***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:** | C5A06 |
| | | **Study Identifier:** | NCT01062477 |
| **Proprietary Vaccine Name:** | DTaP//PRP-T Combined Vaccine (ACTACEL) | | |

**Title of the Study:**

Safety and Immunogenicity of the Sanofi Pasteur's DTaP//PRP-T Combined Vaccine (ACTACEL) versus Local DTaP and Hib Conjugate (Act-HIB) Monovalent Vaccine as a Three-dose Primary and Booster Vaccinations in Healthy Infants in China.

**Study centres:** 2 sites in China

**Publications:** None at the time of report writing

**Study period:**

Date of First enrollment: (***Primary series***) 27 Jan. 2010 (***Booster***) - 09 Jun. 2011

Date of Last visit (contact): (***Primary series***) 03 Sep. 2010 (***Booster***) 29 Sep. 2011

**Development phase:** Phase III

**Methodology / Trial Design:**

This was a randomized, open-label, three-arms, controlled multi-center Phase III study.

Infants were randomly allocated in one of the three study groups in a balanced allocation (1:1:1 ratio) as follows:

**Group 1:** subjects received DTaP//PRP-T combined vaccine (ACTACEL) at 2, 3 and 4 months of age and will receive a booster dose at 18-20 months of age.

**Group 2:** subjects received DTaP//PRP-T combined vaccine (ACTACEL) at 3, 4 and 5 months of age and will receive a booster dose at 18-20 months of age.

**Group 3**: subjects received the control vaccines (Wuhan's DTaP and Act-HIB) at 3, 4 and 5 months of age and will receive a booster dose at 18-20 months of age.

Since the number of related SAEs, Grade 3 adverse reactions and unsolicited non-serious AEs after the primary vaccination series did not reach any of the safety criteria for study discontinuation, the Sponsor issued a decision for continuation of the booster series.

**Objectives:**

**Primary objective(s):**

- To demonstrate the non-inferiority in terms of seroprotection rates for diphtheria, tetanus and PRP of ACTACEL vaccine administered at 2, 3 and 4 months of age or administered at 3, 4 and 5 months of age *versus* Wuhan's DTaP and Act-HIB vaccine given concomitantly, 1 month after the three-dose primary vaccination.
- To demonstrate the superiority in terms of seroconversion rates for PRN and FIM 2 and 3 pertussis of ACTACEL vaccine administered at 2, 3 and 4 months of age or administered at 3, 4 and 5 months of age *versus* Wuhan's DTaP and Act-HIB vaccine given concomitantly, 1 month after the three-dose primary vaccination.

**Primary endpoint:**

*One month after the third dose of study vaccine(s):*

- Anti-diphtheria antibody titers ≥0.1 IU/mL (ELISA)
- Anti-tetanus antibody titers ≥0.1 IU/mL (ELISA)
- Anti-PRP antibody titers ≥1.0 µg/mL (ELISA)
- Anti-PRN antibody titers ≥4-fold increase from pre-dose 1 level (ELISA)
- Anti-FIM (2 and 3) antibody titers ≥4-fold increase from pre-dose 1 level (ELISA).

**Secondary objective(s):**

*Immunogenicity*:

- To describe in each group the immunogenicity of the study vaccines 1 month after the primary vaccination
- To describe in each group the immunogenicity of the study vaccines just before the booster vaccination and 1 month after the booster vaccination.

*Safety*:

To describe the safety after administration of the study vaccines.

**Secondary endpoint:**

*One month after the third dose of study vaccine(s):*

- Anti-diphtheria antibody titers ≥0.01 IU/mL (ELISA)
- Anti-tetanus antibody titers ≥0.01 IU/mL (ELISA)
- Anti-PRP antibody titers ≥0.15 µg/mL (ELISA)
- Anti-PT antibody titers ≥4-fold increase from pre-dose 1 level (ELISA)
- Anti-FHA antibody titers ≥4-fold increase from pre-dose 1 level (ELISA)
- Individual antibody titers (for all antibody titers)
- Individual antibody titers ratio* (for anti-PT, anti-FHA, anti-PRN and anti-FIM [2 and 3] antibody titers).

* post-dose 3 / pre-dose 1 vaccination titers

*Before and one month after the booster dose of the study vaccine(s):*

- Anti-diphtheria antibody titers ≥0.01 IU/mL, ≥0.1 IU/mL and ≥1.0 IU/mL (ELISA)
- Anti-tetanus antibody titers ≥0.01 IU/mL, ≥0.1 IU/mL and ≥1.0 IU/mL (ELISA)
- Anti-PRP antibody titers ≥1.0 µg/mL and ≥0.15 µg/mL (ELISA)
- Individual antibody titers (for all antibody titers).

*One month after the booster dose of the study vaccine(s):*

- Anti-PT, anti-FHA, anti-PRN and anti-FIM (2 and 3) antibody titers ≥4-fold increase from pre-booster level (ELISA)
- Individual antibody titers ratio* (for anti-PT, anti-FHA, anti-PRN and anti-FIM [2 and 3] antibody titers).

*titers ratio = post-booster dose titer/ pre-booster dose titer

**Secondary endpoints (Safety)**

The secondary endpoints for the safety evaluation in each study group are:

- The occurrence, intensity and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported within 30 minutes after each vaccination.
- The occurrence, time to onset, number of days of occurrence and intensity of solicited (terms pre-listed in the CRF) injection site and systemic reactions occurring between D0 and D7 after each injection.
- The occurrence, nature (MedDRA preferred term), maximum intensity, duration and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) non-serious AEs from vaccination day to next study visit.

The occurrence, nature (MedDRA preferred term), relationship to vaccination, and seriousness of any serious AE (SAE) occurring throughout the trial period

**Sample size** (Number of Subjects):

Planned: **Group 1 -** 352 ; **Group 2 -** 352 **; Group 3 -** 352

Enrolled: **Group 1:** 352 **Group 2 – 352 ; Group 3:** 352

**Schedules of Vaccination and Specimen Collection:**

**Group 1:** subjects received DTaP//PRP-T combined vaccine (ACTACEL) at 2, 3 and 4 months of age and will receive a booster dose at 18-20 months of age. Six visits (V) will be performed.

**Group 2:** subjects received DTaP//PRP-T combined vaccine (ACTACEL) at 3, 4 and 5 months of age and will receive a booster dose at 18-20 months of age. Seven visits (V) will be performed.

**Group 3:** subjects received the control vaccines (Wuhan's DTaP and Act-HIB) at 3, 4 and 5 months of age and will receive a booster dose at 18-20 months of age. Seven visits (V) will be performed.

For antibody determinations, two blood samples (BL) of approximately 3-4 mL each were taken in each group:

- before the first dose (BL01),
- 1 month after the third dose (BL02).

Two additional blood samples will be taken in each group before and after booster vaccination.

- just before the booster dose (BL03)
- 1 month after the booster dose (BL04).

**Duration of Participation in the Trial:**

The expected total duration of follow-up (first visit to last visit) for a subject was of approximately 17 to 19 months

**Product Under Investigation:** ACTACEL (Act-HIB reconstituted with TRIPACEL/DAPTACEL) manufactured by sanofi pasteur.

Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate) Reconstituted with Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed (DTaP//PRP-T

**Form/Dose/Route:** Freeze-dried PRP-T (lyophilized powder for injection) reconstituted with liquid suspension of DTaP (suspension for injection) / 0.5 mL / Intramuscular (IM)

**Batch number:** C3536AC

**Control Product:** DTaP combined vaccine (Diphtheria, Tetanus and Acellular Pertussis Combined Vaccine, Adsorbed) manufactured by Wuhan Institute of Biological Products; Wuhan, China.

**Form/Dose/Route:** Suspension of DTaP / 0.5 mL / IM into the right deltoid as per current manufacturer label/description

**Batch number:** 20090514-1

**Control Product:** PRP-Tetanus conjugate vaccine (Act-HIB™) manufactured by sanofi pasteur.

Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate)

**Form/Dose/Route:** Freeze-dried PRP-T reconstituted with the injectable saline solution / 0.5 mL / IM into the anterolateral aspect of the right thigh

**Batch number:** E0106-F01

**Other Product(s):** Not applicable

**Assessment method:**

**Immunogenicity**

Anti-diphtheria and anti-tetanus antibody titers were measured by ELISA method and expressed in IU/mL.

Anti-pertussis (anti-PT, anti-FHA, anti-PRN and anti-FIM [2 and 3]) antibody titers were measured by ELISA method and expressed in IU/mL (for PT, FHA and PRN) or in U/mL (for FIM 2 and 3).

Anti-*Haemophilus influenzae* type b (anti-PRP) antibody titers were measured by ELISA method and expressed in µg/mL.

**Safety**

- Immediate reactions

The subject was kept under medical supervision for 30 minutes after each vaccination. The onset of any injection site and/or systemic reactions within these 30 minutes was recorded by trial personnel.

- Local and systemic adverse events (AEs)

The subject/parents(s)/legal representative recorded any injection site and systemic reactions/events occurring after each vaccination, on the day of vaccination and daily for the following 7 days in a diary card (DC). The occurrence of any other AE between 8 days and next visit after each vaccination was also recorded on the DC. All safety information was transcribed in the CRF by the Investigator following a physical examination of the subject and an interview with the subject/parents(s)/
legal representative at the following visit. For systemic events, the causal relationship to the vaccine was evaluated by the Investigator as either related or not related. Severity of AEs was assessed according to the China State Food and Drug Administration (SFDA) requirements and Sponsor standard severity scale.

- Serious adverse events (SAE)

Information on SAEs was collected from inclusion until the end of the study.

## Statistical methods

**Analysis of immunogenicity**

***Primary Endpoints***

Non-inferiority of the tested study vaccine (the sanofi pasteur's DTaP//PRP-T combined vaccine administered at 2, 3, and 4 months of age and at 3, 4, and 5 months of age) was assessed over the reference vaccines (Wuhan's DTaP and Act-HIB administered at 3, 4, and 5 months of age) for diphtheria, tetanus and PRP on the primary criteria, 1 month after the three-dose primary vaccination. For each of these antigens, the non-inferiority was demonstrated if the 95% CI of the difference (study vaccine *minus* control vaccines) lay entirely above the clinically acceptable limit for non-inferiority (-5%) (alpha = 2.5%).

Superiority of the study vaccine (the sanofi pasteur's DTaP//PRP-T combined vaccine administered at 2, 3, and 4 months of age and at 3, 4, and 5 months of age) was assessed over the reference vaccines (Wuhan's DTaP and Act-HIB administered at 3, 4, and 5 months of age) for PRN and FIM 2 and 3 pertussis on the primary criteria, 1 month after the three-dose primary vaccination. For each of these antigens, the superiority was demonstrated if the 95% CI of the difference (study vaccine *minus* control vaccines) lay entirely above 0 (alpha = 2.5%).

The primary objective was reached if the non-inferiority was proven for diphtheria, tetanus and PRP and superiority was proven for PRN, FIM 2 and 3 pertussis in at least one of the two groups. It could then be concluded that the study vaccine administrated at 2, 3 and 4 months of age or at 3, 4 and 5 months of age was non-inferior to the control vaccines in terms of seroprotection rates for diphtheria, tetanus and PRP and superior in terms of seroconversion rates for PRN and FIM 2 and 3.

***Secondary Endpoints***

The following criteria are described at each time point of available blood samples:

- Seroprotection and seroconversion rates are calculated with their 95% CIs using the exact binomial method.
- Geometric mean titers (GMTs) and geometric mean titer ratios (GMTRs) are calculated with their 95% CIs using the normal approximation of the Log10 titers, followed by a back transformation.
- Reverse Cumulative Distribution Curves of individual titers are presented.

**Analysis of safety**

The analysis is descriptive. For each safety criteria, the percentage of subjects with the criteria (i.e. with a given symptom) is computed with its 95% CI. Safety endpoints are described after each injection.

**Sample size**

As per requirement of the Chinese Health Authorities, the sample size was set to 300 evaluable subjects per group for safety surveillance. Under the assumption that around 15% of subjects would not be evaluable, 1056 subjects i.e. 352 per group were enrolled.

Blood samples were planned to be taken for all the enrolled subjects before the first dose and 1 month after the third dose and therefore all enrolled subjects could potentially be included in the analysis of the primary criteria.

The following table gives the power obtained for each individual test with a sample size of 300 subjects per group. The calculation was based on the primary criteria, i.e. combining non-inferiority and superiority for the seroprotection and seroconversion rates. It has been determined using the Farrington and Manning formula.

The expected response rates of the reference group (Wuhan's DTaP and Act-HIB administered at 3, 4 and 5 months

of age) have been taken arbitrarily as similar to those observed in study E2I42 conducted in Republic of China *versus* a DTaP-IPV//PRP-T combined vaccine (Pentaxim, per-protocol population, 1 month after the third vaccination).

| Evaluation Criteria | Expected rate in reference group* | Clinically acceptable limit for non inferiority (δ) | Power achieved with N=300 subjects per group |
|---|---|---|---|
| Anti-Diphtheria ≥ 0.1 IU/mL | 99.6% | 5% | >99.9% |
| Anti-Tetanus ≥ 0.1 IU/mL | 100% | 5% | >99.9% |
| Anti-PRP ≥ 1.0 µg/mL | 99.6% | 5% | >99.9% |
| Anti-PRN ≥ 4-fold increase | NA | NA | >99.9% |
| Anti-FIM (2 and 3) ≥ 4-fold increase | NA | NA | >99.9% |
| | | Global power | >99.9% |

**study E2I42 – Group C (Wuhan's DTacP, Act-HIB™ and IMOVAX Polio™ at 3, 4 and 5 months of age)*

A total of 300 evaluable subjects per group ensured a global power of at least 99%.

**Results summary:**

**Disposition of subjects**

A total of 1056 subjects were included (352 in each group). A total of 65 subjects had an early termination, 10 subjects in Group 1 (one subject non-compliant, nine subjects voluntarily withdrawn), 25 subjects in Group 2 (one subject non-compliant, 24 subjects voluntarily withdrawn) and 30 subjects in Group 3 (three subjects for SAE, one subject non-compliant, 26 subjects voluntarily withdrawn). A total of 342 subjects in Group 1, 327 subjects in Group 2 and 322 subjects in Group 3 completed the primary vaccination phase.

During the booster vaccination phase, among the 991 subjects who completed the primary vaccination phase, 42 subjects had an early termination: 13 subjects in Group 1 (one subject for SAE, three subjects non-compliant with the protocol, nine subjects voluntarily withdrawn), 14 subjects in Group 2 (two subjects non-compliant, 12 subjects voluntarily withdrawn) and 15 subjects in Group 3 (one subject for SAE, two subjects non-compliant, 12 subjects voluntarily withdrawn). A total of 334 subjects in Group 1, 319 subjects in Group 2 and 311 subjects in Group 3 received a booster dose and 329 subjects in Group 1, 313 subjects in Group 2 and 307 subjects in Group 3 completed the booster vaccination phase.

**Demographic characteristics:**

**Primary vaccination phase**: There were 48.9%, 54.3% and 53.3% male subjects and 51.1%, 45.7% and 46.7% female subjects in Group 1, Group 2 and Group 3, respectively. The male/female ratio was slightly higher in Group 2 (1.19) and Group 3 (1.14) than in Group 1 (0.96).

The median age was 2.4 months in each group. The age ranged from 1.9 months to 3.0 months in each group.

The median weight was 5.7 kg in each group. The weight ranged from 4.1 kg to 8.1 kg in Group 1, from 3.9 kg to 7.8 kg in Group 2, and from 4.2 kg to 7.7 kg in Group 3.

**Booster vaccination phase**: At Visit 06 (day of booster vaccination), the median age was 18.6 months in Group 1, 18.7 months in Group 2 and 18.6 months in Group 3.

***Immunogenicity (***Primary objective)

After the three-dose primary vaccination, the seroprotection/seroconversion rates for diphtheria, tetanus, PRP, PRN and FIM (2 and 3) of each study group, the differences between the groups and their 95% CIs are presented in the Per Protocol (PP) Analysis Set.

After the third dose, all subjects (100%) achieved a seroprotective anti-diphtheria antibody titer ≥0.1 IU/mL in the three groups. All subjects, except one subject in Group 3 (99.68%), achieved a seroprotective anti-tetanus antibody titer ≥0.1 IU/mL in the three groups. Seroprotection rates against PRP (antibody titer ≥1.0 µg/mL) were 94.86% in Group 1, 97.18% in Group 2 and 99.37% in Group 3. Seroconversion rates against PRN (≥4-fold increase in anti-PRN antibody titers from pre-dose 1 level) were 99.70% in Group 1, 99.69% in Group 2 and 100% in Group 3. Seroconversion rates against FIM 2 and 3 (≥4-fold increase in anti-FIM 2 and 3 antibody titers from pre-dose 1 level) were 100% in Group 1 and Group 2 and 97.48% in Group 3.

Compared to Wuhan's DTaP and the Sanofi Pasteur's Hib tetanus conjugate (Act-HIB) administered concomitantly at 3, 4 and 5 months of age, the non-inferiority of the Sanofi Pasteur's DTaP//PRP-T combined vaccine

administered at 2, 3 and 4 months of age is statistically demonstrated for diphtheria, tetanus, but not for PRP and its superiority is demonstrated for FIM (2 and 3), but not for PRN.

Similarly, compared to Wuhan's DTaP and the Sanofi Pasteur's Hib tetanus conjugate (Act-HIB) administered concomitantly at 3, 4 and 5 months of age, the non-inferiority of the Sanofi Pasteur's DTaP//PRP-T combined vaccine administered at 3, 4 and 5 months of age is statistically demonstrated for diphtheria, tetanus and PRP, and its superiority is demonstrated for FIM (2 and 3), but not for PRN.

However, since seroconversion rate against PRN was unexpectedly 100% after vaccination with the reference vaccine (the presence of PRN antigen was not mentioned in the composition of the Wuhan's DTaP vaccine), it was not possible to demonstrate a superiority of any schedule over the reference vaccines. In this case, only a statistical test of non-inferiority would have been pertinent. It must also be noted that only one subject in Group 1 and Group 2 did not seroconvert against PRN, and one of these two subjects had high pre-dose 1 and post-dose 3 anti-PRN antibody titers (11.6 IU/mL and 39.4 IU/mL, respectively).

Overall, in the PP Analysis Set, the non-inferiority in terms of seroprotection rates of the Sanofi Pasteur's DTaP//PRP-T combined vaccine is demonstrated for diphtheria, tetanus and PRP over the reference vaccines (Wuhan's DTaP and Act-HIB). The superiority in terms of seroconversion rates of the Sanofi Pasteur's DTaP//PRP-T combined vaccine is demonstrated for FIM (2 and 3).
The main analysis was done in the PP Analysis Set. A sensitivity analysis was also performed in the Full Analysis set (FAS). Results and conclusions in the FAS were similar to those obtained in the PP Analysis Set.

The seroprotection/seroconversion rates for diphtheria, tetanus, PRP, PRN and FIM (2 and 3) of each study group, the differences between the groups and their 95% CIs are presented in the Per Protocol (PP) Analysis Set After the third dose, all subjects (100%) achieved a seroprotective anti-diphtheria antibody titer ≥0.1 IU/mL in the three groups. All subjects, except one subject in Group 3 (99.68%), achieved a seroprotective anti-tetanus antibody titer ≥0.1 IU/mL in the three groups. Seroprotection rates against PRP (antibody titer ≥1.0 µg/mL) were 94.86% in Group 1, 97.18% in Group 2 and 99.37% in Group 3. Seroconversion rates against PRN (≥4-fold increase in anti-PRN antibody titers from pre-dose 1 level) were 99.70% in Group 1, 99.69% in Group 2 and 100% in Group 3. Seroconversion rates against FIM 2 and 3 (≥4-fold increase in anti-FIM 2 and 3 antibody titers from pre-dose 1 level) were 100% in Group 1 and Group 2 and 97.48% in Group 3.

Compared to Wuhan's DTaP and the sanofi pasteur's Hib tetanus conjugate (Act-HIB) administered concomitantly at 3, 4 and 5 months of age, the non-inferiority of the sanofi pasteur's DTaP//PRP-T combined vaccine administered at 2, 3 and 4 months of age is statistically demonstrated for diphtheria, tetanus, but not for PRP and its superiority is demonstrated for FIM (2 and 3), but not for PRN.

Similarly, compared to Wuhan's DTaP and the sanofi pasteur's Hib tetanus conjugate (Act-HIB) administered concomitantly at 3, 4 and 5 months of age, the non-inferiority of the sanofi pasteur's DTaP//PRP-T combined vaccine administered at 3, 4 and 5 months of age is statistically demonstrated for diphtheria, tetanus and PRP, and its superiority is demonstrated for FIM (2 and 3), but not for PRN.

However, since seroconversion rate against PRN was unexpectedly 100% after vaccination with the reference vaccine (the presence of PRN antigen was not mentioned in the composition of the Wuhan's DTaP vaccine), it was not possible to demonstrate a superiority of any schedule over the reference vaccines. In this case, only a statistical test of non-inferiority would have been pertinent. It must also be noted that only one subject in Group 1 and Group 2 did not seroconvert against PRN, and one of these two subjects had high pre-dose 1 and post-dose 3 anti-PRN antibody titers (11.6 IU/mL and 39.4 IU/mL, respectively).

Overall, in the PP Analysis Set, the non-inferiority in terms of seroprotection rates of the sanofi pasteur's DTaP//PRP-T combined vaccine is demonstrated for diphtheria, tetanus and PRP over the reference vaccines (Wuhan's DTaP and Act-HIB). The superiority in terms of seroconversion rates of the sanofi pasteur's DTaP//PRP-T combined vaccine is demonstrated for FIM (2 and 3).
The main analysis was done in the PP Analysis Set. A sensitivity analysis was also performed in the Full Analysis set (FAS). Results and conclusions in the FAS were similar to those obtained in the PP Analysis Set.

**Secondary objectives**

After the third dose, GMTs increased significantly from pre-dose 1 against each vaccine antigen in each group.

Slight differences were observed in terms of anti-diphtheria, anti-tetanus, anti-PT and anti-FHA GMTs between groups. Anti-PRP GMTs were 1.5 to 2 times higher in Group 3 than in Group 1 and Group 2. Anti-FIM (2 and 3) GMTs were approximately 3 times higher in both groups 1 and 2 as compared to Group 3. Anti-PRN GMTs

reached comparable values in the three groups (close to 44-45 IU/mL), suggesting again that the immune response against PRN antigen was similar in the three groups.

All subjects (100%) achieved a ≥4-fold increase in anti-PT antibody titers from pre-dose 1 (seroconversion) except two subjects in Group 3 (99.4%). Seroconversion rates against FHA (≥4-fold increase in antibody titers from pre-dose 1 level) were high and similar in the three groups, i.e. 97.6% in Group 1, 98.4% in Group 2 and 99.1% in Group 3.

Conclusions were similar in the FAS and the PP Analysis Set.

- More than 1 year after the three-dose primary vaccination, GMTs were low in the three groups against each vaccine antigen. Seroprotection rates against diphtheria (≥0.1 IU/mL) and against tetanus (≥0.1 IU/mL) were low and similar in the three groups. However most subjects still had antibody titers ≥0.01 IU/mL. Most subjects still had long-term seroprotective anti-PRP antibody titers (≥1.0 µg/mL) in Group 1 (81.7%), Group 2 (85.9%) and Group 3 (87.8%).
- One month after the booster dose, a marked increase in GMTs was observed against each vaccine antigen in the three groups. Anti-diphtheria and anti-tetanus GMTs were similar in the three groups. Anti-PRP GMTs were higher in Group 3 than in Group 1. Anti-PRN GMTs were similar in the three groups. Anti-PT, anti-FHA, and anti-FIM (2 and 3) GMTs were higher in Group 1 and Group 2 than in Group 3.
- One month after the booster dose, seroprotective anti-diphtheria (≥0.1 IU/mL), anti-tetanus (≥0.1 IU/mL) and anti-PRP (≥1.0 µg/mL) antibody titers were observed in all subjects (100%) in the three groups, except for one subject in Group 3 for anti-diphtheria.
- The seroconversion rates (≥4-fold increase in antibody titers from pre-booster dose level) were high and similar in Group 1, Group 2 and Group 3 against PT (99.7%, 98.7% and 98.4%, respectively), FHA (97.9%, 95.8% and 97.0%, respectively), PRN (97.9%, 98.1% and 100.0%, respectively) and FIM (2 and 3) (100.0%, 99.4% and 97.7%, respectively).

The antibody response was similar in Group 1 and Group 2 against each vaccine antigen after booster vaccination.

**Safety – Secondary objectives:**

Primary vaccination:

The incidence of solicited injection site reactions and systemic reactions was similar in the three groups. Grade 3 injection site reactions and systemic reactions were reported in a similar proportion of subjects in the three groups.

Each type of injection site reaction (tenderness, erythema and swelling) was reported in a similar proportion of subjects in the three groups. In the three groups, tenderness was the most frequent injection site reaction, followed by erythema. Swelling was less frequent. The incidence of injection site reactions (especially tenderness) tended to decrease after each injection. Most of the solicited injection site reactions occurred within 4 days after vaccination, were transient (≤3 days), and of Grade 1 severity. The incidence of Grade 3 injection site reactions was low. Overall, after the three-dose primary vaccination, Grade 2 or Grade 3 tenderness was reported after 3.4% to 6.8% of vaccine injections, Grade 2 or Grade 3 erythema was reported after 1.7% to 4.6% of vaccine injections, and Grade 2 or Grade 3 swelling was reported after 1.7% to 4.4% of vaccine injections.

Fever, vomiting, crying abnormal, drowsiness, appetite lost and irritability were reported in a similar proportion of subjects in the three groups. Fever and crying abnormal were the most frequent solicited systemic reactions, followed by irritability. Vomiting, drowsiness and appetite loss were less common. The incidence of each type of systemic reaction decreased with each vaccine injection, except fever between the second and third injection in Group 1 and Group 2. Most of the solicited systemic reactions occurred within 4 days after vaccination, were transient (≤3 days), and of Grade 1 severity. As for solicited injection site reactions, the incidence of Grade 3 systemic reactions was low in the three groups. Overall, after the three-dose primary vaccination, Grade 2 or Grade 3 fever was reported after 7.6% to 10.2% of vaccine injections, Grade 2 or Grade 3 irritability after 6.1% to 10.2% of vaccine injections, Grade 2 or Grade 3 crying abnormal after 5.6% to 9.1% of vaccine injections, and Grade 2 or Grade 3 vomiting after 6.8% to 8.6% of vaccine injections. Grade 2 or Grade 3 drowsiness (after 0.7% to 1.9% of vaccine injections) and appetite lost (after 1.2% to 1.7% of vaccine injections) were less frequent.

One subject (0.3%) in Group 2 experienced an immediate unsolicited AE (Grade 1 cough) within 30 minutes after the first injection of the study vaccine. Cough resolved spontaneously on D1 and was assessed as related to vaccination by the Investigator.

Unsolicited events were reported in a similar proportion of subjects in Group 1 (70.7%), Group 2 (73.4%) and

Group 3 (72.0%). Unsolicited non-serious events were most often classical diseases or symptoms of the infancy (upper respiratory tract infection, nasopharyngitis, bronchitis, diarrhoea, enteritis, fever and cough). The incidence of unsolicited non-serious AEs assessed by the Investigator as related to vaccination was low (4.3% in Group 1, 3.9% in Group 2, and 1.5% in Group 3). Unsolicited non-serious reactions consisted mainly of injection site reactions (injection site induration most often), and less frequently of systemic reactions (diarrhoea, vomiting, cough, rash, urticaria). Only one unsolicited non-serious adverse reaction (AR) was rated as Grade 3 for one subject in Group 2 (induration which resolved spontaneously within 9 days).

A total of 20 subjects (5.7%) in Group 1, 17 subjects (5.1%) in Group 2 and 13 subjects (4.0%) in Group 3 experienced at least one SAE after any vaccine injection. None of the SAEs was deemed to be related to either of the study vaccines.

A total of 16 subjects (nine in Group 2 and seven in Group 3) experienced SAEs before the first injection.

The most frequent SAEs were bronchitis and bronchopneumonia. Other SAEs were reported, such as pneumonia, enteritis, bronchiolitis, hand-foot-mouth disease, acute respiratory tract infection, hydrocephalus, perianal abscess, pharyngitis, intussusception, thrombocytopenic purpura, iron deficiency anemia and leucopenia. All subjects recovered without sequelae, except one subject in Group 1 who died of critical hand-foot-mouth disease more than 2 months after the third injection. Three SAEs in Group 3 led to study termination: one perianal abscess, one thrombocytopenic purpura (which both occurred before the first injection) and one bronchopneumonia (which occurred after the first injection).

From 1 month post-primary vaccination to booster vaccination

Four SAEs were reported in four subjects. Two SAEs led to death: a critical hand-foot-mouth disease (already described in the primary vaccination section), and a leukemia. The other SAEs (bronchitis and bronchopneumonia) did not lead to study discontinuation and the subjects recovered without sequelae. None of these four SAEs were assessed as related to the vaccination by the Investigator or by the Sponsor.

**Booster vaccination**

The incidence of solicited injection site reactions and systemic reactions was similar in the three groups. Grade 3 injection site reactions and systemic reactions were reported in a similar proportion of subjects in the three groups. Each type of injection site reaction (tenderness, erythema and swelling) was reported in a similar proportion of subjects in the three groups. In all groups, tenderness was the most frequent injection site reaction, followed by erythema. Swelling was less frequent. All solicited injection site reactions occurred within 4 days after vaccination, most reactions were transient (≤3 days), and of Grade 1 severity. The incidence of Grade 3 injection site reactions was low (3.0%, 1.6% and 1.3% of subjects in Group 1, Group 2 and Group 3, respectively).

Each type of solicited systemic reaction (fever, vomiting, crying abnormal, drowsiness, appetite lost and irritability) was reported in a similar proportion of subjects in the three groups. Fever was the most frequent solicited systemic reaction, followed by appetite loss, crying abnormal and irritability. Vomiting and drowsiness were less common. Most solicited systemic reactions occurred within 4 days after vaccination, were transient (≤3 days), and of Grade 1 severity. As for solicited injection site reactions, the incidence of Grade 3 systemic reactions was low in the three groups (2.1%, 1.9%, and 1.6% of subjects in Group 1, Group 2, and Group 3, respectively).

No immediate unsolicited AE was reported within 30 minutes after booster vaccination.

Unsolicited events were reported in a similar proportion of subjects in Group 1, Group 2 and Group 3, which were most often classical diseases of the childhood (nasopharyngitis, upper respiratory tract infection, pharyngitis, fever, diarrhoea and enteritis). Few unsolicited non-serious adverse events were assessed as related to vaccination by the Investigator in Group 1 (0.9%) (injection site induration, diarrhoea, nasopharyngitis). No unsolicited reaction was assessed as Grade 3.

After booster vaccination, only one SAE (fever) was reported in Group 1, which was assessed as related to vaccination by the Investigator. The subject recovered without sequelae.

**Conclusions**

**Primary Vaccination Phase:**

- The study showed the non-inferiority in terms of seroprotection rates of the Sanofi Pasteur's DTaP//PRP-T combined vaccine administered at 2, 3 and 4 months of age (Group 1), or at 3, 4 and 5 months of age (Group 2) when compared to Wuhan's DTaP and the Sanofi Pasteur's Hib tetanus conjugate (Act-HIB) vaccines administered at 3, 4 and 5 months of age (Group 3) for diphtheria, tetanus and PRP, and the superiority in terms of seroconversion rates for FIM (2 and 3), but not for PRN. For PRN, despite high seroconversion rates in both groups 1 and 2 (99.7%), it was not possible to demonstrate a superiority of the Sanofi Pasteur's DTaP// PRP-T combined vaccine versus reference vaccine due to an unexpected 100% seroconversion rate in Group 3.
- After the three-dose primary vaccination, a marked increase of GMTs was recorded in the three groups against each vaccine antigen.
- The seroprotection rates against diphtheria, tetanus and PRP and the seroconversion rates against PT, FHA, PRN and FIM (2 and 3) were high after administration of the Sanofi Pasteur's DTaP// PRP-T combined vaccine at 2, 3 and 4 months of age, or at 3, 4 and 5 months of age.
- Sanofi Pasteur's DTaP// PRP-T combined vaccine was well tolerated in toddlers when given at 2, 3, and 4 months of age or at 3, 4, and 5 months of age. Its safety profile was similar to that of the reference vaccines. The incidence of Grade 3 solicited adverse reactions (injection site or systemic reactions) was low.
- None of the SAEs was assessed as related to vaccination by the Investigator and the Sponsor.

Since the number of related SAEs, Grade 3 adverse reactions and unsolicited non-serious AEs after the primary vaccination series did not reach any of the safety criteria for study discontinuation, the Sponsor issued a decision for continuation of the booster series.

**Booster Vaccination Phase:**

- Sanofi Pasteur's DTaP//PRP-T combined vaccine (ACTACEL) was highly immunogenic for all antigens when given as a booster dose to 18-20 months old toddlers primed with the same vaccine antigens administered as a three-dose primary vaccination at 2, 3 and 4 months of age, or at 3, 4 and 5 months of age.
- After booster vaccination with Sanofi Pasteur's DTaP//PRP-T combined vaccine, a marked increase of GMTs was recorded against each vaccine antigen. All subjects achieved seroprotective antibody titers against diphtheria (≥0.1 IU/mL), tetanus (≥0.1 IU/mL) and PRP (≥1.0 µg/mL). High seroconversion rates (≥4-fold increase in antibody titer from pre-booster level) against PT, FHA, PRN and FIM (2 and 3) were observed. The response after booster was similar in toddlers primed with Sanofi Pasteur's DTaP//PRP-T combined vaccine at 2, 3 and 4 months of age or at 3, 4 and 5 months of age.
- After booster vaccination with Sanofi Pasteur's DTaP//PRP-T combined vaccine, the seroprotection rates against diphtheria, tetanus and PRP and the seroconversion rates against PT, FHA, PRN and FIM (2 and 3) were similar to that of the control vaccines (Wuhan's DTaP vaccine and Sanofi Pasteur's Hib tetanus conjugate [Act-HIB]).
- Sanofi Pasteur's DTaP//PRP-T combined vaccine (ACTACEL) was well tolerated in toddlers when given as a booster dose at 18-20 months of age, as already observed after the three-dose primary vaccination.
- The frequency of Grade 3 solicited injection site and systemic adverse reactions was very low and similar after administration of Sanofi Pasteur's DTaP//PRP-T combined vaccine and of the control vaccines.
- After booster vaccination, only one SAE (fever) was reported in Group 1, which was assessed as related to vaccination by the Investigator. The subject recovered without sequelae.

**Date of Report**: (Primary series) 23 May 2011 (booster phase) 28 Sep. 2012