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Application Type	Original Submission
STN	125563/0
CBER Received Date	13 August 2014
PDUFA Goal Date	12 August 2015
Division / Office	Division of Vaccines and Related Product Applications (DVRPA) Office of Vaccines Research and Review (OVR)
Committee Chair	Rana Chattopadhyay, Ph.D., Chair, BLA Committee
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Priority Review	N/A
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Review Completion Date / Stamped Date	4 May 2015
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Applicant	MCM Vaccine Company
Proper Name	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate and Recombinant Hepatitis B Vaccine
(Proposed) Trade Name	(b) (4)
Dosage Form(s) and Route(s) of Administration	Three-dose immunization series consists of a 0.5 mL intramuscular injection, administered at 2, 4, and 6 months of age
Indication(s) and Intended Population(s)	Active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to <i>Haemophilus influenzae</i> type b (Hib) in infants and children from 6 weeks through 4 years of age.

Table of Contents

1. Executive Summary	7
1.1 Introduction	7
1.2 Brief Overview of BLA Submission	7
1.3 Major Statistical Issues and Conclusions	8
1.4 Conclusions	8
1.5 Summary.....	8
2. Clinical and Regulatory Background.....	9
3. Submission Quality and Good Clinical Practices	9
3.1 Submission Quality and Completeness	9
3.2 Compliance with Good Clinical Practices and Data Integrity.....	9
4. Significant Efficacy/Safety Issues Related to Other Review Disciplines.....	9
5. Sources of Clinical Data and Other Information Considered in the Review	9
5.1 Review Strategy.....	9
5.2 BLA Documents that Serve as the Basis for the Statistical Review	9
5.3 Overview of Clinical Trials/studies	9
6. Discussion of Individual Studies/Clinical Trials	10
6.1 Pivotal Study #1: Protocol 005	10
6.1.1 Objectives.....	11
6.1.2 Design Overview.....	11
6.1.3 Population	12
6.1.4 Study Treatments or Agents Mandated by the Protocol.....	12
6.1.5 Sites and Centers	13
6.1.6 Surveillance/Monitoring.....	13
6.1.7 Endpoints and Criteria for Study Success	13
6.1.8 Statistical Considerations and Statistical Analysis Plan.....	15
6.1.9 Study Population and Disposition	16
6.1.10 Efficacy Analyses.....	17
6.1.11 Subgroup Analyses.....	21
6.1.12 Safety Analyses	21
6.2 Pivotal Study#2: Protocol 006.....	24
6.2.1 Objectives.....	24
6.2.2 Study Design	25
6.2.3 Population	25
6.2.4 Study Treatments or Agents Mandated by the Protocol.....	25
6.2.5 Sites and Centers	26
6.2.6 Surveillance/Monitoring.....	26
6.2.7 Endpoints and Criteria for Study Success	26
6.2.8 Statistical Considerations and Statistical Analysis Plan.....	26
6.2.9 Study Population and Disposition	27
6.2.10 Efficacy Analyses.....	27
6.2.11 Subgroup Analyses.....	29
6.2.12 Safety Analyses	29

7. Integrated Efficacy.....	29
7.1 Background and Design.....	29
7.2 Overview of Efficacy.....	30
7.3 Subgroup Analyses for GMTs PostDose 3 Infant Series	31
7.4 Efficacy Conclusions.....	32
8. Integrated Safety	32
8.1 Safety Design, Data, and Disposition.....	32
8.2 Safety Results	33
8.2.1 Overall Adverse Events.....	33
8.2.2 Solicited Injection-Site AEs	34
8.2.3 Solicited Systemic AEs	35
8.2.4 Serious Adverse events	36
8.2.5 Deaths.....	36
8.3 Subgroup Analyses	37
8.4 Safety Conclusions	38
9. Additional Statistical Issues	38
10. Overall Conclusions.....	38
Appendix-1	39
Appendix-2	41
Appendix 3	42

List of Tables

Table 1: General Information about Phase IIb/III Studies.....	10
Table 2: Vaccine Administration by Vaccination Group [PR5I (N=981), Control (N=484)].....	12
Table 3: Primary Endpoints and Pre-specified Non-inferiority Margins for all PR5I Antigens	14
Table 4: Subject Disposition (All randomized subjects).....	17
Table 5: Non-Inferiority Analysis of PR5I Antigen Responses One Month Postdose 3 Compared to Control (PP-RW Population)	18
Table 6: Non-Inferiority Analysis of Pertussis Antigen Responses One Month after Toddler Dose: PR5I versus Control (PP-RW Population).....	19
Table 7: Clinical Adverse Event Summary After Any Infant Dose Vaccination (All Subjects as Treated Population, N_{PR5I}=981, N_{Control}=484)	22
Table 8: Solicited Injection-Site Adverse Events and Solicited Systemic Adverse Events (Incidence > 0%), Day 1 to Day 5, Following Any Infant Dose Vaccination (All Subjects as Treated Population, N_{PR5I}=981, N_{Control}=484).....	23
Table 9: Vaccine Administration by Vaccination Group [Lot A, n=800; Lot B, n=797; Lot C, n=809; Control, n=402]: Lot Consistency Study	25
Table 10: Lot Consistency Analysis of GMT Based on ANCOVA Model at One Month Postdose 3 (PP-RW Population).....	28
Table 11: Subjects' Demographic Characteristics (All Randomized Subjects) (Protocols 005 and 006).....	30
Table 12: Analysis of PR5I Antigen Responses at One Month Postdose 3 (PP-RW Population) (Protocols 005 and 006).....	30
Table 13: Analysis of Pertussis Antigen Responses at One Month after Toddler Dose (PP-RW Population) (Protocols 005 and 006).....	31
Table 14: Summary of Immunogenicity results [GMT (95% CI), n] One Month Postdose 3 (Infant Series) by PR5I Antigen, in Race and Sex Subgroups (PP-RW Population) (Protocols 005 and 006)	31
Table 15: Subject Disposition, Pooled Safety Population (Protocols 005 and 006).....	33
Table 16: Clinical Adverse Event Summary after Any Infant Dose Vaccination (All Subjects as Treated Population, N_{PR5I} = 3380, N_{Control} = 885) (Protocols 005 and 006).....	34
Table 17: Solicited Injection-Site Adverse Events and Solicited Systemic Adverse Events (Incidence > 0% in One or More Vaccination Groups) Day 1 to Day 5 Following Any Infant Dose Vaccination (All Subjects as Treated Population, N_{PR5I}=3380, N_{Control}=885) (Protocols 005 and 006)	35
Table 18: Subjects with Any Solicited Systemic Adverse Events by Vaccination (Incidence > 0% in One or More Vaccination Groups) Day 1 to Day 5 Following Each Infant Dose Vaccination (All Subjects as Treated Population) (Protocols 005 and 006).....	36
Table 19: Clinical Adverse Event Summary by Race and Gender Subgroups after Any Infant Dose Vaccination (All Subjects as Treated Population) (Protocols 005 and 006).....	37
Table 20: Subjects' Prevaccination GMTs by Study Group (PP-RW Population)	42

List of Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
ANCOVA	Analysis of covariance
ASaT	All Subjects as Treated
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CSR	Clinical study report
DTaP	Diphtheria, tetanus, and acellular pertussis
DTwP	Diphtheria, tetanus, and whole cell pertussis
(b) (4)	
FAS	Full Analysis Set
FDA	Food and Drug Administration
FHA	Filamentous haemagglutinin
FIM	Fimbriae types 2 and 3
FPE	First Patient Entered
GCI	Sanofi Pasteur Global Clinical Immunology
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMT	Geometric mean titer
HBsAg	hepatitis B surface antigen
HepB	hepatitis B
HepB (b) (4)	hepatitis B (b) (4)
Hib	<i>Haemophilus influenzae</i> type b
HRP	Horseradish peroxidase
ICH	International Conference on Harmonization
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intramuscular(ly)
IPV	Inactivated poliovirus
IRT	Interactive Response Technology
IU	Infectious units
LLOQ	Lower limit of quantification/quantitation
LPLV	Last Patient Last Visit
MI ANCOVA	Analysis of covariance with multiple imputation for missing baseline titers
(b) (4)	
mIU/mL	Milli-International units per milliliter
Mos	Months
MRL	Merck Research Laboratories
n	Number of subjects included in each category

N	Number of subjects vaccinated in each group
NAb	Neutralizing antibody
NI	Non-inferiority
PP	Per-Protocol
PP-OW	Per Protocol-Original Windows
PP-RW	Per Protocol-Revised Windows
PRN	Pertactin
PRP	Polyribosylribitol phosphate
PT	Pertussis toxoid
(b) (4)	
SAP	Statistical Analysis Plan
SD	Standard Deviation
SNA	Serum neutralizing antibody
SOC	System Organ Class
ULOQ	Upper limit of quantification/quantitation
USA	United States of America

1. Executive Summary

1.1 Introduction

The product PR5I (also referred to as V419) is a hexavalent vaccine and has the target use of active immunization against 6 childhood diseases -- diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *H. influenzae* type b -- with the convenience of 1 injection, administered as a 3-dose infant series at 2, 4, and 6 months of age. The vaccine is a combination vaccine containing components of vaccines licensed in the USA and/or European Union (EU). Currently in the USA, PEDIARIX[®] (GlaxoSmithKline), a pentavalent vaccine containing DTaP, IPV, and hepatitis B, and PENTACEL[®] (Sanofi Pasteur Limited), a pentavalent vaccine containing DTaP, IPV, and Haemophilus influenza type b (Hib), are the licensed combination vaccines with the greatest number of antigens.

The product PR5I is co-developed by Sanofi Pasteur and Merck Sharp & Dohme Corp. Sanofi Pasteur submitted this Biologics License Application (BLA) titled “Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine (DTaP-IPV-Hib- HepB)” on August 13, 2014.

1.2 Brief Overview of BLA Submission

This submission included two pivotal Phase III clinical studies, Protocols 005 and 006, conducted in the USA, to support approval of the BLA. The submission was in accordance with the Agency’s comments provided (on January 24, 2008) for the pre-IND meeting information package. Further information appears in section 5.3 of this review. Protocol 005 was designed to assess the safety, tolerability, and immunogenicity of PR5I when given as an infant series at 2, 4, and 6 months of age concomitantly with Prevnar 13[®] and RotaTeq[®]. The control was the licensed PENTACEL[®] + RECOMBIVAX HB[®] component vaccines. The primary immunogenicity endpoint was obtained at 1 month after 3rd vaccination (postdose 3). The study enrolled 1440 healthy infants of age between 46 days and 89 days and subjects were randomized at a 2:1 ratio to receive either PR5I or the component vaccine Control. Protocol 006 enrolled healthy infants (N=2800) and was designed to evaluate the safety, tolerability, and lot-to-lot consistency of three manufacturing lots of PR5I administered on an infant series schedule the same as that in Protocol 005. After the 3-dose infant series, the toddler dose of DAPTACELL[®] in Protocol 005 or PENTACEL in Protocol 006 was administered for the evaluation of pertussis response. Details of the study designs are included in this review in sections 6.1.2 for Protocol 005 and 6.2.2 for Protocol 006. Overall, the submitted results supported the primary immunogenicity objectives and clinical lot consistency, and suggest no concern about PR5I’s general safety profile compared to the licensed control regimen.

1.3 Major Statistical Issues and Conclusions

In BLA 125563, the safety and immunogenicity data were included for pivotal studies. The statistical analyses were performed for the non-inferiority evaluation of primary immunogenicity endpoints with pre-specified margins. For safety, the analyses mostly used descriptive statistics. The endpoints are described in sections 6.1.7 (Protocol 005) and 6.2.7 (Protocol 006) of this review. In the primary analysis evaluating the non-inferiority of postdose 3 response, the effects of baseline titer, vaccination group, and brand of birth dose hepatitis B vaccine were controlled by using ANCOVA. The statistical analysis also assessed clinical lot consistency of 3 manufacturing lots based on the pre-specified margins (0.67 to 1.5) for the geometric mean titer (GMT) ratios obtained for each pair of 3 lots. It is to be noted that the baseline titer, which was a covariate for postdose3 titer in the ANCOVA, was itself a response variable with postdose 3 titer as one of the covariates in the regression method used for imputing missing baseline titers.

The quality of the submission was sufficient for a statistical evaluation. Based on the applicant's analyses of the pivotal studies' data, the conclusions outlined below were drawn.

1.4 Conclusions

In healthy infants who received 3 doses of PR5I at 2, 4, and 6 months followed by DAPTACEL and PedvaxHIB at 15 months of age:

1. The immune response at 1 month post-dose 3 of the 3-dose infant series of vaccination by PR5I was non-inferior to that for the licensed Control regimen, for all the pre-specified endpoints, except for GMT of the FHA antigen.
2. At the toddler dose following the 3-dose infant series of vaccination, the pertussis response rates and GMTs in PR5I vaccinees were non-inferior to those observed in the licensed Control group.
3. Although not a primary endpoint per the Statistical Analysis Plan (SAP), the inactivated poliovirus response rate for each serotype (IPV1, IPV2, IPV3) was 100%, and the lower bound of the two-sided 95% CI of the rate exceeded 90%.
4. The three manufacturing lots of PR5I met the pre-specified statistical criterion of clinical lot consistency, based on the GMT of each pre-specified antigen.
5. The general safety profile of PR5I appeared to be comparable with that of its licensed component vaccines.

1.5 Summary

Overall, based on the pivotal studies, the immunogenicity and lot consistency objectives were met, and no major concern regarding the general safety profile of PR5I was discerned.

2. Clinical and Regulatory Background

Please refer to the medical officer's review.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The quality of the submission was sufficient to enable a statistical evaluation.

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issues with respect to immunogenicity or safety data in the pivotal studies were noted.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

Not applicable.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This submission included the clinical study reports of Protocols 005 and 006. These two were the pivotal studies to support the approval of the BLA and were reviewed. Statistical aspects of immunogenicity and safety, as well as the lot-to-lot consistency were reviewed.

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

The submission (STN 125563/0) was received on 13 August 2014. It is located in the EDR. The clinical study reports, electronic data sets, and other related materials are located in modules 2 and 5. The reviewed documents also included STN 125563/0.6, Section # 1.11.4 received on 9 April 2015 as efficacy information Amendment.

5.3 Overview of Clinical Trials/studies

Final formulations of PR5I hexavalent vaccine were used in three clinical studies, Protocols 004, 005, and 006, conducted in Canada and the USA. Protocol 004 was a Phase IIb study conducted in Canada. Upon its successful completion, Protocols 005 and 006 were conducted as pivotal Phase III studies to support PR5I licensure in the USA. A brief overview of the three studies is provided below (Table 1).

Table 1: General Information about Phase IIb/III Studies

Study	Objectives, design and schedules	Study Population	# subjects randomized	Conclusions
004 Phase IIb (Canada)	Open-label, multicenter, randomized, active-comparator controlled Phase II study to evaluate immunogenicity and safety of PR5I when given concomitantly with Prevnar. Subjects were randomized into one of three groups: <u>Group A</u> : Received PR5I and Prevnar at 2, 4, 6, and 15 months. <u>Group B</u> : Received PR5I at 2, 4, 6, and 15 months; Prevnar at 3, 5, 7, and 16 months. <u>Group C</u> : Received PENTACEL, ENGERIX-B and Prevnar at 2, 4, and 6 months; PENTACEL and Prevnar at 15 months.	Infants 42 to 99 days old	460	Final formulation of PR5I has acceptable immunogenicity and tolerability profile when given concomitantly with Prevnar.
005 Phase III (U.S.)	Open-label, multicenter, randomized, active-comparator controlled Phase III study to evaluate safety, tolerability and immunogenicity of PR5I <u>PR5I group</u> received PR5I at 2, 4, 6 months followed by DAPTACEL and PedvaxHIB at 15 months. <u>Control group</u> received PENTACEL at 2, 4, 6 months and RECOMBIVAX HB at 2 and 6 months followed by DAPTACEL and ActHIB at 15 months.	Infants* 46 to 89 days old	Randomized: 1473 PR5I: 986 Control: 487	Met immunogenicity objectives and comparable safety profile with control
006 Phase III (U.S.)	Partially double-blind, multicenter, randomized, active comparator controlled, lot-to-lot consistency Phase III study to evaluate safety, Tolerability and immunogenicity of PR5I. <u>PR5I groups</u> received PR5I (3 different lots to assess lot consistency) at 2, 4, 6 months and PENTACEL at 15 months. <u>Control group</u> received PENTACEL at 2, 4, 6, and 15 months and RECOMBIVAX HB at 2 and 6 months.	Infants* 46 to 89 days old	Randomized: 2808 PR5I: 2406 Control: 402	Met lot-to-lot consistency, acceptable immunogenicity and showed comparable safety with control

*Subjects who received birth dose of hepatitis B vaccine under standard medical care.
Source *Summary of Clinical Efficacy-prophylaxis, page 23-27 of the submission.*

In addition to the above Phase IIb/III studies in North America, two studies (Protocol 007 and Protocol 008), using non-USA schedules and non-USA licensed control vaccines, were not considered by CBER to contribute substantially to the evaluation of PR5I for use in the USA and as such will not be used to support USA licensure. CBER concurred during the end-of-phase-II clinical meeting that Protocol 005 and Protocol 006 would be the pivotal studies.

6. Discussion of Individual Studies/Clinical Trials

6.1 Pivotal Study #1: Protocol 005

Title: A Phase III Randomized, Open-Label, Active Comparator Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V419 in Infants When Given at 2, 4, and 6 Months Concomitantly with Prevnar 13 and RotaTeq.

6.1.1 Objectives

Primary Immunogenicity Objectives:

1. To compare the immunogenicity of PR5I with the component vaccine Control(s) (refer to section 6.1.4 for dose information).
2. To compare the immunogenicity of pertussis responses at one month after the Toddler dose of DAPTACEL after receiving an infant series of either 3 doses of PR5I or PENTACEL.
3. To demonstrate that the inactivated poliovirus (IPV) response rate is acceptable after receiving an infant series of 3 doses of PR5I. (This objective was not mentioned in V419 Study 005, SAP, 18-Jan 2013, page 7 of 66.)

Selected Key Secondary Immunogenicity Objectives:

1. To compare anti-polyribosylribitol phosphate (PRP) responses elicited by PR5I with the component vaccine Control(s).
2. To evaluate the immunogenicity of RotaTeq when administered concomitantly with PR5I.

Safety Objective:

To assess the safety and tolerability of PR5I or the component vaccine Control(s) when given concomitantly with the licensed vaccines Prevnar 13 and RotaTeq in healthy infants.

6.1.2 Design Overview

Study 005 was an open-label, multicenter, randomized, active-comparator controlled Phase III study conducted in the USA to evaluate the safety, tolerability, and immunogenicity of PR5I. The study population was planned on a 2:1 (PR5I vs Control) randomization of approximately 1440 healthy infants aged 46 to 89 days at the time of study entry for Dose 1. Each infant received a dose of monovalent hepatitis B vaccine at birth or <1 month of age, as part of standard medical care outside of the current study.

Subjects in the PR5I group received PR5I, Prevnar 13, and RotaTeq at 2, 4, and 6 months; and DAPTACEL and PedvaxHIB at 15 months.

Subjects in the Control group received PENTACEL, Prevnar 13, and RotaTeq at 2, 4, and 6 months, RECOMBIVAX HB at 2 and 6 months, followed by DAPTACEL and ActHIB at 15 months.

Blood samples, for serologic evaluation, were collected at 4 time points (pre-dose 1, 4 to 6 weeks after the 3rd dose (i.e., after completion of the infant series), prior to the toddler vaccination, and 4 to 6 weeks after the toddler dose). Vaccination schedules in each group are presented in Table 2.

Table 2: Vaccine Administration by Vaccination Group [PR5I (N=981), Control (N=484)]

Group	Vaccine administered	Dose	Route of Administration	Visit 1 2 months ^a	Visit 2 4 months ^b	Visit 3 6 months ^{c,d}	Visit 6 15 months ^e
PR5I	PR5I ¹	0.5 mL	IM	X	X	X	
PR5I	DAPTACEL ²	0.5 mL	IM				X
PR5I	PedvaxHIB ³	0.5 mL	IM				X
PR5I	Pevnar 13 ⁴	0.5 mL	IM	X	X	X	X
PR5I	RotaTeq ⁵	2.0 mL	Oral	X	X	X	
Control	PENTACEL ⁶	0.5 mL	IM	X	X	X	
Control	RECOMBIVAX HB ⁷	0.5 mL	IM	X		X	
Control	DAPTACEL ²	0.5 mL	IM				X
Control	ActHIB ⁸	0.5 mL	IM				X
Control	Pevnar 13 ⁴	0.5 mL	IM	X	X	X	X
Control	RotaTeq ⁵	2.0 mL	Oral	X	X	X	

¹PR5I=V419=DTaP-IPV-Hib-HepB

²DAPTACEL = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed.

³Liquid PedvaxHIB = *Haemophilus b* Conjugate Vaccine (Meningococcal Protein Conjugate).

⁴Pevnar 13 = Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein).

⁵RotaTeq = Rotavirus Vaccine, Live, Oral, Pentavalent.

⁶PENTACEL = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, IPV, and *Haemophilus b* Conjugate (Tetanus Toxoid Conjugate) Vaccine.

⁷RECOMBIVAX HB = recombinant hepatitis B vaccine.

⁸ActHIB = *Haemophilus b* Conjugate Vaccine (Tetanus Toxoid Conjugate).

DTaP = Diphtheria, tetanus, and acellular pertussis, HepB = Hepatitis B, Hib = *Haemophilus influenzae* type b, IM=Intramuscular, IPV=inactivated poliovirus.

Reviewer's note: For Per Protocol population with revised windows (PP-RW) (SAP, Prot 005, page 5 of 66), ^areceived vaccine from 46 to 89 days of age, ^breceived vaccine from 42 to 84 days after Dose1, ^creceived vaccine from 42 to 84 days post Dose 2, ^dpostdose 3 serology 28 to 51 days instead of 28 to 37 days after vaccination, ^epost toddler dose serology 28 to 51 days instead of 28 to 37 days after vaccination. For Per Protocol population with original days of window (PP-OW), the vaccination-window was Days 46 to 74 after the previous vaccination, and a blood draw sample window of Days 28 to 44 following dose 3 or the Toddler dose. The period 28-37 days was mentioned in Table 9-1 of the CSR 005, page 46.

Source Adapted from the CSR, Protocol 005, page 7.

6.1.3 Population

At the time of enrollment (baseline), the study population consisted of healthy infants as determined by the investigator, who were 46 to 89 days old (on the day of Dose 1) and who

- received one dose of hepatitis B monovalent vaccine outside the study context at birth or up to approximately one month of age and met the criteria for being in the study. All subjects could attend all scheduled visits and could comply with all study procedures, and
- provided voluntary written informed consent from a parent/legal representative, who had access to a telephone and was able to complete all study questionnaires.

The complete listing of inclusion and exclusion criteria, as stated in the protocol, can be found in Appendix-1 of this review.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Each 0.5 mL dose of PR5I contains the following in a sterile, single-dose, liquid, and preservative-free formulation for intramuscular injection.

- 20 µg of pertussis toxoid (PT)
- 20 µg of filamentous haemagglutinin (FHA)

- 3 µg of pertactin (PRN)
- 5 µg of fimbriae Types 2 and 3 (FIM)
- 3 µg of polyribosylribitol phosphate polysaccharide coupled to the outer membrane complex of *Neisseria meningitidis* (PRP-OMPC)
- 10 µg of hepatitis B surface antigen (HBsAg)
- 15 Lf of diphtheria toxoid
- 5 Lf of tetanus toxoid
- 29, 7, and 26 –D antigen Units of Inactivated Poliovirus (IPV) Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett), respectively, by a D-antigen (b) (4) assay (equivalent to 40, 8, and 32 D-antigen units, respectively, by the (b) (4) assay) and
- (b) (4) µg of aluminum.

PR5I was administered as a 0.5-mL intramuscular injection in a 3-dose infant series given at 2, 4, and 6 months of age in the USA. Further details about licensed components can be found in Appendix-2.

6.1.5 Sites and Centers

The study was conducted at 39 centers in the USA, and the recorded primary therapy period was 20 April 2011 to 09 May 2013.

6.1.6 Surveillance/Monitoring

Please see the medical officer's review.

6.1.7 Endpoints and Criteria for Study Success

Immunogenicity

Subjects' serum specimens were tested for responses to PR5I antigens listed in Table 3 and as well for the Rotavirus strains, at different time points of immunogenicity endpoints.

The endpoints for the primary hypothesis of immunogenicity against all PR5I components were the response rates and GMTs against all PR5I components as listed in Table 3. The hypotheses are described in section 6.1.8.

To demonstrate non-inferiority of immune response to PR5I compared to Control, the study's success criteria required that for all primary endpoints, the lower bounds of the 2-sided 95% CIs of the post-vaccination response-rate differences (PR5I group – Control group) and of the GMT ratios (PR5I vs. Control) exceed the corresponding pre-specified margins.

For primary analysis, the test of hypotheses was based on results from the Per Protocol (PP) population that used revised vaccination and blood draw windows. Details about revised windows are provided in section 6.1.10.

Table 3: Primary Endpoints and Pre-specified Non-inferiority Margins for all PR5I Antigens

Time Point	Antigen	Primary endpoint	Non-inferiority margin (δ)	Assumed true response rates (P) or SD	Power(%)
Postdose 3	PRP	% with titer $\geq 1.0 \mu\text{g/mL}$	10%	85%	99.7
Postdose 3	PRP	% with titer $\geq 0.15 \mu\text{g/mL}$	5%	97%	99.8
Postdose 3	HBsAg	% with titer $\geq 10 \text{ mIU/mL}$	10%	95%	>99.9
Postdose 3	Diphtheria	% with titer $\geq 0.1 \text{ IU/mL}$	10%	90%	>99.9
Postdose 3	Tetanus	% with titer $\geq 0.1 \text{ IU/mL}$	5%	97%	99.8
Postdose 3	Pertussis-PT	% vaccine response [†]	10%	85%	99.7
Postdose 3	Pertussis-PT	GMT	1.5	0.69	>99.9
Postdose 3	Pertussis-FHA	% vaccine response	10%	80%	99.8
Postdose 3	Pertussis-FHA	GMT	1.5	0.76	>99.9
Postdose 3	Pertussis-FIM	% vaccine response	10%	85%	99.7
Postdose 3	Pertussis-FIM	GMT	1.5	0.93	>99.9
Postdose 3	Pertussis-PRN	% vaccine response	10%	75%	97.4
Postdose 3	Pertussis-PRN	GMT	1.5	1.18	>99.9
Postdose 3	IPV1	% with NAb [®] $\geq 1:8$ dilution	5%	97%	99.8
Postdose 3	IPV1	% with NAb $\geq 1:8$ dilution	90% [‡]	97%	>99.9
Postdose 3	IPV2	% with Nab $\geq 1:8$ dilution	5%	97%	99.8
Postdose 3	IPV2	% with Nab $\geq 1:8$ dilution	90% [‡]	97%	>99.9
Postdose 3	IPV3	% with Nab $\geq 1:8$ dilution	5%	97%	99.8
Postdose 3	IPV3	% with Nab $\geq 1:8$ dilution	90% [‡]	97%	>99.9
Toddler dose	Pertussis-PT	% vaccine response	10%	85%	99.6
Toddler dose	Pertussis-PT	GMT	1.5	0.73	>99.9
Toddler dose	Pertussis-FHA	% vaccine response	10%	85%	99.6
Toddler dose	Pertussis-FHA	GMT	1.5	0.65	>99.9
Toddler dose	Pertussis-FIM	% vaccine response	10%	85%	99.6
Toddler dose	Pertussis-FIM	GMT	1.5	0.85	>99.9
Toddler dose	Pertussis-PRN	% vaccine response	10%	85%	99.6
Toddler dose	Pertussis-PRN	GMT	1.5	0.88	>99.9

[†]The pertussis vaccine response was defined as follows: (1) If prevaccination antibody concentration < 4× lower limit of quantification (LLOQ), then the postvaccination antibody concentration was $\geq 4 \times \text{LLOQ}$, (2) If prevaccination antibody concentration $\geq 4 \times \text{LLOQ}$, then the postvaccination antibody concentration was \geq pre-immunization levels. The pre-immunization level was defined as the antibody titer at pre-Dose .

[®] Neutralizing Antibodies.

[‡]Lower bound limit for acceptability regarding IPV responses in the PR5I group (Study 005 SAP, page 10).

Time point Postdose 3 was one month after the third dose; Toddler dose was one month after Toddler dose.

LLOQ = Lower limit of quantification, NAb = Neutralizing antibodies, SD=Standard deviation of natural logarithm of antibody titers.

Source: Study 005 SAP, page 9, 18 Jan 2013.

Safety

The safety endpoints included measurements of temperatures from Day 1 through Day 5 following each vaccination, solicited adverse events (local and/or systemic), unsolicited adverse events from Day 1 through Day 15, serious adverse events monitored up to 180 days following completion of the infant series, and serious adverse events and deaths throughout the study. From these were computed the general summary of descriptive safety statistics. Safety evaluation was not designed to have statistical power, the results are best viewed as descriptive, and any reference to statistical significance should not be interpreted inferentially since no pre-specified hypotheses were tested.

6.1.8 Statistical Considerations and Statistical Analysis Plan

Treatment assignment

Subjects of the study population (approximately 1440 infants who had received a dose of monovalent hepatitis B vaccine as part of standard medical practice at birth or up to one month of age and aged 46 to 89 days at the time of study entry for Dose 1) were randomized in a 2:1 ratio to:

- PR5I group where subjects received PR5I, Prevnar 13, and RotaTeq at 2, 4, and 6 months followed by DAPTACEL, PedvaxHIB, and Prevnar 13 at 15 months, or
- Control group where subjects received the same vaccine regimen as the PR5I group with respect to concomitant vaccines, but received PENTACEL at 2, 4, and 6 months and RECOMBIVAX HB at 2 and 6 months followed by DAPTACEL, Prevnar 13, and ActHIB at 15 months.

Statistical hypotheses tested (for primary immunogenicity)

- Response Rates: For each of the response rates postdose 3 listed in Table 3, the non-inferiority for PR5I is established by rejecting $H_0: \Delta \leq -\delta$ against $H_a: \Delta > -\delta$, where Δ is the post-vaccination response-rate difference (PR5I group – Control group), with δ as the margin for non-inferiority comparison. The pre-specified δ values are listed in Table 3.
- Geometric Mean Titers: For each of the GMTs postdose 3 listed in Table 3, the non-inferiority for PR5I is established by rejecting $H_0: \rho \leq 0.67$ against $H_a: \rho > 0.67$, where ρ is the post-vaccination GMT ratio (PR5I group / Control group) and 0.67 corresponds to a $\frac{2}{3}$ -fold change in the ratio.

For overall success, the criteria required that for all primary endpoints, the lower bound of the 2-sided 95% CI for Δ and for the GMT ratio (ρ) must exceed the corresponding pre-specified margins. The study's overall power for testing all primary hypotheses was 92.6%, with 94.5% power regarding the hypothesis of non-inferiority of PR5I at Postdose 3 and 98.4% regarding the hypothesis for non-inferiority after the Toddler dose. Table 3 provides power for individual hypotheses for components. No multiplicity adjustment was performed because the success of the study required success on all primary hypothesis tests. The evaluation of the non-inferiority hypothesis tests for primary immunogenicity was based on the PP population with a revised vaccination-window (PP-RW). More about this window follows from section 6.1.10.

Statistical analysis

For each primary endpoint of response rate and its non-inferiority evaluation, the p-value and 95% CI for the response rate difference (PR5I - Control) were evaluated taking into account the brand/type of birth dose hepatitis B vaccine. For response rate difference, the method by Miettinen and Nurminen (Comparative analysis of two rates. *Statistics in Medicine* 1985:213-226) was used. For non-inferiority in terms of GMT endpoints, the GMT ratios and 95% CIs were obtained from the ANCOVA statistical method, where the log-transformed postdose 3 titer was the dependent variable and the log-transformed prevaccination titers, treatment group and brand/type of birth dose hepatitis B vaccine were the fixed effect variables. The prevaccination

(i.e., baseline) titer, although a covariate in ANCOVA, did not have marked variation in terms of GMTs between arms (Appendix 3). The missing values among the baseline titers were reported to be from 1.7% to 4.0% of subjects for different antigens (STN 125563/0.6, Section # 1.11.4, Table 2, received on 9 April 2015). Previously, the applicant expected such percentage with missing values to be up to 25% (IND 14496/0.51, Section # 1.12.4, page 6). The applicant attributed the missing values to limitations in serum volume in 2-month-old infants and the large number of antigens tested for the study.

These missing values were multiply imputed by vaccination group, which is consistent with the null hypothesis for a non-inferiority assessment. In the multiple imputation procedure, each missing value under the assumption of missing at random is replaced by a set of plausible values (20 in this application) that represent the uncertainty about the value to be imputed, thus giving rise to multiple completed data sets. Each of the completed data sets is then analyzed by using standard statistical procedures. The analysis results so obtained from the individual completed data sets are then combined in the final analysis, thereby generating results for valid statistical inference. The procedures followed Rubin's method (*Multiple Imputation for nonresponse surveys*, 1987. New York: Wiley) and required use of both PROC MI and PROC MIANALYZE procedures in the SAS software.

In the applicant's multiple imputation step, the missing baseline titers were replaced by plausible values drawn from a population predicted by a regression model where the log-transformed baseline titer was the dependent variable (i.e., the variable being imputed) and the log-transformed postdose 3 titer was included as an independent variable along with covariates age, gender, race, weight, and brand/type of birth dose hepatitis B vaccine. This approach resulted in the estimates of treatment effect reported in Table 5.

Supportive analyses of antibody titers were performed by the applicant, using an approach proposed by Liang and Zeger (Longitudinal data analysis of continuous and discrete response for pre-post designs. *Sankhya* 2000:134-138), but those analyses are not described in this review.

Assay measurements

The assay range was defined by the lower limit of quantitation (LLOQ) and the upper limit of quantitation (ULOQ). The applicant stated that the antibody titer values reported as < LLOQ by the testing laboratory were replaced by $0.5 \times \text{LLOQ}$ for calculating GMTs; the replacement values were $0.5 \times \text{LLOQ}$ for a numerator and $1.0 \times \text{LLOQ}$ for a denominator when calculating GMT ratios. For both numerator and denominator < LLOQ, both were converted in the same manner as described. Values greater than ULOQ were assigned to the ULOQ.

6.1.9 Study Population and Disposition

Demographic characteristics at baseline

A total of 1473 subjects were randomized at a 2:1 ratio to either the PR5I group (N=986) or the control group (N=487). There were slight differences in the subjects' demographic characteristics between the two groups with regard to sex and race. In the two respective PR5I and Control groups, 51.4% and 56.1% were males, 77.6% and 82.5% were whites, and 15.6% and 10.9% were blacks. The means \pm standard deviations (SDs) of the infants' age were

65.6±7.5 days and 65.0±6.9 days, with age ranges of 46-89 days and 47-87 days, in the PR5I group and Control group, respectively.

Disposition of subjects

The details are included in Table 4 below. Of the 1473 randomized subjects, 1384 subjects (94.0%) completed all 3 doses of the infant series (PR5I/ Control) and all doses of the concomitant associated study vaccines per study design in Table 2, with 924 subjects (93.7%) receiving PR5I vaccine and 460 subjects (94.5%) receiving Control vaccine. There were 1264 (85.8%) subjects completing the toddler doses. Among those who discontinued between the infant series and toddler dose (n=121, 8.2%), the majority were lost to follow-up or were individual withdrawals.

Table 4: Subject Disposition (All randomized subjects)

	PR5I (N=981) n (%)	Control (N=484) n (%)	Total (N=1465) n (%)
Screened	-	-	1587
Randomized subjects	986	487	1473
Received all 3 doses of the Infant Series (PR5I/ Control)	924 (93.7)	460 (94.5)	1384(94.0)
Received all 3 doses of the Infant Series (PR5I/ Control) and all doses of concomitant study vaccines	924 (93.7)	460 (94.5)	1384(94.0)
Did not complete the Infant Series (PR5I/ Control)	57 (5.8)	24 (4.9)	81(5.5)
Reason for Withdrawal: [1]			
Adverse Event	1 (0.1)	1 (0.2)	2(0.1)
Death	1 (0.1)	1 (0.2)	2(0.1)
Lost to Follow-up	13 (1.3)	7 (1.4)	20(1.4)
Non-compliance with Study Drug	2 (0.2)	1 (0.2)	3(0.2)
Physician Decision	3 (0.3)	1 (0.2)	4(0.3)
Protocol Violation	22 (2.2)	9 (1.9)	31(2.1)
Withdrawal by Subject	15 (1.5)	4 (0.8)	19(1.3)
Discontinued between the Infant Series and Toddler Dose	81 (8.2)	40 (8.2)	121(8.2)
Reason for Withdrawal: [1]			
Lost to Follow-up	51 (5.2)	23 (4.8)	74(5.1)
Non-compliance with Study Drug	1 (0.1)	0 (0.0)	1(0.1)
Physician Decision	6 (0.6)	3 (0.6)	9(0.6)
Protocol Violation	5 (0.5)	3 (0.6)	8(0.5)
Withdrawal by Subject	18 (1.8)	10 (2.1)	28(1.9)
Other	0 (0.0)	1 (0.2)	1(0.1)
Completed Toddler Dose vaccinations [2]	844 (85.6)	420 (86.2)	1264 (85.8)

[1] Percentages were based on the number of randomized subjects who received at least 1 dose of PR5I or Control.

[2] Received Toddler Dose of DAPTACEL, monovalent Hib vaccine, and concomitant study vaccines (including subjects who received vaccines at non-study visits).

Percentages were based on the number of randomized subjects.

One primary reason for discontinuation per subject was reported, Other - Other criteria specified in the protocol that is not met by the subject. mos = months, N = Number of subjects vaccinated, n = Number of subjects in analysis.

Source Adapted from the CSR Protocol 005, Page 87.

6.1.10 Efficacy Analyses

Immunogenicity data sets

Two per protocol (PP) populations were used, namely PP-RW and PP-OW, described below.

The two PP populations had the same definition -- specifically, all subjects who met the inclusion criteria, who were not protocol violators and had serology results within the specified day ranges -- except for their day ranges (windows) for vaccinations and blood draw samples.

1. For PP-RW (PR5I: 765 subjects, i.e., 77.6% of 986 randomized subjects; Control: 382 subjects, i.e., 78.4% of 487 randomized subjects):

- vaccination-window was Days 42 to 84 after the previous vaccination, and a blood draw sample window of Days 28 to 51 following dose 3 or the Toddler dose.

2. For PP-OW (PR5I: 716 subjects, i.e., 72.6% of 986 randomized subjects; Control: 354 subjects, i.e., 72.7% of 487 randomized subjects):

- vaccination-window was Days 46 to 74 after the previous vaccination, and a blood draw sample window of Days 28 to 44 following dose 3 or the Toddler dose.

For primary immunogenicity analyses, the hypothesis tests were based on the results from the PP-RW population. The results from the PP-OW population were for supportive purpose. The applicant contended that the revised window was based on results from earlier Phase II studies, would allow more vaccinees to contribute to immunogenicity data in the PP analyses, and was chosen prior to the final lock of the database.

3. Full Analysis Set (FAS) population: The Applicant also performed supportive analyses based on the Full Analysis Set (FAS) population, which includes all randomized subjects with available serology data.

6.1.10.1 Analyses of Primary Efficacy Endpoints

Table 5 shows the primary immunogenicity results based on the PP-RW population. The non-inferiority (NI) analysis results regarding PR5I response rates and GMT antibodies at one month postdose 3 for the PP-RW population are provided. The results show that the lower bounds of the 2-sided 95% CIs about the group differences or GMT ratios (PR5I vs Control) exceeded the

Table 5: Non-Inferiority Analysis of PR5I Antigen Responses One Month Postdose 3 Compared to Control (PP-RW Population)

		PR5I N=924	PR5I N=924	Control N=460	Control N=460	Estimated Difference/ GMT Ratio (95% CI)	NI margin	Conclusion: Non- inferiority Criterion Met/Not Met
Antigen	Endpoint	n	Estimated Response	n	Estimated Response			
PRP	% with titer ≥ 1.0 $\mu\text{g/mL}$	765	84.99	382	75.31	9.68 (4.83, 14.83)	-10%	Met
PRP	% with titer ≥ 0.15 $\mu\text{g/mL}$	765	97.26	382	92.39	4.87 (2.23, 8.14)	-5%	Met
HBsAg	% with titer ≥ 10 mIU/mL	688	99.42	353	98.58	0.84 (-0.35, 2.74)	-10%	Met
Diphtheria	% with titer ≥ 0.1 IU/mL	786	82.44	393	86.28	-3.84 (-8.02, 0.66)	-10%	Met
Tetanus	% with titer ≥ 0.1 IU/mL	787	99.87	390	99.48	0.39 (-0.28, 1.74)	-5%	Met
PT	% vaccine response [1]	796	98.12	391	98.45	-0.33 (-1.80, 1.60)	-10%	Met
PT	GMT	810	109.61	400	85.41	1.28 (1.20, 1.38)	0.67	Met
FHA	% vaccine response [1]	796	87.33	391	92.04	-4.70 (-8.14, -0.97)	-10%	Met
FHA	GMT	810	46.59	400	72.28	0.64 (0.59, 0.70)	0.67	Not Met
PRN	% vaccine response [1]	794	79.34	390	82.01	-2.67 (-7.27, 2.23)	-10%	Met
PRN	GMT	808	55.77	400	66.81	0.83 (0.73, 0.95)	0.67	Met
FIM	% vaccine response [1]	796	90.20	391	86.15	4.05 (0.23, 8.28)	-10%	Met
FIM	GMT	809	235.87	400	184.40	1.28 (1.15, 1.42)	0.67	Met
IPV1	% with Nab $\geq 1:8$ dilution	806	100.00	398	98.24	1.76 (0.85, 3.59)	-5%	Met
IPV2	% with Nab $\geq 1:8$ dilution	801	100.00	399	99.74	0.26 (-0.22, 1.42)	-5%	Met
IPV3	% with Nab $\geq 1:8$ dilution	790	100.00	396	99.75	0.25 (-0.24, 1.41)	-5%	Met

[1] For pertussis vaccine response definition, refer to footnote in Table 3.

CI = Confidence interval, GMT = Geometric mean titer, N = Number of subjects vaccinated, n = Number of subjects included in the analysis, Nab = Neutralizing antibodies, NI = Non-inferiority, PP-RW = Per-protocol-Revised Window (defined as vaccination window Days 42 to 84 after the previous vaccination and a blood draw sample window of Days 28 to 51 following Dose 3 or the Toddler dose),

Source Adapted from the CSR Protocol 005, page 117-118.

corresponding pre-specified NI margins for all antigens except for FHA. For the FHA antigen, the GMT ratio's lower bound of 0.59 did not exceed the margin of 0.67 and the NI criterion was not met.

The pertussis vaccine response, in addition to being evaluated at post dose 3 of infant series, was also evaluated at one month after the Toddler dose following study's primary objectives (ref. section 6.1.1).

Non-inferiority criteria were met for the pertussis vaccine response rates and antibody GMTs, at one month after the toddler dose of DAPTACEL following the infant series of PR5I/Control. The analyses based on the PP-RW population are included in Table 6. The lower bounds of the 2-sided 95% CIs for the differences (PR5I - Control) in vaccine response rates and GMT ratios between the PR5I and the Control groups exceeded the pre-specified NI margins, indicating that the PR5I group was non-inferior to the Control group in terms of pertussis responses. It is noted that for the PRN GMT, the observed lower bound of 0.68 was close to the NI margin 0.67, but did exceed it.

Table 6: Non-Inferiority Analysis of Pertussis Antigen Responses One Month after Toddler Dose: PR5I versus Control (PP-RW Population)

		PR5I (N=843)	PR5I (N=843)	Control (N=420)	Control (N=420)	Estimated Difference/ GMT Ratio (95% CI)	NI Margin	Conclusion: Non- inferiority Criterion Met/Not met
Antigen	Endpoint	n	Estimated Response	n	Estimated Response			
PT	% vaccine response	701	99.28	349	97.40	1.88 (0.39, 4.18)	-10%	met
PT	GMT	713	126.90	356	90.78	1.40 (1.28, 1.52)	0.67	met
FHA	% vaccine response	699	94.44	350	93.14	1.30 (-1.67, 4.78)	-10%	met
FHA	GMT	710	87.52	357	87.54	1.00 (0.91, 1.10)	0.67	met
PRN	% vaccine response	701	93.00	351	93.41	-0.41 (-3.46, 3.10)	-10%	met
PRN	GMT	713	108.48	358	139.71	0.78 (0.68, 0.89)	0.67	met
FIM	% vaccine response	700	97.30	351	91.12	6.18 (3.26, 9.78)	-10%	met
FIM	GMT	713	657.28	358	415.00	1.58 (1.41, 1.78)	0.67	met

Source CSR Protocol 005, page 122

IPV Response Rate.

Also, from Table 5, the inactivated poliovirus (IPV) response rates ($\geq 1:8$) in the PR5I group were 100% for all IPV antigens (1, 2, and 3), and each rate had a 2-sided 95% CI lower bound of 99.5%, indicating that the acceptability criterion was met. It was defined in the protocol that the IPV response rate was acceptable if its 2-sided 95% CI lower bound was $> 90\%$. The analysis was not listed as one of the primary objectives in the SAP, however.

The above conclusions from Table 5 and Table 6 did not change based on the applicant's supportive analyses obtained from the PP-OW and FAS populations (results not shown in this review).

Adjusted vs. Unadjusted Analyses.

Following the pre-specified Statistical Analysis summarized in section 6.1.8, the applicant evaluated the non-inferiority of PR5I responses, adjusting for the brand of birth dose of hepatitis

B vaccine and pre-vaccination titers, with results provided in Table 5 (for postdose 3) and Table 6 (for Toddler dose) of this review. The applicant submitted the same non-inferiority analyses without the said adjustment (STN 125563/0.6, page 8-16), based on CBER's request. The results from the unadjusted and adjusted analyses were found to be very close by arm and the two analyses led to no difference in primary analysis conclusions. Detailed unadjusted results are not included in this review; however, a few key results are described below.

For the PT antigen, the unadjusted GMTs postdose3 by arm (PR5I, Control) were, respectively, (110.40, 86.54), compared to the respective, adjusted postdose3 GMTs (109.61, 85.41) shown in Table 5. The corresponding unadjusted vs. adjusted GMTs, by arm (PR5I, Control), were (48.17, 74.44) vs. (46.59, 72.28) for the FHA antigen, (56.22, 66.16) vs. (55.77, 66.81) for the PRN antigen, and (235.62, 185.54) vs. (235.87, 184.40) for the FIM antigen. The unadjusted results are shown in STN 125563/0.6, pages 8-16, and the adjusted results are included in Table 5 of this review. From the unadjusted vs. adjusted comparisons, the results were similar for the Toddler dose also, but are not shown here. Similar results were expected, given no marked variation in the infants' pre-vaccination GMTs across arms (Appendix-3).

6.1.10.2 Analyses of Secondary Endpoints

1. To compare anti-polyribosylribitol phosphate (PRP) responses elicited by PR5I with the component vaccine Control(s).

The secondary analysis of non-inferiority of anti-PRP response rate (% with ≥ 0.15 $\mu\text{g/mL}$) at one month postdose3 was basically the same when the response rate was analyzed as one of the primary endpoints postdose3, except that in the secondary analysis the NI margin was widened to -10%. An observed response rate difference (PR5I – Control) of 4.87% (95% CI: 2.23%, 8.14%), which already met the -5% NI margin in the primary analysis automatically met the -10% margin in the secondary analysis. With regard to anti-PRP titers one month postdose3, the GMT ratio (PR5I/Control) was 1.62 (95% CI: 1.32, 1.98), with the lower bound of the 2-sided 95% CI for the ratio exceeding 0.67, indicating a non-inferior response in the PR5I group compared to the Control group. The applicant obtained these results based on the PP-RW population, but had similar results when based on the PP-OW and FAS populations (results not shown).

2. To evaluate the immunogenicity of RotaTeq when administered concomitantly with PR5I.

For anti-rotavirus IgA, the GMT was 282.5 for the PR5I group (n=522) and 277.9 for the Control group (n=274), resulting in the GMT ratio (PR5I/ Control) of 1.02 (95% CI: 0.83, 1.24). The lower bound of the 2-sided 95% CI exceeded the threshold 0.67, thereby indicating non-inferior response to RotaTeq in the PR5I group compared to the Control group. The findings were similar when obtained from the PP-OW and FAS populations (results not shown).

6.1.10.3 Reviewer's Comment and Overall Conclusions about Efficacy

Reviewer's Comment/Observations

In PP-RW analyses, 17.8% to 30.2% of subjects were excluded for different antigen endpoints at one month postdose 3 in the PR5I group, and 17.9% to 27.5% in the Control group. In PP-OW

analyses, these exclusion rates ranged from 22.9% to 34.6% in the PR5I group, and from 24.0% to 32.6% in the Control group. For RotaTeq IgA endpoint one month postdose 3, the exclusion rates were 47.1% in the PR5I group and 43.7% in the Control group. For the toddler dose, PP-RW population, the exclusion rates were around 28% in both study groups. In the same context, for study 006, such exclusions of subjects in different antigen endpoints ranged from 20.9% to 28.9% at one month postdose3 and from 27.4% to 40.0% at one month after the toddler dose, regardless of study group, for the PP-RW population. The most common reasons for the exclusions were reported as Vaccination out of day range (window), Received incomplete or incorrect study vaccine regimen for the PR5I/ Control group, and Sample not collected. The submission did not indicate whether any approach to compensate for such exclusions was taken, except for multiple imputation for missing baseline titers.

Efficacy Conclusions

1. Based on the study's immunogenicity measurements at 1 month postdose3 of the 3-dose infant series of vaccination:
 - a. Non-inferiority criteria were met with regard to immune response rates among the PR5I vaccinees when compared to Control, for all antigens (Table 5).
 - b. Non-inferiority criteria were met with regard to GMTs among the PR5I vaccinees when compared to Control, for all antigens except for the FHA antigen (Table 5).
2. For the toddler dose with DAPTACEL, the pertussis response rates and GMTs among subjects vaccinated with the 3-dose infant series of PR5I vaccine met non-inferiority criteria compared to the licensed Control (Table 6).
3. All IPV response rates were 100% (Table 5). Each rate had 95% CI lower bound > 90% (section 6.1.10.1).

6.1.11 Subgroup Analyses

In the presence of an array of endpoints for all antigens (Table 3), the submission included demographic subgroup analyses of efficacy based on the integration of pivotal phase III studies, Protocols 005 and 006. The submission mentioned that such integration was supported at the End of Phase II Clinical Meeting with CBER in January 2008. Section 7 presents the antibody GMT summaries by antigens for race and sex subgroups from the Integrated Population.

6.1.12 Safety Analyses

6.1.12.1 Overall Adverse Events

An overall summary of adverse events (AE) is provided in Table 7. As the table shows, 95.5% of the PR5I vaccinees (936/980) experienced one or more adverse events (AEs) during the first 15 Days after any infant dose of vaccination. The rate was 93.4% (451/483) in the Control group. For solicited injection-site AEs and solicited systemic AEs during Day 1 to Day 5, respectively, the arm-wise (PR5I, Control) percentages were (83.8%, 80.5%) and (92.3%, 89.4%). Serious AEs occurred to 21 (2.1%) subjects in the PR5I group, compared to 8 (1.7%) subjects in the Control group, during Day 1 to Day 15 of vaccination. Of these, one subject in the PR5I group had an apparent life threatening event on Day 1 and Day 3 after the first dose, and the

investigator could not rule out the relatedness to study vaccines due to the timing of the onset of the serious adverse event. However, the adverse event did resolve (CSR 005, page 170). There were no vaccine related serious AEs in the Control group.

**Table 7: Clinical Adverse Event Summary After Any Infant Dose Vaccination
(All Subjects as Treated Population, N_{PR5I}=981, N_{Control}=484)**

	PR5I n (%)	Control n (%)	Difference (95% CI)
Number of subjects with known values after any vaccination.	980	483	-
With one or more adverse events (Day 1 to Day 15)	936 (95.5)	451 (93.4)	2.1 (-0.3, 5.0)
Injection-site adverse events (Day 1 to Day 15)	824 (84.1)	390 (80.7)	3.3 (-0.7, 7.7)
Solicited injection-site adverse events (Day 1 to Day 5)	821 (83.8)	389 (80.5)	3.2 (-0.9, 7.6)
Systemic adverse events (Day 1 to Day 15)	918 (93.7)	439 (90.9)	2.8 (-0.0, 6.0)
Solicited systemic adverse events (Day 1 to Day 5)	905 (92.3)	432 (89.4)	2.9 (-0.1, 6.3)
With vaccine-related adverse events (Day 1 to Day 15) [1]	926 (94.5)	446 (92.3)	2.2 (-0.5, 5.2)
With serious adverse events (Day 1 to Day 15)	21 (2.1)	8 (1.7)	0.5 (-1.2, 1.9)
With serious adverse events (Day 1 after Dose 1 to Day 181 after Dose 3)	53 (5.4)	31 (6.4)	-1.0 (-3.8, 1.4)
Who died [2]	1 (0.1)	1 (0.2)	-0.1 (-1.1, 0.4)
Discontinued due to an adverse event [2]	1 (0.1)	1 (0.2)	-0.1 (-1.1, 0.4)

[1] Determined by the investigator to be related to the vaccine.

[2] This category included adverse events that occurred after any infant dose vaccination up to before the Toddler vaccination.

Percentages were based on the number of subjects in the population.

N = Number of vaccinated subjects, n = Number of subjects in each category.

Source Adapted from the CSR Protocol 005, page 140.

During the longer period from Day 1 to Day 181 following any infant dose, serious AEs were reported for 53 (5.4%) subjects in the PR5I group and 31 subjects (6.4%) in the Control group. For at least 60% of the subjects with these AEs, the illnesses were infections and infestations, dehydration, respiratory, thoracic, and mediastinal disorders. Two deaths occurred during the trial, one a 23-week old multiracial male randomized to the PR5I group and reportedly died of positional asphyxia ^{(b) (6)} days post dose 2; the other one was a 12-week old white female with a history of premature birth (born at 31 weeks), randomized to the Control group and died ^{(b) (6)} days post dose 1 with reported diagnoses of pneumonia, aspiration, cardiac arrest, and respiratory arrest. None of the deaths was reported as related to study vaccination by the investigator. Additionally, two subjects discontinued, one in each arm, having vaccine-related non-serious AEs (injection-site erythema and irritability of moderate intensity), but the AEs were reportedly resolved within less than 48 hours of vaccination.

6.1.12.2 Solicited Injection-Site AEs

Table 8 provides information on solicited injection-site adverse events during Day 1 to Day 5 following any dose of the infant series. The solicited injection-site erythema AEs occurred to 48.8% of the 980 PR5I vaccinees, and to 42.2% of the 483 Control subjects. These percentages by arm (PR5I and Control) were respectively 73.4% and 71.8% for injection-site pain, and 40.1% and 34.8% for injection-site swelling. The data showed, in the PR5I group, excess percentages of 6.5% (95% CI: 1.1%, 11.9%) and 5.3% (95% CI: 0.0, 10.5) of subjects experiencing injection-site erythema and swelling, respectively, compared to Control. But large proportions ($\geq 89\%$) of these AEs had erythema/swelling of less than 2.5 cm, and pain of mild or moderate intensity.

Table 8: Solicited Injection-Site Adverse Events and Solicited Systemic Adverse Events (Incidence > 0%), Day 1 to Day 5, Following Any Infant Dose Vaccination (All Subjects as Treated Population, N_{PR5I}=981, N_{Control}=484)

	PR5I n (%)	Control n (%)	Difference (95% CI)
Subjects with known values after any vaccin	980	483	-
Injection-site erythema	478 (48.8)	204 (42.2)	6.5 (1.1, 11.9)
Injection-site pain	719 (73.4)	347 (71.8)	1.5 (-3.3, 6.5)
Injection-site swelling	393 (40.1)	168 (34.8)	5.3 (0.0, 10.5)
Maximum Temperature (≥ 39.5 C, rectal)	19 (2.0) *	4 (0.9) *	1.2 (-0.3, 2.4)
Systemic AE Crying	733 (74.8)	349 (72.3)	2.5 (-2.2, 7.5)
Systemic AE Decreased appetite	479 (48.9)	209 (43.3)	5.6 (0.2, 11.0)
Systemic AE Irritability	814 (83.1)	395 (81.8)	1.3 (-2.8, 5.6)
Systemic AE Pyrexia	465 (47.4)	166 (34.4)	13.1 (7.7, 18.3)
Systemic AE Somnolence	726 (74.1)	346 (71.6)	2.4 (-2.3, 7.4)
Systemic AE Vomiting	252 (25.7)	104 (21.5)	4.2 (-0.5, 8.7)

N = Number of vaccinated subjects, n = Number of subjects in each category.

*Number of subjects with temperature data were 949 in PR5I and 470 in Control.

Source Adapted from the CSR Protocol 005, pages 142,148, 155.

6.1.12.3 Solicited Systemic AEs

Table 8 also provides solicited systemic adverse events during Day 1 to Day 5 following any dose of the infant series. As seen from Table 7, 905 (92.3%) subjects in the PR5I group and 432 (89.4%) subjects in the Control group experienced one or more solicited systemic AEs by Day 5 of any dose. The most frequent AEs were Crying (74.8% in PR5I vs 72.3% in Control), Irritability (83.1% vs. 81.8%), and Somnolence (74.1% vs 71.6%). Pyrexia (fever) was reported by 47.4% subjects in the PR5I group and 34.4% subjects in the Control group. The difference of 13.1% (95% CI: 7.7%, 18.3%) was statistically significant. A large proportion of these AEs were reported as mild/moderate in intensity. Additionally, for solicited systemic AEs after each dose in the PR5I group, the AEs did not show increased frequency with subsequent vaccinations. However, for pyrexia, the frequency increased from 16% at post vaccination visit 1 to 26.6% at post vaccination visit 2 and remained at that level at post vaccination visit 3. In the Control group, such an increase was not observed; the percentages at the three vaccination visits were respectively 12.6%, 16.4%, and 16.2%. As will be seen later in section 8, similar trends and frequencies were observed in the integrated safety analysis.

Furthermore from Table 8, 19 (2.0%) vaccinees out of 949 in the PR5I group reported severe elevated temperature ($\geq 39.5^{\circ}\text{C}$, rectal route) following any dose in the infant series compared to 4 (0.9%) subjects out of 470 in the Control group. Based on the reviewer's calculation using an exact test, the relative risk of elevated temperature (PR5I vs. Control) was 2.35 (95% CI: 0.86, 10.40). The observed lower bound (0.86) being less than 1.0 made excess risk inconclusive; with regard to the risk's clinical significance, the reviewer defers to the clinical reviewer. A similar relative risk of 2.14 (95% CI: 1.11, 4.58) was observed based on the larger integrated population, as will be seen in section 8.2.3.

6.1.12.4 Subgroup Analyses

The post hoc subgroup analyses of safety were performed by race and sex, with details provided as part of the integrated safety analysis in section 8.3. The results were consistent with the overall safety results.

6.1.12.5 Safety Conclusions

Overall, the PR5I group reported one or more adverse events in 95.5% of the subjects, compared to 93.4% in the Control group, during Day 1 to Day 15 following any dose of vaccination in the infant series. For the Day 1 to Day 5 period following any infant dose, the percentage of subjects reporting solicited injection-site AEs were 83.8% in the PR5I group compared to 80.5% in the control group; for solicited systemic AEs the rates were 92.3% and 89.4% for the PR5I and Control groups, respectively. Of the solicited injection site AEs, the PR5I group experienced more frequently injection erythema and swelling than the control group, with a rate difference of 6.5% and 5.3%, respectively. These events were mostly mild or moderate in intensity. The PR5I vaccinees also had more frequent pyrexia compared to the control group, with the rate difference being 13.1% (95% CI: 7.7%, 18.3%). The pyrexia events, however, were also mostly reported as mild or moderate in intensity. The study reported no vaccine related deaths. One subject in the PR5I group had a vaccine related serious adverse event after the first dose, but it was eventually resolved. Given all these findings, the general safety profile of PR5I appears to be comparable to that of the Control group.

6.2 Pivotal Study#2: Protocol 006

TITLE: A Phase III Randomized, Partially Double-Blind, Active-Comparator-Controlled, Lot-to-Lot Consistency Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V419 in Healthy Infants When Given at 2, 4, and 6 Months Concomitantly with Prevnar 13 and RotaTeq.

6.2.1 Objectives

Primary Objective:

To evaluate the consistency of the Postdose 3 immune response to 3 manufactured lots of PR5I when given at 2, 4, and 6 months of age with respect to geometric mean titers (GMTs).

Primary Hypothesis:

Three manufacturing lots (Lots A, B, and C) of PR5I induce similar GMTs to all antigens contained in PR5I at one month after the third dose of PR5I, when given concomitantly with Prevnar 13 and RotaTeq.

The statistical criterion requires that, for each of the PR5I antigens, the 2-sided 95% CIs of the GMT ratios between any 2 lots be within the equivalence margin (0.67 to 1.5).

Safety Objective:

To describe the safety profile associated with the administration of each dose of PR5I or the component vaccine Control when given concomitantly with Prevnar 13 and RotaTeq.

6.2.2 Study Design

This was a randomized, partially double-blind, active comparator-controlled, lot-to-lot consistency study based on a total of 2808 healthy infants. The infants were 46 to 89 days old at enrollment and had a dose of monovalent hepatitis B vaccine at birth or <1 month of age, as part of standard medical practice. The parent/legal representatives of the infant subjects voluntarily provided written informed consent. The subjects were randomized at a 2:2:2:1 ratio to one of 4 vaccination groups: Lot A, Lot B, Lot C, or Control. Lots A, B, and C were 3 different manufacturing lots of the PR5I vaccine. Inclusion of the Control group where the subjects received licensed component vaccines, made possible for an overall comparison of all PR5I vaccinees regardless of clinical lots with Control vaccinees, even though lot consistency evaluation was the study's primary objective.

Subjects in each lot group (N≈800) received PR5I, Prevnar 13 and RotaTeq at 2, 4, and 6 months, and PENTACEL and Prevnar 13 at 15 months. Subjects in the Control group (N=402) received PENTACEL, Prevnar 13 and RotaTeq at 2, 4, and 6 months, RECOMBIVAX HB at 2 and 6 months, and PENTACEL and Prevnar 13 at 15 months (Table 9). The study personnel and subjects were blinded to individual lot assignments, but aware of assignment to PR5I vs. Control.

Table 9: Vaccine Administration by Vaccination Group [Lot A, n=800; Lot B, n=797; Lot C, n=809; Control, n=402]: Lot Consistency Study

Group	Vaccine Administered	Dose	Route of Administration	Visit 1 2 months	Visit 2 4 months	Visit 3 6 months	Visit 6 15 months
PR5I Lot A	PR5I ¹	0.5 mL	IM	X	X	X	
PR5I Lot A	PENTACEL ²	0.5 mL	IM				X
PR5I Lot A	Prevnar 13 ³	0.5 mL	IM	X	X	X	X
PR5I Lot A	RotaTeq ⁴	2.0 mL	Oral	X	X	X	
PR5I Lot B	PR5I ¹	0.5 mL	IM	X	X	X	
PR5I Lot B	PENTACEL ²	0.5 mL	IM				X
PR5I Lot B	Prevnar 13 ³	0.5 mL	IM	X	X	X	X
PR5I Lot B	RotaTeq ⁴	2.0 mL	Oral	X	X	X	
PR5I Lot C	PR5I ¹	0.5 mL	IM	X	X	X	
PR5I Lot C	PENTACEL ²	0.5 mL	IM				X
PR5I Lot C	Prevnar 13 ³	0.5 mL	IM	X	X	X	X
PR5I Lot C	RotaTeq ⁴	2.0 mL	Oral	X	X	X	
Control	PENTACEL ²	0.5 mL	IM	X	X	X	X
Control	RECOMBIVAX HB ⁵	0.5 mL	IM	X		X	
Control	Prevnar 13 ³	0.5 mL	IM	X	X	X	X
Control	RotaTeq ⁴	2.0 mL	Oral	X	X	X	

¹ PR5I = V419 = DTaP-IPV-Hib-HepB.

² PENTACEL = DTaP, IPV, and *Haemophilus b* Conjugate (Tetanus Toxoid conjugate) Vaccine.

³ Prevnar 13 = Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein).

⁴ RotaTeq = Rotavirus Vaccine, Live, Oral, Pentavalent.

⁵ RECOMBIVAX HB = recombinant hepatitis B vaccine.

DTaP = Diphtheria, tetanus, and acellular pertussis, HepB = Hepatitis B, Hib = *Haemophilus influenzae* type b, IM = Intramuscular, IPV = Inactivated poliovirus.

Source: CSR Protocol 006, page 6.

6.2.3 Population

Same as in previous section 6.1.3.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Same as in previous Section 6.1.4.

6.2.5 Sites and Centers

The study was conducted at 73 centers in the USA. The recorded study period was from 11 May 2011 (First Patient Entered) to 26 July 2013 (Last Patient Last Visit).

6.2.6 Surveillance/Monitoring

Please refer to the medical officer's review.

6.2.7 Endpoints and Criteria for Study Success

Primary Immunogenicity

The primary immunogenicity endpoints for evaluating the primary hypothesis of lot consistency were the GMTs for all antigens contained in PR5I one month after the third dose of PR5I. The hypothesis was stated in section 6.2.1.

The statistical criterion for establishing lot consistency required that, for each of the PR5I antigens, the 2-sided 95% CIs of the GMT ratios between any 2 lots be contained within the specified equivalence margin (0.67 to 1.5).

Safety

The safety endpoints included measurements of temperatures and solicited adverse events (local and/or systemic) from Day 1 through Day 5 following each vaccination, adverse events recorded from Day 1 through Day 15 following each vaccination, serious adverse events monitored up to 180 days following completion of the infant series, and serious adverse events and deaths throughout the study. Safety evaluation was not designed to have statistical power; thus only descriptive statistics are provided.

6.2.8 Statistical Considerations and Statistical Analysis Plan

Lot consistency evaluation was based on GMTs. The objective was to establish that the GMT ratios in 3 lot-pairs are contained within the interval (0.67, 1.5) for all antigens. The study planned 680 evaluable subjects per lot for 92% overall power.

The GMT ratio and 95% confidence interval (CI) for each pair of the 3 lots were calculated based on an ANCOVA model, where log-transformed postvaccination titer was the dependent variable and log-transformed prevaccination titers, lot group, and actual brand of birth dose hepatitis B vaccine received (i.e., RECOMBIVAX HB or Other/Unknown) were used as fixed effect variables. Missing prevaccination (i.e., baseline) titers were imputed and analyzed by using the SAS PROC MI and PROC MIANALYZE procedures. Relevant details are provided in section 6.1.8.

As primary analysis, lot consistency based on GMTs one month postdose 3 was established by using the per-protocol (PP) population, which used the revised (PP-RW) vaccination-window of Days 42 to 84 after the previous vaccination and a blood draw sample window of Days 28 to 51

following Dose 3 or the Toddler dose. Further details about the PP population and revised windows were provided in section 6.1.10.

6.2.9 Study Population and Disposition

Demographic characteristics at baseline

A total of 2808 subjects were randomized at a 2:2:2:1 ratio to one of the 3 different PR5I lot groups or the Control group. The proportions of males varied from 52.9% to 54.1% in the PR5I groups, compared to 46.5% in the Control group. Overall, across the four groups, whites comprised 67.8% of subjects, blacks were 9.4%, and the remaining 23.0% included multi-racial and others. The mean age was 64.5 (SD=6.5) days (range: 46 to 89 days) and average weight was 5.3 (SD=0.7) kg (range: 3 to 9 kg).

Disposition of subjects

The study screened 3019 subjects for participation. Of these, 2808 were randomized. A total of 2600 (92.6%) randomized subjects completed all 3 doses of the infant series (PR5I/ Control). Among those who did not complete the series (7.1%), the majority (85.4%) were lost to follow-up or subject withdrawal. These proportions were similar across the PR5I lot groups and the control group. Additionally, 82.9% subjects (ranging 81.3% to 84.3% in the PR5I lots and control groups) completed the toddler doses. Among those who discontinued between the infant series and the toddler dose (n=271, 9.7%), the majority (85.9%) were lost to follow-up or subject withdrawal.

6.2.10 Efficacy Analyses

6.2.10.1 Primary Immunogenicity Analyses of Lot Consistency Based on GMTs of PR5I Antigens at One Month Postdose 3

The lot GMTs induced by PR5I at one month postdose3 and the GMT ratios in lot-pairs are provided by antigen in Table 10 for the PP-RW population, as the primary analyses. The lower and upper limits of the 2-sided 95% CI of the GMT ratios for each lot-pair and antigens were within the equivalence margin (0.67 to 1.5), thus supporting lot consistency among the 3 manufacturing lots. The applicant provided similar, supportive results based on the PP-Original Windows (PP-OW) population and Full Analysis Set (FAS) population, but are not included in this review.

Table 10: Lot Consistency Analysis of GMT Based on ANCOVA Model at One Month Postdose 3 (PP-RW Population)

Antigen	Lot A n GMT	Lot B n GMT	Lot C n GMT	Lot A/Lot B Ratio (95% CI)	Lot A/Lot C Ratio (95% CI)	Lot B/Lot C Ratio (95% CI)	Lot Consistency Criteria Met?
PRP	604 5.51	596 6.10	595 6.59	0.91 (0.77, 1.08)	0.86 (0.72, 1.02)	0.94 (0.79, 1.12)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
HBsAg	588 1195.96	599 1376.86	580 1414.52	0.87 (0.76, 0.98)	0.85 (0.74, 0.96)	0.98 (0.86, 1.11)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
Diphtheria	622 0.37	625 0.36	618 0.38	0.95 (0.84, 1.07)	0.97 (0.86, 1.09)	1.02 (0.90, 1.14)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
Tetanus	622 1.59	609 1.63	612 1.55	0.97 (0.91, 1.04)	1.02 (0.95, 1.09)	1.05 (0.98, 1.13)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
PT	647 100.83	634 96.82	622 98.52	1.03 (0.96, 1.10)	1.02 (0.95, 1.09)	0.99 (0.92, 1.06)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
FHA	644 43.98	631 49.19	628 56.93	0.89 (0.83, 0.96)	0.78 (0.72, 0.83)	0.87 (0.81, 0.94)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
PRN	632 51.30	616 52.32	611 54.78	0.97 (0.87, 1.09)	0.93 (0.83, 1.05)	0.96 (0.85, 1.08)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
FIM	641 228.78	632 286.74	623 283.28	0.78 (0.72, 0.85)	0.80 (0.73, 0.87)	1.02 (0.93, 1.11)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
IPV1	630 579.77	632 684.68	628 666.18	0.86 (0.76, 0.96)	0.88 (0.79, 0.99)	1.03 (0.92, 1.15)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
IPV2	630 1212.40	632 1276.56	633 1359.78	0.94 (0.84, 1.05)	0.91 (0.82, 1.02)	0.98 (0.87, 1.09)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
IPV3	624 901.70	625 851.34	625 825.31	1.06 (0.92, 1.22)	1.09 (0.95, 1.26)	1.03 (0.90, 1.19)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes

CI = Confidence interval, GMT = Geometric mean titer, n = Number of subjects included in the analysis

Source Adapted from the CSR Protocol 006, pages10-11.

6.2.10.2 Secondary Immunogenicity Analysis of Non-Inferiority of PR5I Antigen Responses One Month Postdose 3

The applicant also provided non-inferiority (NI) analysis of the PR5I antigen responses at one month postdose 3 for the PP-RW population. The results and the conclusions made were consistent with those observed in the pivotal 005 study (Table 5). The lower limits of the 2-sided 95% CIs for the differences (PR5I vs. Control) were above the corresponding pre-specified NI margins for all pre-specified endpoints and antigens at one month postdose 3, except for the FHA antigen measured in GMT. Non-inferiority was observed for the pertussis response as well at one month after the toddler dose of PENTACEL, except for the GMT for the PRN antigen. Overall, these results were mostly consistent with those based on the PP-OW and FAS populations.

6.2.10.3 Efficacy Conclusions

In healthy infants who received 3 doses of PR5I at 2, 4, and 6 months administered concomitantly with Prevnar and RotaTeq, followed by PENTACEL and Prevnar 13 at 15 months of age, the following conclusions about immunogenicity can be drawn.

1. As the primary objective, the consistency of the 3 clinical lots was demonstrated based on GMTs at one month postdose 3 for all antigens contained in PR5I. The lower and upper limits of the 2-sided 95% CIs of the GMT ratios in lot-pairs for all antigens were within the pre-specified equivalence margin (0.67, 1.5).
2. In the secondary analyses, the applicant's results showed that the immune responses induced by PR5I in 3-dose infant series of vaccination met the criteria for non-inferiority with respect to the licensed control for all pre-specified endpoints (postdose 3), except for the GMT of the FHA antigen. Similar comparability in pertussis responses after the toddler dose of PENTACEL following the 3-dose infant series was observed, except for GMT of the PRN antigen.

6.2.11 Subgroup Analyses

The applicant included demographic subgroup analyses of efficacy based on the Integrated Population of pivotal phase III studies, Protocols 005 and 006. Section 7 presents GMT summaries by antigens for race and sex subgroups, using the integrated efficacy data base.

6.2.12 Safety Analyses

These analyses are included in section 8, based on integration of safety data from the pivotal phase III studies, Protocols 005 and 006. The two studies used a USA immunization schedule and USA licensed comparator vaccines.

7. Integrated Efficacy

7.1 Background and Design

The two pivotal studies (Protocol 005 and Protocol 006) were very similar in study design and study population, used a common USA immunization schedule and USA licensed comparator vaccines, and had common immunogenicity and safety measurements. Therefore, these similarities allowed pooling of the immunogenicity and safety information across the two studies, to provide summary immunogenicity and safety profiles about PR5I.

Study 006 had a control group added to the three PR5I lot groups. This made the study's design basically similar to the two-arm design used in the pivotal study 005. In each study, the PR5I or licensed control vaccines were used in an infant series followed by a toddler dose [DAPTACEL with the concomitant vaccinations PedvaxHIB/ActHIB in study 005 and PENTACEL in study 006, with Prevnar13 as common] for pertussis vaccination at 15 months of age. The two licensed vaccines, DAPTACEL and PENTACEL, were reported in the application to have generally similar pertussis response rates. Also, besides design similarities, both studies enrolled

infants 46 to 89 days of age who had received one dose of monovalent hepatitis B vaccine as part of the standard medical practice not related to the current study. The duration of both studies was about 14 months for each subject, i.e., to 16 months of age.

The results below are from the pooled immunogenicity data of the two studies. The integrated population (N=3392 in PR5I, N=889 in control) as shown in Table 11 had generally comparable demographic characteristics. Overall, in both study groups, the majority of the subjects were white (71.7%), 11.0% black, almost half were male (52.6%), and mean age and weight were respectively 65.0 days and 5.2 kg. at the first vaccination or study visit.

Table 11: Subjects' Demographic Characteristics (All Randomized Subjects) (Protocols 005 and 006)

	PR5I	Control	Total
	n (%)	n (%)	n (%)
Number of Subjects with known values in population	3392	889	4281
Male	1790 (52.8)	460 (51.7)	2250 (52.6)
Age (days) [1]: Mean±SD, range	64.9±6.8, 46 to 89	64.7±6.8, 46 to 87	64.8±6.8, 46 to 89
Weight (kg) [2]: Mean±SD, range	5.3±0.7, 3 to 9	5.2 ±0.7, 3 to 8	5.2 ±0.7, 3 to 9
Race			
Black	380 (11.2)	91 (10.2)	471 (11.0)
White	2400 (70.8)	671 (75.5)	3071 (71.7)
Multiracial+Other	612 (18.0)	127 (14.3)	739 (17.3)

[1] Age was calculated as the integer value of (date of vaccination dose 1- date of birth). For the subjects who were randomized and did not receive any vaccination, age was calculated as the integer value of (date of visit 1 – date of birth).

[2] Not included in summary statistics: 5 subjects in PR5I and 2 subjects in Control had unknown weights.

Source Adapted from Summary of Clinical Safety, page 21 of the submission.

7.2 Overview of Efficacy

Based on the integrated population, the results for the primary immunogenicity endpoints supported non-inferiority for PR5I compared to Control, both post dose 3 (Table 12) and after

Table 12: Analysis of PR5I Antigen Responses at One Month Postdose 3 (PP-RW Population) (Protocols 005 and 006)

Antigen	Endpoint	PR5I (N=3156)	PR5I (N=3156)	Control (N=830)	Control (N=830)	Estimated Diff./ GMT Ratio (95% CI)
		n	Estimated Response	n	Estimated Response	
PRP	% with titer > 1.0 µg/mL	2560	86.59	670	78.03	8.55 (5.07, 12.36)
PRP	% with titer > 0.15 µg/mL	2560	97.98	670	94.84	3.15 (1.51, 5.33)
HBsAg	% with titer > 10 mIU/mL	2455	99.73	639	98.84	0.89 (0.25, 2.19)
Diphtheria	% with titer > 0.1 IU/mL	2651	84.37	694	87.25	-2.88 (-5.70, 0.32)
Tetanus	% with titer > 0.1 IU/mL	2630	99.92	690	98.95	0.97 (0.40, 2.17)
PT	% vaccine response [1]	2557	98.45	680	98.11	0.34 (-0.65, 1.84)
PT	GMT	2713	101.86	709	82.12	1.24 (1.18, 1.30)
FHA	% vaccine response [1]	2632	87.39	695	92.09	-4.70 (-7.05, -1.98)
FHA	GMT	2713	46.33	712	70.40	0.66 (0.62, 0.70)
PRN	% vaccine response [1]	2518	79.43	676	78.35	1.08 (-2.49, 4.93)
PRN	GMT	2667	54.60	703	58.93	0.93 (0.85, 1.01)
FIM	% vaccine response [1]	2614	89.86	689	86.58	3.28 (0.46, 6.49)
FIM	GMT	2705	246.29	709	177.04	1.39 (1.30, 1.49)
IPV1	% with NAb > 1:8 dilution	2696	100.00	705	98.95	1.05 (0.48, 2.24)
IPV2	% with NAb > 1:8 dilution	2696	100.00	706	99.91	0.09 (-0.07, 0.81)
IPV3	% with NAb > 1:8 dilution	2664	100.00	700	99.70	0.30 (0.07, 1.17)

N = Number of subjects vaccinated, n = Number of subjects included in the analysis; Analysis methods same as stated in section 6.1.8.

Source Adapted from Integrated Analysis of Efficacy, page 80 of the submission.

Table 13: Analysis of Pertussis Antigen Responses at One Month after Toddler Dose (PP-RW Population) (Protocols 005 and 006)

		PR5I (N=2845)	PR5I (N=2845)	Control (N=746)	Control (N=746)	Estimated Diff./ GMT Ratio
Antigen	Endpoint	n	Estimated Response	n	Estimated Response	(95% CI)
PT	% vaccine response	2317	98.79	603	98.04	0.75 (-0.34, 2.45)
PT	GMT	2457	114.36	627	93.15	1.23 (1.15, 1.31)
FHA	% vaccine response	2368	95.01	611	94.66	0.36 (-1.54, 2.79)
FHA	GMT	2452	92.40	628	99.27	0.93 (0.87, 0.99)
PRN	% vaccine response	2309	92.48	609	91.89	0.59 (-1.82, 3.49)
PRN	GMT	2459	106.84	629	140.50	0.76 (0.70, 0.83)
FIM	% vaccine response	2364	94.51	615	90.39	4.12 (1.55, 7.19)
FIM	GMT	2459	523.59	629	362.31	1.45 (1.34, 1.56)

N = Number of subjects vaccinated, n = Number of subjects included in the analysis; Analysis methods same as stated in section 6 1.8.
 Source Adapted from *Integrated Analysis of Efficacy*, page 85 of the submission.

the toddler dose of pertussis following the infant series (Table 13). As in study 005 (Table 5), the lower bound of the GMT ratio for the FHA antigen (0.62) remained lower than the non-inferiority margin 0.67 in the pooled analysis.

7.3 Subgroup Analyses for GMTs PostDose 3 Infant Series

For the race and sex subgroups, the antibody GMT summaries are provided in Table 14. The pertussis GMTs (PT, FHA, PRN, FIM) as well as GMTs for the IPV antigens in the PR5I and Control groups tended to be higher among blacks than among whites. The GMTs, however, did not show marked male-female differences within the PR5I group or Control group, except that possibly for the IPV antigens, with females appearing to have higher GMTs.

Table 14: Summary of Immunogenicity results [GMT (95% CI), n] One Month Postdose 3 (Infant Series) by PR5I Antigen, in Race and Sex Subgroups (PP-RW Population) (Protocols 005 and 006)

Race

Antigen	White	White	Black	Black
	PR5I (N=2253)	Control (N=632)	PR5I (N=353)	Cont. (N=83)
	GMT (95% CI) [1]	GMT (95% CI) [1]	GMT (95% CI) [1]	GMT (95% CI) [1]
	n	n	n	n
PRP	5.12 (4.76, 5.50) 1835	3.12 (2.68, 3.63) 510	8.3 (6.8, 10.1) 260	3.5 (2.2, 5.6) 57
HBsAG[2]	1188.0 (1127.0, 1252.2) 1746	468.8 (414.8, 530.0) 486	1409.4 (1214.7, 1635.4) 248	706.2 (466.3, 1069.4) 54
Diphtheria[2]	0.34 (0.32, 0.35) 1901	0.34 (0.31, 0.38) 532	0.43 (0.37, 0.50) 268	0.52 (0.38, 0.71) 59
Tetanus [2]	1.78 (1.72, 1.84) 1885	1.02 (0.95, 1.09) 529	2.39 (2.19, 2.62) 265	1.42 (1.12, 1.79) 60
PT	94.5 (92.0, 97.1) 1952	80.6 (77.0, 84.4) 545	153.9 (142.2, 166.6), 277	127.2 (111.1, 145.7) 61
FHA	48.2 (46.6, 49.8) 1952	71.5 (67.3, 76.1) 548	52.6 (47.9, 57.8) 277	90.5 (74.5, 109.8) 61
PRN	50.8 (48.4, 53.3) 1909	54.9 (50.1, 60.2) 540	81.9 (72.2, 93.0) 275	105.9 (85.3, 131.5) 61
FIM	238.5 (229.5, 247.9) 1943	167.2 (154.9, 180.4) 545	366.6 (328.7, 408.9) 278	314.2 (251.0, 393.3) 61
IPV1[2]	651.4 (620.6, 683.6) 1936	253.2 (225.2, 284.8) 542	1052.7 (930.3, 1191.2) 276	308.0 (205.0, 462.6) 60
IPV2[2]	1215.8 (1158.9, 1275.5) 1934	790.8 (721.6, 866.5) 543	1884.0 (1645.3, 2157.3) 274	1613.2 (1238.2, 2101.8) 61
IPV3[2]	818.0 (773.9, 864.6) 1906	666.7 (602.5, 737.6) 537	1265.8 (1094.6, 1463.8) 273	1423.3 (996.6, 2032.6) 60

Sex (Table 14 contd.)

Antigen	Male	Male	Female	Female
	PR5I (N=1653)	Control (N=421)	PR5I (N=1503)	Control (N=409)
	GMT (95% CI) [1] n	GMT (95% CI) [1] n	GMT (95% CI) [1] n	GMT (95% CI) [1] n
PRP	5.4 (5.0, 5.9) 1345	3.0 (2.5, 3.6) 348	6.1 (5.6, 6.7) 1215	3.9 (3.2, 4.7) 322
HBsAG[2]	1270.3 (1194.7, 1350.7) 1299	431.8 (369.3, 504.9) 328	1229.7 (1148.3,1316.9) 1156	617.4 (530.6, 718.4) 311
Diphtheria[2]	0.34 (0.32, 0.36) 1395	0.35 (0.32, 0.40) 356	0.37 (0.35, 0.40) 1256	0.38 (0.34, 0.42) 338
Tetanus [2]	1.92 (1.85, 1.99) 1376	1.08 (1.00, 1.17) 357	1.80 (1.73, 1.87) 1254	1.06 (0.97, 1.17) 333
PT	102.8 (99.6, 106.2) 1429	87.3 (82.6, 92.4) 366	101.2 (97.7, 104.9) 1284	82.0 (77.0, 87.4) 343
FHA	51.9 (50.0, 54.0) 1424	74.7 (69.2, 80.6) 370	46.4 (44.6, 48.4) 1289	73.1 (67.8, 78.9) 342
PRN	52.4 (49.5, 55.5) 1396	63.2 (56.8, 70.5) 366	55.3 (52.1, 58.8) 1271	54.9 (49.0, 61.6) 337
FIM	249.0 (238.1, 260.5) 1419	171.7 (156.7, 188.1) 367	263.0 (250.6, 276.1) 1286	191.9 (173.9, 211.8) 342
IPV1[2]	615.3 (582.4, 650.0) 1416	243.4 (211.8, 280.0) 365	786.2 (740.0, 835.2) 1280	297.7 (254.3, 348.5) 340
IPV2[2]	1200.3 (1134.8, 1269.7) 1418	795.4 (709.3, 892.0) 365	1505.4 (1419.6,1596.5) 1278	921.3 (820.6, 1034.4) 341
IPV3[2]	750.0 (706.9, 806.4) 1399	626.9 (551.8, 712.1) 363	1022.6 (956.3, 1093.5) 1265	858.9 (753.4, 979.2) 337

[1] The 95% CI for GMT was based on the t-distribution of the natural log-transformed antibody titer.

[2] The summaries at pre-vaccination are based on data from Protocol 006 only. The antibody titers for these antigens were not measured pre-vaccination in Protocol 005.

N = Number of subjects vaccinated, n = Number of subjects included in the analysis,

Source Adapted from *Integrated Analysis of Efficacy, pages 89-92, 107-111 of the submission.*

7.4 Efficacy Conclusions

Overall, from the integrated analyses, the applicant showed that the infant series of PR5I vaccination induced non-inferior immune response to that of the licensed control regimen for all but one pre-specified primary endpoint postdose 3 (Table 12). The integrated analyses supported as well the non-inferiority of pertussis response after the toddler dose of pertussis vaccination by either DAPTACEL or PENTACEL following the infant series (Table 13). The 2-sided 95% CI lower bounds for the comparisons exceeded the pre-specified non-inferiority margins. Non-inferiority was not met for the postdose3 GMT for FHA; the 2-sided 95% CI lower bound of the GMT ratio (0.62) was lower than the required margin of 0.67.

8. Integrated Safety

8.1 Safety Design, Data, and Disposition

Section 7.1 of this review briefly described similarities of the two pivotal studies, Protocol 005 and Protocol 006, in terms of study design, study population, and common immunogenicity and safety measurements. The results below are from the pooled safety database of these two studies.

Regarding subject disposition, from Table 15, a total of 4606 subjects were screened, 4281 were randomized, of which 3392 subjects received PR5I vaccine and 889 subjects received the

Control vaccine. Overall, 93.1% of subjects completed the infant series and concomitant vaccinations in either arm. Among non-completers (6.5%), the dominant reasons reported were subject withdrawal and lost to follow up. There were 3593 (83.9%) subjects completing the toddler dose vaccinations. Similarly, among those who discontinued between the infant series and toddler dose (n=392, 9.2%), the majority were due to lost to follow-up or individual withdrawal.

Table 15: Subject Disposition, Pooled Safety Population (Protocols 005 and 006)

	PR5I n (%)	Control n (%)	Total n (%)
Screened	-	-	4606
Randomized subjects	3392	889	4281
Received all 3 doses of the Infant Series (PR5I/Control)	3156 (93.0)	830 (93.4)	3986 (93.1)
Received all 3 doses of the Infant Series (PR5I/Control) and all doses of concomitant study vaccines	3154 (93.0)	830 (93.4)	3984 (93.1)
Did not complete the Infant Series (PR5I/Control)	224 (6.6)	55 (6.2)	279 (6.5)
Reason for Withdrawal:			
Adverse Event	6 (0.2)	1 (0.1)	7 (0.2)
Death	5 (0.1)	1 (0.1)	6 (0.1)
Lost to Follow-up	59 (1.7)	20 (2.3)	79 (1.9)
Non-compliance with Study Drug	2 (0.1)	1 (0.1)	3 (0.1)
Physician Decision	9 (0.3)	1 (0.1)	10 (0.2)
Protocol Violation	31 (0.9)	12 (1.4)	43 (1.0)
Withdrawal by Subject	110 (3.3)	19 (2.1)	129 (3.0)
Other	2 (0.1)	0 (0.0)	2 (0.0)
Discontinued between the Infant Series and Toddler Dose	311 (9.2)	81 (9.1)	392 (9.2)
Reason for Withdrawal:			
Adverse Event	2 (0.1)	0 (0.0)	2 (0.0)
Lost to Follow-up	181 (5.4)	46 (5.2)	227 (5.3)
Non-compliance with Study Drug	1 (0.0)	0 (0.0)	1 (0.0)
Physician Decision	8 (0.2)	3 (0.3)	11 (0.3)
Protocol Violation	19 (0.6)	6 (0.7)	25 (0.6)
Technical Problems	14 (0.4)	3 (0.3)	17 (0.4)
Withdrawal by Subject	86 (2.5)	22 (2.5)	108 (2.5)
Other	0 (0.0)	1 (0.1)	1 (0.0)
Completed Toddler Dose vaccinations	2846 (83.9)	747 (84.0)	3593 (83.9)

One primary reason for discontinuation per subject was reported.

n = Number of subjects in each category.

Source Adapted from *Integrated Analysis of Safety, page 21-22 of the submission*

8.2 Safety Results

8.2.1 Overall Adverse Events

An overall summary of adverse events (AE) combined from the two pivotal studies is provided in Table 16. From this table, 94.9% of the PR5I vaccinees and 92.8% of Control subjects experienced one or more AEs during the first 15 days after any infant dose of vaccination. For solicited injection-site AEs and solicited systemic AEs, during Day 1 through Day 5, the arm wise (PR5I, Control) percentages of subjects with AEs were, respectively, (81.7%, 80.6%) and (91.7%, 88.6%), and the AE rates seemed similar across study groups. Serious AEs occurred to 42 (1.3%) subjects in the PR5I group and to 11 (1.1%) subjects in the Control group (discussed in section 8.2.4 below). A total of 7 infant deaths were reported; 6 (0.2%) were in the PR5I group, reporting AEs of asphyxia, hydrocephalus, sepsis, sudden infant death syndrome, and

pneumonia, and 1 (0.1%) was in the Control group, reporting an AE of cardiac arrest. The study investigator did not consider these deaths to be related to study vaccinations. Nine subjects (0.2%) discontinued due to an adverse event, 8 in the PR5I group and 1 in the Control group; most of these AEs were non-serious and resolved, and there were three serious AE cases which the study investigator considered as not related to study vaccines (Summary of Clinical Safety, page 74, 81-86 of the submission). Please refer to the medical officer’s review for more details regarding these AEs.

Table 16: Clinical Adverse Event Summary after Any Infant Dose Vaccination (All Subjects as Treated Population, N_{PR5I} = 3380, N_{Control} = 885) (Protocols 005 and 006)

	PR5I n(%)	Control n(%)	Difference[2,3] (95% CI)
Number of subjects with known values after vaccination	3370	880	
With one or more adverse events (Day 1 to Day 15)	3195 (94.9)	818 (92.8)	2.1 (0.2,4.3)
Injection-site adverse events (Day 1 to Day 15)	2764 (82.2)	711 (80.8)	1.4 (-1.6,4.6)
Solicited injection-site adverse events (Day 1 to Day 5)	2749 (81.7)	709 (80.6)	1.2 (-1.9,4.4)
Systemic adverse events (Day 1 to Day 15)	3150 (93.5)	795 (90.1)	3.4 (1.3,5.9)
Solicited systemic adverse events (Day 1 to Day 5)	3090 (91.7)	782 (88.6)	3.1 (0.8,5.8)
With vaccine-related adverse events (Day 1 to Day 15)	3145 (93.4)	808 (91.6)	1.8 (-0.2,4.2)
With serious adverse events (Day 1 to Day 15)	42 (1.3)	11 (1.1)	0.2 (-0.8,0.9)
With serious adverse events (Day 1 after Dose 1 to Day 181 after Dose 3)	143 (4.3)	45 (4.5)	-0.2 (-2.0, 1.3)
Who died [2]	6 (0.2)	1 (0.1)	0.1 (-0.5,0.3)
Discontinued due to an adverse event [1]	8 (0.2)	1 (0.1)	0.2 (-0.4,0.4)

[1] This category included adverse events that occurred after any infant dose vaccination up to before the Toddler vaccination.

[2] Difference was PR5I group minus Control group.

[3] Estimated rate and difference were based on Miettinen & Nurminen method stratified by studies.

N = Number of vaccinated subjects, n = Number of subjects in each category.

Source Adapted from Summary of Clinical Safety, page 26 of the submission.

8.2.2 Solicited Injection-Site AEs

Table 17 provides information on solicited injection-site adverse events during Day 1 to Day 5 following any dose of the infant series. The solicited injection-site erythema AEs occurred to 46.0% of 3370 PR5I vaccinees, and to 41.3% of 880 Control subjects. These percentages according to arms were respectively 71.2% and 72.0% for injection-site pain, and 36.4% and 34.6% for injection-site swelling. The data showed that in the PR5I group, an increased percentage of 4.7% (95% CI: 0.8%, 8.6%) of subjects experienced injection-site erythema compared to the Control. Nevertheless, a large proportion ($\geq 93.3\%$) of these AEs had erythema of less than 2.5 cm (Summary of Clinical Safety, page 28 of the submission).

Table 17: Solicited Injection-Site Adverse Events and Solicited Systemic Adverse Events (Incidence > 0% in One or More Vaccination Groups) Day 1 to Day 5 Following Any Infant Dose Vaccination (All Subjects as Treated Population, N_{PR5I}=3380, N_{Control}=885) (Protocols 005 and 006)

	PR5I n (%)	Control n (%)	Difference[1][2] (95% CI)
Subjects with known values after any vaccination	3370	880	
Injection-site erythema	1543 (46.0)	366 (41.3)	4.7 (0.8, 8.6)
Injection-site pain	2393 (71.2)	633 (72.0)	-0.8 (-4.3, 2.9)
Injection-site swelling	1218 (36.4)	305 (34.6)	1.8 (-2.0, 5.5)
Maximum Temperature (≥ 39.5 C, rectal)	74 (2.3)*	9 (1.2)*	1.1 (-0.1, 1.9)
Systemic AE Crying	2520 (74.8)	637 (72.4)	2.3 (-1.1, 5.9)
Systemic AE Decreased appetite	1638 (48.6)	397 (45.9)	2.7 (-1.3, 6.6)
Systemic AE Irritability	2743 (81.5)	712 (80.5)	1.0 (-2.0, 4.3)
Systemic AE Pyrexia	1590 (47.2)	298 (33.6)	13.6 (9.7, 17.3)
Systemic AE Somnolence	2475 (73.5)	637 (72.7)	0.8 (-2.7, 4.4)
Systemic AE Vomiting	889 (26.3)	203 (23.8)	2.6 (-0.9, 5.9)

[1] Difference was PR5I group minus Control group.

[2] Estimated rate and difference were based on Miettinen & Nurminen method stratified by studies.

N = Number of vaccinated subjects, n = Number of subjects in each category.

*Number of subjects with temperature data were 3257 in PR5I and 848 in Control.

Source Adapted from Summary Clinical Safety, pages 28-35, 50 of the submission .

8.2.3 Solicited Systemic AEs

Table 17 also provides solicited systemic adverse events during Day 1 to Day 5 following any dose of the infant series. Table 16 showed that a total of 3090 (91.7%) subjects in the PR5I group and 782 (88.6%) subjects in the Control group experienced one or more solicited systemic AEs within 5 days of any dose. From Table 17, the most frequent AEs were Crying (74.8% in PR5I vs 72.4% in Control), Irritability (81.5% vs. 80.5%), and Somnolence (73.5% vs 72.7%). Pyrexia, which occurred to 47.2% of the PR5I subjects compared to 33.6% of the Control group, showed a statistically significant difference of 13.6% (95% CI: 9.7%, 17.3%). Nevertheless, the majority of these AEs were reported as mild/ moderate in intensity (Summary Clinical Safety, page 36 of submission). Additionally, for solicited systemic AEs after each dose in the PR5I group (Table 18), the AEs did not show increased frequency with vaccination visits, but for pyrexia, the frequency increased from 18.1% at post vaccination visit 1 to 27.4% at post vaccination visit 2 and remained almost at that level (28.0%) at post vaccination visit 3. By contrast, in the Control group, the percentages at the three visits were respectively 13.9%, 17.1%, and 17.1%, showing only a slight increase in trend.

Referring again to Table 17, a total of 74 (2.3%) vaccinees out of 3257 in the PR5I group reported severe elevated temperature ($\geq 39.5^{\circ}\text{C}$, rectal route) by Day 5 following any dose in the infant series, compared to 9 (1.2%) subjects out of 848 in the Control group. It appears that the PR5I vaccinees, overall, were more likely to have elevated temperature compared to the Control subjects (RR=2.14, 95% CI: 1.11, 4.58) (reviewer's calculation based on an exact test).

Table 18: Subjects with Any Solicited Systemic Adverse Events by Vaccination (Incidence > 0% in One or More Vaccination Groups) Day 1 to Day 5 Following Each Infant Dose Vaccination (All Subjects as Treated Population) (Protocols 005 and 006)

	Vaccination 1	Vaccination 1	Vaccination 2	Vaccination 2	Vaccination 3	Vaccination 3
	PR5I (N=3380)	Control (N=885)	PR5I (N=3234)	Control (N=854)	PR5I (N=3156)	Control (N=830)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with known values after any vaccn	3370	880	3221	849	3134	825
With one or more solicited systemic adverse events	2766 (82.1)	708 (80.5)	2492 (77.4)	619 (72.9)	2297 (73.3)	554 (67.2)
Crying	1815 (53.9)	472 (53.6)	1651 (51.3)	411 (48.4)	1462 (46.6)	347 (42.1)
Decreased appetite	1020 (30.3)	248 (28.2)	819 (25.4)	184 (21.7)	761 (24.3)	178 (21.6)
Irritability	2157 (64.0)	571 (64.9)	1955 (60.7)	492 (58.0)	1778 (56.7)	437 (53.0)
Pyrexia	611 (18.1)	122 (13.9)	883 (27.4)	145 (17.1)	877 (28.0)	141 (17.1)
Somnolence	2005 (59.5)	520 (59.1)	1618 (50.2)	395 (46.5)	1342 (42.8)	337 (40.8)
Vomiting	503 (14.9)	118 (13.4)	420 (13.0)	98 (11.5)	329 (10.5)	66 (8.0)

N = Number of vaccinated subjects, n = Number of subjects in each category.

Source Adapted from Summary of Clinical Safety, page 38 of the submission.

8.2.4 Serious Adverse events

The pooled data of the two studies reported serious adverse events (SAEs) with 143 subjects (4.3%) in the PR5I group and 45 subjects (4.5%) in the Control group (Table 16). These SAEs occurred between Day 1 after Dose 1 and Day 181 after Dose 3. For Day 1 to Day 15 after any dose, the number of subjects with one or more SAEs were 42 (1.3%) and 11 (1.1%) in the PR5I and Control groups, respectively. No notable difference in SAE rates between groups was observed.

The most frequent serious adverse events from Day 1 after Dose 1 to Day 181 after Dose 3 in the PR5I group included Pyrexia, Bronchiolitis, Croup infections, Gastroenteritis, Respiratory syncytial virus bronchiolitis, febrile convulsion. Those in the Control group were bronchiolitis/syncytial virus bronchiolitis, croup infections, and dehydration. An SAE of Kawasaki's disease was reported in the Control arm (Summary of Clinical Safety, page 60-64 of submission).

Vaccine related serious adverse events after any infant dose were reported from 6 subjects (0.2%) vaccinated with PR5I, with none in the control group. An excess risk for PR5I relative to Control was not established; the 95% CI lower bound of the RR was 0.42, which was much below 1.0, the value of RR for equality of risks between groups. Of the 6 subjects, one had intussusception, which the study investigator considered to be related to Rotateq, and the rest had pyrexia, diarrhea, or febrile convulsion.

8.2.5 Deaths

A total of 7 infant deaths were reported; 6 (0.2%) were in the PR5I group, reporting AEs of asphyxia, hydrocephalus, sepsis, sudden infant death syndrome, and pneumonia, and 1 (0.1%) was in the Control group, reporting an AE of cardiac arrest. The study investigator did not consider any of these deaths to be related to study vaccinations. Also, 9 subjects discontinued due to an adverse event, 8 in the PR5I arm and 1 in the Control arm; most of these AEs were

non-serious and resolved, but three serious AE cases were considered by the study investigator to be not related to study vaccines (Summary of Clinical Safety, page 74, 81-86 of submission).

8.3 Subgroup Analyses

A clinical summary of AEs is provided by subgroups of race and sex in Table 19. It appears that, despite an overall insignificance of differences (PR5I – Control) in different AE rates, the overall AE rates reported among Blacks (88.9%) receiving PR5I seemed lower to some extent when compared to Whites (96.1%) (rate difference=7.1%, 95% CI: 4.2%, 10.7%). Otherwise, the overall rates of different AEs appeared similar across different subgroups.

Table 19: Clinical Adverse Event Summary by Race and Gender Subgroups after Any Infant Dose Vaccination (All Subjects as Treated Population) (Protocols 005 and 006)

Race

	White	White	Black	Black	*Multi-Racial +Other	*Multi-Racial +Other
	PR5I (N=2389)	Control (N=667)	PR5I (N=380)	Control (N=91)	PR5I (N=611)	Control (N=127)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects with known values after vaccination	2381	664	380	89	609	127
With one or more adverse events (Day 1 to Day 15)	2287 (96.1)	625 (94.1)	338 (88.9)	78 (87.6)	570 (93.6)	115 (90.6)
Injection-site adverse events (Day 1 to Day 15)	2014 (84.6)	543 (81.8)	292 (76.8)	72 (80.9)	458 (75.2)	96 (75.6)
Solicited injection-site adverse events (Day 1 to Day 5)	2007 (84.3)	542 (81.6)	288 (75.8)	72 (80.9)	454 (74.5)	95 (74.8)
Systemic adverse events (Day 1 to Day 15)	2258 (94.8)	612 (92.2)	328 (86.3)	75 (84.3)	564 (92.6)	108 (85.0)
Solicited systemic adverse events (Day 1 to Day 5)	2222 (93.3)	604 (91.0)	316 (83.2)	72 (80.9)	552 (90.6)	106 (83.4)
With vaccine-related adverse events (Day 1 to Day 15)	2259 (94.9)	620 (93.4)	328 (86.3)	75 (84.3)	558 (91.6)	113 (89.0)
With serious adverse events (Day 1 to Day 15)	34 (1.4)	9 (1.4)	4 (1.1)	2 (2.2)	4 (0.6)	0 (0.0)
With serious adverse events (Day 1 after Dose 1 to Day 181 after Dose 3)	99 (4.2)	35 (5.3)	24 (6.3)	8 (9.0)	20 (3.3)	2 (1.6)
Who died	3 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)
Discontinued due to an adverse event	4 (0.2)	1 (0.2)	1 (0.3)	0 (0.0)	3 (0.5)	0 (0.0)

Sex

	Male	Male	Female	Female
	PR5I (N=1786)	Control (N=457)	PR5I (N=1594)	Control (N=428)
	n (%)	n (%)	n (%)	n (%)
Number of subjects with known values after vaccination	1782	456	1588	424
With one or more adverse events (Day 1 to Day 15)	1680 (94.3)	421 (92.3)	1515 (95.4)	397 (93.6)
Injection-site adverse events (Day 1 to Day 15)	1445 (81.1)	352 (77.2)	1319 (83.1)	359 (84.7)
Solicited injection-site adverse events (Day 1 to Day 5)	1437 (80.6)	352 (77.2)	1312 (82.6)	357 (84.2)
Systemic adverse events (Day 1 to Day 15)	1657 (93.0)	411 (90.1)	1493 (94.0)	384 (90.6)
Solicited systemic adverse events (Day 1 to Day 5)	1620 (90.9)	402 (88.2)	1470 (92.6)	380 (89.6)
With vaccine-related adverse events (Day 1 to Day 15)	1652 (92.7)	413 (90.6)	1493 (94.0)	395 (93.2)
With serious adverse events (Day 1 to Day 15)	23 (1.3)	8 (1.8)	19 (1.2)	3 (0.7)
With serious adverse events (Day 1 after Dose 1 to Day 181 after Dose 3)	84 (4.7)	24 (5.3)	59 (3.7)	21 (5.0)
Who died	4 (0.2)	0 (0.0)	2 (0.1)	1 (0.2)
Discontinued due to an adverse event	5 (0.3)	1 (0.2)	3 (0.2)	0 (0.0)

N = Number of vaccinated subjects, n = Number of subjects in each category.

Source Adapted from Summary of Clinical Safety, page 109 and 126 of the submission.

8.4 Safety Conclusions

Based on the submitted results of the pooled data, the overall safety profile of PR5I appears to be comparable with that of the licensed Control.

The study reported injection site erythema occurring in a slightly higher proportion of PR5I subjects compared to Control (difference in proportions = 4.7%, 95% CI: 0.8%, 8.6%; Table 17) after any dose of vaccination, but the majority of these AEs were of mild or moderate intensity (Clinical Summary of Safety, page 28 of submission).

The PR5I vaccinees experienced Pyrexia in a significantly higher proportion of subjects compared to Control (difference in proportions = 13.6%, 95% CI: 9.7, 17.3; Table 17) during Day1 to Day 5 after any dose, but mostly the pyrexia was mild or moderate in intensity (Clinical Summary of Safety, page 38 in submission).

A total of 7 deaths were reported, 6 (0.2%) in the PR5I group and 1 (0.1%) in the Control group, but none was considered by the study investigator to be related to study vaccine.

9. Additional Statistical Issues

None.

10. Overall Conclusions

Immunogenicity

Overall, the applicant's results showed that PR5I in the 3-dose infant series of vaccination induced non-inferior immune response compared to the licensed Control, for all but one specified primary endpoint postdose 3 (Table 5) and for pertussis response after the toddler dose following the infant series (Table 6). Non-inferiority was not met for GMT of the FHA antigen postdose 3, where the lower bound of the 95% CI of the GMT ratio (0.59) was lower than the non-inferiority margin of 0.67. These results were supported by the integrated population's results on the PR5I vs. Control comparisons of the endpoints (Tables 12 and 13, last columns).

The lot-to-lot consistency of 3 manufacturing lots was demonstrated in terms of GMTs, using pre-specified criteria. The lower and upper limits of the 2-sided 95% CIs of the GMT ratios in lot-pairs for all antigens were contained within the equivalence margins (0.67, 1.50), i.e., the GMT ratios excluded 1.5-fold changes in all antigens (Table 10).

Safety

The studies reported no deaths that were deemed to be vaccine related by the investigators. It is noted that the PR5I vaccinees experienced significantly higher incidence of pyrexia (rate difference = 13.1%, 95% CI: 7.7%, 18.3%; Table 8) compared to the Control subjects. However,

the reported pyrexia cases were mostly mild or moderate. Overall, the safety profile of PR5I was comparable with the Control.

Appendix-1

Inclusion Criteria

The subject must have met the following criteria to participate in the study:

1. Subject is a healthy infant and is greater than or equal to 46 days and less than or equal to 89 days of age on the day of inclusion.
2. Subject has received only one dose of monovalent hepatitis B vaccine, outside of the study context prior to or at one month of age and it is documented in subject's medical history.
3. Subject's parent/legal guardian understands the study procedures, alternate treatments available, risks involved with the study, and voluntarily agrees to participate by giving written informed consent.
4. Subject's parent/legal guardian is able to read, understand, and complete study questionnaires (i.e., the VRC).
5. Subject is able to attend all scheduled visits and to comply with the study procedures.
6. Subject's parent/legal guardian has access to a telephone.

Exclusion Criteria

The subject was excluded from participation if he/she met any of the following criteria. For criteria with an asterisk (*), a subject could return to be entered into the study once these criteria no longer applied.

1. Subject is currently participating or has participated in a study with an investigational compound or device within 4 weeks of expected first dose of PR5I/component vaccine Control(s).
2. Subject's parent/legal guardian plans to enroll the subject in another clinical study during the present study period.
3. Subject has history of congenital immunodeficiency or acquired immunodeficiency (e.g., human immunodeficiency virus, splenomegaly).
4. Prior to study enrollment, subject has received or is expected to receive immunosuppressive agents (e.g., substances or treatments known to diminish immune response such as radiation therapy, antimetabolites, cyclophosphamide, azathioprine, methotrexate, any chemotherapy, cyclosporine, leflunomide (Arava[®]), tumor necrosis factor- α antagonists, monoclonal antibody

therapies (including rituximab [Rituxan[®]]) intravenous gamma globulin, antilymphocyte sera, or other therapy known to interfere with the immune response).

5. Subject has received 1) systemic immunomodulatory steroids (> the equivalent of 2 mg/kg total daily dose of prednisone) since birth, or 2) any dose of systemic immunomodulatory steroids within 7 days prior to entering study or 3) is expected to require systemic immunomodulatory steroids through the course of the study. Subjects using non-systemic corticosteroids (e.g., topical, ophthalmic, inhaled) will be eligible for vaccination.

6. Subject has a history of leukemia, lymphoma, malignant melanoma, or myeloproliferative disorder.

7. Subject has known or suspected hypersensitivity to any of the vaccine components or history of a life-threatening reaction to a vaccine containing the same substances as the study vaccines or concomitant vaccines.

8. Subject has chronic illness that could interfere with study conduct or completion.

9. Subject has received any immune globulin, blood, or blood-derived products since birth.

10. Subject has received more than one dose of monovalent hepatitis B vaccine or hepatitis B based combination vaccine prior to study entry.

11. Subject has received vaccination prior to study entry with any DTaP or whole cell pertussis-(DTwP) based combination vaccines, Hib conjugate, poliovirus, pneumococcal conjugate or pneumococcal polysaccharide, rotavirus, or combination thereof.

12. *Subject has had a febrile illness within 24 hours prior to enrollment or a rectal temperature $\geq 38.0^{\circ}\text{C}$ [$\geq 100.4^{\circ}\text{F}$] at Visit 1.

13. *Subject has been vaccinated with any non-study vaccine (e.g., inactivated, conjugated or live virus vaccine) within 30 days prior to enrollment, except for inactivated influenza vaccine, which will be permitted 15 days or more prior to enrollment.

14. Subject has coagulation disorder contraindicating IM vaccination.

15. Subject has clinically significant findings on review of systems (medical history) determined by Investigator or sub-Investigator to be sufficient for exclusion.

16. Subject has developmental delay or neurological disorder at the time of enrollment (by medical history).

17. Subject or his/her mother has a medical history of HBsAg seropositivity.

18. Subject has history of Hib, hepatitis B, diphtheria, tetanus, pertussis, poliomyelitis, rotavirus, or pneumococcal infection.

19. Subject's parent/legal guardian is unlikely to adhere to study procedures, keep appointments, or is planning to relocate during the study.

20. Any contraindication to the concomitant study vaccines (RotaTeq and Prevnar 13).

(Source: CSR Protocol 005, pages 47-48 of submission)

Appendix-2

Each 0.5 mL dose of PENTACEL contained the following ingredients:

- 20 µg of PT
- 20 µg of FHA
- 3 µg of PRN
- 5 µg of FIM
- 10 µg of PRP of Hib covalently bound to ^{(b) (4)} µg of tetanus protein
- 15 Lf of diphtheria toxoid
- 5 Lf of tetanus toxoid
- IPV: 40 D-antigen Units Type 1 (Mahoney), 8 D-antigen Units Type 2 (MEF-1), 32 D-antigen Units Type 3 (Saukett), and
- 1.5 mg of aluminum phosphate.

Recombivax HB, RotaTeq, and PedvaxHIB were manufactured by Merck Sharp & Dohme Corp. PR5I, PENTACEL, DAPTACEL, and ActHIB were manufactured by Sanofi Pasteur Limited.

Each 0.5 mL dose of Recombivax HB was formulated to contain 5 µg of HBsAg.

RotaTeq was a 2 mL solution for oral administration of 5 live human-bovine reassortant rotaviruses which contains a minimum of 2.0 to 2.8 x 10⁶ infectious units (IU) per reassortant dose, depending on the serotype, and not greater than 116 x 10⁶ IU per aggregate dose.

Each 0.5 mL dose of PedvaxHIB was formulated to contain the following:

- 7.5 µg of Hib PRP
- 125 µg of *Neisseria meningitidis* OMPC, and
- 225 µg of aluminum as amorphous aluminum hydroxyphosphate sulfate (previously referred to as aluminum hydroxide), in 0.9% sodium chloride.

Each 0.5 mL dose of DAPTACEL was formulated to contain the following:

- 15 Lf diphtheria toxoid
- 5 Lf tetanus toxoid
- Acellular pertussis antigens
- 10 µg detoxified PT
- 5 µg FHA
- 3 µg PRN
- 5 µg FIM

Each 0.5 mL dose of ActHIB was formulated to contain 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid and 8.5% of sucrose when reconstituted with saline diluent.

All vaccines used in this study was prepared, packaged, and labeled in accordance with Good Manufacturing Practice, ICH guidelines for GCP, and applicable local laws/regulations.

All vaccine supplies were shipped to the sites, stored, distributed and handled in accordance with the study protocol and Good Pharmacy Practices.

(Source: CSR Protocol 005, pages 49-51 of submission)

Appendix 3

Table 20: Subjects' Prevaccination GMTs by Study Group (PP-RW Population)

Antigen	PR5I GMT (95% CI) n	Control GMT (95% CI) n
PRP	0.13 (0.12, 0.14) 943	0.13 (0.11, 0.14) 466
PT	3.62 (3.43, 3.83) 955	3.49 (3.23, 3.78) 469
FHA	6.93 (6.43, 7.46) 961	7.06 (6.36, 7.84) 472
PRN	5.80 (5.35, 6.29) 961	6.12 (5.41, 6.92) 471
FIM	10.64 (9.61, 11.79) 960	10.41 (8.97, 12.07) 472
Rotavirus (IgA response)	0.80 (0.75, 0.84) 784	0.72 (0.67, 0.77) 391

Source Adapted from Tables 14-14, 14-18, 14-20, the CSR Protocol 005, pages 217-224.