

BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125089/593
CBER Received Date	November 17, 2015
PDUFA Goal Date	September 16, 2016
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name	Anuja Rastogi, MD MHS
Review Completion Date / Stamped Date	September 14, 2016
Supervisory Concurrence	Lucia Lee, MD Jeff Roberts, MD
Applicant	Sanofi Pasteur, Inc.
Established Name	Meningococcal (Groups A,C,Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine
(Proposed) Trade Name	Menactra®
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each 0.5 mL dose contains serogroup A, C, Y, and W-135 meningococcal capsular polysaccharides [PSs] (4 ug of each PS) conjugated to approximately 48 ug of diphtheria toxoid
Dosage Form(s) and Route(s) of Administration	Liquid solution supplied in 0.5 mL single-dose vials, intramuscular injection
Dosing Regimen	<p>Primary Vaccination:</p> <ul style="list-style-type: none"> • Children 9 through 23 months of age: Two doses, three months apart. • Individuals 2 through 55 years of age: A single dose; <p>Booster Vaccination:</p> <ul style="list-style-type: none"> • A single booster dose for individuals 15 through 55 years of age at continued risk for meningococcal disease, if at least 4 years have elapsed since the prior dose. <p>With this application there are no new proposed dosing regimens.</p>
Indication(s) and Intended Population(s)	<p>Menactra is indicated for active immunization to prevent invasive meningococcal disease caused by <i>Neisseria meningitidis</i> serogroups A, C, Y and W-135. Menactra is approved for use in individuals 9 months through 55 years of age. Menactra does not prevent <i>N meningitidis</i> serogroup B disease.</p> <p>With this application there are no new proposed indications.</p>
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	Adverse Event
ACIP	Advisory Committee on Immunization Practices
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
Daptacel	DAPTACEL® Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi Pasteur Ltd., Toronto, ON, Canada):
DIS	Division of Inspections and Surveillance
ELISA	Enzyme-Linked Immunosorbent Assay
ES	Executive Summary
FAS	Full Analysis Set
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practices
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titers
GMFR	Geometric Mean Fold Rise
GRMP	Good Review Management Principles
hSBA	Serum Bactericidal Assay using human complement
IPOL®	Poliovirus Vaccine Inactivated (Sanofi Pasteur SA, Lyon, France)
IPV	Inactivated Poliovirus Vaccine
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
IVR	Interactive Voice Response system
JMP	JMP®, statistical analysis software program
MedDRA	Medical Dictionary for Regulatory Activities
Menactra®	Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA):
OCOD	Office of Communication Outreach and Development (CBER)
PD	Pharmacodynamics
PI	Package Insert
PK	Pharmacokinetics
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PP	Per Protocol Analysis Set
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategy
RMS/BLA	Regulatory Management System for the Biologics License Application
RTF	Refuse to File
SAE	Serious Adverse Event
SAS	Safety Analysis Set
sBLA	Supplemental Biological License Application

1. Executive Summary

Sanofi Pasteur submitted safety and immunogenicity data from Study MTA43 evaluating the co-administration of DAPTACEL® (Daptacel) and Menactra® in children 4 years through 6 years of age at either the same visit or sequentially 30 days apart. Daptacel is a combination vaccine which contains adsorbed diphtheria and tetanus toxoids and four pertussis antigens (PT,FHA, FIM, PRN) and is indicated for use in infants and children aged 6 weeks through 6 years of age to protect against diseases caused by *Bordetella pertussis*, *Clostridium tetani*, and *Corynebacterium diphtheriae*. Menactra is a diphtheria toxoid conjugated quadrivalent meningococcal vaccine containing serogroup-specific A, C, Y, W-135 polysaccharide antigens and is indicated for the active immunization of individuals 9 months through 55 years of age for the prevention of invasive disease cause by *Neisseria meningitidis* vaccine serogroups.

The data from Study MTA43 were used to support approval of two labeling supplements, 125089/593 for Menactra and 103666/5377 for Daptacel. The applicant is seeking to update both package inserts to include study data in Section 6 (Adverse Reactions), Section 14 (Clinical Studies), and Section 5 (Warning and Precautions) which includes language on the preferred sequence that these two vaccines should be administered.

The US Advisory Committee on Immunization Practices (ACIP) currently recommends the routine administration of a 5th dose of a DTaP containing vaccine, such as Daptacel, in children 4-6 years of age at the time of school entry. Vaccination with a meningococcal quadrivalent conjugate vaccine, such as Menactra, is only recommended for use in children 4 through 6 years of age if they are at high risk for meningococcal disease due to an underlying condition or if they are at increased risk due to travel. The applicant's rationale to conduct the study was to assess the safety and immunogenicity of administration of Menactra when administered with Daptacel at the time of school entry.

Study MTA43 enrolled ~880 healthy US children 4 years through 6 years of age who were randomized to one of three study groups. All subjects received three study vaccines, Menactra, Daptacel, and an inactivated poliovirus vaccine-IPV over two study visits separated by 30 days. Each group was administered 2 study vaccines at Visit 1, and the 3rd study vaccine alone at Visit 2, as follows:

	Group A	Group B	Group C
Visit 1 (Day 0)	Daptacel + IPV	Daptacel + Menactra	IPV + Menactra
Visit 2 (Day 30)	Menactra	IPV	Daptacel

The immune response generated to each vaccine component was assessed 30 days after the respective vaccination in each study group. The primary immunogenicity objectives evaluated immune responses generated to the tetanus, diphtheria, and meningococcal vaccine components when Menactra and Daptacel are co-administered at the same visit, as compared to when each vaccine is administered with IPV. The secondary immunogenicity objectives evaluated the immune response to each pertussis antigen when the two vaccines were co-administered at the same visit, and the response hSBA GMTs response when Menactra was administered one month after Daptacel compared to when Menactra administered one month before Daptacel. The evaluation of safety was descriptive and included 7 day post-vaccination assessment of solicited local and systemic reactions, 30 days post-vaccination assessment of unsolicited AEs, and monitoring of serious adverse events throughout the study duration.

The study objectives evaluating the seroresponse rates to the diphtheria toxin (% participants with antibody concentrations > 1.0 IU/mL) and tetanus toxin (% participants with antibody concentrations > 1.0 IU/mL), in addition to the immune responses to PT, FHA, and PRN pertussis (GMCs) antigenic components of Daptacel when co-administered with Menactra at the same visit were met, but the non-inferiority criteria for the evaluation of FIM pertussis antigen was missed by a small margin. When Menactra was co-administered with Daptacel, the non-inferiority criteria for the evaluation of hSBA GMT responses to meningococcal serogroups A, C, and W were met, but the criteria for serogroup Y was missed by a small margin. The observed responses to meningococcal serogroup Y and to FIM pertussis antigen are unlikely to be of clinical significance based on the review other immunologic parameters, including hSBA GMTs and other pertussis antigen responses, respectively.

The hSBA responses to vaccine antigens in Menactra when it was administered 30 days after Daptacel did not meet the non-inferiority criteria for all four serogroups when compared to the hSBA response to Menactra when it was administered 30 days before Daptacel. These findings are clinically relevant and suggest immune interference in the meningococcal responses when Daptacel is administered before Menactra. Reduced hSBA responses to all four meningococcal serogroups were not observed after co-administration of Menactra+ Daptacel.

The most frequently reported solicited local reaction at either the Menactra or Daptacel injection site across all groups was pain, reported in 52% - 72% of subjects at the Daptacel site, and 52%-61% of subjects at the Menactra site. The most frequently reported solicited systemic reaction across all groups was myalgia across all study groups, reported in 25.8% to 46.2% of subjects following administration of Daptacel alone or with a concomitant vaccine, and in 24.2% to 37.3% subjects following administration of Menactra alone or with a concomitant vaccine.

The reported rates and types of unsolicited AEs are similar to that seen in the general population for children 4-6 years of age. None of the 3 reported SAEs were considered related to study vaccination and there were no death reported during the study.

In summary, the most significant finding from this study was the reduced meningococcal hSBA responses to all vaccine serogroups when Menactra was administered 30 days after Daptacel. These findings are important as only those individuals at increased risk for meningococcal disease are recommended to receive meningococcal quadrivalent vaccination. For example individuals with persistent deficiencies in the common complement pathway have ~10,000 fold increased risk for meningococcal disease.¹ If quadrivalent meningococcal conjugate vaccination with Menactra is required prior to school entry as well, then the timing of vaccination with Menactra and with Daptacel would need to be considered by the health care provider in order to prevent sub-optimal immune response to Menactra vaccination.

Statistically reduced hSBA responses to meningococcal serogroups A, C, W and Y could translate to reduced protection against meningococcal disease when Menactra is administered 30 days after Daptacel, as compared to when these two vaccine are administered in the reverse order. In order to mitigate this risk to children who may receive both vaccines in close proximity to each other at the time of school entry, the reviewer recommends that the Section on Drug Interactions in the Menactra and Daptacel package inserts include language reflecting the immune interference to meningococcal hSBA responses when Menactra is administered 30 days after Daptacel.

¹ CDC. Prevention and Control of Meningococcal Disease, Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR, 2013; 62(RR.02):1-22..

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Subgroup analyses based on sex indicated that immune responses were generally similar between males and females across study groups for the majority of analyses. When comparing the meningococcal hSBA GMT immune response to serogroup Y by sex in the study group receiving Menactra+Daptacel, the hSBA GMT responses in females were numerically higher than what were observed in males (hSBA GMTs: 25.3 [18.2-35.2] in females vs 13.0 [9.3-18.1] in males). In addition, in the study group receiving Menactra alone 30 days after Daptacel, the hSBA GMT responses to Serogroup C in females were also higher than what was observed in males (hSBA GMTs: 4.4 [3.1, 6.3] in females vs 2.6 [2.3, 2.9] in males). Though the confidence intervals for the hSBA GMTs in both sets of comparisons did not overlap, definitive conclusions cannot be made about these numerical differences because the sample size for these analyses were small (~61-77 subjects/group). Subgroup analyses based on race were of limited utility due to the higher proportion of Caucasian enrolled subjects compared to other racial groups.

2. Clinical and Regulatory Background

Menactra is a diphtheria toxoid conjugated quadrivalent meningococcal vaccine containing serogroup-specific A, C, Y, W-135 polysaccharide antigens. The vaccine was first licensed for use in the US in 2005, and is currently indicated for the active immunization of individuals 9 months through 55 years of age for the prevention of invasive disease cause by *Neisseria meningitidis* vaccine serogroups. It is approved for use as a single dose in individuals 2 years to 55 years and for two doses in children 9 months to 23 months.

Meningococcal conjugate (A,C,Y, W) quadrivalent vaccines, such as Menactra, are currently recommended by the ACIP only for use in persons with high risk conditions, including those with persistent deficiencies in the common complement pathway who have a 10,000 fold increased risk for meningococcal disease, and for those at increased risk for disease due to travel to endemic regions.²

With this current application, Sanofi Pasteur has submitted data from Study MTA43, which was designed to evaluate antibody responses to vaccine antigens contained in Menactra and Daptacel when they are co-administration at the same visit or sequentially administration 30 days apart in children prior to school entry (4-6 years of age). The applicant is seeking to update the package inserts to include data from this study in Section 6 (Adverse Reactions) and Section 14 (Clinical Studies), as well as a preference on the order in which the two vaccines should be administered in Section 5 (Warning and Precautions).

2.1 Disease or Health-Related Conditions Studied

Meningococcal Disease^{3,4,5}

Neisseria meningitidis, a gram negative endotoxin producing diplococcal bacteria exclusively infects humans. Transmission occurs by aerosolized droplet or contact with nasopharyngeal secretions from colonized individuals. Common clinical symptoms include fever, neck stiffness, headache, altered mental status, myalgia, and vomiting. The course of meningococcal disease is wide-ranging, from an initial nonspecific febrile illness to a rapidly progressive fulminant

2 High risk conditions: anatomic asplenia (including sickle cell disease), persistent complement component deficiency. Increased risk: persons who travel or reside in countries in which meningococcal disease is hyperendemic or epidemic.

3 Pace, D, Pollard AJ. Meningococcal disease: Clinical presentation and sequelae. *Vaccine*. 2012 May 30;30 Suppl 2:B3-9.

4 CDC. Active Bacterial Core Surveillance (ABCs) Report: *Neisseria meningitidis*, 2012.

5 CDC. Prevention and Control of Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62(RR02);1-22.

infection with multi-organ involvement, sepsis, and possibly death within hours. Overall case fatality rate is 10-15%. In 2012, the ABC's surveillance program by the Centers for Disease Control and Prevention (CDC) estimated a meningococcal disease rate of 0.15/100,000 (480 cases), and death rate of 0.02/100,000 (75 deaths). Incidence of disease is highest in infants <1 year of age (4.3/100,000), adolescents 11-18 yo (0.4/100,000), young adults 19-21 yo (0.5/100,000), and elderly adults >65 years (0.4/100,000). Serogroup B causes ~60% of disease in infants <1yo; serogroups C, Y, and W cause 73% of cases in individuals >11 yo; and serogroup Y causes ~60% of disease in adults >65 yo. Based on CDC surveillance data, serogroup specific meningococcal disease in 2014 for children 2 yo - 4 yo and children/adolescents 5 yo to 17 yo were only reported for Serogroup B and C disease, and not for other serogroups. The rates for Serogroup B disease were 0 & 0.03%, and the rates for Serogroup C disease were 0.14% & 0.01%, for 2yo - 4yo children and 5yo – 17yo children, respectively⁶. The effectiveness of serogroup A, C, Y, and W meningococcal vaccine is measured by serum bactericidal activity using human complement (hSBA), which is considered the relevant serologic marker to infer effectiveness of meningococcal conjugate vaccines.

2.2 Currently Available, Pharmacologically Unrelated Treatments for the Proposed Indications

In the U.S, pharmacologic treatment of meningococcal disease is empiric therapy with a broad-spectrum antibiotic, such as a third generation cephalosporin. After positive identification of the meningococcal infection and susceptibilities have been determined, treatment may be switched as needed. Prophylactic antibiotic use with rifampin or ciprofloxacin is often prescribed in the settings of outbreaks or during epidemics.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are three meningococcal vaccines licensed in the United States for the prevention of invasive meningococcal disease due to serogroup A, C, Y and W. The first to be licensed in the US was Menomune® (MPSV4) in 1981, manufactured by Sanofi Pasteur, it is a meningococcal polysaccharide (ACWY) vaccine. Subsequently Menactra® was the first conjugated quadrivalent (ACWY) meningococcal vaccine to be licensed in 2005. Menveo®, manufactured by Novartis Vaccines and Diagnostics was the 2nd conjugate (to CRM) quadrivalent (ACWY) meningococcal vaccine to be licensed in the US. MenHibrix® manufactured by GlaxoSmithKline (GSK) Biologics was licensed in 2013 for active immunization for the prevention of invasive disease caused by meningococcal serogroups C and Y and haemophilus influenzae type b (Hib). Trumenba®, manufactured by Wyeth Pharmaceuticals, Inc was licensed in 2014 for active immunization to prevent invasive disease caused by meningococcal serogroup B, and Bexsero® manufactured by Novartis Vaccines and Diagnostics was licensed in 2015 for active immunization to prevent invasive disease caused by meningococcal serogroup B.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Menactra is currently approved for use in the U.S. for individuals 9 months to 55 years of age for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W-135. Menactra is also licensed for use in over 45 countries (mostly for individuals 2 years through 55 years of age).

⁶ CDC's Active Bacterial Core Surveillance (ABCs) Report for *Neisseria meningitidis* for 2014 in the U.S., children 2yo to 4 yo and 5yo to 17yo: calculated rates per 100,000 population

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

- Efficacy supplement 125089/593 (Menactra): official date for CBER receipt was 17 November 2015, and was determined to be acceptable for filing on 14 January 2016.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission of efficacy sBLA 125089/593 was adequately organized and integrated to accommodate the conduct of a complete review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Study MTA43 was conducted in accordance with Good Clinical Practice and International Committee on Harmonization guidelines. The informed consent form contained all the essential element of informed consent as stated in 21CFR 50.25. The final protocol used for the trial was version 3.0, dated 21 August 2006. Institutional Review Board approval was provided by



The Bioresearch Monitoring Program at CBER conducted study site inspections of three clinical investigators at the following sites: Nationwide Children’s Hospital in Columbus Ohio (sites 19, 20, 21, and 23), University Health Care Center in Syracuse New York (sites 46 and 47), and Arkansas Pediatric Clinic in Little Rock, Arkansas (site 51). During these inspections GCP violations were not identified and the data audit portion of the inspections verified the validity of safety and immunogenicity data collected at the respective study sites.

3.3 Financial Disclosures

Covered clinical study (name and/or number): MTA43		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/> <input type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>28</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

This supplemental BLA did not include new CMC information.

4.2 Assay Validation

Validation reports and other additional relevant data were submitted to the BLA and cross-referenced INDs, and were sufficient to support the adequate performance of the assays. The samples from Study MTA43 were analyzed in 2006 and 2007. No aberrant or unusual data were noted in the clinical study reports that would indicate performance issues with the assays. The assay reviewer recommends that the package insert include a recommendation that Menactra not be administered one month after Daptacel and defers final wording in each package insert to the review committee..

4.3 Nonclinical Pharmacology/Toxicology

This supplemental BLA did not include new pharmacology/toxicology information.

4.4 Clinical Pharmacology

This supplemental BLA did not include new clinical pharmacology information.

4.4.1 Mechanism of Action

The use of immunogenicity data to support the effectiveness of meningococcal vaccines has been discussed at two Vaccines and Related Biological Products Advisory Committee (VRBPAC) meetings. In September 1999, the committee concurred that a serological marker could be used to infer effectiveness of new meningococcal conjugate vaccines in children 2 years of age and older. In a second meeting on April 6-7, 2011, the committee concluded that serum bactericidal activity with human complement (hSBA) could be used as an immune measure to infer effectiveness of meningococcal conjugate vaccines in children younger than 2 years of age. In addition, the committee concluded that seroresponse achieved at or above a pre-defined hSBA titer could be considered evidence that the meningococcal-specific functional antibodies measured post-vaccination were protective against systemic infection. From a regulatory perspective, serum bactericidal activity measured using extrinsic human complement (hSBA) is viewed as a clinically meaningful endpoint, protection against invasive disease caused by meningococcal strains similar to the test strain used in the assay

Both of the vaccines evaluated in this submission (Menactra and Daptacel) contain a diphtheria toxoid component.⁷ Published clinical data⁸ suggests that the immune response to vaccine antigens may be altered by the concomitant administration of certain conjugate vaccines when they contain the same carrier protein. The mechanism of action that has been proposed for this immune interference is associated with increased carrier protein specific T helper cell activity. The immunity that develops to the common carrier protein may then suppress the immune response to a polysaccharide antigen conjugated to the same carrier.

4.4.2 Human Pharmacodynamics

Not applicable.

4.4.3 Human Pharmacokinetics

Not applicable.

4.5 Statistical

The statistical reviewer verified the results of the primary and secondary objectives. Further comment on the overall impression of study findings was deferred to the clinical reviewer, including the appropriateness of the proposed revisions to the Menactra and Daptacel package inserts.

4.6 Pharmacovigilance

Not applicable.

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

5.1 Review Strategy

The sBLA was submitted electronically, and included one study, MTA43. The clinical, labeling, financial disclosure information sections of the application were reviewed with a detailed analysis of the study report, pertinent line listings, case report forms, and datasets. As noted in Section

⁷ The carrier protein conjugated to each meningococcal capsular polysaccharide in Menactra is diphtheria toxoid

⁸ Knuf, et al. Comparative effects of carrier proteins on vaccine-induced immune response. Vaccine 29 (2011)4881-4890..

3.1, the applicant submitted one clinical study, MTA43 to support revisions to the package insert for Menactra and Daptacel. Though the clinical data for both efficacy supplements were reviewed in parallel, the regulatory/background, risk/benefit, and labeling discussions were reviewed in the context of each product.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following modules of the sBLA were reviewed:

125089 (Menactra):

- Am.593.0 (10/27/2015)
 - Module 1:
 - Financial Certification-FDA Form 3454
 - Debarment Certification
 - Financial Certification
 - Draft Labeling
 - Module 2:
 - Clinical Overview
 - Summary of Clinical Safety
 - Summary of Clinical Efficacy
 - Synopses of Individual Studies
 - Module 5:
 - Final CSR: MTA43
 - Protocol: MTA43
 - Sample Case Report Form
 - Appendix 3: List of Independent Ethics Committees & Institutional Review Boards
 - Appendix 4: Sample Subject Information Sheets and Informed Consent Forms
 - Appendix 5: List and Description of Investigators and Other Important Trial Participants
 - Appendix 6: Signatures of Principal and Coordinating Investigators
 - Appendix 7: List of Subjects Receiving Investigational Products
 - Appendix 19: Narratives of Deaths, Serious Adverse Events, and Other Significant Adverse Events
 - JMP analysis dataset: adverse events
- Am 593.1 (11/20/2015)
 - Module 1
 - Form FDA 3397-User Fee Cover Sheet
- Am 593.6 (4/2/2016)
 - Module 5
 - Response to Information Request pertaining to Subgroup Analyses
- Am 593.7 (5/26/2016)
 - Module 5
 - Response to Information Request pertaining to comparison of hSBA GMTs in Group A and Group B
- Am 593.8 (8/10/2016)
 - Module 5
 - Response to Information Request pertaining to Group C hSBA GMTs compared to historical data
- Am 593. (8/26/2016)
 - Module 1
 - Draft Labeling Text

5.3 Table of Studies/Clinical Trials

Study MTA43 was submitted as part of this efficacy labeling supplement.

5.4 Consultations

During the review of this sBLA, no external input was sought.

5.4.1 Advisory Committee Meeting (if applicable)

An Advisory Committee meeting was not convened during the review of this sBLA.

5.5 Literature Reviewed

Literature reviewed as part of the clinical review of this efficacy supplement has been cited throughout this review document.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: MTA43

Immunogenicity and Safety of Meningococcal (Serogroups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra®) in Children Aged 4 to 6 Years in the US when Administered Concomitantly with a Fifth Dose Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Daptacel®)

6.1.1 Objectives (Primary, Secondary, etc)

The following study objectives were pre-specified by the applicant as either primary, secondary, and observational. The primary and secondary immunogenicity objectives included hypotheses testing, while the secondary safety and observational objectives were considered descriptive.

Primary Immunogenicity Objective:

To determine whether the concomitant administration of 2 vaccines, Daptacel and Menactra, induces antibody responses to diphtheria and tetanus and to meningococcal serogroups A, C, Y, and W-135 that are non-inferior to those observed when each vaccine is administered with IPV (IPOL®): vaccine to children aged 4 to < 7 years old.

Secondary Immunogenicity Objectives:

1. To determine whether the concomitant administration of 2 vaccines, Daptacel and Menactra vaccine, induces anti-pertussis (PT, FHA, FIM, and PRN) responses non-inferior to those measured when Daptacel is administered with IPV vaccine.
2. To determine whether sequential administration of Menactra vaccine 30 days after Daptacel with IPOL vaccines induces antibody responses to serogroups A, C, Y and W that are non-inferior to those measured when Menactra vaccine is administered with IPV vaccine.

Secondary Safety Objectives:

To compare the rate of fever ($\geq 100.4^{\circ}\text{F}$ [$\geq 38^{\circ}\text{C}$]) when Daptacel and Menactra vaccines are administered concomitantly to the rate of fever when Daptacel is administered with IPV vaccine.

Observational Immunogenicity Objectives:

1. To describe the antibody titers against diphtheria, tetanus, and each of the pertussis antigens (PT, FHA, FIM, and PRN) 30 days after DAPTACEL vaccination in Study Groups A, B, and C (see Table 1).
2. To describe the antibody titers against meningococcal serogroups (A, C, Y, and W) 30 days after Menactra vaccine administration in Groups A, B, and C.
3. To describe the antibody titers against poliovirus Types 1, 2, and 3 thirty days after IPOL vaccine administration in Groups A, B, and C

Observational Safety Objectives:

To describe the safety profile (immediate unsolicited adverse events (AEs) within 30 minutes of each study vaccination, solicited injection site and systemic reactions within 7 days of each study vaccination, unsolicited injection site reactions and unsolicited systemic AEs within 30 days of each study vaccination, and SAEs for 30 days after the last study vaccinations.

6.1.2 Design Overview

Study MTA43 was a Phase 2, randomized, modified double-blind 3-arm, parallel-group, comparative, multi-center study in healthy children 4 years through 6 years of age in the US evaluating the concomitant administration of Menactra and DAPTACEL. Study participants were administered three vaccines during the study, including Menactra, DAPTACEL, and an inactivated poliovirus vaccine (IPV). Three study groups were included in the study design and each group was administered 2 of the study vaccines concomitantly at Visit 1, and the 3rd study vaccine alone 30 days later at Visit 2. Subjects were randomly assigned to one of the 3 groups using the Interactive Voice Response (IVR) system which generated a random list of subject numbers and randomized treatment assignments for each participating site using a block randomization approach. The study groups and assigned treatments were as follows:

Table 1: MTA43 Study Groups

	Group A N:353	Group B N: 353	Group C N=175
Visit 1 (Day 0)	Daptacel + IPV	Daptacel + Menactra	IPV + Menactra
Visit 2 (Day 30)	Menactra	IPV	Daptacel

Source: Adapted from sBLA 125089/593, Clinical Study Report MTA43, Table 3.1 on p.58.
N: total number of subjects randomized to each group (Source: Table 4.3, page 99)

The study staff administering the study vaccine were not blinded,⁹ but the study staff monitoring safety following the administration of study vaccines were blinded to treatment assignments, therefore the study was considered modified double-blind. Subjects were followed for safety for the duration of the study (Day 60) and blood samples were collected at Visit 2 (Day 30) and Visit 3 (Day 60) for immunogenicity evaluations.

The applicant’s assessments of immunogenicity objectives evaluating meningococcal antibody responses were done on a subset of subjects from Group A and B when compared to Group C

⁹ The physical appearance of the study vaccines are different. A designated study personnel who will be unblinded to treatment assignment will vaccinate the subject with the assigned study vaccine(s) in the left or right arm, as specified by the protocol for each study vaccine. This study personnel will not be responsible for any other study related assignments, but is responsible for recording the administration of each vaccine in the Investigational Product Accountability Record Form.

subjects. A programmer (from the applicant) who was not otherwise involved in trial conduct had access to the group randomization lists generated by the IVR system. The programmer randomly chose 177 subjects each from Groups A and B, and these subjects were tested for hSBA and were compared to samples from all subjects in Group C.

Reviewer Comment:

- *The study design and blinding/randomization schemes were adequate to evaluate the protocol specified study objectives.*
- *Prior to school entry, the following vaccines are recommended for use in children 4-6 years of age by the ACIP:*
 - *5th dose of a DTaP-containing vaccine and a 4th dose of IPV-containing vaccine*
 - *If the 4th dose of a DTaP containing vaccine is administered at 4 years of age or after, then the 5th dose is not necessary*
 - *If the 3rd dose of IPV is administered at 4 years of age or older, then the 4th dose is not required; if all 4 IPV doses are administered before 4 years of age, then an additional dose should be administered 4-6 years of age.*
 - *2nd doses Varicella and Measles, Mumps and Rubella (MMR) vaccines*
 - *The 2nd dose of MMR vaccine may be administered before 4 years of age, if the at least 4 weeks have elapsed since the 1st dose*
 - *The 2nd dose of Varicella vaccine may be administered before 4 years of age, if at least 3 months have elapsed since the 1st dose*
 - *The sponsor's rationale for evaluating DTaP and IPV vaccines in this study was that these vaccines are commonly administered to children 4-6 years of age at one office visit. As described above a dose of DTaP containing vaccine and a dose of IPV containing vaccine are required at 4-6 years of age, while doses of MMR and Varicella do not have to be administered at 4-6 years of age if a child had received two doses of the respective vaccines prior to this age.*
- *Menactra is only recommended for use in children 4-6 years of age by the ACIP if they are at high risk to developing invasive meningococcal disease due to an underlying condition, or have an increased risk due to travel to endemic areas. As described in the next section, the study population evaluated was healthy children, and not those who were immunocompromised nor those who were necessarily at an increased risk for meningococcal disease.*
- *IPV was administered to all subjects (as recommended by ACIP). Also, administration of IPV maintained the study blind (i.e., at both vaccination visits, each study group received the same # of injections) and it was not anticipated to interfere with the immune responses to Menactra and Daptacel.*
- *As shown in the table above, the study also evaluated the sequential administration of Daptacel(+IPV) followed by Menactra, and sequential administration of Menactra(+IPV) followed by Daptacel.*
- *The study did not evaluate the immune response to Menactra administered to children younger than 4 years of age following Daptacel. It also did not evaluate the immune response to Menactra administered to persons <11 years of age following other diphtheria toxoid-containing vaccines.*

6.1.3 Population

Subjects were eligible to participate if they were healthy children between the ages of 4 years old and <7 years old whose parents or legal guardians provided informed consent and had documented prior vaccination with a 4th dose of DTaP vaccine series. Subjects were excluded

from participation if they had serious chronic disease (e.g., cardiac, renal, neurologic, metabolic, rheumatologic, psychiatric, hematologic), known or suspected impairment of immunologic function, acute medical illness with or without fever within the last 72 hours or an oral temperature $\geq 100.4^{\circ}\text{F}$ ($\geq 38^{\circ}\text{C}$) at the time of enrollment, history of documented invasive meningococcal disease or previous meningococcal vaccination, received a 5th dose of any tetanus/diphtheria/pertussis-containing vaccine or a 4th dose of IPV prior to the study, received immunoglobulin or other blood products within the last 3 months; or received injected or oral corticosteroids, or other immunomodulator therapy within 6 weeks of the study vaccines (individuals on a tapering dose schedule of oral steroids lasting < 7 days and individuals [e.g., asthmatics] on a short schedule of oral steroids lasting 3 to 4 days may be included in the trial as long as they have not received more than 1 course within the last 2 weeks prior to enrollment), received oral or injected antibiotic therapy within the 72 hours prior to any blood draw, suspected or known hypersensitivity to any of the study vaccines, components, history of serious or life-threatening reaction to the study vaccines or a vaccine containing the same substances, thrombocytopenia or a bleeding disorder contraindicating IM vaccination, unavailable for the entire study period, or unable to attend the scheduled visits or to comply with the study procedures, enrolled in another clinical trial, diagnosed with any condition, which, in the opinion of the investigator, would pose a health risk to the subject or interfere with the evaluation of the vaccine, received any other vaccine 30 days prior to the first study vaccination or scheduled to receive any vaccination during the course of the study, or personal or family history of Guillain-Barré Syndrome.

6.1.4 Study Treatments or Agents Mandated by the Protocol and Directions for Use

The following study vaccines were administered during the study:

- Menactra®: Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA):
 - Each 0.5mL dose contains:
 - 4ug Serogroup A meningococcal capsular polysaccharide
 - 4ug Serogroup C meningococcal capsular polysaccharide
 - 4ug Serogroup Y meningococcal capsular polysaccharide
 - 4ug Serogroup W-135 meningococcal capsular polysaccharide
 - ~48ug Diphtheria toxoid protein
 - (b) (4) Sodium phosphate
 - (b) (4) Sodium chloride
 - Up to 0.5mL Water for injection
 - Lots number: U2139AA
 - Administration: Intramuscular, deltoid muscle
- DAPTACEL® Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Daptacel): (Sanofi Pasteur Ltd., Toronto, ON, Canada):
 - Each 0.5 mL dose contains
 - Active Ingredients:
 - 10ug Pertussis Toxoid (PT)
 - 5ug Filamentous Hemagglutinin (FHA)
 - 3ug Pertactin (PRN)
 - 5ug Fimbriae Types 2 and 3 (FIM)
 - 15 Lf Diphtheria Toxoid
 - 5 Lf Tetanus Toxoid
 - Other ingredients:
 - 0.33 mg Aluminum phosphate (as the adjuvant)

- 3.3 mg 2-Phenoxyethanol
 - Lots number: C2377A
 - Administration: Intramuscular, deltoid muscle
- IPOL®: Poliovirus Vaccine Inactivated (IPV) (Sanofi Pasteur SA, Lyon, France):
 - Each dose contains
 - Active Ingredients:
 - 40 D antigen units Poliovirus Type 1
 - 8 D antigen units Poliovirus Type 2
 - 32 D antigen units Poliovirus Type 3
 - Other ingredients:
 - 0.5% 2-phenoxyethanol
 - 0.02% Formaldehyde
 - Lots numbers: Z0420
 - Administration: Intramuscular, deltoid muscle

Two vaccines were administered concomitantly at the same study visit but in different arms, while the 3rd vaccine was administered 30 days later. The designated arms for each vaccine's intramuscular injection are as follows by study visit:

- Visit 1 (Day 0):
 - Group A: Daptacel-left arm; IPV-right arm
 - Group B: DAPTAEL-left arm; Menactra-right arm
 - Group C: IPV-left arm; Menactra-right arm
- Visit 2 (Day 30):
 - Group A: Menactra-right arm
 - Group B: IPV-left arm
 - Group C: Daptacel-right arm

6.1.6 Sites and Centers

There were 45 US study sites included in this study, of which 5 centers did not enroll any subject.

6.1.7 Surveillance/Monitoring

Schedule of Events: The following list includes the scheduled visits and telephone contacts with the subjects, including trial activity associated with each visit/contact:

Visit 1-Day 0: Informed Consent; review of eligibility criteria, medical/vaccination history; physical examination, concomitant therapy, review of contraindications (review of antibiotics prior to study vaccination/blood draw); Vaccinations as per study group assignment; 30 minutes observation (unsolicited reactions), Diary Card#1 provided, Memory Aid #1 provided.

Telephone Contact 1-Day 8 (window: Visit 1+8days): Parents/legal guardian instructed to mail Diary Card to trial center; review of concomitant therapy; review solicited reactions through 7 days post-vaccination, review unsolicited adverse events.

Visit 2- Day 30 (window:+7 days): Memory Aid #1 collected, contraindications review; concomitant therapy, blood sample collection (5mL); Vaccinations as per group assignment; 30 minutes observation (unsolicited reactions); Diary Card#2 provided, Memory Aid #2 provided.

Telephone Contact 2-Day 38 (window: Visit 2+8days): Parents/legal guardian instructed to mail Diary Card#2 to trial center; review of concomitant therapy; review solicited reactions through 7 days post-vaccination, review unsolicited adverse events.

Visit 3-Day 60 (window: +7 days): review concomitant therapy, review unsolicited adverse events, Memory Aid #2 collected, blood sample collection (5mL), complete Termination Record/Final Visit section in the CRF.

The safety surveillance/monitoring included the following:

- Immediate post-vaccination: subjects were observed for the 30 minute post-vaccination. Any AE that occurs in this 30 minute period was recorded on the unsolicited systemic AE page of the Case Report Form as occurring on Day 0, and 'immediate yes' box was checked. Any SAE observed in this time period was reported as any other SAE.
- Solicited Local and Systemic Reactions: after vaccination subjects were provided with a safety diary card, a digital thermometer¹⁰, and a flexible ruler and instructions on how to use all of these. The subject recorded solicited reactions from Days 0 to Day 7 after vaccination which included daily temperature measurements. Each solicited reaction was measured daily, intensity was graded, and the action taken, if any was reported for each event.
 - Solicited injection site reactions included redness, pain, & swelling
 - Solicited systemic reactions included pyrexia¹¹, headache, malaise, myalgia
- Unsolicited Adverse Events from Day 0 to 30 days post-vaccination: Subjects recorded any medical event that may occur from Day 0 to Day 30 on the diary card. For each adverse event, the following information will be collected: start/stop dates; intensity of the event; action taken for each AE
- Serious Adverse Events: All SAEs were collected and assessed throughout the trial from the time of study inclusion until 30 days after the last study visit.

Immunogenicity Evaluations:

- Blood sample collections (each 5mL) were on Day 30 (+7days) after the Visit 1 vaccinations and on Day 60 (+7 days).
- Antibody titers/concentration against antigens contained in the Menactra, Daptacel, and IPV vaccine were measured as follows by the applicant:
 - Antibodies to meningococcal serogroups A,C,Y and W by serum bactericidal antibody assay using human complement (hSBA).
 - (b) (4)
 - Antibodies to diphtheria toxin
 - Anti-Diphtheria antibodies were measured by a seroneutralization assay. The LLOQ is (b) (4)

¹⁰ Route of measurement: As per protocol the temperature measurement route was specified to be done by oral route, and that tympanic or axillary thermometry should not be used.

¹¹ Intensity scale for fever: Mild $\geq 38.0C$ to $\leq 38.5C$; Moderate $\geq 38.5C$ to $\leq 39.5C$; Severe $\geq 39.5C$

- Antibodies to tetanus toxoid
 - Anti-Tetanus antibodies were measured by ELISA. The LLOQ for the anti-Tetanus ELISA is (b) (4)
- Antibody titers against pertussis antigens (PT, FHA, FIM, and PRN)
 - Anti-PT, FHA, PRN, and FIM (2&3) antibodies were measured by ELISA. The LLOQs for the anti-PT, PRN, and FIM ELISAs is (b) (4) and the LLOQ for the anti-FHA ELISA is (b) (4)
- Antibody titers against poliovirus Types 1, 2, and 3
 - Antibodies to poliovirus Types 1, 2, and 3 were measured by serum neutralization assay. The measures of interest were the percentage of subjects with neutralizing antibody titers $\geq 1:8$ serum dilutions and titers were expressed as the reciprocal dilution.

6.1.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints:

- Percentage of subjects with antibody titers against diphtheria (measured by neutralization assay) and tetanus (measured by ELISA) ≥ 1.0 IU/mL 30 days after Daptacel vaccination in Group A (Visit 1: Daptacel + IPV) and Group B (Visit 1: Daptacel + Menactra)
 - *Study Success Criteria:* If the upper limit of the 2-sided 95% CI of ($p_A - p_B$) < 0.05 , non-inferiority was concluded.

Reviewer Comment: Serum diphtheria antitoxin level of ≥ 1.0 IU/mL measured by neutralization assay have been associated with long-term protection against diphtheria.¹² A tetanus antitoxin concentration ≥ 0.1 IU/ml measured by ELISA has been considered protective in clinical trials evaluating DTaP containing vaccines, including Daptacel.¹³

- Geometric mean antibody titers (GMTs) against meningococcal serogroups A, C, Y, and W-135 (measured by hSBA) 30 days after Menactra vaccination in Group C (Visit 1: Menactra + IPV) and Group B subset (Visit 1: Menactra + Daptacel)
 - *Study Success Criteria:* If the upper limit of the 2-sided 95% CI of the GMT ratio (GMT_C/GMT_B) computed separately for each of the serogroups was < 2 , non-inferiority was concluded.

Reviewer Comment: The study success criteria for the evaluation of meningococcal hSBA responses to each vaccine serotype was based on the upper limit of the 95%CI of the ratio of hSBA GMTs for Group C/Group B < 2 , and not a pre-specified threshold titer

Secondary Immunogenicity Endpoints:

- Geometric mean antibody concentrations (GMCs) against the pertussis antigens (PT, FHA, FIM, and PRN) (measured by ELISA) 30 days after Daptacel vaccination in Group A (Visit 1: Daptacel + IPV) and Group B (Visit 1: Daptacel + Menactra)
 - *Study Success Criteria:* If the upper limit of the 2-sided 95% CI of the adjusted GMC ratio (GMC_A/GMC_B) for each of the antigens was < 1.5 , non-inferiority was concluded.

¹² Wharton M, et al. Diphtheria Toxoid. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th ed. Philadelphia, PA: W. B. Saunders 2004 p. 211-28

¹³ Daptacel package insert (website accessed August 23, 2016):

<http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM103037.pdf>

Reviewer Comment: *The study success criteria for the evaluation of the immune response to pertussis antigens was based on the upper limit of the 95%CI of the ratio of GMCs for Group A/Group B <1.5, which is consistent with regulatory precedence with regard to the evaluation of the immune responses to pertussis antigens in DTaP containing vaccines.*

- GMTs against meningococcal serogroups A, C, Y, and W (measured by hSBA) 30 days after Menactra vaccine administration in Group C (Visit 1: Menactra + IPV) and Group A subset (Visit 2: Menactra alone).
 - *Study Success Criteria:* If the upper limit of the 2-sided 95% CI of the GMT ratio (GMTC/GMTA) computed separately for each of the serogroups was < 2, non-inferiority was concluded.

Secondary Safety Endpoints:

The occurrence, time to onset, number of days of occurrence, and intensity of fever ($\geq 38^{\circ}\text{C}$) between Day 0 and Day 7 after each injection. No hypotheses testing and analyses were descriptive.

Observational Immunogenicity Endpoints: No hypotheses testing and analyses were descriptive.

- Percentage of subjects with antibody titers against diphtheria (measured by seroneutralization assay) and tetanus (measured by ELLISA) ≥ 0.1 IU/mL and ≥ 1.0 IU/mL 30 days after Daptacel vaccination in Groups A, B, and C
- GMCs against pertussis antigens PT, FHA, FIM, and PRN (measured by ELISA) 30 days after Daptacel vaccination in Groups A, B, and C as.
- Antibody responses against meningococcal serogroups A, C, Y, and W (measured by hSBA) 30 days after Menactra vaccine administration in Group A subset, Group B subset, and Group C
- Antibody responses against poliovirus Types 1, 2, and 3 (measured by serum neutralization assay) 30 days after IPV administration in Groups A, B, and C

Observational Safety Endpoints: No hypotheses testing and analyses were descriptive.

- Solicited local reactions Day 0 to Day 7 (injection site pain, erythema, arm swelling)¹⁴
- Solicited systemic reactions Day 0 to Day 7 (fever, headache, malaise, myalgia)¹⁵
- Unsolicited AEs by MedDRA¹⁶ preferred terms within 30 minutes of vaccination, and from Day 0 to Day 30 after each vaccination, with relationship to vaccination
- SAEs throughout trial duration

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculations:

With 310 evaluable subjects/per study group for Groups A and B, and 160 evaluable subjects in Group C and an anticipated 10% non-evaluable subjects during the study, a total of 867 subjects (345/per study group for Groups A and B, and 177 in Group C) was needed to be enrolled in order to provide 780 evaluable subjects in the study. A programmer from the applicant who was not involved in the trial had access to the group randomization list, generated by the IVR system,

¹⁴ Grading scale: Pain: mild-easily tolerated, moderate-sufficiently discomforting to interfere with normal behavior or activities, severe-incapacitating unable to perform usual activities; Erythema & Swelling: mild- 1.0in, moderate- ≥ 1.0 to <2in, severe- ≥ 2 in
¹⁵ Pyrexia: mild ≥ 38.0 C to ≤ 38.5 C, moderate >38.5 C to ≤ 39.5 C, Severe- >39.5 C; Headache/Malaise/Myalgia: mild-noticeable but does not interfere with daily activities, moderate- interferes with daily activities, severe- prevents daily activities

¹⁶ Medical Dictionary for Regulatory Activities (MedDRA)

and using a SAS program generated a randomly chosen subset of 177 subjects each from Group A and B. Following the 1st vaccinations from Group B and the 2nd vaccination from Group A, the blood sample from these subjects were tested for hSBA and compared to samples from Group C.

Handling of Missing Data:

For computational purposes, any pre-vaccination or post-vaccination titer reported as < LOD (limit of detection [LOD]) was converted to a value of 0.5 LOD to calculate the GMTs. Missing data was not replaced. All subjects in the appropriate population with immunogenicity data were included in the immunogenicity analyses. No test for outliers was performed.

Significant Changes in the Conduct of the Study or Planned Analyses

The original approved version of the protocol was Version 2.0, dated 24 May 2006. The major changes with each new version are as follows:

- Version 3.0 (21 Aug 2006):
 - Added subsets to Group A and B for assessment of antibody responses using a serum bactericidal assay with human complement (rather than rabbit complement), and how clarified how these subsets would be generated and analyzed for the statistical analyses
 - Clarified information to be collected at Telephone Contact 1 and 2 and Visit 2
 - Clarified that missing data would not be replaced; blinding and code breaking procedures; procedure to follow for concomitant vaccinations, that applicant would provide pipettes for making aliquots of serum
 - Revised sample site numbers
 - Clarified that study coordinators must not change or add any data on the Diary Cards
 - Updated investigator and study site information.

Reviewer Comment: *CBER's review of Protocol MTA43 submitted under IND 7162, Amendment 217 had recommended that the assessment of meningococcal antibody responses using serum bactericidal assay be conducted using human complement, and not rabbit complement.*

6.1.10 Study Population and Disposition

A total of 881 subjects were enrolled in Study MTA43 (first visit first subject: 16 October 2006 and last visit last subject on 14 September 2007).

6.1.10.1 Populations Enrolled/Analyzed

Analysis Sets:

- Safety Analysis Set (SAS): all subjects who received at least 1 dose of study or control vaccine and had any available safety data. All subjects were analyzed according to the vaccine they actually received. Any safety data elements that were not documented for a given subject were reported as missing.
- Intent-to-Treat (ITT): all subjects included in the trial who received at least one injection of Menactra or Daptacel and had at least 1 valid blood sample test result. For immunogenicity results for meningococcal A,C,W, and Y serogroups, subjects were from either Group B or C to be tested for hSBA. Subjects who received a vaccine different from that assigned were analyzed according to the vaccine received. Subjects who received mixed regimens were removed from the analyses and their serology results were listed separately. The ITT population was used for the secondary analyses of the immunogenicity endpoints.

- Per-Protocol Analysis Set (PP): all subjects who satisfied the inclusion/exclusion criteria, received the assigned injections on Day 0 (Visit 1) and Day 30 (Visit 2), had blood drawn on Day 30 and Day 60 and had blood drawn within the specified time windows and had any valid serology results, did not have any protocol violations, or had 1 or more protocol violations that did not affect the subject’s immunogenicity response, and for any immunogenicity results for meningococcal serogroups A,C,W, and Y, the subject was randomized to study group C or a subset of Group B . The PP population was used for the primary analyses for the immunogenicity endpoints.

6.1.10.1.1 Demographics

Table 2: MTA43 Subject Demographics, By Group (%)

	Group A* N= 353	Group B* N=353	Group C* N=175
Subject who received any study vaccine n (%)	352 (100.0)	353 (100.0)	174 (100.0)
Sex:			
-% Male	180 (51.1)	171 (48.4)	102 (58.6)
-% Female	172 (48.9)	182 (51.6)	72 (41.4)
Age			
-Mean	4.5 (0.48)	4.5 (0.51)	4.5 (0.49)
-Median	4.3	4.3	4.4
-Range	4, 6	4, 6	4, 6
Racial origin:			
-Asian	3 (0.9)	0 (0.0)	1 (0.6)
-Black	44 (12.5)	41 (11.6)	23 (13.2)
-Caucasian	280 (79.5)	287 (81.3)	137 (78.7)
-Hispanic	4 (1.1)	5 (1.4)	2 (1.1)
-American Indian/Alaska Native	0 (0.0)	2 (0.6)	1 (0.6)
-Native Hawaiian/ or other Pacific Islander	1 (0.3)	1 (0.3)	1 (0.6)
-Other	20 (5.7)	17 (4.8)	9 (5.2)

Source: Adapted from sBLA 125089/593, Clinical Study Report MTA43, Table 4.3 on p. 99. * Subjects were included in the study group they were randomized to. N: total number of subjects in the analysis population per group. Group A: Visit 1-Daptacel + IPV, Visit 2- Menactra . Group B: Visit 1- Daptacel + Menactra, Visit 2- IPV. Group C: Visit 1- IPV+Menactra, Visit 2- Daptacel. The number of subjects in the analyses population who received any study vaccine during the study was used as the denominator for the percentages per group. Two subjects were randomized to Group A and C, but did not receive any study vaccines.

Reviewer Comment:

The age range of all study participants was from 4 to 6 years of age, and the mean age for enrolled subjects was 4.5 years. The proportion of males to females was similar in Group A and B (~48-51% males versus ~49-52% females), but for Group C, there were ~58% males compared to ~41% females, but the sample size for Group C was smaller than that of both other groups. There majority of subjects were Caucasian (~78%-81%) followed by Black (11.6%-13.2%). Across all groups, the proportion of Hispanic subjects was low, ~1%, which is not representative of recent US census reports¹⁷ for this racial group (currently 17.6%). Overall the demographic characteristics across groups were similar.

17 Based on data from United Census Bureau official website from <http://www.census.gov/newsroom/facts-for-features/2016/cb16-ff16.html> (as of Aug 20, 2016)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

This section is not applicable to the enrolled study population.

6.1.10.1.3 Subject Disposition

There were 881 subjects enrolled in the study, which included 353 subjects in Group A, 353 subjects in Group B, and 175 subjects in Group C. The following table provides the number of subjects enrolled, vaccinated, and included in the analyses populations, in addition to the number of subjects discontinued for cited reasons.

Table 3: Study MTA43 Disposition of Subjects-Enrolled Population

Population	Group A* (N= 353) n(%)	Group B* (N=353) n(%)	Group C* (N=175) n(%)
Received any study vaccine	341 (100)	344 (100)	169 (100)
Safety Population	341 (100)	344 (100)	169 (100)
Completed Study	321 (94.1%)	315 (91.6)	165 (97.6)
Discontinued (due to)	20 (5.9)	29 (8.4)	4 (2.4)
-SAE	0	2 (0.6)	0
-AE	0	1 (0.3)	0
-Protocol Deviation	7 (2.1)	9 (2.6)	1 (0.6)
-Lost to follow-up	4 (1.2)	7 (2.0)	1 (0.6)
-Voluntary Withdrawal (not due to AE)	15 (4.4)	20 (5.8)	5 (3.0)
ITT Population	326 (95.6)	324 (94.2)	164 (97.0)
-excluded from PPP	76 (22.3)	86 (25.0)	43 (25.4)
PP Population (PPP)	250 (73.3)	238 (69.2)	121 (71.6)

Source: Adapted from sBLA 125089/593, Clinical Study Report MTA43, Table 4.1 on p. 96. N: total number of subjects who received at least one dose of study vaccine and for whom data are available, each subjects is analyzed in the study group corresponding to the vaccines received. Percentages are based on N. n: number of subjects. % percentages of subjects. PPP: Per Protocol Population. *Group A: Visit 1-Daptacel + IPV, Visit 2- Menactra . Group B: Visit 1- Daptacel + Menactra, Visit 2- IPV. Group C: Visit 1- IPV+Menactra, Visit 2- Daptacel

Safety Population: 854 subjects included

27 enrolled subjects were excluded for the following reasons:

- 2 subjects did not receive any study vaccine (1 subject each in Groups A and C)
- 2 subject received mixed vaccine (1 subject each from Groups A and B)
- 23 subjects- blinding was compromised (Group A: 10 subjects, Group B: 8 subjects; Group C: 5 subjects)

ITT Population: 814 subjects included

40 enrolled subjects were excluded for the following reasons

- 23 subjects did not give blood (Group A: 2 subjects; Group B: 20 subjects: Group C: 1 subject)
- 17 subjects did not receive the Menactra and Daptacel vaccinations (13 subjects in Group A and 4 subjects in Group C)

PP Population: 609 subjects included

272 enrolled subjects excluded for the following protocol violations:

- 235 subjects did not have one or both blood samples collected in the specified time window (Group A: 84 subjects (23.9%), Group B: 103 subjects (29.2%); Group C: 48 subjects (27.6%)

- 23 subjects had blinding issues¹⁸ (Group A: 10 subjects; Group B: 8 subjects, Group C: 5 subjects)
- 7 subjects met at least one exclusion criteria (Group A: 7 subjects; Group B: 3 subjects, Group C: 2 subjects)
- Received antibiotic within 3 days of blood draw (Group A: 7 subjects; Group B: 5 subjects, Group C: 1 subject)

There were two subjects who were excluded from both the safety and immunogenicity analyses because they received vaccines that cannot be classified under any of the study groups (Subject 033-00013, and Subject 043-0005).

Reviewer Comment: *There were 53 subjects who withdrew from the study prior to its completion. The most frequent reason was 'voluntary withdrawal not associated with an adverse event,' which was distributed equally across groups (9 subjects in Group A: 2.6%; 9 subjects in Group B: 2.9%; and 2 subjects in Group C: 1.2%. This next most frequent reason for study withdrawal was protocol violations (17 subjects). Two subjects in Group B withdrew due to Serious Adverse Events due to rhabdomyosarcoma and pancytopenia; and one subject withdrew from Group B due to unsolicited AE due to upper respiratory tract infection/conjunctivitis/cyst on right ear. These events are discussed under Safety Section 6.1.12.7. Overall the rates of study discontinuations associated with adverse events were low.*

6.1.11 Immunogenicity Analyses

The immune responses to vaccine antigenic components generated 30 days after the corresponding study vaccinations (Menactra, Daptacel, & IPV) were measured as follows:

- hSBA GMTs to meningococcal serogroups A,C,W, and Y
- Proportion of subjects with anti-diphtheria concentrations ≥ 1.0 IU/mL
- Proportion of subjects with anti-tetanus concentrations ≥ 1.0 IU/mL
- GMCs to each pertussis antigen (PT,FHA, FIM, and PRN)
- GMTs against poliovirus Types 1, 2, and 3

6.1.11.1 Analyses of Primary Endpoint(s)

Diphtheria and Tetanus Seroresponse: Group B (Daptacel+Menactra)

The primary analyses evaluated the immune responses to diphtheria and tetanus vaccine components in Daptacel when it was co-administered with Menactra (Group B) compared to when it was co-administered with IPV 30 days before Menactra (Group A) as measured by the percentage of subjects with tetanus and diphtheria antitoxin levels ≥ 1.0 IU/ml.¹⁹ The non-inferiority criteria for meeting this objective were if the upper limit of the 2-sided 95% CI of the difference in percentages of subjects (pGroup A-pGroup B) was less than 5%. p= the percentage of subjects with tetanus and diphtheria antitoxin antibody levels ≥ 1.0 IU/mL, respectively.

The following table provides the results for the percentage of subjects with tetanus and diphtheria antitoxin levels ≥ 1.0 IU/ml 30 days after receiving a dose of Daptacel by group based on the Per Protocol Population.

¹⁸ At site 046, it was found the person who administered the vaccine was also the same person who collected the safety information for the excluded subjects. Therefore these subjects were excluded from the ITT and safety analyses.

¹⁹ A protective antitoxin level for diphtheria is considered 1.0 IU/ml, while a protective antitoxin level for tetanus is considered ≥ 0.1 IU/ml.

Table 4: Percentage of Subjects with Antitoxin Concentrations against Diphtheria & Tetanus ≥ 1.0 IU/mL 30 days After Concomitant Administration of Daptacel+Menactra (Study Group B) vs. Daptacel +IPV (Study Group A), by Group – PPP

	Group A* (N=250)	Group B* (N=238)	Upper Limit of 2-sided 95% CI for Difference in % (Group A-Group B)
	% [95%CI]	% [95%CI]	
Subjects with diphtheria antitoxin concentration ≥ 1.0 IU/mL	99.6% [97.8,100.0]	100% [98.5,100.0]	0.4
Subjects with tetanus antitoxin concentration ≥ 1.0 IU/mL	99.2% [97.1, 99.9]	99.2% [97.0, 99.9]	1.6

Source: Adapted from sBLA 125089/593, Clinical Study Report MTA43, Table 5.1 on p.102. Subjects analyzed according to the vaccines they actually received rather than in the groups originally randomized to. PPP: per protocol population. N: total number of subjects in study population per group. %: percentage. *Group A: Visit 1-Daptacel + IPV, Visit 2- Menactra . Group B: Visit 1- Daptacel + Menactra, Visit 2- IPV. Group C: Visit 1- IPV+Menactra, Visit 2- Daptacel

Reviewer Comment: *The primary objectives evaluating the seroresponse rates to the diphtheria and tetanus antigenic components in Daptacel were met as the upper limit of the 2-sided 95% CI for the difference in the percentage of subjects with antibody levels ≥ 1.0 IU/mL (study group A-study group B) was $< 5\%$, respectively, for diphtheria and tetanus antigens. A high number of study subjects who were co-administered Daptacel+Menactra at the same visit achieved the pre-specified antitoxin level ≥ 1.0 IU/mL for both tetanus and diphtheria.*

hSBA responses to Meningococcal Serogroups: Group B (Daptacel+Menactra)

The primary objective was to evaluate the serum bactericidal (human complement) responses to meningococcal serogroups A, C, Y, and W in Menactra when it was co-administered with Daptacel (Group B) compared to when it was co-administered with IPV 30 days before Daptacel (Group C) as measured by hSBA GMTs. The non-inferiority success criteria for meeting this objective was if the upper limit of the 2-sided 95% CI of the GMT ratio of Group C/Group B for each serogroup was < 2 .

The following table provides the hSBA GMT results for each serogroup 30 days after receiving a dose of Menactra by group and the upper limit of the 95% CI of the GMT ratio of Group C/Group B, based on the Per Protocol Population. It also includes the percentage of subjects with antibody titers $\geq 1:8$ against each serogroup by group, which are descriptive analyses.

Table 5: Meningococcal Serogroup Specific hSBA GMTs and Percentage of Subjects with hSBA titers $\geq 1:8$, 30 days after Menactra alone (Group A), Menactra+Daptacel (Group B), and Menactra+IPV (Group C), and NI Criteria Group C/Group B, - PPP

Sero-Group	Group A* (N=250)	Group B* (N=238)	Group C* (N=121)	Upper Limit of 2-sided 95% CI for Ratio of GMTs (Group C/Group B)
	GMT [95%CI] (M) $\geq 1:8$ [95%CI]	GMT [95%CI] (M) $\geq 1:8$ [95%CI]	GMT [95%CI] (M) $\geq 1:8$ [95%CI]	
A	6.7 [5.7, 8.0] (137) 49.6% [41.0,58.3]	10.8 [8.7, 13.3] (131) 67.2% [58.4,75.1]	10.4 [8.1,13.3] (104) 64.4% [54.4, 73.6]	1.3 -
C	3.3 [2.7, 3.9] (138) 20.3% [13.9,28.0]	8.1 [6.3, 10.5] (131) 50.4% [41.5, 59.2]	7.8 [5.8,10.7] (103) 50.5% [40.5, 60.5]	1.4 -
Y	6.5 [5.1, 8.2] (138) 44.2% [35.8,52.9]	18.1 [14.2, 22.9] (131) 80.2% [72.3, 86.6]	26.2 [20.0,34.4] (104) 88.5% [80.7, 93.9]	2.1 -
W	8.4 [6.7, 10.6] (138) 55.1% [46.4, 63.5]	22.8 [18.5, 28.1] (131) 87.8% [80.9, 92.9]	21.7 [16.6,28.4] (104) 82.7% [74.0,89.4]	1.3 -

Source: Adapted from sBLA 125089/593, Clinical Study Report MTA43, Table 5.2 on p.103, Table 5.8 on p.114, and Table 5.9 on p. 115. Subjects analyzed according to the vaccines they actually received rather than in the groups originally randomized to. PPP: per protocol population. N: total number of subjects in study population per group. M: total # of subjects in the analysis population who had a valid serology results for the antigen at the reported time point. *Group A: Visit 1-Daptacel + IPV, Visit 2- Menactra . Group B: Visit 1- Daptacel + Menactra, Visit 2- IPV. Group C: Visit 1- IPV+Menactra, Visit 2- Daptacel

Reviewer Comment:

- *The primary objective evaluating the hSBA immune responses to Menactra in Group B compared to Group C was met for Serogroup A, C and W if the upper limit of the 2-sided 95% for the ratio of GMTs (study group C/study group B) was <2. The co-administration of Menactra+Daptacel at the same visit was noninferior to the administration of Menactra+IPV with regard to the hSBA response to meningococcal serogroups A, C, and W.*
- *The ratio of GMTs Group C/Group B for Serogroup Y was 1.4 [1.0, 2.1], therefore non-inferiority was not met for this serogroup.*
 - *As shown in the table for Serogroup Y the GMT and % $\geq 1:8$ were 18.1 and 80.2% for Group B, and 26.2 and 88.5% for Group C, respectively. The statistical demonstration of non-inferiority was missed only slightly, as the sample size was small. The clinical relevance of these findings is unclear, though important as one-third of all reported meningococcal cases in the US are due to Serogroup Y, in addition to Serogroups B and C.²⁰*
- *Group C served as a control group for the evaluation of meningococcal responses in this study. As described in the table above, the antibody responses to Menactra (GMT and % $\geq 1:8$) in Group C appear to be lower than expected based on historical data. The applicant responded to a CBER information request (dated 03 Aug 2016) pertaining to these observations with a compilation of historical data from past studies which included hSBA GMT point estimates against serogroup A, C, W, and Y one month following a single dose of Menactra in subjects of similar age (4-5yo and 4-6yo).²¹ When compared to the hSBA GMT responses seen in ~120 subjects in Group C, the responses observed in these other studies were generally similar in a combined total of 150 subjects.²²*

6.1.11.2 Analyses of Secondary Endpoints

Response to Pertussis Antigens: Group B (Daptacel+Menactra)

The secondary analyses evaluated the immune responses to pertussis antigens (PT, FHA, FIM, and PRN) in Daptacel when it was administered concomitantly with Menactra (Group B) compared to when it was administered 30 days before Menactra (Group A) as measured by GMCs to pertussis antigens. The non-inferiority criteria for meeting this objective was if the upper limit of the 2-sided 95% CI of the GMC ratio of Group A/Group B for each pertussis antigen was <1.5.

The GMCs of antibodies generated against each pertussis antigen across groups and the upper limit of the 2-sided 95% CI of the GMC ratio of Group A/Group B for each pertussis antigen is provided in the table below:

20 CDC. Prevention and Control of Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62(RR02);1-22.

21 STN 125089/593.8 (on 10Aug2016).

22 The applicant notes that comparisons to historical data be qualified by non-contemporaneous hSBA testing, and that such comparisons do not account for differences in study populations, sample size, geography, and post vaccinations

Table 6: GMCs of Antibodies against Each Pertussis Antigen (ELISA-EU/mL), 30 days after Daptacel+IPV (Group A), Daptacel+Menactra (Group B), and Daptacel alone (Group C), - PPP

Ag	Group A* (N=250)	Group B* (N=238)	Group C* (N=121)	Upper Limit of 2-sided 95%CI of Ratio of GMCs (Group A/Group B)
	GMC (M) [95%CI]	GMC (M) [95%CI]	GMC (M) [95%CI]	
PT	70.0 (243) [63.0, 77.8]	71.0 (236) [63.8,79.0]	73.0 (117) [61.9, 86.0]	1.1
FHA	133 (246) [117, 152]	145 (237) [127,165]	131 (118) [110,156]	1.1
FIM	123 (243) [92.5, 164]	113 (238) [84.0, ,151]	95.2 (116) [60.4,150]	1.6
PRN	115 (247) [97.0, 136]	118 (238) [102,137]	119 (137) [107, 175]	1.2

Source: Adapted from sBLA 125089/593, Clinical Study Report MTA43, Table 5.7 on p.109. Subjects analyzed according to 1) the vaccines they actually received rather than in the groups originally randomized to. Ag Antigen. PPP per protocol population. N total number of subjects in study population per group. M total # of subjects in the analysis population who had a valid serology results for the antigen at the reported time point. *Group A Visit 1-Daptacel + IPV, Visit 2- Menactra. Group B Visit 1- Daptacel + Menactra, Visit 2- IPV. Group C Visit 1- IPV+Menactra, Visit 2- Daptacel

Reviewer Comment:

- *The secondary objective evaluating the immune response to PT, FHA, and PRN pertussis antigens in Daptacel was met, with an upper limit of the 2-sided 95% CI for the ratio of GMCs (study group A/study group B) <1.5. For these 3 pertussis antigens, the antibody responses following co-administration Daptacel+Menactra was noninferior to corresponding responses following the co-administration of Daptacel+IPV. The upper limit of the 2-sided 95% CI for the ratio of GMCs for FIM was 1.6; therefore non-inferiority was not met for this pertussis antigen.*
- *As described in Section 6.1.1 of this review, an observational objective for this study was the analyses of GMCs against each pertussis antigens (PT, FHA, FIM and PRN) 30 days after Daptacel vaccination in each group, the results of which are shown in the table above. The GMCs to each pertussis antigen were numerically similar across groups with overlapping 95% CIs.*
- *Serologic correlates of protection for pertussis have not been established.*

hSBA Responses to Meningococcal Serogroups: Group A (Menactra 30 days after Daptacel)

The secondary analyses evaluated the hSBA responses to meningococcal serogroups A,C,Y, and W in Menactra when it was administered 30 days after Daptacel (Group A) compared to when it was administered 30 days before Daptacel (Group C). The non-inferiority criteria for meeting this objective was if the upper limit of the 2-sided 95% CI of the GMT ratio of Group C/Group A for each serogroup was <2.

The following table provides the hSBA GMT results for each serogroup 30 days after receiving a dose of Menactra by group based on the Per Protocol Population, and the upper limit of the 95% CI of the GMT ratio of Group C/Group A. It also includes the percentage of subjects with antibody titers $\geq 1:8$ against each serogroup by group, which were descriptive analyses.

Table 7: Meningococcal Serogroup Specific hSBA GMTs and Percentage of Subjects with hSBA titers $\geq 1:8$, 30 days after Menactra alone (Group A), Menactra+Daptacel (Group B), and Menactra+IPV (Group C), and NI Criteria Group C/Group A -PPP

Sero-Group	Group A* (N=250)	Group B* (N=238)	Group C* (N=121)	Upper Limit of 2-sided 95% CI for Ratio of GMTs (Group C/Group A)
	GMT [95%CI] (M) % $\geq 1:8$ [95%CI]	GMT [95%CI] (M) % $\geq 1:8$ [95%CI]	GMT [95%CI] (M) % $\geq 1:8$ [95%CI]	
A	6.7 [5.7, 8.0] (137) 49.6% [41.0,58.3]	10.8 [8.7, 13.3] (131) 67.2% [58.4,75.1]	10.4 [8.1,13.3] (104) 64.4% [54.4, 73.6]	2.1 -
C	3.3 [2.7, 3.9] (138) 20.3% [13.9,28.0]	8.1 [6.3, 10.5] (131) 50.4% [41.5, 59.2]	7.8 [5.8,10.7] (103) 50.5% [40.5, 60.5]	3.4 -
Y	6.5 [5.1, 8.2] (138) 44.2% [35.8,52.9]	18.1 [14.2, 22.9] (131) 80.2% [72.3, 86.6]	26.2 [20.0,34.4] (104) 88.5% [80.7, 93.9]	5.8 -
W	8.4 [6.7, 10.6] (138) 55.1% [46.4, 63.5]	22.8 [18.5, 28.1] (131) 87.8% [80.9, 92.9]	21.7 [16.6,28.4] (104) 82.7% [74.0,89.4]	3.7 -

Source: Adapted from sBLA 125089/593, Clinical Study Report MTA43, Table 5.4 on p.105; Table 5.8 on page 114; and Table 5.9 on page 115. Subjects analyzed according to the vaccines they actually received rather than in the groups originally randomized to. PPP: per protocol population. N: total number of subjects in study population per group. M: total # of subjects in the analysis population who had a valid serology results for the antigen at the reported time point. *Group A: Visit 1-Daptacel + IPV, Visit 2- Menactra . Group B: Visit 1- Daptacel + Menactra, Visit 2- IPV. Group C: Visit 1- IPV+Menactra, Visit 2- Daptacel

Reviewer Comment: *The secondary objective evaluating the hSBA immune response to Menactra was not met for all 4 serogroups, with an upper limit of the 2-sided 95% CI for the ratio of GMTs >2.0.*

- *The most pronounced difference in GMTs across groups was observed for Serogroup Y (GMT ratio of 4.0 [2.8, 5.8]), where the entire 95% CI was > 2.0 (inclusive of lower and upper limits).*
- *The ratio of GMTs across groups for Serogroup A was 1.5 [1.1, 2.1], and only marginally missed the pre-defined study success criteria.*
- *There was a statistically significant decrease in the hSBA antibody responses to meningococcal serogroups, most notably for Serogroups C, W, and Y when Daptacel was administered 30 days before Menactra as compared to when Menactra was administered 30 days before Daptacel.*
 - *These observed findings suggest that the immune response to the each meningococcal capsular polysaccharide in Menactra was suppressed when Daptacel was administered 30 days before Menactra. As discussed in Section 4.4.1 (Mechanism of Action), the meningococcal capsular polysaccharide components of Menactra are conjugated to diphtheria toxoid carrier proteins. Published clinical data suggests that immune response to vaccine antigens may be altered by the concomitant administration of certain conjugate vaccines when they contain the same carrier protein (diphtheria toxoid). The proposed mechanism of action is that an amplified carrier protein specific T helper cell response may suppress the immune responses to polysaccharide antigens conjugated to the carrier protein, suggesting immune interference.*

6.1.11.3 Subpopulation Analyses

The applicant provided demographic subgroup analysis on data generated from Study MTA43 as a response to an information request.²³ Subgroup analyses by site were not provided due to

²³ Information Request emailed on 28 March 2016. The applicant provided a response which included subgroup analysis data by sex and race at each visit for each group on 18 April 2016 under STN 125089/593.6.

insufficient sample size at each site, as enrollment at each site varied. Additional subgroup analyses by age were also not conducted since the population was homogeneous (median age 4.3 years of age [range 4, 6]).

Subgroup analyses of immunogenicity study findings based on sex were generally similar between male and females across study groups for the majority of analyses. When comparing the meningococcal hSBA GMT results by sex against Serogroup Y in Study Group B (Menactra+Daptacel), and against Serogroup C in Study Group A (Menactra alone 30 days after Daptacel), the responses in females were numerically higher than what was observed in males. For females in Study Group B the hSBA GMT response to Serogroup Y was 25.3 [18.2-35.2] and in males it was 13.0 [9.3-18.1]. For females in Study Group A, the hSBA GMT response to Serogroup C was 4.4 [3.1, 6.3] and in males it was 2.6 [2.3, 2.9]

Reviewer Comment: For the observed numerical differences in hSBA GMTs based on sex in Study Group A (Serogroup C) and Study Group B (Serogroup Y), the confidence intervals around the hSBA GMTs did not overlap. The number of females and males in Study Group B that were available for comparisons of hSBA GMTs against meningococcal serogroup C were ~66 subjects for each subpopulation. The number of females in Study Group C was 61 subjects and the number of males was 77 subjects. Definitive conclusions can not be made on the observed numerical differences in GMT point estimates because the sample sizes for these analyses were small

Subgroup analyses of immunogenicity data based on race were of limited utility because the majority of subjects in the Per Protocol analysis set were Caucasian (~78%-81%).

6.1.11.4 Dropouts and/or Discontinuations

Missing data were not replaced. See Section 6.1.10.1.3 for a review of subject withdrawals.

6.1.11.5 Observational Analyses

The following immunogenicity analyses were additional observational that were not described above in the context of the primary and/or secondary immunogenicity objectives. These results are considered descriptive.

Anti-diphtheria and Anti-tetanus Antibody Concentration: % ≥ 0.1 IU/mL & ≥ 1.0 IU/mL

Analyses of the proportion of subjects with antibody titers against diphtheria and tetanus ≥ 0.1 IU/mL and ≥ 1.0 IU/mL 30 days after Daptacel vaccination was evaluated in Group A, B, and C. The percentage of subjects with diphtheria antitoxin concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL was ~100% and 99.6%-100%, respectively across all groups for the PP population. The percentage of subjects with tetanus antitoxin concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL was ~100% and 98.3% - 99.2%, respectively across all groups for the PP population.

Reviewer Comment: The proportion of subjects with antibody titers against diphtheria and tetanus ≥ 0.1 IU/mL and ≥ 1.0 IU/mL 30 days after Daptacel vaccination was high across all groups.

Poliovirus Antibody GMTs

Analyses of GMTs against the 3 poliovirus serotypes 30 days after IPV vaccination was evaluated in Groups A, B, and C. The GMT generated to each poliovirus type 30 days after IPV vaccination, as measured by serum neutralization assay were reported for each group for the PP population. The GMT point estimates are as follows with 95% CI:

- Type 1:
 - Group A: 5094.8 [4427.8, 5862.4]
 - Group B: 5767.0 [4982.7, 6674.9]
 - Group C: 4885.1 [4013.2, 5946.4]
- Type 2:
 - Group A: 5209.5 [4549.0, 5966.0]
 - Group B: 6195.6 [5325.3, 7208.1]
 - Group C: 5373.6 [4461.0, 6472.8]
- Type 3:
 - Group A: 6777.5 [5766.9, 7965.2]
 - Group B: 7815.9 [6601.0, 9254.5]
 - Group C: 5843.0 [4523.4, 7547.6]

Reviewer Comment: *The GMT responses to each poliovirus type after IPV vaccination were similar across groups. The immune responses to IPV do not appear to have been suppressed when administered with Daptacel or Menactra when compared to the immune response to IPV when it was administered alone. The immune response to IPV was not anticipated to affect the antibody responses to antigens contained in the other two vaccines.*

6.1.12 Safety Analyses

6.1.12.1 Methods

The analysis dataset used to evaluate safety data was the Safety Analysis Set, which included all subjects who received at least 1 dose of study or control vaccine and had any available safety data. All subjects were analyzed according to the vaccine they actually received.

As discussed in Section 6.1.7, safety data collection included the following:

- Immediate adverse events during the 30 minutes post-vaccination time period
- Solicited Local and Systemic Reactions during the 7 days after vaccination and included monitoring of the following:
 - Solicited injection site reactions included redness, pain, swelling, extensive arm swelling (joint swelling)
 - Solicited systemic reactions included pyrexia²⁴, headache, malaise, myalgia
- Unsolicited Adverse Events during the 30 days after vaccination.
- Serious Adverse Events throughout the duration of the trial-which is 90 days (30 days after the last Study Visit at Day 60).

6.1.12.2 Overview of Adverse Events

Solicited Adverse Events

Solicited local and systemic adverse event data were collected for 7 days post-vaccination after each study vaccination on a diary card. The rates of solicited local (injection site) reactions for each study vaccine administered at either Visit 1 or Visit 2 were reported separately. As discussed in Section 6.1.4 of this review the arm that each study vaccine was administered was pre-specified as follows:

Visit 1(Day 0):

- *Group A: Daptacel-left arm; IPV-right arm*
- *Group B: DAPTAEL-left arm; Menactra-right arm*

²⁴ Intensity scale for fever: Mild $\geq 38.0C$ to $\leq 38.5C$; Moderate $\geq 38.5C$ to $\leq 39.5C$; Severe $\geq 39.5C$

- Group C: IPV-left arm; Menactra-right arm
- Visit 2 (Day 30):

- Group A: Menactra-right arm
- Group B: IPV-left arm
- Group C: Daptacel-right arm

The following table provides an overview of the rates of solicited local (injection site) after vaccination with either Daptacel or Menactra at either Visit 1 or 2. These are results are descriptive without pre-specified study success criteria.

Table 8: Reactogenicity Rates: Percentage of Subjects with Any & Severe Solicited Local Adverse Events for 7 Days Post-vaccination by Vaccine & Group (at Visit 1 or 2) –Safety Population

Local Adverse Events ^Δ		Daptacel injection site			Menactra injection site		
		Group A* N=328	Group B* N=327	Group C* N=165	Group A* N=328	Group B* N=327	Group C* N=165
		% [95%CI]	% [95%CI]	% [95%CI]	% [95%CI]	% [95%CI]	% [95%CI]
Pain	Any	71.7% [66.5, 76.5]	69.4% [64.1, 74.3]	52.1% [44.2, 60.0]	52.2% [46.6, 57.5]	60.9% [55.4, 66.2]	56.0% [48.1, 63.7]
	Severe	0.6% [0.1, 2.2]	0.6% [0.1, 2.2]	0 [0, 2.2]	0.6% [0.1, 2.2]	0.3% [0.0, 1.7]	1.2% [0.1, 4.3]
Erythema	Any	48.8% [43.3, 54.3]	48.8% [43.3, 54.3]	25.8% [19.2, 33.2]	24.8% [20.2, 29.9]	31.3% [26.3, 31.3]	18.7% [13.1, 25.4]
	≥2 in	22.7% [18.3, 27.6]	22.1% [17.8, 27.0]	11.0% [6.7, 16.9]	7.5% [4.8; 10.9]	4.9% [2.8, 7.8]	3.6% [1.3, 7.7]
Swelling	Any	34.2% [29.1, 39.6]	33.1% [28.1, 38.5]	19.8% [13.9, 26.7]	18.1% [14.0, 22.7]	20.1% [15.9, 24.8]	12.7% [8.1, 18.8]
	≥2 in	16.4% [12.5, 20.8]	12.5% [9.1, 16.5]	6.2% [3.0, 11.1]	5.9% [3.6, 9.1]	5.5% [3.3, 8.5]	3.0% [1.0, 6.9]

Source: Adapted from sBLA 125089/593, Clinical Study Report MTA43, Table 6-4 on p. 127 and Table 6.5 on p 130. *Group A: Visit 1-Daptacel + IPV, Visit 2- Menactra. Group B: Visit 1- Daptacel + Menactra, Visit 2- IPV. Group C: Visit 1- IPV+Menactra, Visit 2- Daptacel.

N: number of subjects who received at least one study vaccination on the visit reported. IPV solicited reaction rates not included.

Δ: Grading scale for solicited local reactions: Pain: mild-easily tolerated, moderate-sufficiently discomforting to interfere with normal behavior or activities, severe-incapacitating unable to perform usual activities; Erythema & Swelling: mild- 1.0in, moderate-≥1.0 to <2in, severe- ≥2 in.

Reviewer Comment:

➤ **Menactra site reactogenicity:**

- The most frequent solicited local reaction at the Menactra injection site across all groups was pain, seen in ~52%-61% of all subjects. Most reported pain was mild or moderate in severity.
- The rates of reactogenicity of Menactra+IPV were numerically lower than Menactra+Daptacel.
- The rates of ‘any’ & ‘severe’ erythema in Group B (Menactra+Daptacel) were 31% & 5%, in Group C (Menactra+IPV) were 19% and 4%, and in Group A (Menactra alone) were 25% & 7.5%.

Table 9: Reactogenicity Rates: Percentage of Subjects with Any & Severe Solicited Systemic Adverse Events for 7 Days Post-vaccination by Group & Visit –Safety Population

Systemic Adverse Events ^Δ		Group A* N=328 % [95%CI]		Group B* N=327 % [95%CI]		Group C N= 165 % [95%CI]	
		Visit 1 Day 0	Visit 2 Day 30	Visit 1 Day 0	Visit 2 Day 30	Visit 1 Day 0	Visit 2 Day 30
		Headache	Any	14.5% [10.9, 18.8]	8.4% [5.6, 12.0]	12.7% [9.3, 16.8]	6.6% [4.2, 10.0]
	Severe	0.6% [0.1, 2.2]	0.3% [0, 1.7]	0.3% [0, .7]	0.6% [0.1, 2.3]	0 [0, 2.2]	0.6% [0, 3.4]
Malaise	Any	26.0% [21.3, 31.1]	14.3% [10.7, 18.6]	24.5% [20.0, 29.6]	14.9% [11.2, 19.3]	26.7% [20.1, 34.1]	22.7% [16.5, 29.9]
	Severe	2.4% [1.0, 4.7]	1.2% [0.3, 3.1]	0.6% [0.1, 2.2]	2.5% [1.1, 4.9]	3.0% [1.0, 6.9]	1.8% [0.4, 5.]
Myalgia	Any	46.2% [40.8, 51.8]	24.2% [19.6, 29.3]	37.3% [32.0, 42.7]	17.5% [13.4, 22.1]	26.7% [20.1, 34.1]	25.8% [19.2, 33.2]
	Severe	1.8% [0.7, 3.9]	0.6% [0.1, 2.2]	0.9% [0.2, 2.6]	1.0% [0.2, 2.8]	0 [0, 2.2]	0.6% [0.0, 3.4]
Fever**	≥38°	8.2% [5.5, 11.8]	3.8% [2.0, 6.6]	5.5% [3.3, 8.6]	5.6% [3.3, 8.8]	8.0% [4.3, 13.3]	6.9% [3.5, 12.0]
	Any						
	≥39.5°	0.3% [0, 1.7]	0.3% [0, 1.8]	0.9% [0.2, 2.7]	0.3% [0, 1.8]	0 [0, 2.2]	0 [0, 2.3]
	Severe						

Source: Adapted from sBLA 125089/593, Clinical Study Report MTA43, Table 6.6 on p.132 and Table 6.7 on p.134. *Group A: Visit 1-Daptacel + IPV, Visit 2- Menactra. Group B: Visit 1- Daptacel + Menactra, Visit 2- IPV. Group C: Visit 1- IPV+Menactra, Visit 2- Daptacel.

N: number of subjects who received at least one study vaccination on the visit reported. IPV solicited reaction rates not included.
Δ: Grading scale for solicited systemic reactions: Fever: mild ≥38.0 C to ≤38.5 C, moderate >38.5 C to ≤39.5C, Severe- >39.5 C; Headache/Malaise/Myalgia: mild-noticeable but does not interfere with daily activities, moderate- interferes with daily activities, severe- prevents daily activities. ** As per protocol the temperature measurement route was specified to be done by oral route, and that tympanic or axillary thermometry should not have been used.

Reviewer Comment: *The rates of systemic reactions were similar across groups. The most frequently reported reaction was myalgia.*

- *Following the administration of Daptacel alone or with respective concomitant vaccines the most frequently reported systemic reaction was myalgia, reported in 46.2%, 37.3%, and 25.8% of subjects in Groups, A, B, and C, respectively. The majority of the reactions were graded as mild or moderate in severity. Fever (temperature >39.5C) was reported in <1.0% of subjects.*
- *Following the administration of Menactra alone or with the respective concomitant vaccines the most frequently reported systemic reaction was myalgia, reported in 24.2%, 37.3%, and 26.7% of subjects in Groups A, B, and C, respectively. The majority of the reactions were graded as mild or moderate in severity. Fever (temperature >39.5C) was reported in <1.0% of subjects.*

Unsolicited Adverse Events:

Immediate Adverse Events

There were no reports of immediate adverse events that occurred within 30 minutes of the Visit 1 or Visit 2 vaccinations.

Unsolicited AEs 30 days post-vaccination:

All unsolicited AEs reported within 30 days of vaccination were collected using MedDRA 9.0 Preferred Terms and System Organ Class (SOC).

The rates that subjects reported at least one unsolicited AE by Visit and Group are as follows [95% CI]:

- *Visit 1:*
 - Group A: 51.3% [45.9, 56.8]
 - Group B: 48.4% [43.0, 53.8]
 - Group C: 43.8% [36.2, 51.6]
- *Visit 2:*
 - Group A: 35.7% [30.5, 41.1]
 - Group B: 31.7% [26.7, 37.1]
 - Group C: 39.0% [31.5, 46.9]

Unsolicited injection site reactions were notable at the Daptacel site in Group A (12.6%), in Group B (12.8%), and in Group C (10.4%). Unsolicited systemic adverse events after Visit 1 were comparable across groups (42-45%), and after Visit 2 (31-34%). The most frequently reported unsolicited adverse events across all groups and visits were under the SOC of Infections & Infestations and AEs by preferred terms nasopharyngitis, otitis media, and upper respiratory tract infection. Unsolicited AEs under the Respiratory Disorders SOC were also reported frequently, including AEs by preferred terms rhinorrhea and nasal congestion.

Reviewer Comment: *The rates of unsolicited AEs were similar across groups. The reported adverse events are common illnesses seen in 4-6 year old children.*

6.1.12.3 Deaths

There were no deaths during the study.

6.1.12.4 Nonfatal Serious Adverse Events

There were a total of 3 serious adverse events, none of which were considered to be related to study vaccinations by the site investigators. The case narratives for the 3 SAEs were as follows:

- Subject #016-00001: Dehydration
 - 4 yo male received Menactra and IPV vaccines on 6 Feb 2007. He presented to the emergency room on 4 March 2007 (26 days after vaccinations) with croup, fever, decreased oral intake, vomiting, and decreased activity for two days. He was admitted for 3 days for dehydration and improved. He continued in the study.
- Subject # 041-00035: Malignant Rhabdomyosarcoma
 - 5 yo female who received Menactra and Daptacel on 21 March 2007. She presented on 07 April 2007 (17 days after vaccinations) with painless muscle mass on the left inner thigh and was admitted to the hospital. She was diagnosed with embryonal rhabdomyosarcoma stage III and subsequently underwent 15 week IV chemotherapy regimen, followed by tumor resection on 05 July 2007. At the time of reporting, treatment was ongoing and prognosis was good. The subject was discontinued from the study.
- Subject # 041-00021: Pancytopenia
 - 4 yo male who received Menactra and Daptacel on 15 February 2007 and IPV on 22 March 2007. Pertinent recent history includes 3 months of easy bruising and an episode of epistaxis (January 2007) that lasted 20 minutes. In the prior 1 week, the subject had been treated for pneumonia with azithromycin. Three hours after receiving IPV on 22 March 2007, the subject developed scattered bruising and petechial rash on the face, chest. The patient was admitted to the hospital the

same day and diagnostic workup included complete blood count, chest x-ray, and bone marrow aspirate which demonstrated bone marrow failure with macrocytic normochromic anemia (hemoglobin: 7.2g/dl), marked leukopenia (white blood cell count: 1,700/ mm³) and marked thrombocytopenia (12,000/mm³) without evidence of malignancy. The subject was treated with both red blood cell and platelet transfusions, with ongoing bone marrow failure over the next few months. By August 2007 the subjects showed improvement in laboratory parameters and by February 2008 the subjects had recovered hemoglobin levels, though platelet counts were still low. The subject was discontinued from the study.

Reviewer Comment: *In the opinion of the reviewer, the SAEs of dehydration and malignant rhabdomyosarcoma are not related to study vaccinations. Based on the information provided the SAE of pancytopenia/bone marrow failure appears to have developed prior to study participation therefore is also not considered related to study vaccinations.*

6.1.12.5 Adverse Events of Special Interest (AESI)

A search of the JMP adverse event dataset by the reviewer did not generate any common clinical findings associated with meningococcal disease or adverse events associated with Menactra and/or Daptacel vaccinations. For example there were no reports of bacteremia, sepsis, meningitis, pneumonia, syncope, brachial neuritis, and/or Guillain-Barre syndrome. Additionally, there were no reports of whooping cough and/or pertussis, tetanus, or diphtheria infections.

6.1.12.6 Clinical Test Results

Treatment emergent laboratory or vital sign abnormalities were not reported for any subject.

6.1.12.7 Dropouts and/or Discontinuations

There were 53 subjects withdrew from the study prior to its completion. The most frequent reason was voluntary withdrawal not associated with an adverse event, followed by protocol violations. Two subjects in Group B withdrew due to Serious Adverse Events due to rhabdomyosarcoma and pancytopenia which are discussed in Section 6.1.12.4 above.

Subjects #003-00004 in Group B had received Menactra and Daptacel on 25 October 2006, and subsequently developed upper respiratory tract infection (URI) 6 days later, conjunctivitis 7 days later, and a cyst on the right ear 29 days later. The investigator did not consider these events related to study vaccinations and the mother of the subject chose to discontinue participation in the study due to the subject's illness.

Reviewer Comment: *Based on the information provided, the adverse events of URI, conjunctivitis, and right ear cyst in one subject 6-29 days after Menactra+Daptacel vaccinations were considered by this clinical reviewer to be unrelated to the study vaccinations.*

6.1.13 Study Summary and Conclusions

Study MTA43 evaluated concomitant administration of Daptacel+Menactra, sequential administration of Daptacel followed 30 days later by Menactra, and Menactra followed 30 days later by Daptacel. A total of ~880 healthy US children 4 years through 6 years of age were enrolled in the study. The study also included the administration of IPV, which was not expected to interfere with the immune responses to either Menactra or Daptacel. Both Daptacel and IPV are routinely recommended vaccines in children 4-6 years of age, but Menactra is only

recommended by the ACIP for use in 4-6 yo children if they are high risk for meningococcal disease due to an underlying condition or if they are at increased risk due to travel. The applicant's rationale to conduct the study was to assess the safety and immunogenicity of administration of Menactra when administered with Daptacel at the time of school entry.

The characteristics of each study group were similar, including the demographic profile and rates of study discontinuations across groups. Overall immunogenicity findings demonstrate that the sequential administration of Daptacel followed by Menactra resulted in statistically significant decrease in hSBA GMT responses to Serogroup A, C, Y and W. Co-administration of Menactra+Daptacel at the same visit did not demonstrate immune interference, but the non-inferiority criterion for serogroup Y was not met, though marginally. The percentage of subjects with hSBA titers $\geq 1:8$ and GMTs were similar across groups for Serogroup Y. Except for FIM, the non-inferiority criteria for the pertussis antigens were met when Daptacel+Menactra are co-administered. The clinical significance of the immune response to FIM is not known, as serologic correlates of protection for pertussis have not be established. Potential interference to the diphtheria, tetanus, and poliovirus types 1, 2, and 3 immune responses were not demonstrated. The rates of reactogenicity and unsolicited AEs/SAEs do not appear to be significant. The most frequently reported solicited reactions were pain at the injection site and myalgia following any study visit. The reported rates and types of unsolicited AEs are similar to that seen in the general population for children 4-6 years of age. None of the 3 reported SAEs were considered related to study vaccination and there were no death reported during the study..

7. INTEGRATED OVERVIEW OF EFFICACY: NOT APPLICABLE (1 STUDY SUBMITTED)

8. INTEGRATED OVERVIEW OF SAFETY: NOT APPLICABLE (1 STUDY SUBMITTED)

10. CONCLUSIONS

The diminished immune response to Menactra when it is administered 30 days after Daptacel is a significant finding in the submitted data. Although no clinical endpoint data are available to inform the potential risk, these immunogenicity data suggest that receipt of the two vaccines according to this regimen (Menactra 30 days after Daptacel) could lead to increased risk of meningococcal disease in individuals exposed to the pathogen, especially those who are at high risk for meningococcal disease. In order to mitigate this risk to children who may receive both vaccines in close proximity to each other at the time of school entry, the reviewer recommends that the Section on Drug Interactions in the Menactra and Daptacel package inserts include language reflecting the potential for immune interference in the meningococcal hSBA responses when Menactra is administered 30 days after Daptacel.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 10: Risk Benefit Assessment of Menactra and Daptacel Concomitant Administration or Sequential Administration within 30 days

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> Menactra is a diphtheria toxoid conjugated quadrivalent meningococcal vaccine containing serogroup-specific A, C, Y, W-135 polysaccharide antigens and is indicated for the active immunization of individuals 9 months through 55 years of age for the prevention of invasive disease cause by Neisseria meningitidis vaccine serogroups. There is a routine recommendation for a meningococcal quadrivalent conjugate vaccine at 11-12 years of age, followed by a booster dose at 16 years of age. The routine use of Menactra in children younger than 11 years of age is not recommended, but there it is recommended for use a meningococcal quadrivalent conjugate vaccine in children with high risk conditions and or for those at increased risk for disease. Invasive meningococcal disease is a serious condition with high case fatality rate despite antibiotic treatment, and the chronic morbidity many survivors experience as sequelae. Daptacel is a combination vaccine indicated for use in infants and children aged 6 weeks through 6 years of age to protect against diseases caused by <i>Bordetella pertussis</i>, <i>Clostridium tetani</i>, and <i>Corynebacterium diphtheriae</i>. The US Advisory Committee on Immunization Practices (ACIP) currently recommends the routine administration of a 5th dose of a DTaP containing vaccine, such as Daptacel in children 4-6 years of age prior to school entry. Vaccination with a meningococcal quadrivalent conjugate vaccine, such as Menactra is recommend for use in 4-6 yo children if they are at high risk for meningococcal disease due to an underlying condition or if they are at increased risk due to travel. 	<ul style="list-style-type: none"> Invasive meningococcal disease is a rapidly progressive, life-threatening illness and those individuals 4- 6 years who may be at high risk for disease may require vaccination with a quadrivalent meningococcal conjugate vaccine, such as Menactra. Vaccination with a DTaP containing vaccine, such as Daptacel is used for the prevention of infection of <i>Bordetella pertussis</i>, <i>Clostridium tetani</i>, and <i>Corynebacterium diphtheriae</i>. The 5th and final dose is administered at 4-6 years of age prior to school entry. Vaccination to protect against these pathogens is not done again until 11 years of age with Tdap vaccines.
<p>Unmet Medical Need</p>	<ul style="list-style-type: none"> There is a reasonable possibility that children 4- 6 years of age who may be at increased risk for meningococcal disease will receive a dose of Menactra prior to school entry at the office visit that the routine administration of a 5th dose of DTaP would be given. The safety and immunogenicity of co-administration of Menactra and Daptacel at the same visit or within 30 days of each other has not been assessed prior to school entry in children 4- 6 years of age. The evaluation of Menactra with Daptacel at other ages including children <4 years of age and those >6 yo to <11yo has also not been evaluated. 	<ul style="list-style-type: none"> In children entering school at 4-6 years of age, who may be at increased risk for meningococcal disease, may require vaccination with Menactra and Daptacel at either the same visit or within 30 days of each other.
<p>Clinical Benefit</p>	<ul style="list-style-type: none"> One clinical trial in ~880 children 4-6 years of age was submitted. This trial was modified, double-blind, randomized, US multi-center study evaluating the concomitant administration of Menactra and Daptacel at the same visit or within 30 days of each other at separate visits. The study design included hypotheses testing of immune responses to components of both vaccines, including tetanus, diphtheria, 4 pertussis antigens, meningococcal serogroup A,C,W,Y when the two vaccines were administered at the same visit compared to when each vaccine was administered with IPV. The study also evaluated the meningococcal immune response when Menactra was administered 30 days after Daptacel compared to when Menactra was administered 30 days before Daptacel. The evaluation of safety was descriptive. The immune responses to diphtheria, tetanus, PT, FHA, PRN pertussis antigens, meningococcal serogroups A, C, W vaccine components when both vaccines were co-administered at the same visit were non-inferior to the responses observed when each was administered with IPV. The response to serogroup Y missed the non-inferiority criteria marginally when Menactra+Daptacel were administered at the same visit. The anti-FIM GMCs were also slightly lower when Daptacel+Menactra were administered at the same visit. 	<p>The administration of Menactra+Daptacel at the same visit:</p> <ul style="list-style-type: none"> met the NI criteria for Serogroup A,C,and W, but was marginally missed for Serogroup Y. met the NI criteria for tetanus, diphtheria, PT, FHA, and PRN pertussis antigens, but was marginally missed for FIM. did not demonstrate a safety concern may facilitate better vaccine coverage

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> The hSBA GMTs immune responses to meningococcal serogroups A,C,W, Y when Menactra was administered 30 days before Daptacel were not dissimilar to historical data evaluating a single dose of Menactra in children 4-6 yo. The evaluation of solicited, unsolicited and serious adverse events when Menactra and Daptacel were administered at the same visit or within 30 days of each other was not remarkable and no safety signals were identified. The most frequently reported solicited reactions were pain at the injection site and myalgia following any study visit. The reported rates and types of unsolicited AEs are similar to that seen in the general population for children 4-6 years of age. None of the 3 reported SAEs were considered related to study vaccination and there were no death reported during the study. 	
Risk	<ul style="list-style-type: none"> The hSBA responses to Menactra when it was administered 30 days after Daptacel did not meet the non-inferiority criteria for all serogroups when compared to the hSBA response to Menactra when it was administered 30 days before Daptacel. These findings are clinically relevant and suggest immune interference in the meningococcal responses when Daptacel is administered before Menactra. When comparing the meningococcal hSBA GMT results by sex against Serogroup Y in Study Group B (Menactra+Daptacel), and against Serogroup C in Study Group A (Menactra alone 30 days after Daptacel), the responses in females were numerically higher than what was observed in males. The sample sizes for these analyses were small. 	<ul style="list-style-type: none"> Statistically reduced hSBA responses to meningococcal serogroups A, C, W and Y could translate to reduced protection against meningococcal disease when Menactra is administered 30 days after Daptacel. Definitive conclusions cannot be made on the observed numerical differences in meningococcal hSBA GMT point estimates in females versus males in Groups B & C because the sample sizes for these analyses were small
Risk Management	<ul style="list-style-type: none"> In order to mitigate this risk to children who may receive both vaccines in close proximity to each other at the time of school entry, the reviewer recommends that the Section on Drug Interactions in the Menactra and Daptacel package inserts include language reflecting the immune interference to meningococcal hSBA responses when Menactra is administered 30 days after Daptacel. 	<ul style="list-style-type: none"> If both vaccines included data in Section from Study MTA43 in their respective package inserts, then additional language in the Drug Interaction should highlight the immune interference demonstrated when Daptacel is administered 30 days before Menactra.

11.2 Risk-Benefit Summary and Assessment

The benefit of co-administration of both Daptacel and Menactra at the same office visit prior to school entry allows for health care providers to maximize vaccination opportunities for their patient population. The safety evaluations from Study MTA43 do not demonstrate any adverse outcomes. Furthermore the concomitant administration of both vaccines at the same visit does not demonstrate immune interference with regard to the tetanus, diphtheria, pertussis and meningococcal serogroup vaccine components. Therefore, benefit-risk is favorable for co-administration Daptacel and Menactra.

In contrast, the sequential administration of Daptacel followed 30 days later by Menactra resulted in statistically significant lower meningococcal serogroup responses compared to when Menactra was administered 30 days before Daptacel. The diminished immune response to Menactra when it is administered 30 days after Daptacel is a significant concern, especially in those individuals who are at high risk for meningococcal disease. In order to mitigate this risk to children who may receive both vaccines in close proximity at the time of school entry, the reviewer recommends that the Section on Drug Interactions in the Menactra and Daptacel package inserts include language reflecting the potential for immune interference in the meningococcal hSBA responses when Menactra is administered 30 days after Daptacel.

The generalizability of these findings may be limited by the study design which evaluated co-administration of the vaccines in children 4- 6 years of age. The study did not evaluate whether Daptacel interferes with the responses to Menactra when given to children <4 yo and in children >6yo to <11yo. It also did not evaluate the potential for interference that other DTaP containing vaccines may have on meningococcal seroresponses rates when they are administered 30 days before Menactra. Because meningococcal disease is a highly invasive, rapidly progressive, life threatening illness, vaccination must dependably confer immunity, and avoiding potential immune interference should be a primary consideration, especially in high risk individuals. Therefore the data generated from Study MTA43 may be considered relevant to other age groups and other similarly manufactured DTaP containing products.

11.3 Discussion of Regulatory Options

The applicant is seeking to update both package inserts to include study data in Section 6 (Adverse Reactions), Section 14 (Clinical Studies), and Section 5 (Warning and Precautions) which includes language on the preferred sequence that these two vaccines should be administered. The inclusion of language in Section 5 (Warning and Precautions) is not supported by the regulatory guidelines specified under CFR 201.57 for this section, which generally apply to a demonstrated safety concern, rather than immunogenicity findings suggestive of immune interference. The reviewer does support language to be included in Section 7 (Drug Interactions) which describes the reduced meningococcal antibody responses to Menactra if administered one month after Daptacel. The reviewer also supports the addition of language to Sections 6 (Adverse Reactions) and 14 (Clinical Studies).

11.4 Recommendations on Regulatory Actions

Recommend approval of the supplement application based on my review the submitted clinical data of the safety and immunogenicity of concomitant vaccination with Menactra and Daptacel or vaccination with Menactra 30 days prior to Daptacel for the prevention of invasive meningococcal disease which support the protection against diseases caused by *Bordetella pertussis*, *Clostridium tetani*, and *Corynebacterium diphtheriae* in children 4-6 years of age.

11.5 Labeling Review and Recommendations

Menactra label recommendations:

- Inclusion of MTA43 study data in Section 6.1 & Section 14.3
- Inclusion of language on co-administration of both vaccines at same visit or administration of Menactra prior to Daptacel at a separate visit in Section 7.

11.6 Recommendations on Postmarketing Actions

The respective package inserts adequately identify risks associated with the administration of each vaccine. The safety evaluations from Study MTA43 did not identify any new potential risks. Additional risk minimization activities are not required.