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:** E2I29 **Study Identifier:** NCT00254917 **EudraCT Number:** Not applicable
Proprietary Vaccine Name:	PENTAXIM™: Purified diphtheria toxoid, Purified tetanus toxoid, Purified pertussis toxoid (PT), Purified filamentous Haemagglutinin (FHA), enhanced inactivated polioviruses (IPV) type 1, 2, 3, and *Haemophilus influenzae* type b polysaccharide conjugated to tetanus protein (PRP~T)	

Title of the Study: Assessment of the Immunogenicity and Safety of the Sanofi Pasteur DTacP-IPV//PRP~T Combined Vaccine (PENTAXIM™), Administered at 6, 10, and 14 Weeks of Age and Followed by a Booster Dose at 18-19 Months of Age in Healthy Infants Included in Two Study Groups Receiving the Hepatitis B Monovalent Vaccine Either at 0, 6, and 14 Weeks of Age or at 6, 10, and 14 Weeks of Age.

Study centres: 3 sites in Philippines

Publications: None at the time of the report writing

Study period: Date of First enrollment: 22 October 2003
Date of Last visit (contact): 10 September 2004

Development phase: Phase IV

Methodology / Trial Design: Open, randomized, multicenter, controlled trial. Infants were randomly allocated in one of the two study groups as follows:

Group A: subjects received the PENTAXIM™ vaccine at 6, 10, and 14 weeks of age, and the recombinant 10 µg hepatitis B vaccine at 0, 6, and 14 weeks of age.

Group B: subjects received the PENTAXIM™ and the recombinant 10 µg hepatitis B vaccines at 6, 10, and 14 weeks of age.

All infants included were born to HBs antigen seronegative mothers.

All infants included in the study were to receive a booster dose of PENTAXIM™ vaccine at 18-19 months of age.

No Hepatitis B booster vaccination was to be given according to the Philippine National Expanded Program on Immunization (EPI).

Five visits (V01, V02, V03, V04, V05) were performed for the primary vaccination at ≤48 hours of life, 6, 10, 14, and 18 weeks, respectively. Two visits (V06 and V07) are to be performed for the booster vaccination at 18-19 and 19-20 months of age, respectively. At the time of writing this report, the booster vaccination is still ongoing, thus, only the primary series data (V01 to V05) are included in this report. Data from the booster phase (V06 and V07) will be analyzed and appended to this report when the study is completed.

Two blood samples were drawn for antibody determinations in infants before and after the primary vaccination at V01 and V04. Another two blood samples were also planned before and after the booster dose at V06 and V07.

Objectives:

Primary objective:

To demonstrate the non-inferiority in terms of seroprotection rates (D, T, polio types 1, 2 and 3, and PRP) and seroconversion rates (PT, FHA) of PENTAXIM™ *versus* previous data (study E2I03294) with the same product.

Hypothesis:
The study vaccine was inferior in terms of immunogenicity (> pre-specified delta) to the historical control one month after the three-dose primary vaccination.

Secondary objective(s):

1. Immunogenicity:
To describe in each group:
- the immunogenicity of PENTAXIM™ vaccine antigens at Visit 5 (one month after the three-dose primary vaccination), visit 6 (just before the booster dose) and Visit 7 (one month after the booster dose)

- the immunogenicity of the recombinant hepatitis B vaccine antigen at Visit 5 (one month after the three-dose primary vaccination) and visit 6 (14 to 15 months later)

2. Safety:
To describe the safety after each dose of PENTAXIM™ in both groups
To describe the safety after each dose of recombinant hepatitis B vaccine in both groups

Hypotheses:
The secondary objectives involve only descriptive assessments. Therefore, no clinical hypotheses are formulated.

Sample size (Number of Subjects):

	Group A		Group B		Total	
	n	**%**	**n**	**%**	**n**	**%**
N planned	212		212		424	
N included	213	100.0	211	100.0	424	100.0
N completed	200	93.9	187	88.6	387	91.3
N Full Analysis Set	204	95.8	193	91.5	397	93.6

Schedules of Vaccination and Specimen Collection:
Primary series: PENTAXIM™ injection at 6, 10, and 14 weeks of age
Booster injection at 18-19 months of age

Duration of Participation in the Trial:
Approximately 20 months per subject

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/0.5 mL/Intramuscular injection into the anterolateral aspect of the right thigh

Batch number: Commercial batch W1538

Control Product: Not applicable

Other Product(s):
Recombinant hepatitis B vaccine (Recomvax B™ or EUVAX B™) manufactured by LG Life Sciences

Form/Dose/Route:
Liquid/0.5 mL per dose/Intramuscular injection into the anterolateral aspect of the left thigh

Batch number: Commercial batch UVA3002

Criteria for Evaluation:
Primary evaluation criteria (One month after the third dose of the study vaccine):

Seroprotection: anti-Diphtheria titer ≥ 0.01 IU/ml (ELISA), anti-Tetanus titer ≥ 0.01 IU/ml, anti-Polio 1, 2, and 3 titers ≥ 8 (1/dil), anti-PRP titer ≥ 0.15 µg/ml
Seroconversion: at least a 4-fold increase in anti-PT titer and anti-FHA titer.

Secondary evaluation criteria

Immunogenicity

Seroprotection: anti-Diphtheria titer ≥ 0.01 IU/ml and ≥ 0.1 IU/ml, anti-Tetanus titer ≥ 0.01 IU/ml and ≥ 0.1 IU/ml, anti-Polio 1, 2 and 3 titers ≥ 8 (1/dil), anti-PRP titer ≥ 1.0 µg/ml, anti-HBs titer ≥ 10 mIU/ml.
Seroconversion: at least a 2-fold rise in anti-PT titer and anti-FHA titer

Evaluation criteria:

Safety

- Occurrence of any local reaction / systemic adverse event (AE) within 30 minutes after each vaccine injection,
- Occurrence of any solicited local reaction / systemic AE, within 8 days (D0-D7) after each vaccine injection, including immediate AEs,
- Occurrence of any severe solicited local reaction / systemic AE, within 8 days (D0-D7) after each vaccine injection, including immediate AEs,
- Occurrence of any unsolicited AE between D0 and D30 after each vaccine injection,
- Occurrence of any related unsolicited AE between D0 and D30 after each vaccine injection,
- Occurrence of any Serious Adverse Event (SAE) during the study period.

Statistical methods

Analyses were performed as planned in the protocol and the Statistical Analysis Plan (SAP).

Immunogenicity

- Primary criteria analysis: For each antigen, two hypotheses were tested based on the 95% CI of the seroprotection or seroconversion rates. Both hypotheses were tested independently. The type I error was adjusted for each hypothesis at 0.025 (one-sided). The non-inferiority of the study vaccine was demonstrated if the null hypothesis was rejected for each antigen in Group A and Group B.
- Secondary criteria analysis: For each vaccine group the seroprotection/seroconversion rates one month after the third dose of combined vaccine and their 95% CIs were calculated. Antibody titers were further described by GMTs with respective 95% CIs, GMTRs for PT/FHA and Reverse Cumulative Distribution Curves (RCDC).

Safety

The number and the percentage of subjects experiencing at least one and each type of local reaction/systemic AE were calculated. Events were analyzed in terms of relationship to the vaccination, intensity, delay of onset and duration.

Populations analyzed

- Immunogenicity: Per Protocol (PP) set and Full Analysis Set (FAS)
- Safety: all vaccinated subjects (Safety Analysis Set)

Results summary:

This report presents data obtained after the three-dose primary vaccination; data obtained after the booster dose will be appended to this report once the booster phase of the study has been completed and analyzed.

Demography

There were slightly more male infants (56.9%) than female infants (43.1%). The mean (± standard deviation) age at Visit 1 (inclusion day) was 0.15 (± 0.09) weeks. The mean age at Visit 2 (1st combined vaccine dose) was 6.39 (± 0.51) weeks.

Immunogenicity Results

The data presented below are for the PP set.

Primary criteria:

The immunogenicity (in terms of SP/SC rates) was high and similar in both groups for each vaccine antigen, and similar to the immunogenicity observed in Europe (historical control). After the 3rd dose (pooling data of the two groups), anti-PRP ≥ 0.15 µg/mL was observed in 98.7% of subjects. The seroprotection rate for tetanus (≥ 0.01 IU/mL) and polio types 1, 2, and 3 (≥ 8 1/dil U) was 100%, and for diphtheria (≥ 0.01 IU/mL- neutralization assay) was 97.1%. The seroconversion vaccine response rate to pertussis antigens: 4-fold increase in antibody titers from pre- to post-vaccination was 95.1% and 88.8% for PT and FHA respectively, and 2-fold increase was 98.8% and 95.5%, respectively.

The primary objective was reached since the study showed the non-inferiority of Group A or Group B when compared with the historical control (study E2I03 conducted in France) in terms of SP/SC rates. Indeed, the upper limit of the 95% CI for the difference between groups was below 10%, the pre-specified limit for non-inferiority.

The observed 95% CI for the difference between Groups A and B for SP rates was in the range 0% to 1.8%.

Anti-HBs (≥ 10 mIU/mL) was observed in 99.5% and 97.8% in infants vaccinated at 0, 6, and 14 and at 6, 10, and 14 weeks, respectively.

Results were similar in the FAS to those in the PP set.

Secondary immunogenicity criteria:

The immunogenicity (in terms of GMTs) was similar in both groups for each vaccine antigen. After the 3rd dose (pooling data of the two groups), GMTs increased significantly from pre-dose 1 to post-dose 3 for each vaccine antigen. Anti-PRP µg/mL GMT was 1.98 µg/mL. Anti-Polio GMTs (1/dil U) were 552, 754, and 1768 (1/dil U) for types 1, 2, & 3 respectively. Anti-PT and anti-FHA GMTs (EU/mL) increased from 3.08 to 141 EU/mL and from 5.23 to 115 EU/mL, respectively. After the 3rd dose, anti-HBs (mIU/mL) GMTs were 597 mIU/mL and 203 mIU/mL in Groups A (schedule 0, 6, and 14 weeks of age) and B (schedule 6, 10, and 14 weeks of age), respectively.

Results were similar in the FAS to those in the PP set.

Safety and Reactogenicity Results:

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

Only one immediate (within 30 minutes after vaccination) local adverse reaction (erythema of 2 cm) after combined vaccine 2nd injection (at 10 weeks of age in Group A) and one erythema of 4.5 cm after hepatitis B vaccine 2nd injection (at 6 weeks of age in Group A) were reported. Both reactions disappeared within the day of the injection.

Injection site pain was the most common symptom. Indeed, 12.0% and 21.2% of doses given with the combined vaccine were followed by injection site pain in Groups A and B, respectively, and similar to hepatitis B vaccine injection. Severe pain was observed in only 0.5% of doses given in each group. The incidence of redness, swelling, and induration was very low after any doses given and after each dose.

In terms of solicited systemic adverse events, fever and irritability were the most common symptoms observed in only 11.0% – 12.2% of subjects (for fever) and 11.6% – 16.6% of subjects (for irritability). Drowsiness and loss of appetite were reported in 5.4% – 6.5% of doses given with no severe cases reported.

The incidence of fever was low and similar in the two study groups. Only 0.5% of doses given in Group B were followed by fever ≥ 39.5°C (axillary temperature).

After the administration of the combined study vaccine, of 397 subjects with documented doses of vaccine administration, 213 subjects (53.7%) reported at least one unsolicited AE. Of those 213 subjects, only two subjects (both in Group B) were reported to have had at least one unsolicited symptom (fever) assessed by the Investigator as "possibly, probably or definitely" related to the vaccination.

Overall, during the study, six subjects in Group A and nine subjects in Group B experienced at least one SAE. No SAE was reported to be related to the vaccination (combined study vaccine or Hepatitis B vaccine).

Conclusions:

- Sanofi pasteur's DTaP-IPV//Hib combined vaccine (PENTAXIM™) was highly immunogenic for all eight antigens when given at 6, 10, and 14 week of age (WHO EPI) and when given concomitantly with hepatitis B vaccine at either 0, 6, and 14 weeks of age or at 6, 10, and 14 weeks of age.
- The non-inferiority of Sanofi Pasteur's DTaP-IPV//Hib combined vaccine (PENTAXIM™) to the historical control (DTaP-IPV//Hib [PENTAXIM™] at 2, 3, and 4 months of age [study E2I03 France]) was demonstrated for all antigens in each study group.
- Hepatitis B vaccine gave a seroprotection in 97.8% – 99.5% of infants (hepatitis B vaccine given at 0, 6, and 14 weeks of age gave the highest immune response compared to the 6, 10, and 14 weeks of age schedule).

- 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 either 0, 6, and 14 weeks of age or at 6, 10, and 14 weeks of age.

Date of Report: 20 February 2006