

Freeze-dried PRP~T reconstituted with the injectable suspension of DTacP-IPV/0.5mL/ Intramuscular (IM) into the right anterolateral aspect of the thigh

Batch number: Z2044-01

Control Product: Not applicable

Other Product(s):

Recombinant HB vaccine (EUVAX B™) manufactured by LG Life Sciences used routinely by the centre(s)

Form/Dose/Route:

Liquid/0.5 mL per dose/ IM injection into the left anterolateral aspect of the thigh

Batch number: Commercial batch No. UVA05005

Statistical methods

The study was descriptive and therefore usual descriptive statistics (percentages and 95% confidence intervals) were used to assess immunogenicity endpoints.

Sample size:

The statistical analysis was descriptive and therefore, the sample size calculation was not based on any hypothesis testing.

Nevertheless, the sample size was chosen in order to give enough precision to the descriptive results (size of the confidence intervals) and to allow a non-inferential comparison with historical results.

No historical clinical data were available with PENTAXIM™ given at 6, 10 and 14 weeks of age. One study (E2I03294) was carried out with PENTAXIM™ in France, using the 2, 3, 4 months of age schedule. Results of this study are presented in the table below.

Evaluation Criteria:	Rate observed in study E2I03294 (group 2-3-4; [95% CI]
Anti-Diphtheria ≥0.01 IU/mL	100% [95.9 ;100]
Anti-Tetanus ≥0.01 IU/mL	100% [95.9 ;100]
Anti-PT ≥4-fold increase EU/mL	89.6% [81.7 ;94.9]
Anti-FHA ≥4-fold increase EU/mL	89.5% [81.5 ;94.8]
Anti-Polio 1 ≥8 (1/dil)	97.0% [91.5 ;99.4]
Anti-Polio 2 ≥8 (1/dil)	100% [96.4 ;100]
Anti-Polio 3 ≥8 (1/dil)	99.0% [94.6 ;100]
Anti-PRP ≥0.15 µg/mL	98.0% [93.0 ;99.8]

In the present study (E2I41), no inferential comparison was done versus results observed in study E2I03294, but they were used as a basis to allow a clinical comparison.

The sample size was set at 226 enrolled subjects to ensure 180 evaluable subjects (25% drop-out rate for several reasons).

Analysis of immunogenicity:

All criteria were described at each time point of available blood samples:

Seroprotection / seroconversion / vaccine response rates were calculated with their 95% confidence intervals (CIs) using the exact binomial method.

GMTs and GMTR were calculated with their 95% CIs using the normal approximation. Reverse cumulative distribution curves (RCDC) were presented.

Analysis of safety:

Descriptive analysis:

For each safety criteria, the percentage of subjects with the criteria (e.g. with a given symptom) was computed with its 95% CI.

Solicited adverse events occurring between D0 and D7 after each injection were described by daily intensity, time to onset, duration.

Unsolicited events were analyzed by nature (primary System Organ Class and Preferred Term), severity, relationship to vaccination, delay of onset and duration.

MedDRA was used to classify unsolicited adverse experiences and the percentage of subjects with a symptom pertaining to specific Preferred Terms was tabulated. Serious adverse events and discontinuations due to adverse events were described in details.

This clinical and statistical study report was released for the first analysis after completion of the primary vaccination (D0-Visit 1 to D84-Visit 4). This analysis addressed both the immunogenicity and safety evaluation criteria (primary and secondary) after the three doses of the primary vaccination.

A second and final analysis will be performed for the booster phase study.

Results summary:

This interim report presents completed data obtained after the three-dose primary vaccination.

Data obtained after the booster dose will be integrated to this report once the booster phase of the study will be completed and analyzed.

Demography

At visit 1, before the administration of the first dose of the study combined vaccine, there were slightly more male (53.1 %) than female (46.9 %) infants. The mean age (± standard deviation) of the infants at Visit 1 was 45.0 ± 2.9 days i.e., 6.4 weeks approximately.

Immunogenicity results after Primary Series:

The data presented below are for the Full Analysis Set (FAS).

The immunogenicity (in terms of SP/SC rates) was high for each vaccine antigen, and similar to the immunogenicity observed in Europe (historical control). After the third dose, anti-PRP ≥ 0.15 µg/mL was observed in 98.6% of subjects and anti-PRP ≥ 1.0 µg/mL in 90.0% (95%CI 85.2%; 93.7%) of subjects. The seroprotection rate for anti- Diphtheria (≥ 0.01 IU/mL) and for anti-Tetanus (≥ 0.01 IU/mL) was of 99.1% and 100% respectively whereas for anti-Polio types 1, 2 and 3 (≥ 8 [1/dil]) was 100%, 99.1% and 100% respectively. Seroconversion or vaccine response rate to pertussis antigens: 4-fold increase in antibody titers from pre- to post-vaccination was 93.7% and 85.7% for PT and FHA respectively, and 2-fold increase was 97.1% and 92.4%, respectively.

Anti-PRP µg/mL GMT increased from 0.11 µg/mL (before the first injection) to 4.17 µg/mL (after the third injection). Anti-Polio GMTs (1/dil) increased from 18.1 (1/dil) to 440.5 (1/dil), from 20.4 (1/dil) to 458.9 (1/dil), and from 9.9 (1/dil) to 1510.7 (1/dil) for types 1, 2 and 3 respectively. After the third injection, GMTs also increased for PT and FHA vaccine antigens. Indeed, anti-PT and anti-FHA GMTs (EU/mL) increased from 4.9 EU/mL to 321.1 EU/mL and from 5.1 EU/mL to 91.9 EU/mL, respectively.

Safety and Reactogenicity Results after Primary Series:

In terms of solicited adverse reactions or events, sanofi pasteur's DTacP-IPV//PRP~T combined vaccine showed a low reactogenicity when given at 6, 10, and 14 weeks of age with concomitantly with hepatitis B vaccine at 6, 10 and 14 weeks of age or at 0, 6 and 14 weeks of age.

Injection site pain was the most common symptom. Indeed, 17.3% of doses given were followed by injection site pain when given with the combined vaccine. Severe pain was observed after 0.3% of doses given (only two injections were followed by a severe pain). The incidence of erythema and swelling was low after any doses given and after each injection. All solicited injection site reactions occurred within 3 days after vaccination (except one case of erythema/redness occurring between day 4 and day 7).

In terms of solicited systemic reactions, 15.3% of doses given were followed by fever and 13.7% of doses were followed by irritability. Drowsiness was reported after 10.2% of doses given with only one case with reported drowsiness as severe. Only two subjects out of 224 had severe fever (≥39.0 °C, axillary temperature).

After the administration of the combined study vaccine, 119 (53.1%) of 224 subjects with documented doses of vaccine administration reported at least one unsolicited AE. Among these 119 subjects, one subject was reported to have one unsolicited symptom assessed by the Investigator as "related" to vaccination (mild rash macular occurring one day after the first injection and lasted for 7 days).

Throughout the study, 11 subjects experienced at least one SAE. No SAEs were reported as related to the vaccination (combined study vaccine or Hepatitis B vaccine). Most of the SAEs were common adverse events or diagnoses observed in infancy (e.g. bronchopneumonia, bronchiolitis, chikungunya or probable chikungunya), and one case of seizure/convulsion (22 days after the third injection). All subjects with an SAE recovered. No cases of hypotonic hyporesponsive episodes were reported during the safety follow-up period defined in the protocol. No dropouts were observed due to serious or non-serious adverse events.

Conclusions:

- Sanofi pasteur's DTaP-IPV//Hib combined vaccine (PENTAXIM™) was highly immunogenic for all antigens when given at 6, 10, and 14 week of age (WHO EPI), and when given concomitantly with hepatitis B vaccine at 6, 10, and 14 weeks of age or at 0, 6 and 14 weeks of age
- Sanofi pasteur's DTaP-IPV//Hib combined vaccine (PENTAXIM™) shows a similar immunogenicity (in terms of seroprotection or vaccine response rates) to the historical control (DTaP-IPV//Hib [Pentaxim™] at 2, 3, and 4 months of age [study E2I03294 France])
- Sanofi pasteur's DTaP-IPV//Hib combined vaccine (PENTAXIM™) was well tolerated in infants in a 6, 10, and 14-week primary vaccination schedule and when given concomitantly with hepatitis B vaccine at 6, 10 and 14 weeks of age or at 0, 6 and 14 weeks of age.

Date of Report: 24 January 2008.