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

<table>
<thead>
<tr>
<th>Sponsor/ Company:</th>
<th>Sanofi Pasteur</th>
<th>Study Code: IPV26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary Vaccine Name:</td>
<td>Inactivated Poliomyelitis Vaccine (IMOVAX Polio™)</td>
<td>Study Identifier: NCT00885157</td>
</tr>
</tbody>
</table>

**Title of the Study:** Immunogenicity and Safety of Fractional Booster Dose of Sanofi Pasteur’s Inactivated Poliomyelitis Vaccine (IMOVAX Polio) Administered Intradermally versus Full Booster Dose of Inactivated Poliomyelitis Vaccine (IMOVAX Polio) Administered Intramuscularly at 15 to 18 Months of Age in Healthy Toddlers in The Philippines

**Study centre:** 1 site in the Philippines

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

**Study period:**
- Date of First enrollment: 07 April 2009
- Date of Last visit (contact): 28 July 2009

**Development phase:** Phase II

**Methodology / Trial Design:**
Phase II, open-label, two-arms, controlled, mono-center trial in toddlers who completed a three-dose primary series of Inactivated Poliomyelitis Vaccine (IPV) administered by intradermal (ID) or intramuscular (IM) route at 6, 10 and 14 weeks of age during the IPV25 study.

This trial could be initiated because the non-inferiority of the immune responses induced by fractional doses of IMOVAX Polio administered intradermally versus full doses of IMOVAX Polio administered intramuscularly was demonstrated in terms of seroprotection rates (anti-polio 1, 2 and 3 seroneutralizing antibody titers ≥8 (1/dil)) at 1 month after the three-dose primary vaccination series.

All subjects who completed the three-dose primary vaccination series using the route of administration as designated by randomization in the IPV25 study were invited to participate into the present booster dose study.

Toddlers were vaccinated using the route as designated by randomization in the IPV25 study, i.e.:

**Group A:** subjects who received IPV intradermally as primary vaccination series (IPV25) received a fractional booster dose (1/5th of the full dose) of IPV using the same route between 15 and 18 months of age.

**Group B:** subjects who received IPV intramuscularly as primary vaccination series (IPV25) received a full booster dose of IPV using the same route between 15 and 18 months of age.

**Objectives:**

**Immunogenicity**
- To describe in each group the immunogenicity of IMOVAX Polio, administered intradermally or intramuscularly, 1 month after the booster dose given at 15-18 months of age in toddlers previously primed with three doses of IMOVAX Polio vaccine during the IPV25 study.
- To describe in each group the antibody persistence of poliovirus types 1, 2 and 3 (before booster administration), at 15-18 months of age, i.e. approximately 12 to 15 months after the third dose of IPV (IMOVAX Polio) given as primary series in the IPV25 study.

**Safety**
To describe in each group the safety of the booster dose of IMOVAX Polio vaccine administered intradermally or intramuscularly.
Endpoints:

Immunogenicity

- Immediately before booster dose of IMOVAX Polio (approximately 12 to 15 months after the third dose of primary vaccination series), in both groups:
  - Individual anti-polio 1, 2 and 3 antibody titers measured by the polio seroneutralization (SN) assay
- One month after the booster dose of study vaccine, for each polio type (1, 2, and 3):
  - Individual antibody titers measured by the polio SN assay
  - Individual antibody titers ratio*
  - Individual antibody titers $\geq$8 (1/dil)
  - Individual antibody titer $\geq$4-fold rise at V02 compared to V01
  - Individual antibody titers $\geq$4 (1/dil)

*Individual titer ratio: post-booster vaccination / pre-booster vaccination

Safety

The endpoints for the safety evaluation are:

- The occurrence, intensity, and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination.
- The occurrence, time to onset, number of days of occurrence and intensity of solicited (terms pre-listed in the Case Report Form [CRF]) injection site and systemic reactions occurring between D0 and D7 after injection.
- The occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time to onset, duration, intensity and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs from vaccination day to next study visit.
- The occurrence, nature (MedDRA preferred term), relationship to vaccination, outcome and seriousness of any serious AE (SAE) occurring throughout the trial (from V01 to V02).

Statistical methods for objectives: No hypothesis-driven objectives were defined.

Sample size (Number of Subjects):

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number expected</td>
<td>113</td>
<td>115</td>
</tr>
<tr>
<td>Number included for the booster phase</td>
<td>113</td>
<td>112</td>
</tr>
<tr>
<td>Number completed the booster phase</td>
<td>113</td>
<td>111</td>
</tr>
<tr>
<td>Full Analysis Set (FAS)</td>
<td>113</td>
<td>112</td>
</tr>
<tr>
<td>Safety Analysis Set</td>
<td>112</td>
<td>113</td>
</tr>
<tr>
<td>Per Protocol (PP) Analysis Set</td>
<td>111</td>
<td>111</td>
</tr>
</tbody>
</table>

Schedules of Vaccination and Specimen Collection:

Two visits (V01 and V02) and two blood samples (BL01 and BL02) were performed in all toddlers.

**Group A:** subjects who received IPV intradermally as primary vaccination series (IPV25) received a fractional booster dose (1/5th of the full dose) of IMOVAX Polio (IPV) vaccine using the same route between 15 and 18 months of age.

**Group B:** subjects who received IPV intramuscularly as primary vaccination series (IPV25) received a full booster dose of IMOVAX Polio (IPV) vaccine using the same route between 15 and 18 months of age.
Concomitantly, toddlers included in the study received, free of charge, one dose of sanofi pasteur’s commercially available DTwP-Hib vaccine (TETRAct-HIB®), between 12 and 24 months of age. DTwP-Hib vaccine was not part of the study; consequently its safety and immunogenicity were not monitored. This vaccine was administered more than 4 weeks before study vaccination or after V02.

Two blood samples of 2 mL each were taken for anti-poliovirus type 1, 2, and 3 antibody titration:
- Just before the booster dose of study vaccine (BL01-V01),
- One month after the booster dose of study vaccine (BL02-V02)

**Duration of Participation in the Trial:**
The total duration of follow-up for each subject was approximately 28 days.

**Product Under Investigation:**
IPV (IMOVAX Polio™) is manufactured by sanofi pasteur.

**Form/Dose/Route:**
Suspension of IPV/0.1 mL, 1/50 of a 10 full doses vial, i.e. a 5 mL vial/ ID into the right upper arm using the Mantoux technique

**Batch number:** D0051-1

**Control Product:**
IPV (IMOVAX Polio™) is manufactured by sanofi pasteur.

**Form/Dose/Route:**
Suspension of IPV/0.5 mL, pre-filled syringe/IM into the anterolateral area of the right thigh

**Batch number:** B0281-5

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

**Statistical methods**

**Analysis of Immunogenicity**
The analysis was descriptive. The immunogenicity endpoints were described with 95% confidence intervals (CIs) using the following parameters:
- Geometric mean titers (GMTs) before and after the booster dose
- Percentage of subjects with titers above predefined threshold (4; 8) before and after the booster dose
- GM of individual antibody titer ratios (GMTRs) post/pre-booster dose

Reverse cumulative distribution curves (RCDC) were presented.

**Analysis of Safety**
- For each study group, the number and percentage of subjects reporting any solicited injection site reactions or any solicited systemic reactions were summarized by intensity (Grade 1, 2 or 3), number of days of occurrence (1 to 3 days, 4 to 7 days, and ≥ 8 days), and time period of onset (Days 0 to 3, days 4 to 7, and Days 0 to 7 after each vaccination) for each reaction term. Exact two-sided 95% CIs were also calculated for the percentages.
- Unsolicited injection site reactions and unsolicited systemic events were coded by MedDRA preferred term and System Organ Class (SOC). The number and percentage of subjects reporting any of these AEs and the number and percentage of subjects reporting any immediate unsolicited systemic AEs (within 30 minutes after the vaccination) were summarized by study group and intensity for each preferred term and SOC that has at least one report. The number and percentage of subjects reporting unsolicited systemic events (whether immediate or not) were also summarized by relationship to study vaccine.
- The number and percentage of subjects with an SAE were summarized by nature, seriousness criterion, outcome, and relationship to the vaccination.
Results summary:

This report presents data obtained after the booster vaccination. A total of 113 subjects in Group A and 112 subjects in Group B received a booster dose. All subjects completed the booster part, except one subject in Group B who was voluntarily withdrawn after booster vaccination, not for an AE. Two non-compliant subjects in Group A (one subject vaccinated with a measles vaccine, and the other subject vaccinated by mistake via IM route with the full dose of IPV) and one non-compliant subject in Group B (voluntarily withdrawn after booster vaccination) were excluded from the PP Analysis Set, which consisted of 111 subjects in each group.

Demographic Characteristics

The median age at inclusion visit 1 (V01) at the time of the booster vaccine injection was 15.4 months in both groups. The age ranged from 15.0 months to 17.4 months in Group A and from 15.0 months to 17.3 months in Group B. In Group A there were 58 male (51.3%) versus 55 (48.7%) female subjects and in Group B there were 42 male (37.5%) versus 70 (62.5%) female subjects. The imbalance in male to female subjects in Group B occurred purely by chance, and was already observed in the IPV25 study.

Immunogenicity

In both groups, antibody titers had decreased 12 to 15 months after primary vaccination. However, antibody titers were still detectable (antibody titer ≥4 [1/dil]) for the three serotypes in at least 97.3% of subjects in Group A and 99.1% of subjects in Group B. Moreover, seroprotective anti-polio 1, 2 and 3 antibody titers ≥8 (1/dil) were observed in the vast majority of subjects, in 95.5%, 95.5% and 88.3% of subjects, respectively, for Group A and 100.0%, 98.2% and 96.4% of subjects, respectively, for Group B. Anti-polio 1, 2 and 3 seroprotection rates were comparable in Group A and Group B.

One month after booster vaccination, seroprotection rates reached 100% for each polio type 1, 2 and 3 in Group A and Group B. After booster vaccination, a marked increase of antibody titers was observed in Group A and Group B. Anti-polio 1, 2 and 3 GMTs reached respectively 2833.7 (1/dil), 3210.7 (1/dil) and 4498.2 (1/dil) in Group A and 6666.5 (1/dil), 6522.3 (1/dil) and 11952.7 (1/dil) in Group B. The proportion of subjects with more than a 4-fold increase in anti-polio 1, 2 and 3 antibody titer was high and similar in both groups.

Results in the FAS were similar to those in the PP Analysis Set.

Safety:

Solicited Reactions

A total of 61 subjects (54.5%) in Group A and 48 subjects (42.5%) in Group B experienced at least one solicited reaction.

• Injections site reactions:

Solicited injection site reactions were reported more frequently in Group A (49.1% of subjects) than in Group B (30.1% of subjects).

After booster injection, tenderness, erythema and swelling reactions were observed respectively in 28.6%, 38.4% and 8.9% of subjects in Group A and in 21.2%, 11.5% and 1.8% of subjects in Group B.

All solicited injection site reactions occurred within 4 days after vaccination and most lasted 3 days or less and were of Grade 1 severity. None was of Grade 3 severity.

• Systemic reactions:

The proportion of subjects with at least one solicited systemic reaction was similar in Group A (19.6%) and in Group B (24.8%).

Fever (≥38°C, axillary) was observed in 8.0% and 15.0% of subjects in Groups A and B, respectively. The incidence of the other solicited systemic reactions was similar across groups and ranged from 2.7% to 8.0% of subjects in Group A and from 3.5% to 9.7% in Group B.

Most of the solicited systemic reactions occurred within 4 days after vaccination, lasted 3 days or less and were of Grade 1 severity. The incidence of Grade 3 systemic reactions was very low after booster vaccination (in one subject [0.9%] in each group). Grade 3 systemic reactions consisted of fever, transient and isolated in the subject of Group A, or associated to an SAE in the subject of Group B.
Unsolicited AEs/reactions:

No immediate unsolicited events were reported in any group. Unsolicited events (collected between booster injection and the following visit) were reported in similar proportion in Group A (39.3%) and Group B (45.1%). Most of these unsolicited events were systemic and common childhood diseases (upper respiratory tract infection, gastroenteritis). None was of Grade 3 severity and none was assessed by the Investigator as related to vaccination.

Serious Adverse Events (SAEs):

Overall, during the study, two subjects in Group B experienced one SAE each. These SAEs were bronchopneumonia. None was assessed as related to study vaccination by the Investigator or the Sponsor, and all resolved without sequelae. No SAEs were reported in subjects from Group A.

No deaths occurred during the study and no drop outs were reported due to an AE.

Conclusions:

- More than 1 year after the third dose of primary vaccination series with a fractional (1/5) dose of Sanofi Pasteur’s IPV administered intradermally, anti-polio 1, 2 and 3 antibody titers were still protective in a high proportion of subjects.
- After booster vaccination with a fractional dose of IPV administered intradermally at 15 to 18 months of age in subjects previously primed with a fractional dose of IPV administered intradermally, a marked increase of anti-polio 1, 2 and 3 seroneutralizing antibody titers was observed, and all subjects were seroprotected against each polio type 1, 2 and 3.
- The persistence of antibodies after primary vaccination and the anamnestic response after booster vaccination, given as a fractional dose of IPV administered intradermally or a full dose of IPV administered intramuscularly, were similar in terms of seroprotection rates for the three polio types 1, 2 and 3.
- The good safety profile of a fractional dose of IPV administered intradermally or a full dose of IPV administered intramuscularly was confirmed after booster injection. As expected, injection site reactions (mainly erythema) were more frequent in the group of subjects who received the intradermal booster injection, as previously observed in Study IPV25. The incidence of Grade 3 solicited reactions (both injection site and systemic reactions) was very low (only Grade 3 fever was reported in one subject in each group).
- Two subjects in Group B experienced one SAE after booster injection, and none of them was assessed as related to vaccination by the Sponsor or the Investigator.

Date of Report: 09 March 2010