Application Type	Original Application
STN	125525/0
CBER Received Date	March 24, 2014
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Division / Office	DB/OBE
Committee Chair	Matthew Steele, Ph.D.
Clinical Reviewer(s)	Sarah Browne, MD
Project Manager	Juan Lacayo, Ph.D.
Priority Review	NO
Reviewer Name(s)	Ghideon Solomon, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lihan Yan, Ph.D. Team Leader, Bacterial and allergenic team, VEB/DB/OBE
	Dale Horne, Dr.PH, Chief, Vaccine Evaluation Branch, DB/OBE
	Estelle Russek-Cohen, Ph.D. Director, Division of Biostatistics, OBE
Applicant	Sanofi Pasteur
Established Name	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine (DTaP-IPV).
(Proposed) Trade Name	Quadracel
Pharmacologic Class	Bacterial and viral vaccines combined, diphtheria-pertussis-poliomyelitis-tetanus, ATC code J07CA02.
Formulation(s), including Adjuvants, etc	DTaP-IPV has been formulated to contain the following active ingredients per 0.5 mL dose: 15Lf Diphtheria Toxoid (D), 5 Lf Tetanus Toxoid (T), 20 μg Pertussis Toxoid (PT), 20 μg Filamentous

	Haemagglutinin (FHA), 3 µg Pertactin (PRN), 5 µg Fimbriae Types 2 and 3 (FIM), 40 D-antigen units Inactivated Poliovirus (IPV) Type 1 (Mahoney), 8 D-antigen units IPV Type 2 (MEF1), and 32 D-antigen units IPV Type 3 (Saukett).
Dosage Form(s) and Route(s) of Administration	This product is to be administered as a single 0.5 mL dose by intramuscular injection
Dosing Regimen	DTaP-IPV: 1 injection (0.5 mL)
Indication(s) and Intended Population(s)	For active immunization against diphtheria, tetanus, pertussis, and poliomyelitis for use in children 4 to 6 years of age.

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GLOSSARY

AE	Adverse event
AESI	Adverse events of special interest
BL	Blood sample
CDM	Clinical Data Management
CRA	Clinical Research Associate
D	Diphtheria Toxoid
DC	Diary card
dil	Dilution
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EU	ELISA units
FAS	Full Analysis Set
FHA	Filamentous Haemagglutinin
GM	Geometric mean
GMC	Geometric means of concentrations
GMFR	Geometric means of fold rise
GMT	Geometric means of titers
ICF	Informed consent form
IEC	Independent ethics committee
IgG	Immunoglobulin G
IM	Intramuscular
IPV	Inactivated Poliovirus
IRB	Institutional review board
IU	International units
IVRS	Interactive voice response system
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles, mumps, and rubella
NSAIDs	Non-steroidal anti-inflammatory drugs
PFU	Plaque forming units
PP	Per-Protocol
PRN	Pertactin
PT	Pertussis Toxoid
SAE	Serious adverse event
SafAS	Safety Analysis Set
SC	Subcutaneous
T	Tetanus Toxoid
TCID	Median tissue culture infective dose
V	Varicella

1. Executive Summary

Sanofi Pasteur is seeking licensure of their QUADRACEL vaccine, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus (DTaP-IPV) Vaccine as a 5th dose booster in children 4 to 6 years of age. DTaP-IPV, manufactured by Sanofi Pasteur Limited, Toronto, ON, Canada, is a sterile suspension of Diphtheria and Tetanus toxoids and Acellular Pertussis vaccine adsorbed separately on aluminum phosphate combined with Inactivated Poliomyelitis vaccine types 1, 2, and 3 for intramuscular injection.

The pivotal data to support licensure come from study M5I02, which demonstrated the non-inferiority of DTaP-IPV when compared to concomitantly administered DAPTACEL and IPOL.

This memo reviews the immunogenicity and safety data from study M5I02 submitted to support the licensure of DTaP-IPV for administration as a 5th dose booster in US children 4 to 6 years of age.

The results of the study met the pre-specified non-inferiority criteria to show:

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

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.

2. Clinical and Regulatory Background

Currently, two 5-component acellular pertussis pediatric vaccines (manufactured by Sanofi Pasteur) are widely used in the US for primary immunization against diphtheria, tetanus, and pertussis. These include a stand-alone DTaP vaccine, DAPTACEL, and a combination DTaP-IPV/Hib vaccine, Pentacel. Table 1 presents a summary of US-licensed pediatric DTaP and DTaP-IPV vaccines.

Table 1: US-licensed pediatric DTaP-containing vaccines and DTaP-IPV vaccine candidate with respective indications

Vaccine Name	Trade Name	Vaccine Type	US Age Indication	Licensure Date	STN #
DTaP	DAPTACEL	Pediatric	6 weeks – 6 years (before 7th birthday)	14 May 2002	STN: 103666
DTaP-IPV/Hib	Pentacel	Pediatric	6 weeks – 4 years (before 5th birthday)	20 June 2008	STN: 125145
DTaP-IPV	QUADRACEL	Pediatric	4 years – 6 years (before 7th birthday)		

Source: Reviewer's table based on Clinical Overview Report DTaP-IPV

Pentacel vaccine, first licensed in Canada on May 12, 1997, was used exclusively in Canada for the prevention of diphtheria, tetanus, pertussis, and polio for the first 4 doses. The vaccine was also licensed for use in the US on June 20, 2008 as a 4-dose series with a single dose administered at 2, 4, 6, and 15 to 18 months of age.

As a stand-alone vaccine product, the DTaP-IPV component of Pentacel was first registered in Canada on March 20, 1997 for use as a 5th dose booster in children ages 4 to 6 years. It is currently licensed in Australia, Canada, Mexico, and New Zealand under the marketed name QUADRACEL. In the US, DTaP-IPV has been studied extensively in several pivotal, multi- center trials in infant and toddler populations.

As a stand-alone 5th dose booster vaccine in the US, the DTaP-IPV vaccine is expected to provide health- care providers the added flexibility to ensure that their patients are compliant with the recommended DTaP-IPV vaccination schedule from primary series through 5th dose booster with the fewest number of injections. The DTaP-IPV vaccine, which will be marketed in the US as QUADRACEL, will also meet the requirement for the recommended dose of inactivated poliovirus vaccine (IPV) for children 4 to 6 years of age as specified in the US immunization schedule.

2.1 Disease or Health-Related Condition(s) Studied

The target indication for DTaP-IPV is pre-school children ages 4 to 6 years, as a 5th dose booster for active immunization against diphtheria, tetanus, pertussis, and poliomyelitis. The Anatomical Therapeutic Chemical Classification System (ATC) code for QUADRACEL (DTaP-IPV) is J07CA02, and the ATC group is General Anti-Infectives for Systemic Use – Vaccines – Bacterial and Viral Vaccines, Combined - Diphtheria-Pertussis-Poliomyelitis-Tetanus.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The clinical development of this vaccine in the United States was performed under IND 14668, initially submitted in March 25, 2011.

Pre-IND Regulatory Activities
CBER communicated the following to the sponsor during a pre-IND meeting on December 8, 2010:

- The non-inferiority analysis of IPV, diphtheria, and tetanus should be primary endpoints.
- The number of subjects in the pivotal study M5I02 should be increased from 3000 to 5000 for safety
- The assessment of safety of DTaP-IPV should be comprised of the overall descriptive safety analyses, and thus the non-inferiority endpoints for fever were not required.
- Only one concomitant vaccine regimen, ProQuad or M-M-R_{II} + VARIVAX, should be selected.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

Data sources including all materials reviewed (applicant's study reports, data sets analyzed, and literature referenced) were provided electronically and are available in the EDR on the following link:

(b) (4)

5.1 Review Strategy

The BLA is based on safety and immunogenicity data from four studies: one pivotal study (M5I02) and three supportive studies. Section 6 of this review discusses all the relevant statistical information of the pivotal study that reflects the indication sought by the applicant. This study provides the core safety and immunogenicity data to support the licensure of DTaP-IPV as a 5th dose in US children 4 to 6 years of age. Relevant analysis results reported by the applicant and conducted by the reviewer are presented.

5.2 BLA/IND Documents that Serve as the Basis for the Statistical Review

Pivotal Study M5I02 that provides the core safety and immunogenicity data to support the licensure of DTaP-IPV as a 5th dose in US children 4 to 6 years of age is the basis for the statistical review.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

A pivotal study (Study M5I02) and a supportive study (Td508) containing the immunogenicity and safety data were submitted to support licensure of DTaP-IPV for administration as a 5th dose booster in US children 4 to 6 years of age. However, as previously indicated, this statistical review memo is focused on the pivotal study M5I02.

6.1 Study M5I02

6.1.1 Study Objectives

Primary Objectives

- To compare the pertussis (pertussis toxoid [PT], filamentous haemagglutinin [FHA], pertactin [PRN], and fimbriae types 2 and 3 [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 vaccination (Group 2) when administered as a 5th dose.

- 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.
- 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.

Observational Objectives

Immunogenicity

- To present the immune responses (in seroprotection rates, mean fold rise [post-/prevaccination], and reverse cumulative distribution curves [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.
- To present the booster responses and GMTs of subjects in Groups 1 and 2 receiving IPV as 4th dose side-by-side with subjects receiving IPV as 5th dose.

Safety

- To describe the safety profile for Groups 1 and 3 combined, and Groups 2 and 4 combined.
- 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.
- To describe the safety profile of the subjects with and without MMR and V vaccinations in Groups 1 and 3 combined, and Groups 2 and 4 combined.

6.1.2 Overall Trial Design

Study M5I02 was a controlled, multi-center, randomized, open label Phase III study designed to compare the safety and immunogenicity of DTaP-IPV vaccine with DAPTACEL + IPOL vaccines as the 5th dose booster in children ≥ 4 to < 7 years of age in the US and Puerto Rico, who had been previously vaccinated with a 4-dose series of DAPTACEL and/or Pentacel vaccines only (Table 2).

Table 2: Study groups

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

* 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) was to be documented for all subjects.

6.1.3 Study Population

Approximately 3370 subjects were randomized to receive a single dose of DTaP-IPV (Group 1 and Group 3) or DAPTACEL vaccine and IPOL vaccine (DAPTACEL + IPOL) (Group 2 and Group 4); each group also received 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]), if applicable.

Approximately 640 subjects identified as having been vaccinated with a DAPTACEL and/or Pentacel 4-dose series (320 subjects each in Group 1 and Group 2) were assigned to provide a blood sample immediately before vaccination with the study vaccine(s) on Day 0 and again at approximately 28 days after vaccination for immunogenicity assessment; these subjects were also evaluated for safety. In addition, another 2700 subjects with a 4-dose vaccine history of DAPTACEL and/or Pentacel vaccine(s) were followed for safety only (Group 3 and Group 4).

This strategy allowed approximately 640 subjects to be evaluated for immunogenicity and approximately 3340 subjects to be evaluated for safety. For all subjects, immediate and solicited reactions were collected from Day 0 through Day 7, unsolicited adverse events (AEs) from Day 0 until the second visit (Day 28), and SAEs from Day 0 to approximately 180 days thereafter.

6.1.3.1 Selection of Trial Population

Refer to the clinical review for the list of inclusion/exclusion criteria.

6.1.4 Study Treatments Dose and Mode of Administration

Subjects in Group 1 and Group 3 received 0.5 mL each of DTaP-IPV administered intramuscularly in the deltoid of the left arm. For subjects who received MMR and V concomitantly, these vaccines were administered subcutaneously (SC) in the right outer upper arm on Day 0 (Visit 1) of the study.

Subjects in Group 2 and Group 4 received 0.5 mL each of DAPTACEL administered intramuscularly in the deltoid of the left arm, IPOL administered either IM in the deltoid approximately 30 mm below the site of the DAPTACEL injection, or SC in the left outer upper triceps, and, if required, MMR and V administered subcutaneously in the right outer upper arm on Day 0 (Visit 1) of the study.

Randomization/Treatment Allocation Procedures

The randomization list was generated by designated applicant personnel not associated with the trial subjects or with management of the trial. The investigational vaccine was labeled by the applicant with lot numbers.

Designated study site personnel called the interactive voice response system (IVRS) and entered identification and security information. To randomize a participant, the caller entered and confirmed a minimal amount of data in response to IVRS prompts. The IVRS stated the vaccination to assign. Central control of randomization to vaccination and allocation to immunogenicity was maintained by the IVRS.

Subject numbers were recorded on the eCRFs and were not reassigned for any reason. Subject numbers were 8 digits long, with a 3-digit center identifier and a 5-digit subject identifier.

6.1.6 Study Centers and Duration of Study

This study was conducted by multiple investigators at 11 study centers in the United States. The duration of the study per subject was approximately six months: one month of active phase and an additional five months of extended safety follow-up.

6.1.8 Endpoints and Assessment Methods

6.1.8.1 Primary endpoints

Immunogenicity

The primary endpoints for the evaluation of immunogenicity are described below.

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

The booster response rate partially adjusted for individual and population differences in pre-vaccination antibody concentrations. The criteria for demonstrating a booster response were 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 a booster response if they had post-vaccination levels ≥ 4X LLOQ
- Subjects whose pre vaccination antibody concentrations were ≥ LLOQ but < 4X LLOQ, demonstrated a 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 a 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 a booster response and the GMCs was assessed.

The criterion for demonstrating a booster response was as follows:

- Subjects whose pre-vaccination antibody concentrations were < 0.1 IU/mL demonstrated a 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 a 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 a 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 a booster response was assessed. The criterion for demonstrating a booster response was as follows:
   - Subjects whose pre-vaccination antibody concentrations were < 1:8 dilution (dil) demonstrated a booster response if they had post-vaccination levels ≥ 1:8 dil
   - Subjects whose pre-vaccination antibody concentrations were ≥ 1:8 dil, demonstrated a booster response if they had a 4-fold rise (i.e., post-/pre-vaccination ≥ 4).

Efficacy Endpoints
There were no primary objectives for efficacy.

Safety Endpoints
There were no primary objectives for safety.

Secondary endpoints
There were no secondary objectives for immunogenicity, efficacy, or safety

Observational Endpoints and Assessment Methods
Immunogenicity
Endpoints
The following serological endpoints were measured on Day 0 prior to vaccination and 28 days after vaccination in Group 1 and Group 2:

- Geometric mean fold-rises for anti-pertussis, anti-diphtheria, anti-tetanus, and anti-polio
- Seroprotection rates for anti-diphtheria, anti-tetanus, and anti-polio
  - 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
- Reverse cumulative distribution curves (RCDCs) for pertussis (PT, FHA, PRN, and FIM), diphtheria, tetanus, and polio antibody concentrations for pre- (Day 0) and post-vaccination (Day 28).

Safety
The observational endpoints for safety were:

- 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).

6.1.8.2 Measurement methods

Refer to the statistical assay review and clinical review for the immunogenicity antibody concentration measurement methods for the primary and observational endpoints for pertussis (PT, FHA, PRN, and FIM), diphtheria, and tetanus.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The statistical analysis was performed in 3 steps:

First step: - on all immunogenicity data collected at Day 0 and Day 28. This statistical analysis was conducted after all serological samples were received, tested, and the database for the relevant parameters was locked.

Second step: - on all safety data collected within the 28 days following the vaccination (from Day 0 to Day 28) to assess all safety objectives of the study, except for long-term safety (within 6 months post vaccination, Day 180). The overall study database was locked, except for modules associated with SAE collection.

Third step: - after the 6-month follow-up (from Day 0 to Day 180) the database was cleaned and locked to assess the long-term safety in the study.

M5I02 was an open-label study, and a step-based approach to the analysis of immunogenicity and safety data would not lead to a compromise in the scientific integrity of the data. No statistical adjustments were needed because there were no changes to the study design, trial objectives, or planned immunogenicity analyses.

6.1.9.1 Hypotheses and Statistical Methods for Primary Endpoints

Hypotheses for the first Primary Endpoint (Primary Endpoint 1)

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

This primary hypothesis was tested as follows:

- **Primary hypothesis 1A**: H_0: $P_Q - P_D \leq -10\%$ versus H_a: $P_Q - P_D > -10\%$, where P_Q and P_D are the proportion of subjects in the DTaP-IPV group and the DAPTACEL + IPOL group who achieve booster response rates for each pertussis antigen (PT, FHA, PRN, and FIM).

- **Primary hypothesis 1B**: H_0: $GMC_Q / GMC_D \leq 2/3$ versus H_a: $GMC_Q / GMC_D > 2/3$, where GMC_Q and GMC_D are the geometric means of concentrations (GMCs) in the DTaP-IPV group and the DAPTACEL + IPOL group for each pertussis antigen (PT, FHA, PRN, and FIM).

Statistical Analysis for the first Primary Endpoint
Primary hypothesis 1A was based on testing the difference between two proportion parameters. Differences ($P_Q - P_D$) in booster response rates for each pertussis antigen (PT, FHA, PRN, and FIM) and their 2-sided 95% confidence intervals (CIs) were calculated. Non-inferiority of DTaPIPV 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 all pertussis antigens between groups were > -10%.

Primary hypothesis 1B was based on testing the ratio between the 2 post-vaccination GMCs (GMC_Q / GMC_D) for each pertussis antigen and their 2-sided 95% CIs. Non-inferiority of DTaPIPV was demonstrated if the lower limits of the 2-sided 95% CIs of the ratio (DTaP-IPV/DAPTACEL + IPOL) in post-vaccination GMCs for all pertussis antigens between groups were > 2/3.

Hypotheses for Primary Endpoint 2
The primary hypothesis 2 was that anti-diphtheria toxoid and anti-tetanus toxoid booster response rates and GMCs will be non-inferior in subjects who receive DTaP-IPV as a 5^{th} dose when compared to subjects who receive DAPTACEL + IPOL as a 5^{th} dose. Primary hypothesis 2 was tested as follows:

- **Primary hypothesis 2A**: H_0: $P_Q - P_D \leq -10\%$ versus H_a: $P_Q - P_D > -10\%$, where P_Q and P_D are the proportion of subjects in the DTaP-IPV group and the DAPTACEL + IPOL group who achieve anti-diphtheria toxoid and anti-tetanus toxoid booster response rates.
- **Primary hypothesis 2B**: H_0: $GMC_Q / GMC_D \leq 2/3$ versus H_a: GMCQ / GMCD > 2/3, where GMC_Q and GMC_D are the geometric means of concentrations in the DTaP-IPV group and the DAPTACEL + IPOL group for anti-diphtheria toxoid and anti-tetanus toxoid.

Statistical Analysis for Primary Endpoint 2
Primary hypothesis 2A was based on testing the difference between 2 proportion parameters. Differences ($P_Q - P_D$) in booster response rates for anti-diphtheria and anti-tetanus 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) in post-vaccination booster response rates for both anti-diphtheria and anti-tetanus between groups were > -10%.

Primary hypothesis 2B was based on testing the ratio between the 2 post-vaccination GMCs (GMC_Q / GMC_D) for anti-diphtheria and anti-tetanus and their 2-sided 95% CIs. 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 both anti-diphtheria and anti-tetanus between groups were > 2/3.

Hypotheses for Primary Endpoint 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 achieved antibody titers ≥ 1:8 dil (booster response) and GMTs were non-inferior in subjects who received DTaP-IPV as a 5th dose when compared to subjects who received DAPTACEL + IPOL as a 5th dose. The primary hypothesis 3 was tested as follows:

- **Primary hypothesis 3A**: H_0: P_Q - $P_D \leq$ -10% versus H_a: P_Q - P_D > -10%, where P_Q and P_D are the proportion of subjects in the DTaP-IPV group and the DAPTACEL + IPOL group who achieve booster response rates for each polio antigen.
- **Primary hypothesis 3B**: H_0: GMT_Q / $GMT^D \leq 2/3$ versus H_a: GMT_Q / GMT_D > 2/3, where GMT_Q and GMT_D are the geometric means of titers (GMTs) in the DTaP-IPV group and the DAPTACEL + IPOL group for each polio antigen.

Statistical Analysis for Primary Endpoint 3
Primary hypothesis 3A was based on testing the difference between 2 proportion parameters. Differences (P_Q - P_D) in booster response rates for each of the 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) in post-vaccination booster response rates for each polio antigen between groups were > -10%.

Primary hypothesis 3B was based on testing the ratio between the 2 post-vaccination GMTs (GMT_Q / GMT_D) for each polio antigen and their 2-sided 95% CIs. 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 all polio antigens between groups were > 2/3.

Hypotheses for Secondary and Observational Endpoint
No hypothesis testing was performed for observational endpoints, and there were no secondary endpoints.

Statistical Analysis for Observational Endpoints
Immunogenicity
The following immunogenicity analyses were performed:

- Seroprotection rates of the diphtheria, tetanus, and polio antigens following DTaP-IPV vaccination (Group 1) compared with those elicited following DAPTACEL + IPOL vaccinations (Group 2).
- Geometric mean fold rises (and 95% CIs) of the pertussis (PT, FHA, PRN, and FIM), diphtheria, tetanus, and polio antigens following DTaP-IPV vaccination (Group 1) compared 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) compared with those elicited following DAPTACEL + IPOL vaccinations (Group 2).
- RCDCs for the pertussis (PT, FHA, PRN, and FIM), diphtheria, tetanus, and polio antigens following DTaP-IPV vaccination (Group 1) compared 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 solicited systemic reactions were summarized by study group, intensity (Grade 1, Grade 2, or 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 was summarized by study group and intensity for each preferred term, and SOC that had at least one report, as well as by relationship to 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.

In addition, the safety profile was compared between subjects with a 4th and 5th dose of IPV, and between subjects with and without MMR and V vaccinations during the trial.

6.1.9.2 Populations Analyzed

Definition of Populations
Three analysis sets were used: the Per-Protocol (PP) Analysis Set, the Full Analysis Set (FAS), and the Safety Analysis Set (SafAS). These analysis sets are defined below.

Per-Protocol (PP) Analysis Set
Subjects were to be excluded from the PP analysis set for the following reasons:
- Subject did not meet all protocol-specified inclusion/exclusion criteria
- Subject did not receive vaccine

- Subject received a vaccine other than the one that he/she was randomized to receive
- Preparation and/or administration of vaccine was not done as per protocol
- Subject did not receive vaccine in the proper time window
- Subject did not provide a post-dose serology sample in the proper time window
- Subject received a protocol-restricted therapy, medication, or vaccine
- Subject's post-dose serology sample did not produce a valid test result

In the event of a local or national immunization program with an influenza vaccine, subjects who received one or more doses of influenza vaccine at any time during the trial were not to be withdrawn from the trial.

Full Analysis Set (FAS)
The FAS consisted of all subjects who received the study or control vaccine and had at least one valid post-vaccination serology result.

Safety Analysis Set (SafAS)
The SafAS was defined as those subjects who received the study or control vaccine. If the vaccine given to a subject differed from that assigned by randomization, then the safety analyses was conducted according to the vaccine received rather than according to the randomization. If the vaccine given to a subject did not correspond to any study group, that subject was excluded from the SafAS.

Populations Used in Analyses
The immunogenicity analyses were performed on the PP analysis set, and were confirmed on the FAS. In the FAS, subjects were analyzed by the vaccine group to which they were randomized. The safety analyses were performed on the SafAS. Subjects were analyzed according to the vaccine they actually received.

6.1.9.3 Handling of Missing Data and Outliers

Immunogenicity
For computational purposes, any pre-vaccination or post-vaccination concentration (or titer) reported as < LLOQ was converted to a value of 0.5 LLOQ to calculate the GMCs (or GMTs). When fold-rise in antibody levels was calculated, any pre-vaccination value reported as < LLOQ was converted to LLOQ, and any post-vaccination value reported as < LLOQ was converted to a value of 0.5 LLOQ. The LLOQ for anti-PT, PRN, and FIM ELISA was 4 EU/mL and the LLOQ for anti-FHA ELISA was 3 EU/mL.

Missing data were reported as missing and were not replaced. Laboratory values that were outside the typical ranges were validated by the testing laboratory. A statistical search for outliers was not performed.

Reviewer's comment: *The handling of titers <LLOQ for computational purposes were discussed in the protocol and agreed upon during the IND review.*

Safety
Missing safety data were not replaced. All subjects with safety data and all safety data recorded in the eCRFs were included in the safety analyses. No search for outliers was performed by the applicant during the statistical analysis.
Reviewer's comment: No outliers were detected during the reviewer's statistical analysis.

6.1.9.4 Determination of Sample Size and Power Calculation

The total target sample size of the study was approximately 3340; 320 subjects each in Group 1 and Group 2, 2400 subjects in Group 3, and 300 subjects in Group 4. In this age group, the expected drop-out rate is about 10%.

Sample size for immunogenicity endpoints was estimated to show non-inferiority in all primary objectives with 90.1% overall power; calculations assumed one-sided type I error of 0.025. Table 3 presents a summary of the power and sample size calculations.

Table 3: Power and sample size calculation for immunogenicity endpoints

Antigen	Endpoints	Expected Response[1]	NI Definition	Power One-Sided α=0.025, N=285
PT	Booster response rate[2]	0.936	> –10%	99
FHA	Booster response rate[2]	0.892	> –10%	96
PRN	Booster response rate[2]	0.946	> –10%	99
FIM	Booster response rate[2]	0.943	> –10%	99
Diphtheria	Booster response rate[3]	0.988	> –10%	> 99.9%
Tetanus	Booster response rate[3]	0.967	> –10%	> 99.9%
Polio 1	Booster response rate[4]	0.960	> –10%	> 99.9%
Polio 2	Booster response rate[4]	0.960	> –10%	> 99.9%
Polio 3	Booster response rate[4]	0.960	> –10%	> 99.9%
PT	GMC (EU/mL)	86.4 (79.9; 93.5) N=423	> 2/3	> 99.9%
FHA	GMC (EU/mL)	86.5 (78.3; 95.5) N=424	> 2/3	99
PRN	GMC (EU/mL)	173 (155; 193) N=425	> 2/3	98
FIM	GMC (EU/mL)	388 (354; 425) N=424	> 2/3	99
Diphtheria	GMC (IU/mL)	13.3 (12.2; 14.5) N=426	> 2/3	> 99.9%
Tetanus	GMC (IU/mL)	6.58 (6.02; 7.20) N=426	> 2/3	99
Polio 1	GMT (1/dil)	4570 (4099; 5095) N=424	> 2/3	98
Polio 2	GMT (1/dil)	4341 (3909; 4820) N=424	> 2/3	99
Polio 3	GMT (1/dil)	5755 (5130; 6455) N=422	> 2/3	98
Overall				90

[1] Based on post-Dose 5 data from study Td517

[2] Booster response rate for pertussis (PT, FHA, PRN, and FIM) was defined as: subjects with a pre-vaccination antibody concentration < LLOQ, achieving a post-vaccination level ≥ 4X LLOQ; subjects with a pre-vaccination antibody concentration ≥ LLOQ but < 4X LLOQ, achieving a 4-fold rise rate of post-vaccination over the pre-vaccination antibody concentration; subjects with a pre-vaccination antibody concentration ≥ 4X LLOQ, achieving a 2-fold response.

[3] Booster response rate for diphtheria and tetanus was defined as: subjects with a pre-vaccination antibody concentration < 0.1 IU/mL, achieving a post-vaccination level ≥ 0.4 IU/mL; subjects with a pre-vaccination antibody concentration ≥ 0.1 IU/mL but < 2.0 IU/mL, achieving a 4-fold rise rate of post-vaccination over the pre-vaccination antibody concentration; subjects with a pre-vaccination antibody concentration ≥ 2.0 IU/mL, achieving a 2-fold response.

[4] Booster response rate for polio was defined as: subjects with a pre-vaccination antibody concentration < 1:8 dil achieving a post-vaccination level ≥ 1:8 dil; subjects with a pre-vaccination antibody concentration ≥ 1:8 dil, achieving a 4-fold response.

Source: Adapted from - BLA 125525; Clinical Study Report m5i02, p.88

6.1.10 Study Population and Disposition

6.1.10.1 Disposition of Subjects

The first subject in this trial was enrolled on 28 April 2011. The last telephone call was made to a parent/legally acceptable representative to collect 180-day safety data on 30 May 2013.

A summary of subject disposition and reasons for discontinuation of all randomized subjects is presented in table 4.

Table 4: Summary of subject disposition and reasons for discontinuation

	V_1 Group 1 (N=324) n (%)	V_1 Group 3 (N=2419) n (%)	V_1 Total (N=2743) n (%)	V_2 Group 2 (N=327) n (%)	V_2 Group 4 (N=302) n (%)	V_2 Total (N=629) n (%)	Total (N=3372) n (%)
Received study vaccination	323 (99.7)	2411 (99.7)	2734 (99.7)	327 (100.0)	299 (99.0)	626 (99.5)	336 (99.6)
Did not receive study vaccination	1 (0.3)	8 (0.3)	9 (0.3)	0 (0.0)	3 (1.0)	3 (0.5)	12 (0.4)
Full analysis set	303 (93.5)	0 (0.0)	303 (11.0)	302 (92.4)	0 (0.0)	302 (48.0)	605 (17.9)
Safety analysis set	323 (99.7)	2410 (99.6)	2733 (99.6)	327 (100.0)	294 (97.4)	621 (98.7)	3354 (99.5)
Per-protocol analysis set	263 (81.2)	0 (0.0)	263 (9.6)	253 (77.4)	0 (0.0)	253 (40.2)	516 (15.3)
Subjects completed study (28 days)	313 (96.6)	2363 (97.7)	2676 (97.6)	317 (96.9)	291 (96.4)	608 (96.7)	3284 (97.4)
Subjects discontinued	11 (3.4)	56 (2.3)	67 (2.4)	10 (3.1)	11 (3.6)	21 (3.3)	88 (2.6)
Reason for discontinuation*	11 (3.4)	56 (2.3)	67 (2.4)	10 (3.1)	11 (3.6)	21 (3.3)	88 (2.6)
Serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with protocol	2 (0.6)	28 (1.2)	30 (1.1)	4 (1.2)	5 (1.7)	9 (1.4)	39 (1.2)
Lost to follow-up	5 (1.5)	16 (0.7)	21 (0.8)	5 (1.5)	3 (1.0)	8 (1.3)	29 (0.9)
Voluntary withdrawal not due to an AE	3 (0.9)	12 (0.5)	15 (0.5)	1 (0.3)	3 (1.0)	4 (0.6)	19 (0.6)
Subjects completed study (180 day follow-up)	307 (94.8)	2340 (96.7)	2647 (96.5)	312 (95.4)	287 (95.0)	599 (95.2)	3246 (96.3)

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine
* The reason for discontinuation was missing for one subject from Group 1.
Source: Adapted from - BLA 125525; Clinical Study Report m5i02, p.94

6.1.10.2 Protocol Deviations

All Randomized Subjects

A summary of protocol violations for all randomized subjects is presented in Table 5

Table 5: Summary of protocol deviations - All Randomized Subjects

	V_1	V_2	Total
	(N=2743) n (%)	(N=629) n (%)	(N=3372) n (%)
Subjects with one or more protocol violations	168 (6.1)	95 (15.1)	263 (7.8)
Protocol violation:			
Did not meet all protocol-specified inclusion/exclusion criteria	139 (5.1)	54 (8.6)	193 (5.7)
Did not receive vaccine*	13 (0.5)	9 (1.4)	22 (0.7)
Received a vaccine other than the one that he/she was randomized to receive	1 (<0.1)	0 (0.0)	1 (<0.1)
Did not provide a post-dose serology sample in the proper time window†	25 (0.9)	31 (4.9)	56 (1.7)
Subject's serology sample did not produce a valid post vaccination test result†	0 (0.0)	1 (0.2)	1 (<0.1)
Vaccine not usable due to temperature deviation†	8 (0.3)	9 (1.4)	17 (0.5)
Diagnosed with common variable immuno-deficiency disease†	1 (<0.1)	0 (0.0)	1 (<0.1)
Received DAPTACEL and IPOL on different days	1 (<0.1)	0 (0.0)	1 (<0.1)
Subject was randomized to Group 4 (DAPTACEL + IPOL), however they may have received DTaP-IPV	0 (0.0)	5 (0.8)	5 (0.1)

A subject may have more than one protocol violation.

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine

* Includes Groups 1-4 subjects who did not receive study vaccine and Groups 1-2 subjects who did not receive concomitant vaccine.

†These items were assessed for Groups 1-2 subjects only.

Source: Adapted from - BLA 125525; Clinical Study Report m5i02, p.96

Reviewer's comment: *The number of protocol violations or deviations was higher than expected. The applicant provided the following rationale for this high number as "… due to an error which was made during the conversion from paper to electronic medical records (EMR) at one US site. At that time, the medical office staff had routinely transcribed the pertussis-containing vaccines into the EMR system using the generic term "DTaP", and did not enter the specific trade name or lot numbers. The medical office staff changed "DTaP" in the EMR system to "DTaP (DAPTACEL)", thus inaccurately reflecting the actual vaccination history for some study participants."*

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 violations 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 DTaPIPV and DAPTACEL + IPOL, respectively.

The following protocol violation categories had 9 or fewer violators:

- Vaccine not usable due to temperature deviation: 0.3% (8/2743) and 1.4% (9/629) of subjects in DTaP-IPV and DAPTACEL + IPOL, respectively.
- Subjects were randomized to Group 4 (DAPTACEL + IPOL); however, they may have received DTaP-IPV + IPOL: 0% (0/2743) and 0.8% (5/629) of subjects in DTaP-IPV and DAPTACEL + IPOL, respectively.
- Subject's serology sample did not produce a valid post-vaccination test result: 0% (0/2743) and 0.2% (1/629) of subjects in DTaP-IPV and DAPTACEL + IPOL, respectively.

In the DTaP-IPV group, one subject received a vaccine other than the one that he/she was randomized to receive, one subject received DAPTACEL and IPOL on different days, and one subject was diagnosed with common variable immunodeficiency disease.

6.1.10.3 Demographic and Baseline Characteristics

All Randomized Subjects (28-Day Safety Data)

The demographic characteristics for all randomized subjects including sex, age, and race are summarized in Table 6.

Table 6: Demographic characteristics - All Randomized Subjects

	V_1 (N=2743)	V_2 (N=629)	Total (N=3372)
Sex n (%)			
Male	1413 (51.5)	323 (51.4)	1736 (51.5)
Female	1330 (48.5)	306 (48.6)	1636 (48.5)
Age (years)			
Mean (SD)	4.4 (0.5)	4.4 (0.5)	4.4 (0.5)
Median	4.1	4.2	4.1
Min, Max	4.0, 6.6	4.0, 6.3	4.0, 6.6
Race n (%)			
Asian	26 (0.9)	4 (0.6)	30 (0.9)
Black	227 (8.3)	64 (10.2)	291 (8.6)
Caucasian	2101 (76.6)	450 (71.5)	2551 (75.7)
Hispanic	216 (7.9)	52 (8.3)	268 (7.9)
American Indian or Alaska Native	8 (0.3)	1(0.2)	9 (0.3)
Native Hawaiian or other Pacific Islander	12 (0.4)	1(0.2)	13 (0.4)
Other	153 (5.6)	57 (9.1)	210 (6.2)

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine
SD: Standard deviation
Source: Adapted from - BLA 125525; Clinical Study Report m5i02, p.97

Overall, the ratio of males to females was 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%). 8.6% were Black, 7.9% were Hispanic and 7.8% were from other ethnic groups. Ethnicity was well-balanced between both groups.

Immunogenicity Subset (Groups 1 and 2)

The demographic characteristics for the PP analysis set including sex, age, and race are summarized in Table 7.

Table 7: Demographic characteristics - PP Analysis Set

	DTaP-IPV (N=263)	DAPTACEL+IPOL (N=253)	Total (N=516)
Sex n (%)			
Male	144 (54.8)	136 (53.8)	280 (54.3)
Female	119 (45.2)	117 (46.2)	236 (45.7)
Age (years)			
Mean (SD)	4.4 (0.4)	4.4 (0.5)	4.4 (0.5)
Median	4.2	4.1	4.2
Min, Max	4.0, 6.0	4.0, 6.2	4.0, 6.2
Race n (%)			
Black	38 (14.4)	34 (13.4)	72 (14.0)
Caucasian	173 (65.8)	173 (68.4)	346 (67.1)
Hispanic	29 (11.0)	24 (9.5)	53 (10.3)
American Indian or Alaska Native	2 (0.8)	1 (0.4)	3 (0.6)
Other	21 (8.0)	21 (8.3)	42 (8.1)

SD: Standard deviation
Source: Adapted from - BLA 125525; Clinical Study Report m5i02, p.97

Overall, the ratio of males to females was balanced in the PP analysis set as well. Similar proportions were observed in the FAS.

6.1.11 Immunogenicity and Efficacy Results

Immunogenicity
Blood samples were obtained immediately before vaccination (Visit 1) and 28 to 42 days after vaccination (Visit 2) in Groups 1 and 2. The analyses of the antibody responses were performed on both the PP analysis set and the FAS for immunogenicity.

Potential Confounding Effects
In this study, the potential confounding effect from different vaccination histories was taken into consideration during randomization. Both the number of previous DAPTACEL doses (2 levels: 4 doses, less than 4 doses) and the number of previous IPV doses (3 levels: 4 doses, 3 doses, and less than 3 doses) were used as stratification factors. These potential confounders were assigned to the 2 vaccination groups equally through the randomization process, which substantially reduced the confounding effect. In addition, subgroup analyses were proposed to present the summary of post-vaccination booster response rates and summary of pre- and post-vaccination GMCs (or GMTs) at each level of these 2 stratification factors.

Most of the PP analysis set subjects previously had 4 doses of DAPTACEL and 3 doses of IPV. The numbers of subjects from other vaccination history levels were very small, which were as expected since Pentacel was first licensed in 2008. All of these factors

indicated a very minimum potential confounding effect; therefore, additional stratified analyses were not proposed for this study.

6.1.11.1 Primary Objective 1: Pertussis (PT, FHA, PRN, and FIM) Booster Responses and Geometric Mean Concentrations

Booster Response for Pertussis
Table 8 presents the non-inferiority comparisons of booster response rates for the pertussis antigens in the PP analysis set.

Table 8: Non-inferiority comparison of post-vaccination anti-pertussis booster response rates - PP Analysis Set

	V_1 n/M	V_1 %	V_2 n/M	V_2 %	Difference in Rates (%) ($V_1 - V_2$)	(95% CI)	Non-Inferiority Achieved
Anti-PT (ELISA - EU/mL)	240/252	95.2	222/247	89.9	5.4	(0.7; 10.2)	Yes
Anti-FHA (ELISA - EU/mL)	242/255	94.9	217/248	87.5	7.4	(2.5; 12.5)	Yes
Anti-PRN (ELISA - EU/mL)	246/254	96.9	231/248	93.1	3.7	(-0.2; 7.9)	Yes
Anti-FIM (ELISA - EU/mL)	243/250	97.2	230/249	92.4	4.8	(0.9; 9.1)	Yes

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine
n - number of subjects with booster response
M - number of subjects with available data
Note: Non-inferiority is supported by the data if the lower limit of the 2-sided 95% CI is > -10%.
Source: Adapted from - BLA 125525; Clinical Study Report m5i02, p.100

A 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, FHA, PRN, and FIM.

Geometric Mean Concentrations for Pertussis
The 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).

Table 9 presents the non-inferiority comparisons of the GMCs in the PP analysis set. 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).

Table 9: Non-inferiority comparison of post-vaccination anti-pertussis GMCs between groups - PP Analysis Set

	V_1 n	V_1 Geometric Mean	V_2 n	V_2 Geometric Mean	GMC Ratio*	(95% CI)	Non- inferiority Achieved
Anti-PT (ELISA - EU/mL)	261	120.7	252	61.3	1.97	(1.68; 2.31)	Yes
Anti-FHA (ELISA - EU/mL)	263	123.5	253	79.0	1.56	(1.30; 1.88)	Yes
Anti-PRN (ELISA - EU/mL)	262	282.6	252	187.5	1.51	(1.27; 1.79)	Yes
Anti-FIM (ELISA - EU/mL)	260	505.8	253	378.9	1.33	(1.12; 1.60)	Yes

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine
*Ratio = (DTaP-IPV) / (DAPTACEL + IPOL)
n - number of subjects with available data
A non-inferiority criterion is met if the lower limit of the 2-sided 95% CI is > 0.67 (2/3).
Source: Reviewer's analysis based on the submitted data set.

Reviewer's comment: *The reviewer conducted the same analysis with the full analysis set and found similar results.*

6.1.11.2 Primary Objective 2: Diphtheria and Tetanus Toxoid Antibody Responses

Booster Response for Diphtheria and Tetanus

Table 10 presents the non-inferiority comparisons of the anti-tetanus and anti-diphtheria booster response rates between groups in the PP analysis set.

Table 10: Non-inferiority comparison of post-vaccination anti-tetanus and anti-diphtheria booster response rates between groups - PP Analysis Set

	V_1 n/M	V_1 %	V_2 n/M	V_2 %	Difference in Rates* (%)	(95% CI)	Non-Inferiority Achieved
Anti-tetanus (ELISA - IU/mL)	213/253	84.2	209/248	84.3	-0.1	(-6.5; 6.3)	Yes
Anti-diphtheria (TNA - IU/mL)	249/256	97.3	247/249	99.2	-1.9	(-4.8; 0.6)	Yes

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine
*Difference in rates = (DTaP-IPV) – (DAPTACEL+IPOL)
n - number of subjects with booster response
M - number of subjects with available data
A non-inferiority criterion is met if the lower limit of the 2-sided 95% CI is > -10%.
Source: Reviewer's analysis based on the submitted data set.

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).

Table 11 presents the non-inferiority comparisons of anti-tetanus and anti-diphtheria GMCs between vaccination groups in the PP analysis set.

Table 11: Non-inferiority comparison of post-vaccination anti-tetanus and anti-diphtheria GMCs between groups - PP Analysis Set

	V_1 n	V_1 Geometric Mean	V_2 N	V_2 Geometric Mean	GMC Ratio*	(95% CI)	Non- Inferiority Achieved
Anti-tetanus (ELISA-IU/mL)	262	6.4	253	5.5	1.17	(0.998, 1.38)	Yes
Anti-diphtheria (TNA - IU/mL)	262	18.6	253	15.5	1.20	(1.01, 1.42)	Yes

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine

*Ratio = (DTaP-IPV) / (DAPTACEL+IPOL)

n - number of subjects with available data

A non-inferiority criterion is met if the lower limit of the 2-sided 95% CI is > 0.67 (2/3).

Source: Reviewer's analysis based on the submitted data set.

6.1.11.3 Primary Objective 3: Polio Antibody Responses

Booster Response for Polio

Table 12 presents the non-inferiority comparison of the anti-polio types 1, 2, and 3 booster response rates between groups in the PP analysis set.

Table 12: Non-inferiority comparison of post-vaccination anti-polio booster response rates between groups - PP Analysis Set

	V_1 n/M	V_1 %	V_2 n/M	V_2 %	Difference in Rates* (%)	(95% CI)	Non-Inferiority Achieved
Anti-polio 1 (1/dil)	214/249	85.9	204/248	82.3	3.7	(-2.8; 10.1)	Yes
Anti-polio 2 (1/dil)	195/249	78.3	196/248	79.0	-0.7	(-7.9; 6.5)	Yes
Anti-polio 3 (1/dil)	210/247	85.0	210/248	84.7	0.3	(-6.0; 6.7)	Yes

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine

*Rates = (DTaP-IPV) – (DAPTACEL+IPOL)

n - number of subjects with booster response

M - number of subjects with available data

A non-inferiority criterion is met if the lower limit of the 2-sided 95% CI is > -10%.

Source: Reviewer's analysis based on the submitted data set.

Non-inferiority was achieved for polio types 1, 2, and 3.

GMTs for Polio

The pre-vaccination GMTs were similarly low in both study groups, ranging from 90.9 to 214 for all 3 polio types. Post-vaccination GMTs were similarly high in both study groups, ranging from 2731 to 4591 for all 3 polio types. Table 13 presents the non-inferiority comparison of the anti-polio types 1, 2, and 3 GMTs between groups in the PP analysis set. Non-inferiority was achieved for all polio types 1, 2, and 3.

Table 13: Non-inferiority comparison of post-vaccination anti-polio GMTs between groups- PP Analysis Set

	V_1 n	V_1 Geometric Mean	V_2 n	V_2 Geometric Mean	GMT Ratio V_1 / V_2	(95% CI)	Non-Inferiority Achieved
Anti-polio 1 (1/dil)	258	3476.9	253	2730.7	1.27	(1.06; 1.52)	Yes
Anti-polio 2 (1/dil)	258	3490.9	253	3893.6	0.90	(0.750; 1.07)	Yes
Anti-polio 3 (1/dil)	258	4591.4	252	3419.0	1.34	(1.10; 1.64)	Yes

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine

n - number of subjects with available data

A non-inferiority criterion is met if the lower limit of the 2-sided 95% CI is > 0.67 (2/3).

Source: Reviewer's analysis based on the submitted data set

***Reviewer's comment**: Reviewer's analysis results were the same as the applicant's.*

6.1.11.4 Concomitant Medications

A frequency summary of concomitant medication use, based on protocol-defined categories (Category 1 and Category 2) was obtained. Table 14 presents the results by category of concomitant Medication used.

Table 14: Concomitant Medication by Category

Concomitant medication	V_1 n	V_1 %	V_1 (95% CI)	V_2 n	V_2 %	V_2 (95% CI)
Antipyretics/analgesics/non steroidal anti-inflammatory drugs (NSAIDs)	1004	36.7	(34.9; 38.6)	210	33.8	(30.1; 37.7)
Other reportable medication as specified in the protocol	330	12.1	(10.9; 13.4)	82	13.2	(10.6; 16.1)

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine

n - number of subjects experiencing the endpoint listed in the first column

Source: Adapted from - BLA 125525; Appendix 15 to Clinical Study Report m5i02, p.6

There was no notable difference in the use of concomitant medications between the DTaP-IPV group and the DAPTACEL + IPOL group.

6.1.11.6 Immunogenicity Subgroup Analysis for Study M5I02

Ethnicity and Sex

No particular trends were observed in the analysis of GMCs (or titers), GMFR, and 95% CI by ethnicity (Caucasian, Black, and Hispanic) and by sex. Tables 15 and 16 summarize the geometric mean titer values by ethnicity and sex, respectively.

Table 15: Summary of Geometric Mean Titer values by Ethnicity

	V_1 Caucasian	V_2 Caucasian	V_1 Black	V_2 Black	V_1 Hispanic	V_2 Hispanic
Anti-PT	115	59.2	163	89.4	128	50.7
Anti-FHA	112	78.7	172	74.8	165	85.9
Anti-PRN	310	206	251	135	232	199
Anti-FIM	493	381	655	376	469	359
Anti-Tetanus	6.57	5.46	5.59	5.48	7.28	5.29
Anti-Diphtheria	18.4	15.3	18.0	16	17.7	16.3
Anti-Polio 1	3491	3033	3064	1966	4671	2695
Anti-Polio 2	3512	4298	3365	3111	3999	3158
Anti-Polio 3	4642	3555	3007	2724	6766	3494

V_1= DTaP-IPV Vaccine, V_2= DAPTACEL+IPOL Vaccine
Source: Reviewer's table based on the submitted data set focused on 3 major ethnic groups in the study.

Table 16: Summary of Geometric Mean Titer values by Sex

	V_1 Male	V_2 Male	V_1 Female	V_2 Female
Anti-PT	124	62	117	60.5
Anti-FHA	146	89.2	101	68.5
Anti-PRN	269	182	300	194
Anti-FIM	467	334	556	438
Anti-Tetanus	6.52	5.88	6.30	5.05
Anti-Diphtheria	17.7	15.5	19.7	15.5
Anti-Polio 1	3352	3002	3631	2446
Anti-Polio 2	3327	3892	3696	3895
Anti-Polio 3	4347	3597	4900	3222

V_1= DTaP-IPV Vaccine, V_2= DAPTACEL+IPOL Vaccine
Source: Reviewer's table based on the submitted data set

6.1.11.7 Immunogenicity Conclusion

All primary objectives for the M5I02 study were met. DTaP-IPV was shown to be non-inferior to DAPTACEL + IPOL as a 5th dose booster for all immunogenicity parameters evaluated including:

- Anti-pertussis (PT, FHA, PRN, and FIM) GMCs and booster response rates
- Anti-diphtheria and anti-tetanus GMCs and booster response rates
- Anti-poliovirus types 1, 2, and 3 GMTs and booster response rates
- Seroprotection rates for diphtheria, tetanus, and polio were all at or close to 100%.

6.1.12 Safety Results and Evaluation

6.1.12.1 Methods

Post-Vaccination Observation Period

Subjects were observed for 30 minutes after vaccination to ensure their safety. Any AE that occurred during this period was recorded as an immediate event / reaction, and was additionally recorded in the eCRF, as follows:

- **Any injection site AE**, whether or not it was defined as a solicited reaction, was recorded in the eCRF. There was to be no indication of the time to onset; only that the AE occurred on Day 0.
- **A systemic AE that was defined in the DC and eCRF as a solicited reaction** was also recorded in the solicited AE tables of the eCRF, again without specification of the time to onset.
- **Any other systemic AE** that occurred during this period was recorded in the unsolicited AE tables of the eCRF. On this page, there was a checkbox to indicate that the AE was immediate.
- **Any SAE** that occurred during the first 30 minutes post-vaccination was to be reported in the same way as any other SAE and to the applicant, according to the procedures described in the protocol.

Reactogenicity (Solicited Reactions from Day 0 to Day 7 after Vaccination)

After vaccination, subjects' parents/ legally acceptable representatives were provided with a safety DC, a digital thermometer, a measuring tape, and a flexible ruler, and were instructed how to use them. The following items were recorded by the subjects' parent/ legally acceptable representative in the DC on the day of vaccination and for the next 7 days (i.e., Day 0 to Day 7) until resolution:

- Daily temperature, with the route by which it was taken
- Daily measurement or intensity grade of all other solicited injection site and systemic reactions
- Action taken for each event, if any (e.g., medication).

Subjects' parents/ legally acceptable representatives were contacted by telephone 8 days after vaccination to remind them to record all safety information in the DC.

If the timing of the telephone call fell on a weekend or a holiday, the call was made on the next business day. If contact was not made on the designated day, study staff continued calling until contact was made. Every telephone attempt and its outcome were documented in the source document.

6.1.12.2 Safety Analysis Results

Adverse Events

Solicited Reactions between Day 0 and Day 7

Table 17 presents a summary of solicited reactions within 7 days after vaccination in the SafAS.

Table 17: Summary of solicited reactions within 7 days after vaccination-Safety Analysis set

Subjects experiencing at least one:	V_1 n/M	V_1 %	V_1 (95% CI)	V_2 n/M	V_2 %	V_2 (95% CI)
Solicited reaction	2516/2690	93.5	(92.5; 94.4)	553/603	91.7	(89.2; 93.8)
Grade 3 solicited reaction	646/2690	24.0	(22.4; 25.7)	120/603	19.9	(16.8; 23.3)
Solicited injection site reaction	2467/2689	91.7	(90.6; 92.8)	541/603	89.7	(87.0; 92.0)
Grade 3 injection site reaction	573/2689	21.3	(19.8; 22.9)	96/603	15.9	(13.1; 19.1)
Solicited systemic reaction	1713/2689	63.7	(61.9; 65.5)	369/603	61.2	(57.2; 65.1)
Grade 3 systemic reaction	122/2689	4.5	(3.8; 5.4)	39/603	6.5	(4.6; 8.7)

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine
n - number of subjects experiencing the endpoint listed in the first column
M - number of subjects with available data for the relevant endpoint
Source: Adapted from - BLA 125525; Clinical Study Report m5i02, p.136

The percentage of subjects who experienced at least one solicited reaction was similar between vaccination groups: 93.5% and 91.7% of subjects in the DTaP-IPV group and DAPTACEL + IPOL, respectively.

Unsolicited Adverse Events between Day 0 and Day 28
Table 18 presents a summary of the unsolicited serious and non-serious AEs that occurred within 28 days after vaccination.

Table 18: Summary of unsolicited serious and non-serious AEs reported within 28 days after vaccination - Safety Analysis Set

Subjects experiencing at least one:	V_1 n	V_1 %	V_1 (95% CI)	V_1 n AEs	V_2 n	V_2 %	V_2 (95% CI)	V_2 n AEs
Immediate unsolicited AE	25	0.9	(0.6; 1.3)	37	6	1.0	(0.4; 2.1)	13
Grade 3 Immediate unsolicited non-serious AE	0	0.0	(0.0; 0.1)	0	1	0.2	(0.0; 0.9)	1
Immediate unsolicited AR	2	0.1	(0.0; 0.3)	2	1	0.2	(0.0; 0.9)	2
Grade 3 Immediate unsolicited non-serious AR	0	0.0	(0.0; 0.1)	0	0	0.0	(0.0; 0.6)	0
Unsolicited AE	951	34.8	(33.0; 36.6)	1605	191	30.8	(27.1; 34.6)	328
Unsolicited AR	318	11.6	(10.5; 12.9)	402	57	9.2	(7.0; 11.7)	75
Unsolicited non-serious AE	951	34.8	(33.0; 36.6)	1602	190	30.6	(27.0; 34.4)	327
Grade 3 unsolicited non-serious AE	111	4.1	(3.4; 4.9)	151	22	3.5	(2.2; 5.3)	33
Unsolicited non-serious AR	318	11.6	(10.5; 12.9)	402	57	9.2	(7.0; 11.7)	75
Grade 3 unsolicited non-serious AR	13	0.5	(0.3; 0.8)	16	4	0.6	(0.2; 1.6)	4
Unsolicited non-serious injection site AR	265	9.7	(8.6; 10.9)	319	45	7.2	(5.3; 9.6)	58
Grade 3 unsolicited non-serious injection site AR	7	0.3	(0.1; 0.5)	9	2	0.3	(0.0; 1.2)	2
Unsolicited non-serious systemic AE	777	28.4	(26.7; 30.2)	1283	159	25.6	(22.2; 29.2)	269
Grade 3 unsolicited non-serious systemic AE	105	3.8	(3.2; 4.6)	142	20	3.2	(2.0; 4.9)	31
Unsolicited non-serious systemic AR	67	2.5	(1.9; 3.1)	83	13	2.1	(1.1; 3.6)	17
Grade 3 unsolicited non-serious systemic AR	6	0.2	(0.1; 0.5)	7	2	0.3	(0.0; 1.2)	2
SAE	3	0.1	(0.0; 0.3)	3	1	0.2	(0.0; 0.9)	1

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine
n - number of subjects experiencing the endpoint listed in the first column
n AEs - number of AEs
Source: Adapted from - BLA 125525; Clinical Study Report m5i02 p.142

The percentages of subjects who experienced at least 1 unsolicited serious or non-serious AE were similar in both vaccination groups: 34.8% and 30.8% of subjects in the DTaP-IPV and DAPTACEL + IPOL groups, respectively.

6.1.12.3 Deaths

There were no deaths reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

During the course of the study (from 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 at

least one SAE. Of these, 3 (0.1%) subjects in the DTaP-IPV group and 1 (0.2%) subject in the DAPTACEL +IPOL group experienced SAEs between Day 0 and Day 28.

All SAEs were considered by the investigators as not related to the vaccination.

6.1.12.5 Adverse Events of Special Interest (AESI) 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 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 one report of an autoimmune disorder: one subject developed polydipsia and excessive urination 11 days after vaccination with DTaP-IPV, and subsequently was diagnosed with new-onset type 1 diabetes mellitus. The subject had a family history (aunt, uncle, and grandfather) of type 1 diabetes. The event of type 1 diabetes mellitus was assessed by the Investigator as not related to the vaccine. There was no baseline level for glucose.

6.1.12.6 Safety Subgroup Analysis

6.1.12.6.1 Safety Analysis by Sex

Table 19 presents summary of the safety analysis by sex

Table 19: Safety overview after vaccine injection by sex

Subjects experiencing at least one:	V_1 Male	V_2 Male	V_1 Female	V_2 Female
	%	%	%	%
Immediate unsolicited AE	0.5	0.3	1.4	1.7
Immediate unsolicited AR	0.1	0	0.1	0.3
Solicited reaction	93.1	92.3	94.0	91.0
Solicited injection site reaction	91.5	90.7	92.0	88.6
Solicited systemic reaction	61.6	61.7	65.9	60.7
Unsolicited AE	34.4	31.3	35.2	30.2
Unsolicited AR	11.5	7.8	11.8	10.6
Unsolicited non-serious AE	34.4	30.9	35.2	30.2
Unsolicited non-serious AR	11.5	7.8	11.8	10.6
Unsolicited non-serious injection site	9.9	6.3	9.4	8.3
Unsolicited non-serious systemic AE	27.3	26.6	29.7	24.6
Unsolicited non-serious systemic AR	2.2	1.9	2.7	2.3
AE leading to study discontinuation *	0	0	0	0
SAE †	0.9	0.6	0.6	0.3
Death	0	0	0	0

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine
% - percentage of subjects experiencing the endpoint listed in the first column
* - Identified in the termination form as SAE or Other AE
† - All SAEs during the whole trial period are included. Only events within 28 days after vaccination are included in other rows of the table.
Source: Reviewer's table based on Clinical Study Report m5i02

No particular trends were observed in the analysis of safety by sex.

6.1.12.6.2 Safety analysis by Ethnicity

Table 20 presents a summary of safety analysis by ethnicity.

Table 20 : Safety overview after vaccine injection by ethnicity

Subjects experiencing at least one:	**V_1 Caucasian** %	**V_2 Caucasian** %	**V_1 Black** %	**V_2 Black** %	**V_1 Hispanic** %	**V_2 Hispanic** %
Immediate unsolicited	1.1	0.9	0	1.6	0.5	0
Immediate unsolicited	0.05	0.2	0	0	0	0
Solicited reaction	94.5	92.6	87.7	89.7	88.6	88.2
Solicited injection	93.0	90.8	84.0	84.5	86.3	86.3
Solicited systemic	64.7	63.0	59.2	56.9	57.8	52.9
Unsolicited AE	36.5	35.0	29.2	20.3	28.5	13.7
Unsolicited AR	12.7	10.2	8.0	4.7	8.4	5.9
Unsolicited non-	36.5	34.8	29.2	20.3	28.5	13.7
Unsolicited non-	12.7	10.2	8.0	4.7	8.4	5.9
Unsolicited non-	10.6	8.1	6.2	3.1	6.5	3.9
Unsolicited non-	29.6	29.3	25.7	17.2	22.9	9.8
Unsolicited non-	2.7	2.3	2.2	1.6	1.9	2.0
AE leading to study	0	0	0	0	0	0
SAE †	0.7	0.7	2.2	0	0.9	0
Death	0	0	0	0	0	0

V_1- DTaP-IPV Vaccine, V_2- DAPTACEL+IPOL Vaccine
% - percentage of subjects experiencing the endpoint listed in the first
* - Identified in the termination form as SAE or Other AE
† - All SAEs during the whole trial period are included. Only events within 28 days after vaccination are included in other rows of the table.
Source: Reviewer's table based on Clinical Study Report m5i02

No particular trends were observed in the analysis of safety and 95% CI by ethnicity (Caucasian, Black, and Hispanic). The applicant also conducted similar analyses and presented results as an appendix to the study report.

6.1.12.7 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 two 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. No deaths were reported.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary objectives of the study to compare the pertussis, diphtheria, tetanus, and IPV booster responses and GMCs/GMTs after DTaP-IPV vaccination to those elicited after DAPTACEL + IPOL vaccination when administered as a 5th dose have been met, according to the pre-specified non-inferiority criteria.

For pertussis, non-inferiority of DTaP-IPV to DAPTACEL + IPOL was demonstrated both by the booster response rates and the GMC comparisons. Following the 5th dose vaccination, GMC values for subjects in the DTaP-IPV group were higher compared to subjects in the DAPTACEL + IPOL group for all 4 pertussis antigens.

DTaP-IPV was also shown to be non-inferior to the licensed comparator vaccines (DAPTACEL +IPOL) based on the diphtheria and tetanus primary immunogenicity comparisons meeting the pre-specified non-inferiority criteria.

Non-inferiority of anti-poliomyelitis titers, when compared to the standard-of-care (DAPTACEL + IPOL) assessed by the comparison of post-vaccination GMTs and booster response rates, was achieved.

In the context of high seroprotective titers at baseline for all subjects (between 93.1% and 100.0%), the booster administration of IPV resulted in a significant response, illustrated by the GMFR for titers against the 3 polio types, which were between 16.2 and 43.6 in the DTaP-IPV group and between 20.8 and 37.5 in the control group. The proportion of increase for each type (serotype 1, 2, and 3) was similar in both groups.

10.2 Conclusions and Recommendations

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

DTaP-IPV-induced responses were shown to be non-inferior to those following DAPTACEL + IPOL at 28 days post-vaccination with respect to the 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.

The data and the study analysis results support the conclusion that DTaP-IPV vaccine is safe and immunogenic when administered as a 5th dose in children 4 to 6 years of age.