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Sponsor/ Company:	Sanofi Pasteur, Inc.	**Study Code:**	M5I02
		Study Identifiers:	NCT01346293 U1111-1116-4842
Proprietary Vaccine Name:	DTaP-IPV (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus Vaccine)		

Title of the Study:

Safety and Immunogenicity of DTaP-IPV (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus Vaccine) Compared to DAPTACEL® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) + IPOL® (Poliovirus Vaccine Inactivated) as the 5th Dose in Children 4 to 6 Years of Age

Study centre(s):	This was a multi-center, trial involving 64 investigators at 70 sites in the US and Puerto Rico.
Publications:	None at the time of report writing
Study period:	Date of First enrollment: 28 April 2011 Date of Last visit (contact): 30 May 2013
Development phase:	Phase III

Methodology / Trial Design:

This was a controlled, multi-center, randomized, open label, Phase III study designed to compare the safety and immunogenicity of DTaP-IPV to DAPTACEL® + IPOL® as the 5th dose booster in children ≥ 4 to < 7 years of age, who had been previously vaccinated with DAPTACEL and/or Pentacel® vaccine(s).

Approximately 3340 subjects from the US and Puerto Rico were identified for participation in this trial based on vaccine history that included a 4-dose series with DAPTACEL and/or Pentacel vaccine(s). An Interactive Voice Response System (IVRS) was used to randomize subjects into vaccination groups. Approximately 640 subjects were assigned (with a planned capped maximum of 75 subjects per site) to an immunogenicity subset (randomized in a 1:1 ratio to Group 1 and Group 2); these subjects were also evaluated for safety. Groups were balanced based on vaccination history according to the number of DAPTACEL doses and IPV doses. For the immunogenicity subset, the number of doses of IPV was similar between Groups 1 and 2; the date of the last dose of IPV was to be documented. An additional 2700 subjects with a vaccine history of DAPTACEL and/or Pentacel vaccine(s) were assigned to the safety-only subset (randomized in an 8:1 ratio to Group 3 and Group 4).

- Subjects in Group 1 received 3 vaccines concomitantly: a dose of DTaP-IPV vaccine; a dose of M-M-R®$_{II}$ (Measles, Mumps, and Rubella Virus Vaccine Live [MMR]); and a dose of VARIVAX® (Varicella Virus Vaccine Live [V]).
- Subjects in Group 2 received 4 vaccines concomitantly: a dose of DAPTACEL vaccine; a dose of IPOL vaccine; a dose of MMR vaccine; and a dose of V vaccine.
- Subjects in Group 3 received up to 3 vaccines concomitantly: a dose of DTaP-IPV with or without a dose of MMR and V vaccine(s).
- Subjects in Group 4 received up to 4 vaccines concomitantly: a dose of DAPTACEL vaccine, a dose of IPOL vaccine, with or without a dose of MMR and V vaccine(s) (See Table S1).

For subjects in Groups 3 and 4 who had already received 2 doses of MMR and/or varicella vaccine, additional doses of these vaccines were not mandatory as long as complete documentation existed that could verify the subject's MMR/V vaccination status. Only doses of vaccine with written documentation of the date of vaccination were accepted as valid. Parental or legally acceptable representative report of vaccination was not considered adequate documentation. Persons who lacked adequate documentation of vaccination history were to be vaccinated. If information about previous MMR/V vaccination was provided, the vaccine(s) given and the date of receipt were documented in the electronic case report form (eCRF)

Table S1: Study Groups

Randomization scheme	Blood sample	Safety	Visit 1 (Day 0)
Group 1 (N=320)	Yes	Yes	DTaP-IPV + MMR + V
Group 2 (N=320)	Yes	Yes	DAPTACEL + IPOL + MMR + V
Group 3 (N=2400)	No	Yes	DTaP-IPV + MMR* + V*
Group 4 (N=300)	No	Yes	DAPTACEL + IPOL + MMR* + V*

*For subjects in Groups 3 and 4 who had already received 2 doses of MMR and/or varicella vaccine, additional doses of these vaccines were not mandatory as long as complete documentation existed that could verify the MMR/V vaccination status of the subject.

Note: History of Pentacel, DAPTACEL, and IPV (dose number and date of last vaccination) were to be documented for all subjects.

All subjects were observed for 30 minutes after vaccination, and any AEs starting within those 30 minutes were recorded in the eCRF. Solicited adverse events (AEs) were collected from Day 0 to Day 7. Non-serious adverse events (AEs) were assessed for all subjects from Day 0 to Day 28. Serious adverse events (SAEs) were collected from Day 0 to Day 180.

Early Safety Data Review:

This trial did not include an early review of safety data. However, it could have been interrupted at any time if new data about the investigational product became available and was associated with risk to the study participants, and/or on advice of the Sponsor, the Independent Ethics Committees (IECs) /Institutional Review Boards (IRBs), or the governing regulatory authorities in the country where the trial took place.

If the trial had been prematurely terminated or suspended, the Sponsor was to promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial had been prematurely terminated for any reason, the Investigator was to promptly inform the subjects' parents/legally acceptable representatives and was to ensure appropriate therapy and follow-up.

Objectives:

Primary objective(s):

1) To compare the pertussis (PT, FHA, PRN, and FIM) booster responses and geometric mean concentrations (GMCs) (as measured by enzyme-linked immunosorbent assay [ELISA]) following DTaP-IPV vaccination (Group 1) to those elicited following DAPTACEL + IPOL vaccinations (Group 2) when administered as a 5th dose
2) To compare the diphtheria and tetanus booster responses and GMCs (as measured by neutralizing assay and ELISA, respectively) following DTaP-IPV vaccination (Group 1) with those elicited following DAPTACEL + IPOL vaccinations (Group 2) when administered as a 5th dose
3) To compare the IPV booster responses and geometric mean titers (GMTs) (as measured by neutralizing assay) following DTaP-IPV vaccination (Group 1) with those elicited following DAPTACEL + IPOL vaccinations (Group 2) when administered as either a 4th or 5th dose.

Primary endpoint:

1) For each anti-pertussis (PT, FHA, PRN, and FIM) antibody the percentage of subjects demonstrating the booster response and the GMCs were to be measured

The booster response rate partially adjusts for individual and population differences in pre-vaccination antibody concentrations. The criterion for demonstrating a booster response was as follows:

- Subjects whose pre-vaccination antibody concentrations were less than the lower limit of quantitation (< LLOQ) for each anti-pertussis (PT, FHA, PRN, and FIM) antibody demonstrated the booster response if they had post-vaccination levels ≥ 4X LLOQ
- Subjects whose pre-vaccination antibody concentrations were ≥ LLOQ but < 4X LLOQ, demonstrated the booster response if they had a 4-fold rise (i.e., post-/pre-vaccination ≥ 4)
- Subjects whose pre-vaccination antibody concentrations were ≥ 4X LLOQ, demonstrated the booster response if they had a 2-fold response (i.e., post-/pre-vaccination ≥ 2)

2) For diphtheria and tetanus antibodies, the percentage of subjects demonstrating the booster response and the GMCs were to be assessed. The criterion for demonstrating a booster response was as follows:
   - Subjects whose pre-vaccination antibody concentrations were < 0.1 IU/mL demonstrated the booster response if they had a post-vaccination level ≥ 0.4 IU/mL
   - Subjects whose pre-vaccination antibody concentrations were ≥ 0.1 IU/mL but < 2.0 IU/mL demonstrated the booster response if they had a 4-fold rise (i.e., post-/pre-vaccination ≥ 4)
   - Subjects whose pre-vaccination antibody concentrations were ≥ 2.0 IU/mL, demonstrated the booster response if they had a 2-fold response (i.e., post-/pre-vaccination ≥ 2)
3) For IPV antibodies, the GMTs and the percentage of subjects demonstrating the booster response were to be assessed. The criterion for demonstrating a booster response was as follows:
   - Subjects whose pre-vaccination antibody concentrations were < 1:8 dilution (dil) demonstrated the booster response if they had post-vaccination levels ≥ 1:8 dil
   - Subjects whose pre-vaccination antibody concentrations were ≥ 1:8 dil, demonstrated the booster response if they had a 4-fold rise rate (i.e., post-/pre-vaccination ≥ 4)

Observational objectives:

Immunogenicity

1) To present the immune responses (as seroprotection rates, mean fold rise [post-/pre-vaccination], and reverse cumulative distribution curve [RCDCs]) of the pertussis (PT, FHA, PRN, and FIM), diphtheria, tetanus, and polio antigens following DTaP-IPV vaccination (Group 1) side-by-side with those elicited following DAPTACEL + IPOL vaccinations (Group 2) when administered as a 5th dose
2) To present the booster response and GMTs of subjects in Groups 1 and 2 receiving IPV as 4th dose side-by-side with subjects receiving IPV as the 5th dose

Safety

1) To describe the safety profile for Groups 1 and 3 combined, and Groups 2 and 4 combined
2) To describe the safety profile of the subjects with a 4th and 5th dose of IPV in Groups 1 and 3 combined, and Groups 2 and 4 combined
3) To describe the safety profile of subjects with and without MMR and V vaccinations in Groups 1 and 3 combined, and Groups 2 and 4 combined

Observational endpoint:

Immunogenicity:

The following serological endpoints were measured on Day 0 prior to vaccination and 28 days after the vaccination in Group 1 and Group 2:

- Geometric means of fold-rises (GMFR) for anti-pertussis, anti-diphtheria, anti-tetanus, and anti-polio
- Seroprotection rates for anti-diphtheria, anti-tetanus, and anti-polio antibodies
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
  - Anti-tetanus antibody concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
  - Anti-polio types 1, 2, and 3 antibody titers ≥ 1:8 dil
- RCDCs were generated for pertussis (PT, FHA, PRN, and FIM), diphtheria, tetanus, and polio antibody concentrations for pre- (Day 0) and post-vaccination (Day 28)

Safety / Reactogenicity:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination with DTaP-IPV or DAPTACEL + IPOL
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card [DC] and eCRF) injection site reactions (injection site pain, injection site erythema, injection site swelling, change in limb circumference, and extensive limb swelling [ELS]) occurring up to 7 days after vaccination with DTaP-IPV or DAPTACEL + IPOL

- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's DC and eCRF) systemic reactions (fever, headache, malaise, and myalgia) occurring up to 7 days after vaccination with DTaP-IPV or DAPTACEL + IPOL
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs occurring up to 28 days after vaccination with DTaP-IPV or DAPTACEL + IPOL
- Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs occurring throughout the trial (up to 6 months after vaccination)

Sample size (Number of Subjects):

Planned: A total of approximately 3340 subjects were planned to be enrolled into 4 study groups

Enrolled: 3372 subjects were actually enrolled.

Schedules of Vaccination and Specimen Collection:

Vaccination

All subjects were randomized to receive either 1 dose each of DTaP-IPV + MMR + V or 1 dose each of DAPTACEL + IPOL + MMR + V on Day 0. MMR and V vaccines were not required for subjects in Groups 3 and 4 who could provide documentation that they had already received 2 doses of these vaccines.

Blood sampling

Two blood samples were taken from the subjects in Group 1 and Group 2: the first sample was taken immediately before vaccination (Visit 1) and the second 28 to 42 days after vaccination (Visit 2).

Collection of safety data

Each subject was observed for 30 minutes after vaccination and any immediate AEs were recorded in the eCRF. The subject's parent/legally acceptable representative recorded information about solicited reactions from Day 0 to Day 7 post-vaccination, and recorded information about unsolicited AEs from Day 0 to Day 28 in a DC.

- If the subject developed a significant change in limb circumference (> 50 mm from baseline) or ELS (soft tissue swelling that occurred post-vaccination and extended from the injection site to involve an adjacent joint [e.g., the elbow, shoulder joint, or both]) of either arm during the 7-day period after vaccination, the parent/legally acceptable representative was required to contact the site on the same day the change in limb circumference or ELS was observed. If the ELS/joint involvement occurred on the left limb (study vaccine[s] arm), the site was to attempt to arrange for the subject to be seen at the study site within 24 hours to assess the extent of the reaction. Any ELS of the right arm (concomitant vaccines arm) was to be reported as an unsolicited AE. Site staff instructed the parent/legally acceptable representative to continue taking circumference measurements of both arms until the swelling was resolved.
- Staff contacted the subject's parent/legally acceptable representative by telephone at Day 8 (+3 days) to remind them to complete the DC for AEs that may have occurred from Day 0 to 7, to continue recording AE information, and to bring the completed DC with them to the Day 28 visit
- Staff reviewed the Day 0 to 28 safety data with the subject's parent/legally acceptable representative at Day 28 visit and collect the DC
- The subject's parent/ legally acceptable representative recorded information about unsolicited AEs in a memory aid (MA) through 6 months after the last vaccination. Staff contacted the subject's parent/ legally acceptable representative by telephone at 6 months (+14 days) post-vaccination to review AEs that may have occurred. Study staff members determined whether the AE should be classified as an SAE. The non-serious unsolicited AEs were collected in the source document and SAEs were recorded in the source document and transferred to the eCRF.

Duration of Participation in the Trial: The expected total duration of each subject's participation (first visit to last contact) was about 6 months.

Product Under Investigation:

DTaP-IPV®: (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus Vaccine (Sanofi Pasteur Limited, Toronto, ON, Canada)

Composition: Each 0.5 mL dose contains:

Active ingredients:

Diphtheria Toxoid (D):	15 Lf
Tetanus Toxoid (T):	5 Lf
Acellular Pertussis:	
Pertussis Toxoid (PT):	20 µg
Filamentous Haemagglutinin (FHA):	20 µg
Pertactin (PRN):	3 µg
Fimbriae Types 2 and 3 (FIM):	5 µg
Inactivated Poliovirus:	
Type 1 (Mahoney):	40 D-antigen units
Type 2 (MEF-1):	8 D-antigen units
Type 3 (Saukett):	32 D-antigen units

Other ingredients:

Aluminum Phosphate (aluminum 0.33 mg) as the adjuvant:	1.5 mg
2-phenoxyethanol as an excipient:	0.6% v/v
Polysorbate 80:	10 ppm (by calculation)

Form/Dose/Route:

Liquid/0.5 mL/ Intramuscular

Batch number: [redacted]

Control Product 1:

DAPTACEL®: (DTaP) Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi Pasteur Limited, Toronto, ON, Canada)

Composition: Each 0.5 mL dose contains:

Active ingredients:

Diphtheria (D):	15 Lf
Tetanus (T):	5 Lf
Acellular Pertussis:	
Pertussis Toxoid (PT):	10 µg
Filamentous Haemagglutinin (FHA):	5 µg
Pertactin (PRN):	3 µg
Fimbriae Types 2 and 3 (FIM):	5 µg

Other ingredients:

Aluminum phosphate (aluminum 0.33 mg) as the adjuvant:	1.5 mg
2-phenoxyethanol as an excipient:	0.6 % v/v

Form/Dose/Route:

Liquid/0.5 mL/ Intramuscular

Batch number: [redacted]

Control Product 2:

IPOL®: Poliovirus Vaccine Inactivated (Sanofi Pasteur SA, Lyon, France)

Composition: Each 0.5 mL dose contains:

Active ingredients:

Polio Type 1 (Mahoney):	40 D-antigen units
Polio Type 2 (MEF-1)	8 D-antigen units
Polio Type 3 (Saukett)	32 D-antigen units

Other ingredients:

2-phenoxyethanol as preservative:	0.5%
Formaldehyde as preservative:	0.02%

Form/Dose/Route:

Liquid/0.5 mL/ Intramuscular or Subcutaneous

Batch number: [redacted]

Other Product 1:

M-M-R®$_{II}$: (MMR) Measles, Mumps, and Rubella Virus Vaccine Live (Merck & Co., Inc., Whitehouse Station, NJ, USA)

Composition: Each 0.5 mL dose of vaccine is formulated to contain the following active ingredients:

Measles virus:	not less than 1,000 $TCID_{50}$
Mumps virus:	not less than 12,500 $TCID_{50}$
Rubella virus:	not less than 1,000 $TCID_{50}$

Form/Dose/Route:

Lyophilized/0.5 mL/Subcutaneous

Batch number: Commercial lot supplied by the clinical sites

Other Product 2:

VARIVAX®: (V) Varicella Virus Vaccine Live (Oka/Merck) (Merck & Co., Inc., Whitehouse Station, NJ, USA)

Composition: Each 0.5 mL dose of vaccine was formulated to contain a minimum of 1350 PFU of Oka/Merck varicella virus.

Form/Dose/Route:

Lyophilized/0.5 mL/Subcutaneous

Batch number: Commercial lot supplied by the clinical sites

Inclusion Criteria: An individual must fulfill *all* of the following criteria in order to be eligible for trial enrollment:

1) Aged ≥ 4 to < 7 years on the day of inclusion
2) Informed consent form (ICF) has been signed and dated by the parent/guardian before the first study-related procedure
3) Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures
4) Subject has documented completion of 4-dose infant/toddler vaccination series with DAPTACEL and/or Pentacel vaccine(s) only

Exclusion Criteria: An individual fulfilling *any* of the following criteria was to be excluded from trial enrollment:

1) Participation in another clinical trial investigating a vaccine, drug, medical device, or medical procedure in the 4 weeks preceding the trial vaccination
2) Planned participation in another clinical trial during the present trial period
3) Receipt of any vaccine in the 4 weeks preceding the trial vaccination, except for inactivated influenza vaccine, which may be received at least 2 weeks before study vaccines (this exception does not apply to live attenuated influenza vaccines)

4) Planned receipt of any vaccine in the 4 weeks following the trial vaccination, with the exception of inactivated influenza vaccine which may be received beginning 2 weeks after study vaccinations (this exception does not apply to live attenuated influenza vaccines)

5) Receipt of blood or blood-derived products in the past 3 months

6) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

7) History of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C

8) History of diphtheria, tetanus, or pertussis infection, confirmed either clinically, serologically, or microbiologically

9) Known systemic hypersensitivity to any of the vaccines' components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances

10) Laboratory-confirmed thrombocytopenia, contraindicating IM vaccination

11) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination

12) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion

13) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study.

Temporary Contraindications:

A prospective subject was not included in the study until the following conditions and/or symptoms were resolved:

- Febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) or moderate or severe acute illness/infection (according to Investigator judgment) within 24 hours of vaccination

Statistical methods

Immunogenicity

Primary Hypothesis 1

The primary hypothesis 1 was that anti-pertussis booster response rates and GMCs for pertussis antigens (PT, FHA, PRN, and FIM) would be non-inferior in subjects who receive DTaP-IPV as a 5th dose when compared to subjects who receive DAPTACEL + IPOL as a 5th dose.

Booster Response for Pertussis

Non-inferiority of DTaP-IPV was demonstrated if the lower limits of the 2-sided 95% confidence intervals (CIs) of the difference (DTaP-IPV minus DAPTACEL + IPOL) in post-vaccination booster response rates for all pertussis antigens (PT, FHA, PRN, and FIM) between groups were > -10%

GMCs for Pertussis

Non-inferiority of DTaP-IPV was demonstrated if the lower limits of the 2-sided 95% CIs of the ratio (DTaP-IPV / DAPTACEL + IPOL) in post-vaccination GMCs for pertussis antigens (PT, FHA, PRN, and FIM) between groups were > 2/3

Primary Hypothesis 2

The primary hypothesis 2 was that anti-diphtheria toxoid and anti-tetanus toxoid booster response rates and GMCs would be non-inferior in subjects who receive DTaP-IPV as a 5th dose when compared to subjects who receive DAPTACEL + IPOL as a 5th dose.

Booster Response for Diphtheria and Tetanus

Non-inferiority of DTaP-IPV was demonstrated if the lower limits of the 2-sided 95% CIs of the difference (DTaP-IPV minus DAPTACEL + IPOL) in post-vaccination booster response rates for diphtheria and tetanus between groups were > -10%

GMCs for Diphtheria and Tetanus

Non-inferiority of DTaP-IPV was demonstrated if the lower limits of the 2-sided 95% CIs of the ratio (DTaP-IPV / DAPTACEL + IPOL) in post-vaccination GMCs for diphtheria and tetanus between groups were > 2/3

Primary Hypothesis 3

The primary hypothesis 3 was that the immune response to poliovirus vaccine antigens (poliovirus types 1, 2, and 3) in terms of the proportion of subjects who achieve antibody titers ≥ 1:8 dil (booster response) and GMTs would be non-inferior in subjects who receive DTaP-IPV as a 5th dose when compared to subjects who receive DAPTACEL + IPOL as a 5th dose.

Booster response for Polio

Non-inferiority of DTaP-IPV was demonstrated if the lower limits of the 2-sided 95% CIs of the difference (DTaP-IPV minus DAPTACEL + IPOL) in post-vaccination booster response rates for polio types 1, 2, and 3 between groups were > –10%

GMTs for Polio

Non-inferiority of DTaP-IPV was demonstrated if the lower limits of the 2-sided 95% CIs of the ratio (DTaP-IPV / DAPTACEL + IPOL) in post-vaccination GMTs for each polio antigen between groups were > 2/3.

Statistical methods for observational objectives:

Immunogenicity

The following statistical analyses were computed for the specified antibody titers or concentrations:

- Seroprotection rates of the diphtheria, tetanus, and polio antigens following DTaP-IPV vaccination (Group 1) with those elicited following DAPTACEL + IPOL vaccinations (Group 2)
- Geometric mean fold rise (and 95% CIs) of the pertussis, diphtheria, tetanus, and polio antigens following DTaP-IPV vaccination (Group 1) with those elicited following DAPTACEL + IPOL vaccinations (Group 2).
- Percentage of subjects achieving 4-fold rise (and 95% CIs) of the pertussis [PT, FHA, PRN, and FIM], diphtheria, tetanus, and polio antigens following DTaP-IPV vaccination (Group 1) with those elicited following DAPTACEL + IPOL vaccinations (Group 2).
- RCDCs of the pertussis [PT, FHA, PRN, and FIM], diphtheria, tetanus, and polio antigens following DTaP-IPV vaccination (Group 1) with those elicited following DAPTACEL + IPOL vaccinations (Group 2).
- Booster response and GMTs of subjects in Groups 1 and 2 receiving IPV as 4th dose compared to those receiving IPV as 5th dose.

Safety

The number and percentage of subjects reporting any solicited injection site reactions and/or solicited systemic reactions were summarized by study group, intensity (Grade 1, Grade 2, Grade 3), and period (Days 0 to 3, Days 4 to 7, and Days 0 to 7 after each vaccination) for each reaction term. For the time periods in which more than one intensity grade was recorded, the highest intensity grade was used. Exact 2-sided 95% CIs were calculated for the percentages.

Unsolicited AEs and immediate reactions were coded by MedDRA preferred term and system organ class (SOC). The number and percentage of subjects reporting any unsolicited AE were summarized by study group and intensity for each preferred term and SOC that had at least one report, as well as by relationship to the study vaccine. Unsolicited AEs were to be reported from Day 0 through Day 28. SAEs were to be tabulated separately from Day 0 through Day 28 and from Day 0 through Day 180.

Sample Size Calculations

The total sample size of the study was approximately 3340. In this age group, the expected drop out rate is about 10%.

Sample size for immunogenicity endpoints (640 subjects) was estimated to show non-inferiority in all primary objectives with 90.1% overall power.

Results summary: Disposition of Subjects

Disposition of Subjects

All Randomized Subjects

The first subject in this trial was enrolled on 28 April 2011. The last D28 visit for the study took place on 09 January 2013.

A total of 3372 subjects were randomized in this study (324 in Group 1, 327 in Group 2, 2419 in Group 3, and 302 in Group 4). Of these 3372 subjects, 651 subjects were categorized as the immunogenicity subset (Groups 1 and 2) and were scheduled for pre- and post-vaccination blood sample collection. Group 1 subjects were randomized to receive DTaP-IPV; Group 2 subjects were randomized to receive DAPTACEL + IPOL. Safety information was collected for subjects in all groups.

Of the 2743 subjects randomized to receive DTaP-IPV, 99.7% (2734/2743) received the vaccine; of the 629 subjects randomized to receive DAPTACEL + IPOL, 99.5% (626/629) received the vaccine. One subject in Group 1 and 8 subjects in Group 3 did not receive DTaP-IPV. Three subjects in Group 4 did not receive DAPTACEL + IPOL. All subjects in Group 2 received the vaccine.

Of the 3372 subjects randomized in the study, 3354 subjects were included in the Safety Analysis Set (SafAS). Of the subjects randomized to the DTaP-IPV group, 99.6% (2733/2743) were included in the SafAS; of the subjects randomized to the DAPTACEL + IPOL group, 98.7% (621/629) were included in the SafAS.

There were 605 subjects in the Immunogenicity Full Analysis Set (FAS) and 516 subjects in the Per-Protocol (PP) analysis set.

Of the randomized subjects, 97.4% (3284/3372) completed all study activities up to the 28 day safety contact: 97.6% (2676/2743) of subjects in the DTaP-IPV group and 96.7% (608/629) of subjects in the DAPTACEL + IPOL group.

Of the randomized subjects, 96.3% (3246/3372) completed all study activities up to the 180 day safety follow-up phone call: 96.5% (2647/2743) of subjects in the DTaP-IPV group and 95.2% (599/629) of subjects in the DAPTACEL + IPOL group.

Reasons for Withdrawal

A total of 88 subjects were discontinued. These subjects were categorized according to the reasons noted on the termination page in the eCRF.

No subjects were discontinued due to an SAE or AE

The most frequently reported reason for discontinuation from the study was “Non-compliance with the protocol.” Of the total of 39/3372 (1.2%) subjects who were discontinued for non-compliance: 30/2743 (1.1%) in the DTaP-IPV vaccination Groups 1 and 3; and 9/629 (1.4%) in the DAPTACEL + IPOL vaccination Groups 2 and 4.

Of the total number of 29/3372 (0.9%) subjects who discontinued as “Lost to follow-up”: 21/2743 (0.8%) were in the DTaP-IPV vaccination groups, and 8/629 (1.3%) in the DAPTACEL + IPOL vaccination groups.

Of the total number of 19/3372 (0.6%) subjects who were “Voluntary withdrawal not due to an AE”: 15/2743 (0.6%) were in the DTaP-IPV vaccination groups, and 4/629 (0.6%) in the DAPTACEL + IPOL vaccination groups.

The reason for discontinuation was missing for 1 subject from Group 1.

Protocol Deviations

All Randomized Subjects

Of the 3372 subjects randomized to study M5I02, 6.1% (168/2743) of subjects in the DTaP-IPV groups and 15.1% (95/629) of subjects in the DAPTACEL + IPOL groups had at least 1 protocol violation.

Overall, 5.1% (139/2743) of subjects in the DTaP-IPV group and 8.6% (54/629) of subjects in the DAPTACEL + IPOL group did not meet inclusion / exclusion criteria. These numbers were higher than expected and largely due to an error which was made during the conversion from paper to electronic medical records (EMR) at 1 US site. Overall, a total of 178 subjects who did not receive or could not be confirmed to have received 4 doses of DAPTACEL and/or Pentacel prior to the study were mistakenly enrolled: 79 of these subjects were enrolled to the immunogenicity subset and were subsequently excluded from the PP analysis set.

Other common protocol deviations were:

- Subjects who did not provide a post-dose serology sample in the proper time window: 0.9% (25/2743) and 4.9% (31/629) of subjects in DTaP-IPV and DAPTACEL + IPOL, respectively.
- Subjects who did not receive vaccine: 0.5% (13/2743) and 1.4% (9/629) of subjects in DTaP-IPV and DAPTACEL + IPOL, respectively.

Demographic and Baseline Characteristics

All Randomized Subjects

Overall, the ratio of males to females was well-balanced in the All Randomized Subjects set (51.5% [1736/3372] males to 48.5% [1636/3372] females). In the DTaP-IPV and DAPTACEL + IPOL groups, 51.5% (1413/2743) and 51.4% (323/629) of subjects were male, respectively.

The mean age for both groups was 4.4 years, and the majority of the subjects were Caucasian (75.7% [2551/3372]), followed by Black (8.6% [291/3372]), and Hispanic (7.9% [268/3372]). Ethnicity was well-balanced between both groups.

Immunogenicity Subset (Groups 1 and 2)

Overall, the ratio of males to females was well-balanced in the PP analysis set (54.3% [280/516] males to 45.7% [236/516] females). In the DTaP-IPV and DAPTACEL + IPOL groups, 54.8% (144/263) and 53.8% (136/253) of subjects were male, respectively.

In the PP analysis set, the mean age for both groups was 4.4 years, and the majority of the subjects were Caucasian (67.1% [346/516]), Black (14.0% [72/516]), or Hispanic (10.3% [53/516]).

The same trends were observed for the FAS.

Immunogenicity Results

The analyses of the antibody responses were performed in both the PP analysis set and the FAS for immunogenicity. Results for both analysis sets were aligned, followed the same trends, and supported the same conclusions.

Primary Objective 1: Pertussis (PT, FHA, PRN, and FIM) Booster Responses and GMCs

Booster Response for Pertussis

Booster response was experienced by 94.9% to 97.2% of subjects in the DTaP-IPV to each of the pertussis components (PT, FHA, PRN, and FIM) compared to 87.5% to 93.1% in the DAPTACEL + IPOL group. Non-inferiority was achieved for PT (with booster response rate difference 5.4% [95% CI: 0.7% to 10.2%]), FHA (with booster response rate difference 7.4% [95% CI: 2.5% to 12.5%]), PRN (with booster response rate difference 3.7% [95% CI: -0.2% to 7.9%]), and FIM (with booster response rate difference 4.8% [95% CI: 0.9% to 9.1%]).

Results were similar in the FAS.

GMCs for Pertussis

Pre-vaccination GMCs were similar in both study groups. After booster vaccination, the increase in GMC was observed in both study groups, with the subjects in the DTaP-IPV group showing consistently higher post-vaccination levels than the subjects in the DAPTACEL + IPOL group for all 4 pertussis antigens (PT: 121 EU/mL vs. 61.3 EU/mL; FHA: 123 EU/mL vs. 79.0 EU/mL; PRN: 283 EU/mL vs. 187 EU/mL; and FIM: 506 EU/mL vs. 379 EU/mL, respectively). Post-vaccination non-inferiority results were similar for all antigens in the FAS.

GMC ratios ranged from 1.33 to 1.97 for the 4 antigens. Non-inferiority was achieved for each pertussis antigen (PT, FHA, PRN, and FIM). Results were similar in the FAS.

Primary Objective 2: Diphtheria and Tetanus Toxoid Booster Responses and GMCs

Booster Response for Diphtheria and Tetanus

Non-inferiority was achieved for tetanus (with booster response rate difference –0.1% [95% CI: –6.5% to 6.3%]) and diphtheria (with booster response rate difference –1.9% [95% CI: –4.8% to 0.6%]). Results were similar in the FAS.

GMCs for Diphtheria and Tetanus

The pre-vaccination GMCs for tetanus and diphtheria were similar in both study groups. After booster vaccination, the subjects in both groups achieved similarly high GMC/GMT levels (tetanus 6.42 IU/mL vs. 5.48 IU/mL; diphtheria 18.6 IU/mL vs. 15.5 IU/mL for DTaP-IPV and DAPTACEL + IPOL, respectively). Results were similar in the FAS.

Non-inferiority of GMC ratio was achieved for both tetanus (1.17 [95% CI: 0.998 to 1.38]) and diphtheria (1.20 [95% CI: 1.01 to 1.42]). Results were similar in the FAS

Primary Objective 3: Polio Booster Responses and GMTs

Booster Response for Polio

Non-inferiority was achieved for polio type 1 (with booster response rate difference 3.7% [95% CI: –2.8% to 10.1%]), polio type 2 (with booster response rate difference –0.7% [95% CI: –7.9% to 6.5%, and polio type 3 (with booster response rate difference 0.3% [95% CI: –6.0% to 6.7%]). Results were similar in the FAS

GMTs for Polio

The pre-vaccination GMTs were similarly low in both study groups. Post-vaccination GMTs were similarly high in both study groups, ranging from 2731 to 4591 for all 3 polio types. Results were similar in the FAS.

Non-inferiority of GMT ratio was achieved for polio type 1 (1.27 [95% CI: 1.06 to 1.52]), polio type 2 (0.9 [95% CI: 0.750 to 1.07]), and polio type 3 (1.34 [95% CI: 1.10 to 1.64]). Results were similar in the FAS.

Figures S1 and S2 present a summary of all non-inferiority comparisons for the primary objectives.

Figure S1: Non-inferiority comparison of post-vaccination booster response rates – PP Analysis Set

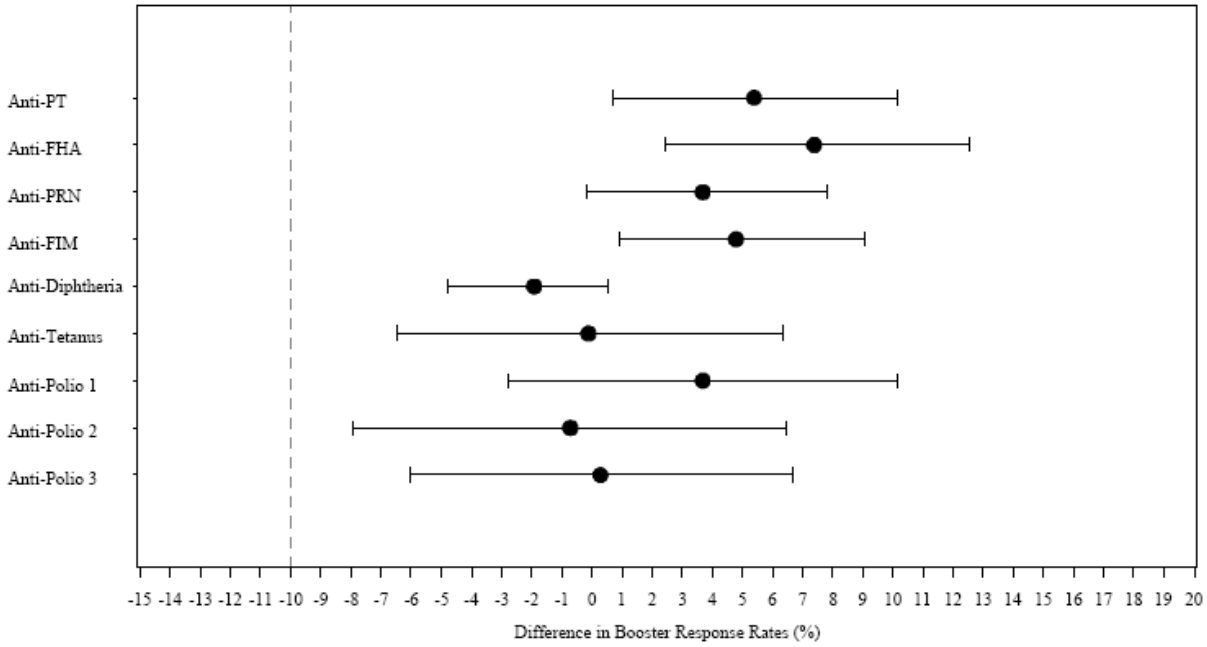
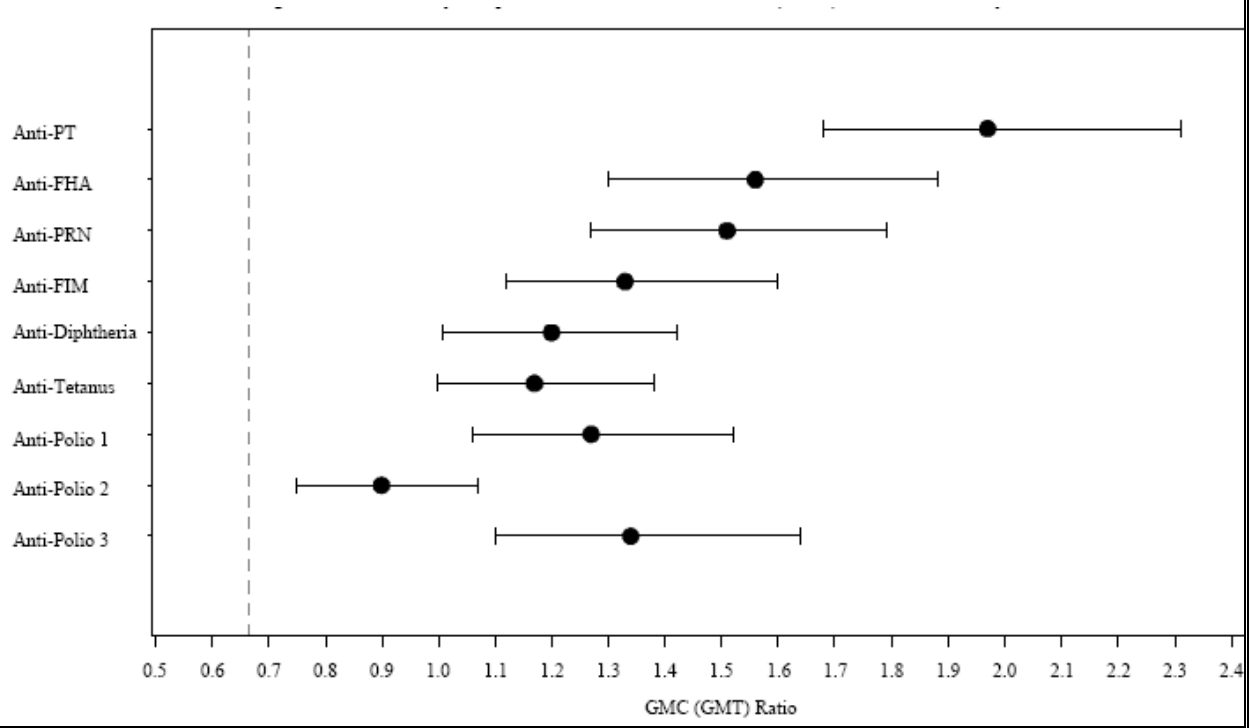


Figure S2: Non-inferiority comparison of post-vaccination GMCs/GMTs – PP analysis set



Observational Objectives

For exploratory purposes, the following immunogenicity endpoints were tested for non-inferiority between the DTaP-IPV group and the DAPTACEL + IPOL group in a similar fashion as the booster response rates in the primary hypothesis: seroprotection rates for tetanus, diphtheria, and polio antigens; 4-fold rise rates for pertussis, tetanus, diphtheria, and polio antigens; and GMFR for pertussis, diphtheria, tetanus, and polio antigens. The comparisons were based on testing the difference between 2 proportion parameters. Differences in seroprotection rates (for tetanus, diphtheria, and polio antigens) and differences in 4-fold rise rates (for pertussis, tetanus, diphtheria, and polio antigens), and their 2-sided 95% CIs were calculated. Non-inferiority of DTaP-IPV was demonstrated if the lower limits of the 2-sided 95% CIs of the difference (DTaP-IPV minus DAPTACEL + IPOL) were > -10%.

Observational Objective 1

Anti-Pertussis 4-Fold Rise Rates

Non-inferiority of 4-fold rise rate difference was achieved for PT (7.8% [95% CI: 2.3% to 13.4%]), FHA (11.3% [95% CI: 4.4% to 18.0%]), PRN (3.5% [95% CI: –2.1% to 9.1%]), and FIM (6.9% [95% CI: 0.5% to 13.2%]). Results were similar in the FAS.

Anti-Pertussis Geometric Means of Fold Rise

The geometric means of fold-rise (GMFR) results for the DTaP-IPV group (range: 13.0 to 16.9) were higher than those for the DAPTACEL + IPOL group (range: 7.16 to 10.8) for each pertussis antigen (PT, FHA, PRN, and FIM). Results were similar in the FAS.

Anti-Tetanus and Anti-Diphtheria Antibody Seroprotection Rates at Level ≥ 0.1 IU/mL

At the 0.1 IU/mL level, pre-vaccination seroprotection rates were present in most subjects for both tetanus and diphtheria in both vaccination groups, ranging from 83.1% to 91.7% of subjects. After booster vaccination, the range rose to 99.2% to 100.0% of subjects in both vaccination groups.

The non-inferiority test for exploratory purposes showed that DTaP-IPV was non-inferior to DAPTACEL + IPOL for tetanus (0.8% [95% CI: –0.8% to 2.8%]) and diphtheria (0.4% [95% CI: –1.1% to 2.2%]). Results were similar in the FAS.

Anti -Tetanus and Anti-Diphtheria Antibody Seroprotection Rates at Level ≥ 1.0 IU/mL

At the 1.0 IU/mL level, which is indicative of long-term protection, the pre-vaccination rates ranged from 28.9% to 36.6% of subjects. After booster vaccination, the range rose to 96.8% to 99.6% of subjects with long-term protection against both tetanus and diphtheria. Results were similar in the FAS.

The non-inferiority test for exploratory purposes showed that DTaP-IPV was non-inferior to DAPTACEL + IPOL for tetanus (2.0% [95% CI: –0.6% to 5.1%]) and diphtheria (0.0% [95% CI: –1.8% to 1.8%]). Results were similar in the FAS.

Anti-Tetanus and Anti-Diphtheria 4-Fold Rise Rates

The non-inferiority test for exploratory purposes showed that DTaP-IPV was non-inferior to DAPTACEL + IPOL for tetanus (0.5% [95% CI: –7.0% to 7.9%]) and diphtheria (–1.5% [95% CI: –5.0% to 2.0%]). Results were similar in the FAS.

Anti-Tetanus and Anti-Diphtheria GMFR

The GMFR for the DTaP-IPV group were similar when compared with the results for the DAPTACEL + IPOL group for each antigen. Results were similar in the FAS.

Anti-Polio Antibody Seroprotection Rates at Level ≥ 1:8 / dil

The non-inferiority test for exploratory purposes showed that DTaP-IPV was non-inferior to DAPTACEL + IPOL for polio type 1 (0.4% [95% CI: –1.1% to 2.2%]), polio type 2 (0.0% [95% CI: –1.5% to 1.5%]), and polio type 3 (0.0% [95% CI: –1.5% to 1.5%]). Results were similar in the FAS.

Anti-Polio GMFR

The GMFR for the DTaP-IPV group were 25.2, 16.2, and 43.6 for types 1, 2, and 3, respectively; the results for the DAPTACEL + IPOL group were 21.1, 20.8, and 37.5 for types 1, 2, and 3, respectively. Results for polio types 1 and 3 were higher in the DTaP-IPV group than in the DAPTACEL + IPOL group, and lower for type 2. Results were similar in the FAS.

Anti-Polio 4-Fold Rise Rates

The non-inferiority test using 4-fold rise rate difference showed that DTaP-IPV was non-inferior to DAPTACEL + IPOL for polio type 1 (3.7% [95% CI: –2.8% to 10.1%]), polio type 2 (–0.7% [95% CI: –7.9% to 6.5%]), and polio type 3 (0.3% [95% CI: –6.0% to 6.7%]). Results were similar in the FAS.

Reverse Cumulative Distribution Curves

RCDCs were generated for pre- and post-vaccination responses to each antigen in both the PP analysis set and FAS. Comparing pre- and post-vaccination responses, both the DTaP-IPV and DAPTACEL + IPOL vaccinations were observed to induce a good immune response for each vaccine antigen, as evidenced by the shift to the right after the booster vaccination.

For each of the 4 pertussis antigens, in the post-vaccination curves, the distribution of antibody concentrations in the DTaP-IPV group shifted further right than those in the DAPTACEL + IPOL group. For the tetanus, diphtheria, and poliovirus antigens, the post-vaccination distribution curves were closer or overlapping between vaccination groups. This further supports the primary observation of non-inferiority between the vaccination groups.

Observational Objective 2

Anti-Polio Booster Response Rates in Subjects after Receiving IPV as 4th or 5th Dose

There was a similar booster response rate for the subjects receiving IPV as the 4th dose between the vaccination groups. The number of subjects who received a 5th dose of IPV was very low.

Pre-vaccination seroprotection rates ≥ 1:8 dil for subjects in the PP analysis set ranged from 93.1% to 99.6% for all 3 polio types in both vaccination groups. Post-vaccination seroprotection rates ranged from 99.6% to 100.0% in both vaccination groups. Results were similar in the FAS.

Anti-Polio GMTs in Subjects after Receiving IPV as 4th or 5th Dose

Most of the subjects received the 4th dose. After vaccination, the GMTs increased for both groups. However, the sample size for the 5th dose was too small to draw meaningful conclusions from the data.

Complementary Outputs

Background doses of DAPTACEL

Subjects with 4 Previous Doses of DAPTACEL

The booster response rates to each antigen (pertussis [PT, FHA, PRN, and FIM], tetanus, diphtheria, and polio types 1, 2, and 3) for subjects in the PP analysis set with 4 previous doses of DAPTACEL were similar in both vaccination groups (booster response rate range for DTaP IPV: 78.9% to 97.5%; booster response rate range for DAPTACEL + IPOL: 80.3% to 99.1%). Results were similar in the FAS.

The pre- and post-vaccination GMCs or GMTs for each antigen (pertussis, tetanus, diphtheria, and polio types 1, 2, and 3) for subjects in the PP analysis set with 4 previous doses of DAPTACEL were similar in both groups. Results were similar in the FAS.

Subjects with Less Than 4 Previous Doses of DAPTACEL (i.e., mixed DAPTACEL/Pentacel background)

There were 12 subjects in the DTaP-IPV group and 15 subjects in the DAPTACEL + IPOL group who had less than 4 previous doses of DAPTACEL. The sample size was too small to draw meaningful conclusions from the data concerning the booster response rate or the GMCs/GMTs. Results were similar in the FAS.

Ethnicity and Gender

Summaries of GMCs (or titers) are presented by ethnicity and gender. No particular trends were observed. A frequency summary of concomitant medication use, based on protocol-defined categories (Category 1 and Category 2) was also provided. There was no difference in the use of concomitant medications between the DTaP-IPV group and the DAPTACEL + IPOL group.

Safety Results

Observational Objective 1

A total of 3372 subjects were enrolled in the study. The safety analyses were performed on the SafAS, which consisted of 3354 subjects (2733 subjects in the DTaP-IPV group and 621 subjects in the DAPTACEL + IPOL group).

Adverse Events

Solicited Reactions between Day 0 and Day 7

Solicited reactions were experienced by 93.5% (2516/2690) of subjects in the DTaP-IPV group and by 91.7% (553/603) of subjects in the DAPTACEL + IPOL group.

Grade 3 solicited reactions were experienced by 24.0% (646/2690) of subjects in the DTaP-IPV group and 19.9% (120/603) of subjects in the DAPTACEL + IPOL group. Grade 3 injection site reactions were experienced by 21.3% (573/2689) of subjects in the DTaP-IPV group, which was higher than that experienced by the 15.9% (96/603) of subjects in the DAPTACEL + IPOL group. This finding was primarily driven by the frequency of Grade 3 injection site erythema, which was consistently higher for the DTaP-IPV recipients compared to the DAPTACEL + IPOL recipients.

Grade 3 solicited systemic reactions were experienced by 4.5% (122/2689) of subjects in the DTaP-IPV group and 6.5% (39/603) of subjects in the DAPTACEL + IPOL group.

Solicited Injection Site Reactions

Solicited injection site reactions were experienced by 91.7% (2467/2689) of subjects in the DTaP-IPV group and by 89.7% (541/603) of subjects in the DAPTACEL + IPOL group. The reactions were mostly of Grade 1 intensity, occurred within 3 days of vaccination, and resolved within 3 days of occurrence.

The most commonly reported reaction was injection site pain, reported by 77.4% (2081/2689) of subjects in the DTaP-IPV group and 76.5% (461/603) of subjects in the DAPTACEL + IPOL group.

Erythema was experienced by 59.1% (1587/2687) of subjects in the DTaP-IPV group, and 53.4% (322/603) of subjects in the DAPTACEL + IPOL group.

Swelling was experienced by 40.2% (1076/2678) of subjects in the DTaP-IPV group and 36.4% (219/602) of subjects in the DAPTACEL + IPOL group.

Change in limb circumference was experienced by 68.1% (1703/2500) of subjects in the DTaP-IPV group and 65.1% (302/464) of subjects in the DAPTACEL + IPOL group.

The percentage of subjects reported as experiencing ELS within 7 days after vaccination was similar between vaccination groups: 1.5% (39/2666) of subjects in the DTaP-IPV group and 1.3% (8/598) of subjects in the DAPTACEL + IPOL group.

Solicited Systemic Reactions

Solicited systemic reactions were experienced by 63.7% (1713/2689) of subjects in the DTaP-IPV group and by 61.2% (369/603) of subjects in the DAPTACEL + IPOL group.

The most commonly reported solicited systemic reactions were myalgia: (53.8% [1445/2688] of subjects in the DTaP-IPV group and 52.6% [317/603] of subjects in the DAPTACEL + IPOL group); followed by malaise: (35.0% [940/2687] of subjects in the DTaP-IPV group and 33.2% [200/603] of subjects in the DAPTACEL + IPOL group); and headache: (15.6% [419/2688] of subjects in the DTaP-IPV group and 16.6% [100/603] of subjects in the DAPTACEL + IPOL group). Most of the solicited systemic reactions were of Grade 1 intensity, occurred within 3 days of vaccination, and resolved within 3 days of occurrence.

Fever was reported in 6.0% (161/2668) of subjects in the DTaP-IPV group and in 6.9% (41/598) of subjects in the DAPTACEL + IPOL group. Most of the fever was of Grade 1 or 2 intensity, occurred within 3 days of vaccination, and resolved within 3 days of occurrence. Grade 3 intensity was experienced by 1.3% (35/2668) of subjects in the DTaP-IPV group and 2.0% (12/598) of subjects in the DAPTACEL + IPOL group. There were very few health care provider contacts due to fever within 7 days of vaccination.

The use of Category 1 medications (antipyretics, analgesics, or non-steroidal anti-inflammatory drugs [NSAIDs]) was similar between the 2 vaccination groups. Their use was reported by 36% (1004/2733) of subjects in DTaP-IPV group and 33.8% (210/621) of subjects in the DAPTACEL + IPOL group.

Unsolicited Adverse Events between Day 0 and Day 28

Immediate Adverse Events

No immediate anaphylactic, life-threatening reactions or other SAEs were observed during the 30 minutes after vaccination time period. Overall, 0.9% (25/2733) of subjects in the DTaP-IPV group and 1.0% (6/621) of subjects in the DAPTACEL + IPOL group experienced at least 1 immediate unsolicited AE.

Immediate Adverse Reactions

Two subjects in the DTaP-IPV group and 1 subject in the DAPTACEL + IPOL group experienced immediate events which were considered as related to the investigational product. All 3 subjects completed the study.

- Subject [redacted] received DTaP-IPV vaccine and experienced Grade 1 flushing (preferred term), which lasted 2 days.
- Subject [redacted] received DTaP-IPV vaccine and experienced Grade 1 macular rash (preferred term – event reported as a red blotch located near the injection site), which lasted 3 days.
- Subject [redacted] received DAPTACEL + IPOL vaccines and experienced Grade 2 hyperhidrosis and nausea (preferred terms) which lasted 1 day.

Unsolicited Adverse Events

Unsolicited AEs within 28 days after vaccination were experienced by 34.8% (951/2733) of subjects in the DTaP-IPV group and 30.8% (191/621) of subjects in the DAPTACEL + IPOL group. Of these, 4.1% (111/2733) in the DTaP-IPV group and 3.5% (22/621) in the DAPTACEL + IPOL group experienced at least 1 Grade 3 unsolicited non-serious AE. Most were assessed as unrelated to the vaccines. Two subjects in the DTaP-IPV group and 1 subject in the DAPTACEL + IPOL group experienced immediate events which were considered as related to the investigational product. All 3 subjects completed the study.

Unsolicited non-serious systemic AEs were experienced by 28.4% (777/2733) of subjects in the DTaP-IPV group and 25.6% (159/621) of subjects in the DAPTACEL + IPOL group. Of these, 3.8% (105/2733) in the DTaP-IPV group and 3.2% (20/621) of subjects in the DAPTACEL + IPOL group experienced at least 1 Grade 3 unsolicited non-serious AE.

The most commonly reported unsolicited AEs were in the SOCs of General Disorders and Administration Site Conditions; Infections and Infestations; and Respiratory, Thoracic and Mediastinal Disorders.

The most commonly reported unsolicited AEs were respiratory or gastrointestinal ailments and infections that affect children The most commonly reported unsolicited AEs by preferred term were cough (5.2% [142/2733] in the DTaP-IPV group and 4.2% [26/621] in the DAPTACEL + IPOL group), injection site induration (5.1% [139/2733] in the DTaP-IPV group and 3.2% [20/621] in the DAPTACEL + IPOL group, and vomiting (3.3% [90/2733] in the DTaP-IPV group and 3.9% [24/621] in the DAPTACEL + IPOL group).

Overall, the incidence and nature of frequently reported unsolicited AEs in the DTaP-IPV group and DAPTACEL + IPOL group was similar.

Unsolicited Adverse Reactions

Unsolicited ARs within 28 days after vaccination were experienced by 11.6% (318/2733) of subjects in the DTaP-IPV group and 9.2% (57/621) of subjects in the DAPTACEL + IPOL group. Of these, 0.5% (13/2733) of subjects in the DTaP-IPV group and 0.6% (4/621) of subjects in the DAPTACEL + IPOL group experienced at least 1 Grade 3 unsolicited non-serious AR.

Unsolicited non-serious injection site ARs (events identified at the injection sites of DTaP-IPV, DAPTACEL, and/or IPOL and that do not include the injection sites of MMR and /or V) were experienced by 9.7% (265/2733) of subjects in the DTaP-IPV group and 7.2% (45/621) of subjects in the DAPTACEL + IPOL group. Of these, 0.3% (7/2733) of subjects in the DTaP-IPV group and 0.3% (2/621) of subjects in the DAPTACEL + IPOL group experienced at least 1 Grade 3 unsolicited non-serious injection site AR.

The most commonly reported unsolicited non-serious ARs were in the SOC General Disorders and Administration Site Conditions. The most commonly reported unsolicited ARs by preferred term were all injection site reactions (events identified only at the injection sites of DTaP-IPV, DAPTACEL and/or IPOL). Injection site induration was the most commonly reported of the ARs (4.9% [135/2733] of subjects in the DTaP-IPV group and 2.7% [17/621] of subjects in the DAPTACEL + IPOL group), followed by haematoma (2.1% [58/2733] of subjects in the DTaP-IPV group and 2.6% [16/621] of subjects in the DAPTACEL + IPOL group), pruritus (1.8% [48/2733] of subjects in the DTaP-IPV group and 1.0% [6/621] of subjects in the DAPTACEL + IPOL group), and warmth (1.3% [36/2733] of subjects in the DTaP-IPV group and 1.6% [10/621] of subjects in the DAPTACEL + IPOL group).

Unsolicited non-serious systemic ARs were experienced by 2.5% (67/2733) of subjects in the DTaP-IPV group and 2.1% (13/621) of subjects in the DAPTACEL + IPOL group. Of these, 0.2% (6/2733) of subjects in the DTaP-IPV group and 0.3% (2/621) of subjects in the DAPTACEL + IPOL group experienced at least 1 Grade 3 unsolicited non-serious systemic AR.

The most commonly reported unsolicited non-serious systemic ARs were in the SOCs Gastrointestinal Disorders, Nervous System Disorders, and Skin and Subcutaneous Tissue Disorders. The most commonly reported unsolicited ARs by preferred term were vomiting (0.5% [13/2733] of subjects in the DTaP-IPV group and 0% in the DAPTACEL + IPOL group), somnolence (0.3% [8/2733] of subjects in the DTaP-IPV group and 0% in the DAPTACEL + IPOL group), and rash (0.1% [3/2733] of subjects in the DTaP-IPV group and 0% in the DAPTACEL + IPOL group), respectively.

In general, the incidence of commonly reported unsolicited ARs in the DTaP-IPV group and DAPTACEL + IPOL group was similar.

Adverse Events of Special Interest Day 0 through Day 28

The important identified risks associated with the use of DTaP-IPV - anaphylactic reaction, convulsion (including febrile convulsion), and hypotonic-hyporesponsive episodes (HHE) - were defined as Adverse Events of Special Interest (AESIs) if they occurred between Day 0 and Day 28 and were to be reported as SAEs. There were no reports of these events within 28 days after vaccination.

In addition, neurological events that were identified as SAEs and autoimmune disorders were also considered as AESIs in this study if they occurred between Day 0 and Day 28. There was 1 report of an autoimmune disorder: Subject [redacted] developed polydipsia and excessive urination 11 days after vaccination with DTaP-IPV, and subsequently was diagnosed with new-onset type 1 diabetes mellitus. [redacted] The event of type 1 diabetes mellitus was assessed by the Investigator as not related to the vaccine.

Subjects who Discontinued due to an Adverse Event

There were no AEs that led to discontinuation from the study.

SAEs – Day 0 through Day 28

A total of 3/2733 (0.1%) subjects in the DTaP-IPV group experienced an SAE within 28 days after vaccination. All 3 subjects required hospitalization and none of the SAEs were considered as related to the vaccine. There was 1 report of an autoimmune disorder.

- Subject [redacted] was reported with lobar pneumonia which lasted 23 days.
- Subject [redacted] was reported with asthma which lasted 53 days.
- Subject [redacted] was diagnosed with new-onset type 1 diabetes mellitus.

SAEs – Day 0 through Day 180

During the course of the study (Day 0 through Day 180), 21 (0.8%) subjects in the DTaP-IPV group and 3 (0.5%) subjects in the DAPTACEL + IPOL group experienced SAEs. Eighteen of the 21 subjects with SAEs in the DTaP-IPV group and all 3 of the subjects in the DAPTACEL + IPOL group required hospitalization. The remaining 3 (0.1%) subjects, all in the DTaP-IPV group and none in the DAPTACEL + IPOL group experienced SAEs which were considered important medical events by the Investigator, but the subjects were not hospitalized.

The 180-day phone call allowed a 14-day window to collect safety data; 1 SAE was reported on Day 181. The subject was included in the total number of subjects with SAEs in the DTaP-IPV group.

One of the hospitalized subjects experienced an AESI within 28 days. In addition to this event of type 1 diabetes, which was described in a previous section, the following SAEs occurred between Day 29 and Day 180 and were considered as significant.

Two subjects experienced SAEs which resulted in hospitalization:

- One subject in the DTaP-IPV group experienced a life-threatening SAE 161 days after vaccination. Subject [redacted] was admitted to the hospital, and subsequently experienced respiratory failure. The subject was diagnosed with respiratory failure secondary to croup/laryngotracheitis. The subject recovered after 6 days
- One subject in the DTaP-IPV group was admitted to the hospital 93 days after vaccination. Subject [redacted] was subsequently diagnosed with Kawasaki disease. The subject was reported as recovered after the 180-day phone call.

Three subjects in the DTaP-IPV group experienced SAEs that were considered by the Investigator as being important medical events. None of these subjects were hospitalized.

- Subject [redacted] was diagnosed with asthma and common variable immune deficiency 50 days after vaccination. The events were ongoing at the time of the 180-day phone call.
- Subject [redacted] presented with symptoms of autism 158 days after vaccination, and a developmental pediatrician subsequently diagnosed autism.
- Subject [redacted] was diagnosed with absence seizure (MedDRA preferred term: petit mal epilepsy) 168 days after vaccination.

Deaths, Other SAEs and Other Significant AEs:

There were no deaths.

Observational Objective 2

The safety profile for subjects who received IPV as the 4th and 5th dose was found to be similar between the DTaP-IPV recipients (Groups 1 and 3) and the DAPTACEL + IPOL recipients (Groups 2 and 4).

Observational Objective 3

The safety profile of subjects without MMR and V vaccinations was similar to the SafAS. The number of subjects who did not receive MMR and V was low in both vaccination groups (76 subjects in the DTaP-IPV group and 13 subjects in the DAPTACEL + IPOL group).

Safety Conclusions

Overall, the rates of immediate unsolicited AEs, solicited reactions (injection site and systemic), unsolicited AEs, and unsolicited ARs within 180 days of vaccination were similar in the DTaP-IPV group compared to those observed for the DAPTACEL + IPOL group. In addition, the incidence of SAEs occurring between 0 to 180 days post-vaccination was low and similar between the 2 vaccination groups; no SAEs were assessed by the study site investigators as being related to vaccination. No anaphylactic reactions, HHEs, or seizures were reported within 28 days after vaccination.

Overall Conclusions

The report presents the safety and immunogenicity of DTaP-IPV administered in children aged 4 through 6 years of age. In study M5I02, children were vaccinated with a single dose of DTaP-IPV or DAPTACEL + IPOL as the 5th dose.

All study objectives were met, in terms of immunogenicity of DTaP-IPV.

- DTaP-IPV booster response rates and GMCs were non-inferior to those of DAPTACEL + IPOL for all pertussis antigens (PT, FHA, PRN, and FIM).

- DTaP-IPV-induced responses were non-inferior to those following DAPTACEL + IPOL at 28 days post-vaccination with respect to evaluated measures of diphtheria, tetanus, and polio immunity.

The administration of DTaP-IPV in children 4 to 6 years old as the 5th dose was well tolerated, with no safety concerns identified and a safety profile similar to the co-administration of DAPTACEL + IPOL.

In conclusion, DTaP-IPV vaccine is safe and immunogenic when administered as a 5th dose in children 4 to 6 years of age.

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