Application Type	Original Application
STN	125563/0
CBER Received Date	August 12, 2014
PDUFA Goal Date	August 12, 2015
Complete Response Letter	November 01, 2015
Resubmission Action Due Date	December 29, 2018
Division / Office	DVRPA /OVRR
Priority Review	No
Reviewer Name(s)	Ann Schwartz, M.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	R. Douglas Pratt, MD MPH Associate Director for Medical Affairs
Concurrence Date / Stamped Date	
Applicant	MCM Vaccine Co. [partnership between Merck Sharp & Dohme Corp. (a subsidiary of Merck and Co., Inc.) and Sanofi Pasteur Inc.]
Established Name	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine
(Proposed) Trade Name	VAXELIS
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants	Suspension for injection, each 0.5 mL dose contains: PT 20 µg FHA 20 µg FIM 5 µg PRN 3 µg Diphtheria 15 Lf Tetanus 5 Lf Vero-derived IPV-Type 1: 29 D-antigen Units Vero-derived IPV-Type 2: 7 D-antigen Units Vero-derived IPV-Type 3: 26 D-antigen Units HBsAg 10 µg PRP-OMPC 3 µg Aluminum (b) (4) µg
Dosing Regimen	Single intramuscular dose at 2,4 and 6 months of age
Indication(s) and Intended Population(s)	Active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by Haemophilus influenzae type b and infection caused by all known subtypes of hepatitis B virus in children 6 weeks through 4 years of age.
Orphan Designated (Yes/No)	No

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GLOSSARY

Abbreviation	Term Definition
ANCOVA	Analysis of covariance
ASaT	All Subjects as Treated
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences Forms for Serious Adverse Events
cLDA	Constrained longitudinal data analysis
CO2	Carbon dioxide
CSR	Clinical study report
DOD	Delta optical density
DTaP	Diphtheria, tetanus, and acellular pertussis
DTwP	Diphtheria, tetanus, and whole cell pertussis
(b) (4)	
ERC	Ethical Review Committee
(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
Hep B	Hepatitis B
HepB (b) (4)	Hepatitis B (b) (4)
Hib	Haemophilus influenzae type b
HRP	Horseradish peroxidase
ICH	International Conference on Harmonization
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intramuscular(ly)
IPV	Inactivated poliovirus
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	Infectious units
LLC	Limited Liability Company
LLOQ	Lower limit of quantification/quantitation
LPLV	Last Patient Last Visit
MAR	Missing at random
MCAR	Missing completely at random
MI ANCOVA	Analysis of covariance with multiple imputation for missing baseline titers
(b) (4)	(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
OD	Optical density
OMPC	Outer membrane protein complex of Neisseria meningitidis
PP	Per-Protocol
(b) (4)	(b) (4)
PP-OW	Per Protocol-Original Windows
PP-RW	Per Protocol-Revised Windows
PRN	Pertactin
PRP	Polyribosylribitol phosphate
PR5I	Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, Haemophilus b conjugate (meningococcal outer membrane protein complex), and hepatitis B (recombinant) vaccine
PT	Pertussis toxoid
(b) (4)	(b) (4)
SAE	Serious Adverse Event
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
VRC	Vaccination Report Card
WHO	World Health Organization

1. Executive Summary

Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B [Recombinant] Vaccine is a hexavalent vaccine co-developed by Sanofi Pasteur Limited. and Merck Sharp & Dohme Corp. The proposed trade name is VAXELIS, with antigenic components notated as DTaP-IPV/Hib-Hep B, and with the acronym of PR5I used to identify the investigational product in the clinical studies and this review. All components of this vaccine are currently in products licensed in the United States (US).

This license application provides data to support the proposed indication for PR5I of active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), infection caused by hepatitis B virus, and invasive disease caused by *Haemophilus influenza* type b (*H. influenzae* /Hib) when administered as a 3-dose series in infants and children 6 weeks through 4 years of age (up to the 5th birthday).

During the clinical development of PR5I, several Phase 1 and Phase 2 studies (non-IND) were conducted to evaluate the safety and immunogenicity of four investigational hexavalent vaccine formulations which were administered to approximately 2000 infants and toddlers. The four investigational vaccine formulations were identical in composition but differed in the dose of (b) (4) The concentrations and associated excipient content of the five DTaP components in all formulations of the vaccine were identical. Two of the studies, (see sections 6.3 and 6.4), in which PR5I was administered as a four-dose series, were reviewed under this application as supportive for safety only. The Phase 2 study V419- 004 administered the final formulation of PR5I as a four-dose series (three infant doses and a toddler dose) and the results supported the initiation of the Phase III clinical development program.

The two Phase 3 comparative trials (V419-005 and V419-006) submitted to support licensure under this application enrolled infants 46 to 89 days of age who had received one dose of monovalent hepatitis B vaccine outside of the study at birth or up to one-month of age. Subjects in both studies received PR5I at 2, 4, and 6 months of age or the comparator Pentacel (DTaP-IPV/Hib) + RECOMBIVAX HB (Hep B) at 2 and 6 months of age, with Pentacel alone at 4 months of age, as a three-dose infant series. Concomitant vaccination with Prevnar 13 (Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) and RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent) was also administered at these study visits per recommendations of the Advisory Committee on Immunization Practices (ACIP) for routine vaccination in this age group.

At 15 months of age, toddler vaccines were administered, with subjects in V419-005 receiving DAPTACEL (DTaP), Prevnar 13 and either PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] or ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)], and subjects in V419-006 receiving Pentacel and Prevnar 13.

Adverse events were monitored after each vaccination as follows for both studies:

- Temperature (daily) Days 1-5 post-vaccination
- Solicited local injection site reactions (erythema, pain, swelling) Days 1-5 post-vaccination
- Solicited systemic adverse events (AEs)(crying, decreased appetite, irritability, somnolence and vomiting) Days 1-5 post-vaccination
- Unsolicited adverse events for 14 days post-vaccination

- Serious Adverse Events (SAEs) from study entry to 6 months following the toddler vaccinations at 15 months of age

The safety evaluation of PR5I was based upon the two Phase 3 studies conducted in the U.S., V419-005 and V419-006, with additional supportive safety data from phase 2 studies (evaluation of SAEs). A total of 4265 subjects (3380 received PR5I and 885 received Control vaccines) from V419-005 and V419-006. Phase 2 studies conducted in Canada enrolled a total of 495 subjects who received the vaccine formulation evaluated in Phase 3 studies compared to 339 subjects in the Control groups.

For both studies, the nature of adverse events following any vaccination with PR5I were similar to what has been seen following administration of the licensed component vaccines and combination vaccines containing the antigens in PR5I. In the Phase 3 studies, V419-005 and V419-006, no imbalances for solicited local injection site reactions (i.e., pain/tenderness, erythema, and swelling) or systemic AEs (i.e., crying, decreased appetite, irritability, somnolence and vomiting) were identified between groups for days 1-5 after each vaccination. There was an increase in the rates of pyrexia after any dose of PR5I in both studies. In the combined Phase 3 studies, rates of fever (defined as ≥38◦C) were increased for PR5I (47.2%) as compared to the Control vaccines (33.6%); [difference 13.6% (95%CI: 9.7, 17.3)]. Of note, the rates of febrile seizures were similar between the groups for Day 0-181 (0.2 study 005 and 0.1 study 006) ; no seizures occurred within 15 days post-vaccination.

The most frequently reported serious adverse event in the 30 days following any vaccination was respiratory syncytial virus bronchiolitis in studies V419-005 and V419-006. The majority of SAEs that occurred during this time period in both studies were due to conditions commonly observed in this age group, including gastroenteritis/dehydration, gastroesophageal reflux disease, respiratory tract infections, and other infections. Adverse events leading to study vaccine discontinuation were reported by 8 subjects (0.2%) in the PR5I group and 1 (0.1%) in the Control group. Death was reported for 6 subjects (0.2%) in the PR5I group and 1 subject (0.1%) in the Control group. No deaths were considered by investigators or this clinical reviewer to be related to the study vaccinations (SIDS, Hydrocephalus, Sepsis, Pneumonia, Asphyxia, and Respiratory/Cardiac Arrest).

In the Phase 2 studies, for which SAEs following each of four doses of PR5I were reviewed, imbalances between the study groups were not identified, and the nature and timing of the reported SAEs did not suggest a causal relationship to vaccination.

Immunogenicity of PR5I was evaluated in the Phase 3, randomized, active-comparator controlled clinical trials (V419-005 and V419-006) described previously. Immunogenicity analyses were based on a per-protocol (PP) approach, excluding subjects based on certain pre-specified criteria. Two PP populations, PP-Revised Windows (PP-RW) and PP-Original Windows (PP-OW), were used in both pivotal studies. The PP-RW population allowed for more subjects to be included in the statistical analyses by extending the windows for blood draws. As pre-specified and in agreement with CBER, the success of the primary endpoints for the pivotal studies was based on the results from the PP-RW population.

For study V419-005, in infants who received 3 doses of PR5I at 2, 4, and 6 months of age (concomitantly with Prevnar and RotaTeq) followed by DAPTACEL and PedvaxHIB at 15 months of age, the immune responses following three doses of PR5I were non-inferior to those of the Control vaccine except for the GMT of the pertussis antigen FHA at one-month post-dose 3. Following the fourth dose of a DTaP vaccine, which completed the primary series of pertussis

vaccinations, the pertussis responses of infants who had received three doses of PR5I were non-inferior to those who had received the Control vaccines. The IPV response rate was 100% following the 3 dose infant series of PR5I.

The immunogenicity findings in study V419-006 (lot consistency study) were similar to those seen in V419-005. Lot consistency was demonstrated with respect to GMTs and response rates for all antigens contained in PR5I. As observed in study V419-005, the immune responses following three doses of PR5I were non-inferior to those of the Control vaccines except for the GMT of the pertussis antigen FHA at one-month post-dose 3. After the Toddler dose, the pertussis responses and GMTs in subjects who received a 3-dose infant series of PR5I were comparable to subjects who received an infant series of a licensed Control vaccine, except for the GMT for PRN antigen which marginally missed the non-inferiority margin.

The failure to meet non-inferiority of the immune response to the pertussis FHA antigen following the three-dose infant vaccinations series in both Phase 3 studies is not thought to affect the effectiveness of PR5I to provide protection against pertussis disease. Since non-inferiority was demonstrated for FHA responses after completion of the 4-dose series (primary series) with the Toddler dose of Pentacel/DAPTACEL, the missed FHA GMT endpoint post-dose 3 is considered of limited clinical significance.
Regarding PRN responses after the Toddler dose in study V419-006, integrated results from the combined studies V419-005 and V419-006 met non-inferiority criteria for PRN prespecified for the individual studies. Therefore, the narrow miss in Study V419-006 for the non-inferiority comparison of PRN responses is also considered of little clinical significance.

The immune responses demonstrated for Prevnar 13 when given concomitantly with PR5I were non-inferior to those seen when Prevnar 13 was given concomitantly with the Control vaccines for 12 out of the 13 antigens, with the GMT for PCV 6B, falling outside the pre-specified immunogenicity criterion. The immune responses demonstrated to RotaTeq (concomitant vaccine) were comparable between the Control vaccine and PR5I cohorts.
Overall, the immune responses in subjects who received a three dose infant series of PR5I were similar to subjects who received the licensed control vaccine for most antigens.

During the review of CMC data, it was noted that the results of the (b) (4) Tests did not meet previously established specifications during the stability testing of PR5I. An extensive investigation into the Out of Specification results led to a Major Amendment to the file. (Please see CMC reviews). The (b) (4) is performed to detect (b) (4) combination vaccines possibly remaining after (b) (4) at the Final Bulk Product release testing stage and for stability monitoring. MCM proposed to replace the (b) (4) test with the (b) (4) Assay. The validity criteria and the concordance of study results, along with acceptance criteria for release final bulk and dose stability monitoring were acceptable and supported the replacement of the (b) (4) with the (b) (4) assay.

During the above CMC investigations, issues were identified with the pertactin (PRN) potency assay and with the use of expired lot of PRP-OMCP as a reference standard. A Complete Response (CR) letter was issued. Subsequently, the CR issues were addressed and supporting information was submitted to the BLA. With the resolution of these CMC issues, the BLA was resubmitted in 29 June 2018, on a six-month review cycle.

Determinations regarding PR5I with respect to the Pediatric Research Equity Act (PREA) considered the availability of currently licensed vaccines which provide protection against diphtheria, tetanus, pertussis, polio, *Haemophilus influenza* type b and hepatitis B. PR5I, if approved, could reduce the number of injections required at any infant visit, which may increase compliance. The Applicant requested partial waivers based upon age groups [infants (less than 6 weeks of age) and children and adolescents (from 5 years to 17 years)]. The request for waiver was granted under the BLA per Section 505B(a)(4)(B)(iii). The Pediatric Review Committee (PeRC) concurred with CBER's evaluation.

No Post-Marketing Commitments (PMC) or Post-Marketing Requirements (PMR) are planned for VAXELIS (PR5I). Post-marketing safety will be monitored by routine pharmacovigilance. (see section 11.6 of this review).

In conclusion, the safety and immunogenicity data from the pivotal studies V419-005 and V419-006, and the supportive safety data from the Phase 2 studies conducted in Canada, support the licensure of VAXELIS (PR5I) in infants and children 6 weeks through 4 years of age.

2. Clinical and Regulatory Background

PR5I has been developed jointly by Sanofi Pasteur, Ltd. and Merck Sharp & Dohme. It is manufactured using modified and/or existing bulk intermediates from vaccines currently licensed in the U.S. by Sanofi Pasteur, Ltd. or Merck & Co, Inc. (See section 2.3 Safety and Efficacy of Pharmacologically Related Products, below.)

2.1 Disease to be Prevented and Available Interventions

The requested indication for PR5I is for active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by *Haemophilus influenza*e type b and infection caused by all known subtypes of hepatitis B virus in children 6 weeks through 4 years of age. A description of each disease follows.

Diphtheria is an acute disease caused by the exotoxin-producing bacterium, *Corynebacterium diphtheriae*. In non-immune persons of all ages, symptoms of diphtheria typically occur after an incubation period of 1 to 5 days. The onset is characterized by the gradual development of a low to moderate fever and a mild, exudative pharyngitis. Transmission occurs through droplets and close physical contact, with humans being the only natural host for C. diphtheria. Persons in all age groups are susceptible to diphtheria if not vaccinated. The epidemiology of diphtheria has changed dramatically, largely attributable to widespread vaccination. In the US, 147,991 cases were reported in 1920 (151 cases/100,000 population) while 5 or fewer cases have been reported annually since 1980 (< 0.002/100,000 population) (1). Diphtheria is a reportable disease in the U.S.

Tetanus is an infectious bacterial disease caused by environmental exposure to *Clostridium tetani*, a ubiquitous spore-forming anaerobic bacillus, which can produce a potent neurotoxin, tetanospasmin. This toxin blocks inhibitory neurotransmitters in the central nervous system and causes the muscular stiffness and spasms typical of generalized tetanus. C. tetani spores are ubiquitous in the environment and may be carried in the intestinal tracts of both humans and animals. Tetanus is not transmitted from person to person. The incubation period varies between 2 days and 2 months, and typically presents as trismus (lockjaw) and sudden, generalized tonic seizures. All age groups can be affected, and case-fatality rates can be high even where modern intensive care is available. The overall tetanus case-fatality rate ranges from 10% to 70%, depending on treatment, age and general health of the patient. Since introduction as a component

of routine childhood immunization in the 1940's, tetanus has steadily declined from as many as 600 annual cases reported nationally to 0.01 per 100,000 between the years of 2000 to 2009 (3). Tetanus is a reportable disease in the US.

Pertussis (whooping cough) is caused by the bacterium *Bordetella pertussis* and is transmitted from infected to susceptible individuals through droplets. The incubation period of pertussis ranges from 6 to 21 days (average 7 to 10 days). Early symptoms of pertussis are similar to a mild upper respiratory tract infection (catarrhal stage), and progress to cough and then to paroxysms of cough (paroxysmal stage) characterized by an inspiratory whoop commonly followed by vomiting. Fever is absent or minimal. Symptoms wane gradually over weeks to months (convalescent stage). The duration of classic pertussis is 6 to 10 weeks, in the pediatric population. Peak incidence of pertussis was in children 1 to 5 years of age: fewer than 20% of cases were in infants, and almost all children had experienced pertussis by 12 years of age. After the introduction of whole-cell pertussis vaccine in the 1940s, pertussis incidence gradually declined, from well over 100,000 cases in the US to an average of 2900 reported cases per year (approximately 1 per 100,000 population) between 1980 and 1990 (4). Since the early 1990s there has been a resurgence of pertussis in North America (5), and young infants who are not fully immunized are at highest risk among all age groups.

Poliomyelitis is an acute infectious and communicable disease caused by poliovirus, which occurs only in humans. Polioviruses are single stranded RNA enteroviruses (Picornaviridae). There are three poliovirus serotypes: 1, 2, and 3. Transmission is person-to- person via fecal-to-oral and oral-to-oral routes with an incubation period from exposure to first symptoms (minor illness) of 3 to 6 days, and from infection to onset of paralytic disease of usually 7 to 21 days, with a range of 3 to 35 days. Infection is more common in infants and young children and occurs at an earlier age among children living in poor hygienic conditions. The case fatality rate is variable and depends primarily on the age groups affected: 5 and 10% case fatality have been reported based on epidemic cases in the early 20th century. Wild-type polio is considered eradicated from the Western Hemisphere, with no wild strain-associated cases reported since 1991 although cases and outbreaks continue to be reported outside the US (8).

Haemophilus influenza is a Gram-negative coccobacillus that enters the body through the nasopharynx. Encapsulated *Haemophilus influenza* has 6 serological types (types a to f); however most invasive disease is caused by type b (Hib). Hib is transmitted primarily by airborne droplets or by direct contact with respiratory secretions. Humans (asymptomatic carriers) are the only known reservoir. The invasive manifestations of Hib infection – namely, meningitis (the most common form of invasive Hib disease), pneumonia and other invasive diseases – occur primarily in infants and toddlers less than 2 years of age. The disease burden is highest among infants 4 to 18 months of age, but invasive Hib disease is occasionally observed in infants aged <3 months and among those aged >5 years. In unvaccinated populations, invasive Hib is the dominant cause of non -epidemic bacterial meningitis during the first year of life. Even with prompt and adequate antibiotic treatment, the case fatality rate of patients with Hib meningitis is 3 to 20%.

Hepatitis B infection is caused by the hepatitis B virus, a member of the hepadnaviridae family, which includes a hepatotropic group of DNA viruses. Most acute cases of hepatitis B infection in children are asymptomatic. Most patients do recover, but the chronic carrier state complicates up to 10% of cases acquired in adulthood. The rate of acquisition of chronic infection depends largely on the mode and age of acquisition and is up to 90% in perinatal cases. Chronic hepatitis cirrhosis and hepatocellular carcinoma are seen with chronic infection.

For infants and children 6 weeks through 4 years of age, the following component and combination vaccines are licensed in the U.S. for prevention of diseases targeted by PR5I (See also Section 2.3 of this review):

- DTaP
  - DAPTACEL (Sanofi Pasteur, Ltd.)
  - INFANRIX (GlaxoSmithKline)

- Diphtheria and Tetanus Toxoids Adsorbed for Pediatric Use (DT)
  - DT, Sanofi Pasteur Inc. and Sanofi Pasteur Limited

- Hib conjugate vaccine
  - ActHIB
  - PEDVAXHIB (Meningococcal Protein Conjugate; Merck)
  - HIBERIX (GlaxoSmithKline)

- Poliovirus Vaccine Inactivated (IPV)
  - IPOL (Sanofi Pasteur Inc.)
  - POLIOVAX (Sanofi Pasteur Limited; not distributed in the U.S.)

- DTaP, Hepatitis B (Recombinant) and IPV Combined
  - PEDIARIX (GlaxoSmithKline)

- DTaP and IPV Combined
  - KINRIX (GlaxoSmithKline)
  - QUADRACEL (Sanofi Pasteur, Limited)

- DTaP, IPV, and Hib conjugate Combined
  - Pentacel (Sanofi Pasteur, Ltd)

- Hepatitis B
  - Recombivax HB (Merck & Co, Inc)
  - ENGERIX-B (GlaxoSmithKline Biologicals)

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

For tetanus, diphtheria and pertussis diseases, the treatment is generally supportive with or without other interventions.

Of the diseases cited above, tetanus is unique in that it is not a communicable disease, but an anaerobic spore widely distributed in the environment. *C. tetani* spores germinate and produce the toxin that is associated with the signs and symptoms of tetanus disease. Therapy to counteract the effects of the circulating toxin on the nervous system is based on a combination of wound care, supportive measures and the use of human tetanus immunoglobulin (TIG). TIG will neutralize circulating toxin and should be given in combination with either a booster dose of Td vaccine or a primary series of vaccination with tetanus toxoid. Appropriate treatment of the nidus of infection should include wound debridement and appropriate antibiotic therapy (usually metronidazole).[1,2]

Infection with *C. diphtheriae* can cause respiratory, cutaneous or asymptomatic infection. Appropriate treatment is dependent upon the location of the infection and clinical manifestation

of the disease. For respiratory diphtheria, if suspected, treatment with antitoxin and antibiotic therapy should be initiated prior to confirmation of diagnosis. Diphtheria antitoxin, which can be obtained only from the CDC, is a hyperimmune antiserum produced in horses that binds to and inactivates diphtheria toxin. The goal of antitoxin therapy is to prevent or mitigate the formation of pseudomembranes in the respiratory tract and prevention of myocarditis and neurologic toxicity.[3]

Treatment of pertussis is largely supportive in nature, but early in disease the use of antibiotics may decrease the duration and severity of cough and reduce the transmission of *Bordetella pertussis (B. pertussis)*. While most adults and adolescents will clear *B. pertussis* within 6 weeks of infection without antibiotics, infants and children should be treated with antimicrobial therapy. Post-exposure prophylaxis is recommended for all household and close contacts of the index case regardless of immunization status. If close contacts are under immunized, the recommended vaccine schedule based on age and previous vaccines received should be initiated concurrently with antibiotic therapy.[4,5]

Since the introduction of universal hepatitis B vaccination in 1991, there has been a dramatic decrease in the incidence of hepatitis B disease in the US. Infants born to mothers who are hepatitis B surface antigen positive, should receive active and passive immunization (ie, hepatitis B vaccine and hepatitis B immune globulin [HBIG]) preferably within 12 hours of birth. During the acute phase of infection medical care is primarily supportive. In children (older than one year of age) who develop chronic hepatitis B antiviral therapy includes pegylated interferon alpha or nucleoside/nucleotide analogs.[6]

The treatment of poliomyelitis is supportive, including pain relief and physical therapy. If respiratory failure develops, mechanical ventilation may be required. Patients with bulbar involvement require close monitoring of cardiovascular status because of the association with blood pressure fluctuations, circulatory collapse, and autonomic dysfunction. Treatment is targeted at support and amelioration of presenting signs and symptoms. The role of anti-enteroviral treatments is unclear at this time.[7]

The treatment of specific syndromes attributable to *H. influenzae* (e.g., meningitis, pneumonia) often requires antibiotic therapy. Beta-lactam antibiotics (e.g., amoxicillin or a second- or third-generation cephalosporin) are the preferred agents if the organism is susceptible. Alternative agents with activity against *H. influenzae* include fluoroquinolones, macrolides, tetracyclines, and aminoglycosides. Resistant strains of *H. influenza* are emerging, and these beta-lactamase–negative, ampicillin-resistant (BLNAR) *H. influenzae* require a different antibiotic approach.[8]

2.3 Safety and Efficacy of Pharmacologically Related Products

The components of the PR5I vaccine are currently components of vaccines licensed in the U.S., either as stand-alone vaccines or as part of combination vaccines. (Please see section 6.1.4 of this review for a description of the products.) Safety and efficacy of these products has been previously evaluated and are summarized in current product packaging inserts for the noted products.

The components of the PR5I Vaccine and related products are presented below:

P- PRP-OMPC Bulk Intermediate, from Liquid PedvaxHIB® (STN BL 103237)
[*Haemophilus influenza* type b Conjugate Vaccine (Meningococcal Protein Conjugate)]
– Merck, Sharp and Dohme, Corp.

R- Hepatitis B Surface Antigen (HBsAg) Bulk Intermediate (also described as HBsAg Bulk Intermediate), from RECOMBIVAX HB® (STN BL 101066) [Hepatitis B Vaccine (Recombinant)] – Merck, Sharp and Dohme, Corp.

5- Five component Acellular Pertussis Adsorbed (Pertussis Toxoid, Filamentous Haemagglutinin, Pertactin, and Fimbriae Types 2 and 3), Diphtheria Toxoid Adsorbed and Tetanus Toxoid Adsorbed Bulk Intermediates. These antigens are used in other US licensed products including, Pentacel® (STN BL 125145), Diphtheria and Tetanus Toxoids Adsorbed Vaccine (STN BL 103944), DAPTACEL® (STN BL 103666), Adacel® (STN BL 125111) and TENIVAC™ (STN BL 103171) – Sanofi Pasteur Limited

I- Inactivated Poliovirus Types 1, 2, and 3 Bulk Intermediate [Poliovirus Vaccine Inactivated], these antigens are used in other US licensed products, including IPOL® (STN BL 103930) – Sanofi Pasteur SA (vIPV)

Of note, the polio antigens for VAXELIS /PR5I [DTaP-IPV/Hib-Hep B] are produced in vero cells, whereas the polio antigens contained in Pentacel [DTaP-IPV/Hib] vaccine are produce in MRC5 cells.

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

PR5I is not currently licensed in the U.S. Under the trade name of 'VAXELIS', this product was granted marketing authorization by the European Medicines Agency (EMA) for use in the EU in February 2016. A Periodic Safety Update Report (PSUR) for the reporting interval 16 February through 15 August 2018 was submitted to the file. There have been no safety-related events reported in the PSUR which would change the current risk/benefit assessment for VAXELIS.

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

- Initial studies during the clinical development of PR5I were not conducted under US Investigational New Drug (IND) submission. The phase 1 and 2 studies (V419-001, V419-002, V419-003, and V419-004) assessed the safety and immunogenicity of four related investigational hexavalent vaccine formulations, varying in dose and formulation, in infants and toddlers under Canadian Health Authority applications. This phase 1/2 program was completed in June 2008.

- End-of-phase 2/Pre-IND Meetings were held with CBER on March 28, 2007, and on January 25, 2008, to discuss the Phase 3 chemistry, manufacturing, and clinical development plan for PR5I.

- An Investigational New Drug Application (IND) was submitted to CBER under BB-IND 14496 on September 21, 2010. The Phase 3 clinical development plan included 4 immunogenicity and safety studies as follows:

    > Two studies (V419- 005 and V419-006) conducted in the United States under IND 14496 were intended to assess the safety, tolerability, and immunogenicity of PR5I when administered concomitantly with licensed pediatric vaccines, and to serve as the pivotal studies for the U.S. licensure. A total of 3380 subjects received at least one dose of PR5I in the U.S. studies.

- Two studies (Protocol 007 and Protocol 008) were conducted in the European Union (EU) to assess the safety, tolerability, and immunogenicity of PR5I when administered concomitantly with licensed pediatric vaccines using EU vaccination schedules. The data from these EU-based studies are intended to support licensure of PR5I in the EU. Initially, the sponsor indicated that these two EU studies would not be submitted as part of the US licensure application. However, CBER requested that the safety data from the EU studies be submitted as information only (not in support of US licensure).

- On June 27, 2013, Sanofi Pasteur submitted a Type C Meeting Request to obtain CBER concurrence on the Chemistry, Manufacturing and Control (CMC) aspects of the license application for PR5I vaccine. In lieu of a meeting, a written response was sent to the sponsor on September 11, 2013 by fax. The Type B (pre-BLA) meeting, which was to gain CBER concurrence on the adequacy of the clinical safety and immunogenicity profile of PR5I to support U.S. licensure and the plan for the timing of submission of certain additional stability data, was held on April 25, 2014.

- Sanofi Pasteur Limited submitted an initial pediatric study plan (iPSP) as an amendment to their IND 14496 on April 17, 2014. The Pediatric Equity Research Committee (PeRC) reviewed the iPSP on June 18, 2014. On June 19, 2014, CBER communicated the PeRC review comments to Sanofi Pasteur Limited and requested the submission of an 'Agreed PSP.' Sanofi Pasteur Limited submitted 'Agreed PSP' on June 20, 2014, which was approved in the PeRC meeting on July 16, 2014. The Agreed PSP was included in the BLA, STN 125563/0.

- The biologics license application (BLA) for PR5I was submitted on August 12, 2014 with the proposed indication of active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* type b as a three-dose series in children from 6 weeks through 4 years of age. The vaccine is manufactured for MCM Vaccine Company, a joint venture between Merck and Sanofi Pasteur Limited. The BLA was initially submitted under Sanofi Pasteur's current license, subsequently changed the applicant to MCM Vaccine Company and a new license number has been issued. Sanofi Pasteur Limited will manufacture DTaP, Sanofi Pasteur SA will manufacture IPV, and Sanofi Pasteur Limited will manufacture the final drug product. Merck will manufacture Hib and Hep B and provide these bulk intermediates to Sanofi. Sanofi Pasteur Inc. will be responsible for submitting information for MCM Vaccine Company. Merck submitted two For Further Manufacturing Use (FFMU) BLAs STN125580/0 (PedvaxHIB, Hib) and STN125581/0 (Recombivax HB, Hep B) including information regarding the manufacture of the bulk intermediates. The FFMU BLAs are cross referenced to the BLA.

- During the review of the BLA, Out-of-Specification (OOS) results for (b) (4) for three lots of filled drug product during the stability monitoring program was noted. This finding was discussed with the Applicant, with a request for further information. On June 25, 2015, MCM responded with completed comprehensive (b) (4) laboratory and product manufacturing investigation review in response to OOS test results for (b) (4) obtained on the stability monitoring program. CBER informed MCM, by a letter on July 06, 2018, that this information constituted a major amendment to the BLA and a new PDUFA due date for November 11, 2015 was set. CBER issued a two-item Complete Response (CR) letter on November 01, 2015, which contained comments on (1) Out-of-Specification pertactin (PRN) potency assay

data for multiple manufactured lots and (2) proposed use of expired lot of PRP-OMCP as a reference standard.

- To address the CMC issues in the Complete Response Letter it was agreed that Sanofi would submit requested information to IND 14496 rather than to the licensing application. On May 25, 2017 an amendment to the IND was submitted which contained the following information:

  > Additional review of the Acellular Pertussis Mouse Immunogenicity Assay and findings to date and a question to seek agreement from CBER for the modification of the Acellular Pertussis Mouse Immunogenicity test to include an age criterion for mice of (b) (4) of age and a weight range of (b) (4) .
  > Additional OOS events in the (b) (4) test and the results of the investigation and a question to seek agreement from CBER for the modifications to the (b) (4) test to reduce the (b) (4) dose and the strategy for replacing the current (b) (4) assay post-licensure.
  > Update to the AlPO4 process description and release (b) (4) of Diphtheria Toxoid Test (b) (4)) to align with licensed Adsorbed Vaccines formulated at Sanofi Pasteur, Toronto site.
  > Proposal for (b) (4) and questions seeking CBER agreement on that proposal, along with submission of associated Quality Amendments to the BLA in order to address the CR letter.

- On August 01, 2017, CBER responded to Sanofi's questions included in the above-mentioned amendment, dated May 25, 2017 to IND 14496. CBER concurred with:

  > The conclusion of the PRN potency investigation and information provided to demonstrate manufacturing lot consistency and control of the assay.
  > The modification of the Acellular Pertussis Mouse Immunogenicity test to include an age criterion for mice of (b) (4) of age and a weight range of (b) (4)
  > The proposal for acceptance of quality amendments to BLA in order to address issues included in the CR letter.

CBER did not agree with:

> The proposed modifications to the (b) (4) test procedure to reduce the (b) (4) dose. The data presented using the 0.5 mg dose shows that the (b) (4) , which results in reduced sensitivity of the test. In addition, the data provided suggests that this modification to the (b) (4) test does not significantly reduce the variability as demonstrated by the (b) (4) invalid rate.
> The proposed strategy for replacing the (b) (4) assay post-licensure as there was insufficient information included in the submission. CBER requested for the validation protocol and final report for the (b) (4) assay and all relevant studies that were used in the development of the (b) (4) assay for use with the PR5I vaccine to be submitted to both IND and BLA as for review.

CBER would be willing to consider the use of an appropriately validated (b) (4) assay in place of the current (b) (4) test prior to licensure of the vaccine.

> The proposal to manufacture (b) (4) for launch purposes implementing the proposed corrective actions for final product PRN immunogenicity and pertussis (b) (4) testing as CBER disagreed on Sanofi's proposal to modify (b) (4) testing. CBER deferred discussion of the (b) (4) until the (b) (4) testing issue has been resolved.

- Sanofi submitted two amendments to IND 14496 on September 11, 2017 and February 14, 2018 containing information on replacement of the (b) (4) Assay in VAXELIS and Quadracel vaccines. CBER sent an Information Request (IR) on May 02, 2018 after reviewing the information included in those amendments. On June 08, 2018, Sanofi submitted response to that IR, satisfactorily addressing all CBER comments. Subsequently, MCM submitted a Quality Amendment to the BLA on June 28, 2018 which proposed to replace the (b) (4) test with the (b) (4) Assay. The (b) (4) Assay is performed to detect (b) (4) Product release testing stage and for stability monitoring. A product acceptance criterion of (b) (4) /0.5 mL dose is proposed for release and (b) (4) /0.5 mL is proposed for stability monitoring.

- MCM submitted a response to the CR letter on June 29, 2018 addressing both the issues of Out-of-Specification pertactin (PRN) potency assay data for multiple manufactured lots and proposed use of expired lot of PRP-OMCP as a reference standard, included in the CR letter. This submission initiated a new 6-month review clock with a Resubmission Action Due date of December 29, 2018.

- The proprietary name for the PR5I vaccine was (b) (4) in the original BLA. On February 14, 2018 Sanofi requested under IND 14496 to withdraw the proprietary name (b) (4) . Following this withdrawal, on February 16, 2018 a Proprietary Name Review (PNR) request to the same IND was submitted requesting a proprietary name change for the product to VAXELIS. CBER, reviewed the request, provisionally approving VAXELIS as the proprietary name of the vaccine on June 19, 2018. Subsequently, on August 27, 2018, MCM submitted to the BLA a PNR request to change the name of the vaccine from (b) (4) to VAXELIS.

2.6 Other Relevant Background Information

As noted in Section 2.5 above, Sanofi Pasteur Inc. and Merck Sharpe and Dome Corporation (subsidiary of Merck & Co., Inc.) have entered into a shared manufacturing agreement as MCM Vaccine Company to have oversight of the development, manufacture, and release of PR5I (proposed trade name VAXELIS). Sanofi Pasteur Inc. will be responsible for publishing of the BLA and submissions to FDA on behalf of MCM Vaccine Co. MCM Vaccine Co. will have responsibility for post approval obligations such as post marketing clinical trials, additional product stability studies, complaint handling, recalls, post market reporting as required under 21 CFR 601.12. MCM Vaccine Co. will also have responsibility for adverse experience reporting. As per the Cooperative Manufacturing guidance (Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics, November 2008), MCM Vaccine Co. is eligible to be the applicant for the Biologics License for PR5I because it had oversight for vaccine

development of PR5I and will also have responsibility for commercial manufacturing of the drug product (formulation, filling, and packaging) by Sanofi Pasteur Limited (Ontario, Canada), which operates as (b) (4) (Contract Manufacturing Organization) for MCM Vaccine Co. There is a shared manufacturing arrangement between the MCM Vaccine Co. and the partner companies supplying the drug substances, Merck Sharp & Dohme Corp (Haemophilus b conjugate and Hepatitis B Surface Antigen) and Sanofi Pasteur Inc. (supplier of Tetanus Toxoid Adsorbed, Diphtheria Toxoid Adsorbed, 5-Component Acellular Pertussis Adsorbed, and Inactivated Vero Trivalent Polio vaccine bulk) to manufacture PR5I. The drug substances are components of vaccines that are currently licensed in United States, as outlined in the table below.

Table 1. STN 125636: Drug Substance used in manufacturing of PR5I

Drug Substance used in manufacturing of PR5I	**US Licensed product(s) that contains drug substance components**	**Application #**
Tetanus Toxoid Adsorbed	Pentacel® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus (MRC-5) and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine /Sanofi Pasteur, Inc.	BLA125145
Diphtheria Toxoid Adsorbed		
5-Component Acellular Pertussis Adsorbed which is composed of five antigens (Fimbriae Types 2 and 3 (FIM) Adsorbed, Pertactin (PRN) Adsorbed, Pertussis Toxoid (PT) Adsorbed, Filamentous Haemagglutinin (FHA) Adsorbed)		
Inactivated Vero Trivalent Polio vaccine bulk (vIPV)	IPOL® (Poliovirus Vaccine Inactivated)/ Sanofi Pasteur, Inc.	BLA103930
Haemophilus b conjugate (PRP-OMPC)	PedvaxHIB® Liquid [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]/ Merck Sharp & Dohme Corp	BLA103237
Hepatitis B Surface Antigen (HBsAg)	RECOMBIVAX HB® [Hepatitis B Vaccine (Recombinant)]/ Merck Sharp & Dohme Corp	BLA101066

Source: STN 125563/0.4 (date 04 November 2014), Section 1.11.1, pages 3.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

Bioresearch Monitoring inspections of six clinical investigators were conducted. Inspections of these clinical investigators did not reveal significant problems that impact the integrity of data

submitted in this BLA. Two sites for study V419-005, enrolling 1473 subjects at 39 United States sites were selected for inspection and represented ~9% of enrolled subjects. For study V419-006, 2808 subjects were enrolled at 73 study centers within the United States. Four sites were selected for BIMO inspection, representing ~10% of the enrolled subjects.

One site for V419-006 (Layton, Utah) was issued a Form FDA 483. The FDA Form 483 listed at least 14 subjects' adverse event data from the diaries were missing or incorrectly transcribed into the case report forms. This inspection was classified as VAI (Voluntary Action Indicated).

3.3 Financial Disclosures

The Financial Disclosures for the two pivotal studies V419-005 and V419-006 to support licensure are presented below.

Covered clinical study (name and/or number): V419-005 (PR505)		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 38 for Sanofi, 47 for Merck		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 for Sanofi, 0 for Merck		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 for Sanofi, 0 for Merck		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from applicant)

Covered clinical study (name and/or number): V419-006 (PR506)		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)

Total number of investigators identified: 57 from Sanofi Pasteur, 77 from Merck		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 from Sanofi Pasteur, 0 from Merck		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 from Sanofi Pasteur, 0 from Merck		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

No significant issues were identified for the manufacture of tetanus, diphtheria, pertussis, *Haemophilus influenza*, hepatitis B and IPV components of PR5I.

4.2 Assay Validation

During the review of CMC data, it was noted that some results of the (b) (4) did not meet previously established specifications during the stability testing of the pertussis toxoid contained in PR5I. MCM proposed to replace the (b) (4) Assay. The validity criteria and the concordance study results along with acceptance criteria for release (b) (4) and dose stability monitoring were acceptable and supported the replacement of the (b) (4) assay. The data submitted to support this change in assays resulted in a Major Amendment to the file.

During the above CMC investigations, issues were identified with the pertactin (PRN) potency assay and with the use of expired lot of PRP-OMCP as a reference standard. A Complete Response (CR) letter was issued. Over the next several years, the CR issues were addressed under the IND 14496 and supporting information was submitted to the BLA. With the resolution of these CMC issues the BLA was resubmitted in 29 June 2018, on a six-month review cycle. Please see corresponding committee member reviews for further information.

4.3 Nonclinical Pharmacology/Toxicology

The experience with other licensed products, which share the antigens produced under the same manufacturing conditions that are found in PR5I, precluded need for non-clinical pharmacology/toxicology data to be submitted to this BLA.

4.4 Clinical Pharmacology

The amount of each antigen formulated in a dose of PR5I represents previously tested and standardized amounts contained in other licensed and approved component and combination vaccines.

4.4.1 Mechanism of Action

Antigenic components of the infectious agents causing diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenza* type b or poliomyelitis are included in this vaccine such that they can induce an active immune response against these pathogens. Specifically, protection to diphtheria and tetanus are conferred by production of neutralizing antibodies against diphtheria and tetanus toxins that are elaborated by *C. diphtheria* and *C. tetani*, respectively. Similarly, neutralizing antibodies against polioviruses 1, 2 and 3 confer protection against poliomyelitis. Immunity to pertussis it is thought to result from the elaboration of antibodies against multiple antigenic targets including PT, FHA, PRN and FIM 2 & 3. Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] is a purified capsular polysaccharide (polyribosylribitol phosphate or PRP) of *Haemophilus influenzae* type b (Haemophilus b, Ross strain) covalently bound to an outer membrane protein complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B inducing a T-dependent enhanced antibody response and immunologic memory. Recombinant hepatitis B surface antigen elicits development of an antibody response to the '*a*' determinant of the surface antigen.

4.5 Statistical

The statistical reviewer verified that the study endpoint analyses and subgroup analyses of efficacy and safety cited by the Applicant were supported by the submitted data.
Please see statistical review for complete details.

4.6 Pharmacovigilance

A review conducted by the Office of Biostatistics and Epidemiology found no concerns for any safety signals.
When the initial BLA was submitted on August 13, 2014, VAXELIS was not licensed in the U.S. or any other country. Therefore, no epidemiological safety study data for VAXELIS were available. In February 2016, VAXELIS was licensed in EU and is currently registered and approved in 31 countries. After MCM responded on June 29, 2018 to the CR letter, dated November 01, 2015, an Information Request was issued to MCM on October 12, 2018, to submit the most recent Periodic Benefit-Risk Evaluation Report (PBRER) to the BLA. In response, MCM submitted the latest Periodic Safety Update Reports (PSUR) to the BLA on October 19, 2018, for Reporting Interval February 16, 2018, to August 15, 2018. During the indicated period, VAXELIS was marketed in Germany, France, the Netherlands and in multiple regions of Spain and Italy. Post-marketing patient exposure was calculated from internal distribution data for the period from February 01, 2018, to July 31, 2018. During the reporting interval of this PSUR, the estimated number of marketed VAXELIS doses distributed between 16-Feb-2018 to 15-Aug-2018 was approximately (b) (4). Approximately 198,919 to (b) (4) individuals are estimated to have been vaccinated, based on the assumption that each individual received 1, 2 or 3 dose(s).

Cumulatively, since non-U.S. market introduction (February 15, 2016) to August 15, 2018, the estimated number of marketed VAXELIS doses distributed worldwide was (b) (4) Approximately 319,518 to (b) (4) individuals are estimated to have been vaccinated, based on the assumptions that each received 1 to 4 doses and that all distributed doses were administered. There are no records of any registration being revoked or withdrawn for safety reasons. During the reporting period of this PSUR, no regulatory or manufacturer actions, changes to the Company Core Safety Information (CCSI) or update to the Investigator's Brochure (IB) related to VAXELIS due to safety reasons have been reported.

Routine pharmacovigilance monitoring is recommended.

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

5.1 Review Strategy

Two Phase 3 studies evaluating safety and immunogenicity (V419-005, see section 6.1 and V419-006, see section 6.2) of PR5I, serve as a basis for approval. The review strategy for V419-005 and V419-006 was to focus on co-primary immunogenicity and safety endpoints and safety assessments comparing administration of PR5I at 2, 4, and 6 months to administration of Pentacel (with RECOMBIVAX HB administered at 2 and 6 months) which is one of the current standards of care in the US. The study design of these studies was similar and allowed for the pooling of safety data. (See Section 8 of this review).
Supportive Phase 2 studies (V419-003, section 6.4 and V419-004, see section 6.5 of this review) performed in Canada, were submitted for the purpose of providing additional safety data in the Toddler age range, with the agreement pre-submittal that immunogenicity data from these studies would not be considered during the review. The focus of the review of the phase 2 studies, V419-003 and V419-004, is primarily to assess the occurrence of SAEs during these studies.

Two additional clinical trials, Studies V419-007 and V419-008, were conducted outside the U.S. During these studies, PR5I was administered on different schedules and dosing regimens, which differed from the indication, dose and regimen sought for approval in the US and differing from schedule used in the studies submitted for licensure. It was decided at the pre-licensure meetings that these studies would not be reviewed or considered as part of the licensure and approval package for PR5I. Additionally, there were 2 studies conducted with PR5I in the United Kingdom and Spain (clinical studies PRI01C and PRI02C, respectively) to evaluate PR5I using country specific immunization schedules and concomitant vaccinations which were submitted to the file, but were not considered as part of the licensing package. Final data and study reports for these four clinical studies were not complete at the time of the original BLA submission.

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

The primary source of data considered for review of this investigational product were documents submitted under STN 125563/0 and amendments to the file. Supportive information on the clinical study protocols was reviewed and referenced under BB IND 14496.
Studies contained under section 5.3.5.1 of the original submission and the presentation of integrated summaries of safety and effectiveness in section 5.3.5.3 were the primary source documents.

Draft labeling was submitted under amendment 4 to the BLA indicating merger status of Merck and SP for product manufacturing and distribution. Further labeling, as well as facsimiles of the carton and containers, were submitted to the file after approval of the trade name VAXELIS.

Concurrent memos from other review team members were consulted.

The following sections were reviewed in support of this application:
Section 5.3.5.1 Final Study Clinical Study Reports
Section 1.9.4 Proposed Pediatric Study Request
Section 1.14.1 Draft Labeling (under amendment 4 to the BLA)
Section 1.16.1 Pharmacovigilance plans
Section 2.5 Clinical Overview
Section 2.7.3 Summary of Clinical Efficacy
Section 2.7.4 Summary of Clinical Safety
Section 5.2 Tabular Listing of all Clinical studies

5.3 Table of Studies/Clinical Trials

Table 2. STN 125636: Primary Studies for Licensure PR5I (V419)

	V419-005	**V419-006 (lot consistency)**	**Total subjects planned**
Number of subjects planned for enrollment (enrolled)	1440 (1465)	2800 (2808)	4200
Number of subjects to receive PR5I planned (Enrolled and vaccinated)	960 (981)	2400 (2232)	3660
Subjects to receive active Control vaccines planned (enrolled and vaccinated)	480* (484)	400^ (370)	880
Randomization	2:1	2:2:2:1	-
Timing of doses of PR5I administered	2,4,6 months	2,4,6 months	-
Concomitant vaccines months 2,4,6	Prevnar 13, RotaTeq	Prevnar 13, RotaTeq	-
Birth dose monovalent Hepatitis B vaccine	yes	yes	-
Fourth dose in series (15 months)	DAPTACEL, PedvaxHIB, Prevnar 13	Pentacel, Prevnar 13	-
Duration	~ 14 months	~ 14 months	-

Reviewer generated table.
*Pentacel at months 2, 4and 6 and Recombivax HB[1] at months 2 and 6, followed by DAPTACEL, Prevnar 13 and ActHIB at month 15
^Pentacel at months 2, 4and 6 and Recombivax HB1 at months 2 and 6, followed by Pentacel and Prevnar 13 at month 15
1 Recombivax HB intended for use in Study V419-005 and -006 manufactured according to an investigational, modified process using (b) (4)

Table 3. STN 125636: Supportive Safety Studies for Licensure PR5I (V419)

Protocol 003 [PR503]	Partially Double-Blind, Randomized, Controlled, Dose-Ranging, Multicenter Study to Evaluate the Safety, Tolerability, and Immunogenicity of 3 Different Formulations of HR5I	756 male and female healthy hepatitis B vaccine-naïve infants, 2 months of age
Protocol 004 [PR504]	A Randomized Trial to Assess the Immunogenicity and Safety of (b) (4) to the Hepatitis B Component and When Given Concomitantly With Prevnar™	460 male and female healthy hepatitis B vaccine-naïve infants, 42 to 89 days of age

5.4 Consultations

No consultations were initiated during the review of the clinical studies.

5.4.1 Advisory Committee Meeting (if applicable)

CBER did not identify issues that required the opinion of an independent panel of experts including the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) or other external consultative groups.

5.5 References

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6. Discussion of Individual Studies/Clinical Trials

Two pivotal studies have been submitted to support the safety and immunogenicity of PR5I for use in the US as a three-dose series in infants at 2, 4, and 6 months of age:

• Study PR505, 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™ (Protocol No: 005-04)
• Study PR506, 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™ (Protocol No.: 006-01)

Studies V419-004 and V410-003 [Phase 2, non-IND studies] were reviewed for safety (serious adverse events) and to support the use of the vaccine to complete a three dose primary series of vaccination in children > 6 months of age.

The results from these studies are reported below.

6.1 Study V419-005 (PR505): Phase 3 study to evaluate Safety and Immunogenicity

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

Dates of study conduct: 20-Apr-2011 (FPE) to 09-May-2013 (LPLV)

The study was conducted at 39 study sites in the U.S.

6.1.1 Objectives

This study was conducted to assess the safety, tolerability, and immunogenicity of PR5I compared to the component vaccine control(s) (US standard-of-care) when given according to the US infant schedule at 2, 4, and 6 months of age followed by a Toddler dose of DAPTACEL and PedvaxHIB at 15 months of age and when administered concomitantly with licensed pediatric vaccines (Prevnar 13 and RotaTeq).

Primary Objectives:
1. To compare the immunogenicity of PR5I with the component vaccine Control(s).
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.

Secondary 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.
3. To describe the safety profile associated with the administration of each dose of PR5I or the component vaccine Control(s) when given concomitantly with Prevnar 13 and RotaTeq.
4. To describe the fever profile after the administration of each dose and after all doses of PR5I or the component vaccine Control(s) when given concomitantly with Prevnar 13 and RotaTeq.
5. To describe the percentage of subjects with solicited injection-site adverse events (i.e., pain, erythema, and swelling), and solicited systemic adverse events (i.e., vomiting, crying abnormal, drowsiness, appetite lost, and irritability) within 5 days after each and any doses of PR5I or the component vaccine Control(s) when co-administered with other recommended vaccines.

6. To describe the incidence of serious adverse events that occurred up to 6 months following the last dose of PR5I or Control (i.e., the 6-month dose).

Tertiary Objectives:
1. To describe the geometric mean titers (GMTs)/geometric mean concentration (GMC) for all antigens in PR5I and the component vaccine Control(s) at Post-dose 3 with 95% confidence interval (CI).
2. To describe the proportion of subjects with anti-PRP ≥ 0.15 μg/mL before the Toddler dose of PedvaxHIB or ActHIB and the proportion of subjects with anti-PRP ≥ 1.0 μg/mL at one-month after the Toddler dose of PedvaxHIB or ActHIB.
3. To describe the response rates to all antigens, except pertussis (i.e., diphtheria, tetanus, and Hib) at one-month after the Toddler dose with 95% CI.

6.1.2 Design Overview
This Phase 3 study is a randomized, active comparator-controlled, open-label, multicenter clinical trial in healthy infants (46 to 89 days of age at enrollment) to assess the safety, tolerability, and immunogenicity of PR5I when administered as an infant series at 2, 4, and 6 months of age; followed by a toddler dose of DAPTACEL, Prevnar 13 and PedvaxHIB at 15 months of age.

- Subjects randomized to the PR5I group received PR5I, Prevnar 13, and RotaTeq at 2, 4, and 6 months followed by DAPTACEL, PedvaxHIB, and Prevnar 13 at 15 months.
- Subjects randomized to the Control group 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. The Control group received the same vaccine regimen as the PR5I group with respect to concomitant vaccines (Prevnar 13 and RotaTeq at 2, 4, and 6 months of age).

The comparator arm of the study represents one of the current standard-of-care regimes in the US, with Pentacel administered as an infant series at 2, 4, and 6 months, and RECOMBIVAX HB administered separately at 2 and 6 months. Subjects that received PR5I received an additional dose of Hepatitis B vaccine when compared to those subjects who received the standard of care [Four doses for subjects in the PR5I cohort versus three doses in the Pentacel cohort]. DAPTACEL was administered in both vaccine groups at 15 months as the Toddler dose of pertussis vaccine. To complete the *Haemophilus influenza* B series subjects who had received the PR5I infant series, were administered PedvaxHIB (Merck) as a toddler dose. ActHIB (Sanofi Pasteur Ltd) completed the series for the Control group to preserve antigenic continuity throughout the Hib vaccination series. Four doses of DAPTACEL or Pentacel vaccine constitutes a primary immunization course for pertussis vaccination for these vaccines. [A PR5I regimen was compared to a 4-dose regimen of Pentacel in a separate study (V419-006), see Section 6.2 of this review]

The open-label design of study 005 was necessary because of the additional vaccination with RECOMBIVAX HB for subjects in the Control group, at 2 and 6 months of age, which did not allow the study groups to remain blinded, (i.e., no placebo vaccination was administered at the 4-month time point in the control group to maintain a blind). US licensed pediatric vaccines, Prevnar 13 and RotaTeq, were administered as concomitant vaccinations to all study participants as part of the study. Prevnar 13 was supplied by the investigator or by the site as needed. All vaccines were administered intramuscularly (IM) except RotaTeq, which is administered orally.

A total of 1473 healthy infants, who had received a dose of monovalent hepatitis B vaccine outside of the study as part of standard medical practice at birth or up to one-month of age, were randomized in a 2:1 ratio to receive either PR5I or the component Control vaccines at 39 US

investigative sites. The brand of Hepatitis vaccine administered at birth was recorded when available. To balance the vaccination groups with respect to the birth dose of Hepatitis B vaccine administered, subjects were randomized to either PR5I or Control group stratified by brand of Hepatitis vaccine given at birth (Recombivax HB versus all other brands + unknown brands). It was recommended that at least thirty days were to have lapsed between the birth dose of any monovalent Hepatitis vaccine and the administration of the first dose of PR5I.

The duration of the study for each subject was approximately 14 months from time of enrollment. It was expected that each subject would during the course of the clinical study: (1) receive all scheduled vaccinations; (2) provide all safety data after receiving each study vaccination (Day 1 through Day 15 after each vaccine dose) via diary card; and (3) have all blood samples collected. The study was considered complete at Visit 7 (after the blood draw). A subject without safety data from the 180-day safety follow-up period was considered to have completed the study assuming the three of the previously mentioned criteria were met.

Blood draws were performed at pre-specified time points as seen in Table 4 below, with specimens of ~3 mL whole blood at Visit 1 and ~5 mL whole blood at Visits 4, 6,and 7. Immunogenicity analyses were done on samples collected immediately prior to administration of Dose 1 (Visit 1), Post-dose 3 (28 to 37 days / Visit 4), immediately prior to administration of the Toddler dose (Visit 6), and after the Toddler dose (28 to 37 days / Visit 7).

Table 4. STN 125636/V419-005: Study Design and Procedures by Vaccination Group (N=1440) *

	Infant Series				**Toddler Dose**	**Close-out visit**
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 6	Visit 7
Group	2 months	4 months	6 months	7 months	15 months	16 months
1 (n=960)	Blood Draw† PR5I Prevnar 13 RotaTeq	Blood Draw† PR5I Prevnar 13 RotaTeq	Blood Draw† PR5I Prevnar 13 RotaTeq	Blood Draw†	Blood Draw† DAPTACEL ActHIB Prevnar 13	Blood Draw†
2 (n=480)	Blood Draw† Pentacel RECOMBIVAX HB Prevnar 13 RotaTeq	 Pentacel Prevnar 13 RotaTeq	 Pentacel RECOMBIVAX HB Prevnar 13 RotaTeq	Blood Draw†	Blood Draw† DAPTACEL ActHIB Prevnar 13	Blood Draw†

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Table 9-1, Section 9, page 44 of 400.
*All subjects received a dose of RECOMBIVAX HB or other monovalent Hepatitis vaccine at birth (outside of the study).
† Blood specimens (~3 mL of whole blood at Visit 1 and ~5 mL whole blood at Visits 4, 6, and 7) used to assess immunogenicity were collected, respectively: immediately prior to administration of Dose 1, Post-dose 3 (28 to 37 days), immediately prior to administration of Dose 4, and after Toddler dose (28 to 37 days). The method of blood draw was to be venipuncture (by vein).
Visit 5 was a telephone contact conducted 180 days after Visit 3.
n = number of subjects.

PR5I, DAPTACEL, PedvaxHIB, Pentacel, and RECOMBIVAX HB were supplied in vials containing the 0.5 mL dose of sterile suspension for intramuscular injection. ActHIB was supplied as a lyophilized powder for reconstitution and after reconstitution was administered IM (dose ~ 0.5 mL). The preferred site for injection for all IM vaccinations was the anterolateral thigh. RotaTeq was supplied in a tube containing 2 mL of dose solution for oral administration. All vaccines were prepared and administered according to the information contained in the currently approved US package inserts.

Changes in the conduct of the study and clinical protocol

There were four protocol amendments which revised the original protocol (dated 03 June 2010). Most of the revisions were the result of advice from CBER regarding the design and conduct of the study under the IND.

Protocol Amendment 1 (005-01), dated 17 Dec 2010; the primary reason for this amendment was to revise the primary objectives and hypotheses as follows:

1. The analysis of the pertussis responses at one-month after a Toddler dose of DAPTACEL was moved from a secondary objective and hypothesis to a primary objective and hypothesis.
2. An additional statistical criterion for the non-inferiority analysis of the anti-PRP response at one-month after the third dose of PR5I or Control was added:
   - Conditional upon meeting one of the previous criteria (which stated that the difference in percent of subjects with anti-PRP ≥ 0.15 μg/mL (PR5I minus Control) is greater than 10%), the difference in percent of subjects with anti PRP ≥ 0.15 μg/mL (PR5I minus Control) is greater than -5%.
3. An acceptability criterion of 90% (lower bound of the 2-sided 95% CI > 90%) for the observed seroprotection rate in the PR5I group was added as a primary endpoint for IPV (Types 1, 2, and 3).

Protocol Amendment 2 (005-02), dated 03 Mar 2011; the primary reason for this amendment was to revise the primary objectives and hypotheses as follows:

1. The statistical criteria for the non-inferiority analysis of the anti-PRP response at one-month after the third dose of PR5I or Control were revised to:
   - The statistical criteria for non-inferior antibody response to PRP require that:
     a) the difference in percent of subjects with anti-PRP ≥ 1.0 μg/mL (PR5I minus Control) is greater than -10%, and
     b) the difference in percent of subjects with anti-PRP ≥ 0.15 μg/mL (PR5I minus Control) is greater than -5%.
2. The analysis of anti-PRP GMTs was moved from a primary endpoint to a secondary endpoint.

Protocol Amendment 3 (005-03), dated 08-Mar-2012; the primary reason for this amendment was to revise the primary objectives and hypotheses as follows:

Section 2.1.1, Primary Objectives:

- Added "(3) to demonstrate that the IPV response rate is acceptable after receiving an infant series of 3 doses of PR5I."

Section 2.1.1, Primary Hypotheses:

- Added "(3) the percentage of subjects with anti-IPV neutralizing antibodies > 1:8 is > 90% in the PR5I group at one-month after the third dose of PR5I."

The statistical criteria for the acceptability of IPV response were that the lower bound of the 2-sided 95% CI for the endpoint is > 90%.

Protocol Amendment 4 (005-04), dated 24-Jan-2013; the primary reasons for this amendment were as follows:

Section 2.7.1, Immunogenicity of PR5I

- Added a new primary statistical analysis method for all GMT analyses (i.e., analysis of covariance with multiple imputation for missing baseline titers [MI ANCOVA]) to account for missing baseline titers due to limited serum volumes obtained from 2-month-old infant subjects at study entry.
- Added a second PP population (referred to as PP-RW) in addition to the existing PP population (referred to as PP-OW) to account for subjects who received study vaccinations and/or blood draws outside of narrow protocol-defined visit windows. The success of the hypothesis test was based on the results from the PP-RW population. PP-RW is defined as the PP population using a 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. PP-OW is defined as the PP population using a vaccination window of 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.

Section 3.5, SAP;

- Added 2 sensitivity analyses: (1) analysis of GMT endpoints with no baseline adjustment and (2) analysis of GMT endpoints based on data from subjects with both baseline and post-vaccination titers to support the ANCOVA MI primary analysis for GMT endpoints.
- Added revised systemic corticosteroid use criteria to the description of protocol violations for which a subject was excluded from the PP population (received systemic corticosteroids at ≥ 2 mg/kg/day prednisone or equivalent for ≥ 14 consecutive days).

6.1.3 Population

The following inclusion criteria were used in the clinical study to enroll eligible subjects.

Inclusion Criteria

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

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 ≥ 38.0°C [≥ 100.4°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™).
*For criteria with an asterisk, a subject could return to be entered into the study once these criteria no longer applied.

6.1.4 Study Treatments or Agents Mandated by the Protocol
(See also Table 4, section 6.1.2 of this review)

PR5I (V419) is presented as a sterile, single-dose, liquid, and preservative-free vaccine comprised of the following components per 0.5 mL dose:

- 20 μg of pertussis toxoid (PT)
- 20 μg of filamentous hemagglutinin (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-Vero cell) 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)
- (b) (4) µg of aluminum

The comparator vaccine, Pentacel (0.5 mL dose) contains the following:

- 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 (MRC5 cells): 40 D-antigen Units Type 1 (Mahoney), 8 D-antigen Units Type (MEF-1), 32 D-antigen Units Type 3 (Saukett),
- 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 10^6 infectious units (IU) per reassortant dose, depending on the serotype, and not greater than 116 x 10^6 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.

Please see the currently approved labeling for the products licensed in the US.

Table 5. STN 125636/V419-005: Clinical Supplies (Presentation/ Lot/Batch Numbers)

Clinical Material	Packaging Lot Number	Batch Number (Formulation number)	Dosage Form/Packaging
PR5I[1]	WL00040773*	(b) (4)	0.5 mL single dose glass vial
RotaTeq[2]	WL00040863 WL00045125	(b) (4)	2 mL single dose plastic tube
Pentacel[3]	WL00040890 WL00046891	(b) (4)	0.5 mL single dose glass vial
RECOMBIVAX HB[4]	WL00040926	(b) (4)	0.5 mL single dose glass vial
ActHIB[5]	WL00047160	(b) (4)	0.5 mL single dose glass vial
PedvaxHIB[6]	WL00047353	(b) (4)	0.5 mL single dose glass vial
DAPTACEL[7]	WL00047033	(b) (4)	0.5 mL single dose glass vial

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Table 9-2, Section 9.4.2, page 51 of 400.
1 PR5I = V419 = DTaP-IPV-Hib-HepB.
2 RotaTeq = Rotavirus Vaccine, Live, Oral, Pentavalent.
3 Pentacel = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, IPV, and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine.
4 RECOMBIVAX HB = recombinant hepatitis B vaccine.
5 ActHIB = Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate).
6 Liquid PedvaxHIB = Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate).
7 DAPTACEL = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed.
DTaP = Diphtheria, tetanus, and acellular pertussis, HepB = Hepatitis B, Hib = *Haemophilus influenzae* type b, IPV = Inactivated poliovirus.
*Identified as lot (b) (4) in CMC submissions (personal communication with CMC reviewer)

6.1.5 Treatments

Subjects were randomized in a 2:1 ratio and received either PR5I or control vaccinations. Subjects in the PR5I group received a 0.5 mL dose of PR5I vaccine along with Prevnar 13 and RotaTeq vaccines at 2, 4, and 6 months followed by administration of DAPTACEL, Prevnar 13, and PedvaxHIB vaccines at 15 months. Subjects in the Control group received a 0.5 mL dose of Pentacel vaccine along with Prevnar 13 and RotaTeq vaccines at 2, 4, and 6 months and a 0.5 mL dose of RECOMBIVAX HB vaccine at 2 and 6 months followed by DAPTACEL, Prevnar 13, and ActHIB vaccines at 15 months. (All subjects had received a birth dose of Hepatitis B vaccine.) All vaccinations were administered IM, except for Rotateq vaccine which was given orally.

Concomitant Medications and Vaccines

The exclusion criteria (section 6.1.3 of this review) addressed specific restrictions regarding drug products which could be administered prior to and during the course of the clinical study. All concomitant medications or drug treatments were to be noted on the subject's case report form.

Antipyretic, analgesic, and non-steroidal anti-inflammatory medications should not have been administered within 48 hours prior to administration of study vaccines (i.e., as prophylaxis

against fever). These medications may have been given in response to fever (temperature ≥ 38.0°C [100.4°F] that followed vaccination at the discretion of the subject's guardian after discussion with the investigator. Use and timing of antipyretics/analgesics and NSIAD were to be recorded on the subject diary card along with any other non-study medications administered.

Administration of non-study licensed pediatric vaccines (e.g., influenza vaccine, measles, mumps, rubella, and varicella vaccines) was permitted during this study provided the following conditions were met:
1. Inactivated influenza vaccine was not administered within 14 days before or within 14 days after any dose of study vaccine.
2. Other inactivated, conjugated, or live non-study licensed pediatric vaccines were not administered within 30 days before or within 30 days after any dose of study vaccine.
3. It was preferred that the toddler vaccines (e.g., measles, mumps, rubella, and varicella vaccines, etc.) were given after the completion of the 6-month safety follow-up period for PR5I (i.e., ~12 months of age or later), if possible.
All non-study vaccines (including inactivated, conjugated, or live vaccines) administered within 30 days prior to receipt of the study vaccine or from Day 1 (day of vaccination) through Day 31 after each study vaccination were recorded on the subject diary card.

6.1.6 Sites and Centers
There were 40 U.S. investigative sites evaluated and considered eligible, which screened a total of 1587 subjects for study participation. Of these, 39 sites randomized a total of 1473 subjects, of whom 1465 received study vaccinations; 8 subjects were randomized but did not receive study vaccination. Baseline numbers were assigned to each subject at a given site (proceeding from lowest to highest number). Allocation of baseline numbers did not allow for skipping or reassigning of numbers. After obtaining informed consent and completing all pre-vaccination procedures (i.e., collection and review of medical history, review of inclusion/exclusion criteria, review of prior medications and non-study vaccines, collection of vital signs, collection of pre-vaccination blood sample), subjects were assigned an allocation/randomization number using the IRT (Interactive Response Technology) system.

6.1.7 Surveillance/Monitoring
This was an open-label un-blinded study with all vaccines and diluents provided as un-blinded products.

Immediate Assessments
Subjects were monitored for 30 minutes following each vaccination for immediate adverse events and/or serious adverse events.

Immunogenicity Assessments
At Visits 4, 6, and 7; blood specimens (~3 mL whole blood at Visit 1, and ~5 mL whole blood at other time points) were used to assess immunogenicity. Samples were collected immediately prior to administration of Dose 1 (Visit 1), Post-dose 3 (28 to 37 days) (Visit 4), immediately prior to administration of Dose 4 (Visit 6), and after the Toddler dose (28 to 37 days) (Visit 7). All subject serum specimens were tested for responses to PR5I antigens (anti-PRP, anti-HBsAg, anti-diphtheria, anti-tetanus, anti-pertussis [PT, FHA, PRN, FIM], anti-polio Type 1, 2, and 3, and total serum IgA to rotavirus). Serum neutralization responses to rotavirus strains G1, G2, G3, G4, and P1A were performed and results provided descriptively.

Due to limited serum volume and the number of antigens to be tested, samples were prioritized based on the priority of study hypotheses and the expected antigen assay variability (primary hypotheses and more variable antigens were prioritized higher).

Subjects' serum specimens were tested for immune responses to antigens in the following priority:

- Anti-pertussis [PT, FHA, PRN, FIM] and anti-PRP at pre-vaccination 1, Post-dose 3, pre- and post-Toddler dose;
- Anti-HBsAg at Post-dose 3, pre- and post-Toddler dose;
- Anti-diphtheria, anti-tetanus, anti-polio Type 1, 2, and 3 at Post-dose 3 and post-Toddler dose;
- Serum neutralization responses to rotavirus strains G1, G2, G3, G4, and P1A at pre-vaccination 1 and Post-dose 3.

Immunogenicity Laboratory Assays

Table 6. Study V419-005 Laboratory assays

(b) (4)				
			(b) (4)	--

Source: Reviewer generated table from Clinical review under IND 14496

Safety Assessments

Adverse events included signs, and symptoms that occurred temporally to vaccination. Standard definitions for serious adverse events were used. The subject's parent(s)/legal representative

recorded all adverse events on the subject diary card, which was supplied at each vaccination visit. All adverse events reported on the subject diary card were reviewed with the study investigator and the subject's parent(s)/legal representative for completeness, accuracy, and clarity at the following study visit.

Subjects were observed for 30 minutes after each vaccination for immediate reactions.

Table 7. STN 125636/ Study V419-005: Safety assessments and timing

Time period post-vaccination*	Safety Parameter Assessed
Days 1-5	Temperature
Days 1-5	Solicited Injection Site Reactions ▪ Pain ▪ Erythema/redness ▪ Swelling Solicited Systemic Reactions ▪ Fever ▪ Vomiting ▪ Abnormal crying ▪ Drowsiness ▪ Appetite loss ▪ Irritability
Days 1-15	Unsolicited Adverse Events
Day 1-180	Serious Adverse Events (SAEs)
Following Toddler dose Day 1-15	SAEs
Throughout study	Deaths

Reviewer generated table.
*After each vaccination

Table 8. STN 125636/Study V419-005: Solicited Local Adverse Events* and Grading Scales

	Injection-Site Pain or Tenderness‡	Injection-Site Erythema (redness)	Injection-Site Swelling
Definition	See severity scale	Presence of redness around the approximate point of needle entry	Swelling at or near the injection-site
Severity scale	Mild = minor reaction when injection site is touched Moderate = cries and protests when injection site is touched Severe = cries when injected limb is moved or the movement of the injected limb is reduced	Mild: < 2.5 cm Moderate: ≥ 2.5 to ≤ 5 cm Severe: > 5 cm	Mild: < 2.5 cm Moderate: ≥ 2.5 to ≤ 5 cm Severe: > 5 cm

Source: STN 125563/0, section 5.3.5.1: V419 Protocol 005-04, Table 9-3 and 9-4, Section 9.5.1.1, page 57 and 58 of 400.
*All adverse events were collected from the time the consent form was signed through 14 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter,
^ Rectal temperature was preferred and recommended. If the temperature taken by the alternative route was ≥ 38.0°C (≥ 100.4°F), it was confirmed with a rectal temperature. Both temperatures and routes were recorded on the subject dairy card. No conversion of temperatures taken by alternative routes was performed.

Table 9. STN 125636/PR505: Solicited Systemic Adverse Events* and Grading Scales

	Temperature^	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥ 38°C	Vomiting does not include spitting up.	Inconsolable crying without a resolution.	Reduced interest in surroundings or increased sleepiness.	See severity scale	An excessive response to stimuli; increased fussiness; whining, and fretfulness despite attempts to comfort the infant and despite parental responses that would normally be soothing.
Severity scale	Mild: ≥ 38°C to ≤ 38.4°C Moderate: ≥ 38.5°C to ≤ 39.4°C Severe: ≥ 39.5°C Rectal	Mild: 1 episode per 24 hours Moderate: 2-5 episodes per 24 hours Severe: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Mild: < 1 hour Moderate: 1-3 hours Severe: > 3 hours	Mild: Sleepier than usual or less interested in surroundings Moderate: not interested in surroundings or did not wake up for a meal Severe: Sleeping most of the time or difficult to wake up	Mild: eating less than normal Moderate: missed 1 or 2 feeds/meals completely Severe: refuses ≥ 3 feeds or refuses most feeds	Mild: easily consolable Moderate: requiring increased attention Severe: inconsolable

Source: STN 125563/0, section 5.3.5.1: V419 Protocol 005-04, Table 9-3 and 9-4, Section 9.5.1.1, page 57 and 58 of 400.
*All adverse events were collected from the time the consent form was signed through 14 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter,
^ Rectal temperature was preferred and recommended. If the temperature taken by the alternative route was ≥ 38.0°C (≥ 100.4°F), it was confirmed with a rectal temperature. Both temperatures and routes were recorded on the subject dairy card. No conversion of temperatures taken by alternative routes was performed.

Serious Adverse Events

Any serious adverse event, including death due to any cause, which occurred following consent through 6 months (~180 days) after last vaccination of PR5I/component vaccine or Control(s) (i.e., the 6-month dose), and through 14 days following administration of vaccines at the Toddler dose, whether or not related to the investigational product. SAEs were to be reported within 24 hours to the Sponsor. All subjects were to be followed for outcome.

6.1.8 Endpoints and Criteria for Study Success

Primary Hypotheses:

1. Compared with subjects who receive licensed component vaccine Control(s) at 2, 4, and 6 months, the subjects who receive PR5I as an infant series at 2, 4, and 6 months have a non-inferior response rate to each antigen contained in PR5I and non-inferior GMTs for pertussis

antibody responses at one-month after the third dose of PR5I/component vaccine Control(s), when given concomitantly with Prevnar 13 and RotaTeq.

> The statistical criteria for non-inferior response rate require that, for each of the PR5I antigens, the lower bound of the 2-sided 95% CI for the difference in rates (PR5I group minus Control group) is greater than the pre-specified margin – δ, where δ is the non-inferior margin (Table 10). The statistical criteria for non-inferior antibody response to pertussis also require that, for pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 and 3 (FIM), the lower bound of the 2-sided 95% CI of the GMT ratios (PR5I group/Control group) is > 0.67.
>
> The statistical criteria for non-inferior antibody response to PRP require that:
> a. the lower bound of the 2-sided 95% CI for the difference in percent of subjects with anti-PRP ≥ 1.0 μg/mL (PR5I group minus Control group) is greater than -10%, (this endpoint is to measure the level thought to be associated with long term protection) and
> b. the lower bound of the 2-sided 95% CI for the difference in percent of subjects with anti-PRP ≥ 0.15 μg/mL (PR5I group minus Control group) is greater than -5%. (this endpoint is to measure the level thought to be associated with initial seroprotection)

2. Compared to subjects who receive licensed component vaccine Control(s) at 2, 4, and 6 months followed by DAPTACEL and ActHIB at 15 months, the subjects who receive PR5I at 2, 4, and 6 months followed by DAPTACEL and PedvaxHIB at 15 months have a non-inferior response rate and non-inferior GMTs for pertussis antibody responses at one-month after the Toddler dose of DAPTACEL.

> The statistical criteria for non-inferior responses to pertussis antigens require that for PT, FHA, PRN, and FIM both:
> a. the lower bound of the 2-sided 95% CI of the difference in response rates (PR5I group minus Control group) is greater than the pre-specified margin –δ, where δ is the non-inferior margin, and
> b. the lower bound of the 2-sided 95% CI of the GMT ratios (PR5I group/Control group) is > 0.67.

3. The percentage of subjects with anti-IPV neutralizing antibodies > 1:8 is > 90% in the PR5I group at one-month after the third dose of PR5I.

> The statistical criterion for the acceptability of IPV response is that the lower bound of the 2-sided 95% CI for the endpoint is > 90%.

Table 10. STN 125636/V419-005: Primary Endpoints and Pre-Specified Non-inferiority Margins for all PR5I Antigens

Time Point	Antigen	Primary Endpoint	Non- inferior Margin (δ)
Post-dose 3	PRP	% with titer ≥ 1.0 μg/mL	10%
		% with titer ≥ 0.15 μg/mL	5%
Post-dose 3	HBsAg	% with titer ≥ 10 mIU/mL	10%
Post-dose 3	Diphtheria	% with titer ≥ 0.1 IU/mL	10%
Post-dose 3	Tetanus	% with titer ≥ 0.1 IU/mL	5%
Post-dose 3	Pertussis–PT	% vaccine response†	10%
		GMT	1.5
Post-dose 3	Pertussis–FHA	% vaccine response	10%
		GMT	1.5
Post-dose 3	Pertussis–FIM	% vaccine response	10%
		GMT	1.5
Post-dose 3	Pertussis–PRN	% vaccine response	10%
		GMT	1.5
Post-dose 3	IPV1	% with neutralizing antibodies (NAb) ≥ 1:8 dilution	5%
			90% ‡
Post-dose 3	IPV2	% with NAb ≥ 1:8 dilution	5%
			90% ‡
Post-dose 3	IPV3	% with NAb ≥ 1:8 dilution	5%
			90% ‡
Toddler dose	Pertussis–PT	% vaccine response	10%
		GMT	1.5
Toddler dose	Pertussis–FHA	% vaccine response	10%
		GMT	1.5
Toddler dose	Pertussis–FIM	% vaccine response	10%
		GMT	1.5
Toddler dose	Pertussis–PRN	% vaccine response	10%
		GMT	1.5

Source: STN 125563/0, section 5.3.5.1: V419 Protocol 005-04, Table S1, V419 Protocol 005-04, page 4 of 400
† The pertussis vaccine response was defined as follows: (1) If pre-vaccination antibody concentration < 4X lower limit of quantification (LLOQ), then the post-vaccination antibody concentration was ≥ 4X LLOQ, (2) If pre-vaccination antibody concentration ≥ 4X LLOQ, then the post-vaccination antibody concentration was ≥ pre-immunization levels. The pre-immunization level was defined as the antibody titer at pre-Dose 1.
‡ Lower bound limit for acceptability.
Time point Post-dose 3 was one-month after the third dose; Toddler dose was one-month after the Toddler dose.
FHA = Filamentous hemagglutinin, FIM = Fimbriae types 2 and 3, GMT = Geometric mean titer of antibody titer, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, LLOQ = Lower limit of quantification, NAb = Neutralizing antibodies, PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid, SD = Standard deviation of natural logarithm of antibody titers.

Secondary Hypotheses:

1. Compared with subjects who receive licensed component vaccine Control(s) at 2, 4, and 6 months, the subjects who receive PR5I as an infant series at 2, 4, and 6 months have non-inferior response rates to PRP and non-inferior GMTs for anti-PRP at one-month after the third dose of PR5I/component vaccine Control(s), when given concomitantly with Prevnar 13 and RotaTeq.

The statistical criteria for non-inferior antibody response to PRP require that:
a. the lower bound of the 2-sided 95% CI for the difference in percent of subjects with anti-PRP ≥ 0.15 μg/mL (PR5I group minus Control group) is > -10%, and
b. the lower bound of the 2-sided 95% CI of the GMT ratio (PR5I group/Control group) is > 0.67.

2. The immunogenicity of RotaTeq in subjects who receive it concomitantly with PR5I as an infant series at 2, 4, and 6 months is non-inferior to the responses observed in subjects who receive RotaTeq concomitantly with the component vaccine Controls at one-month after the third dose of PR5I/component vaccine Control(s).

> The statistical criteria require that, for anti-rotavirus immunoglobulin A (IgA), the lower bound of the 2-sided 95% CI of the antibody GMT ratios (PR5I group/Control group) is > 0.67.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Enrolling 960 subjects to receive PR5I and 480 subjects in the control group, and presuming that 85% of subjects would be evaluable after the third dose and 80% after the toddler dose would give: 816 subjects in the PR5I group and 408 subjects in the control group after the third dose and following the toddler dose, there would be 768 subjects in the PR5I group and 384 in the control group for evaluation.

The power calculations for the non-inferiority GMT endpoints were based on the 2-sample t-test, and the acceptability of IPV response rates was based upon the normal approximation of a binary response. The alpha level of one-sided 0.025 was used for this calculation. Given the study sample size, the power for all the primary hypotheses was 92.6%. For the hypothesis of non-inferiority of PR5I at Post-dose 3, the power was 94.5% and the power was 98.4% regarding the hypothesis for the non-inferiority after the Toddler dose.

The summary of power calculations for the primary hypotheses are presented in the Table 11 below.

Table 11. STN 125636/V419-005: Summary of Power Calculation for the Primary Hypotheses

Time Point	Antigen	Primary Endpoint	Non-inferior Margin (δ)	Assumed True Response Rates (P) or SD	Power (%)
Post-dose 3	PRP	% with titer ≥ 1.0 μg/mL	10%	85%	99.7
		% with titer ≥ 0.15 μg/mL	5%	97%	99.8
Post-dose 3	HBsAg	% with titer ≥10 mIU/mL	10%	95%	>99.9
Post-dose 3	Diphtheria	% with titer ≥ 0.1 IU/mL	10%	90%	>99.9
Post-dose 3	Tetanus	% with titer ≥ 0.1 IU/mL	5%	97%	99.8
Post-dose 3	Pertussis–PT	% vaccine response[†]	10%	85%	99.7
		GMT	1.5	0.69	>99.9
Post-dose 3	Pertussis–FHA	% vaccine response	10%	80%	98.8
		GMT	1.5	0.76	>99.9
Post-dose 3	Pertussis–FIM	% vaccine response	10%	85%	99.7
		GMT	1.5	0.93	>99.9
Post-dose 3	Pertussis–PRN	% vaccine response	10%	75%	97.4
		GMT	1.5	1.18	>99.9
Post-dose 3	IPV1	% with NAb ≥1:8 dilution	5%	97%	99.8
			90% [‡]	97%	>99.9
Post-dose 3	IPV2	% with NAb ≥1:8 dilution	5%	97%	99.8
			90% [‡]	97%	>99.9
Post-dose 3	IPV3	% with NAb ≥ 1:8 dilution	5%	97%	99.8
			90% [‡]	97%	>99.9
Toddler dose	Pertussis–PT	% vaccine response	10%	85%	99.6
		GMT	1.5	0.73	>99.9

Time Point	Antigen	Primary Endpoint	Non-inferior Margin (δ)	Assumed True Response Rates (P) or SD	Power (%)
Toddler dose	Pertussis–FHA	% vaccine response	10%	85%	99.6
		GMT	1.5	0.65	>99.9
Toddler dose	Pertussis–FIM	% vaccine response	10%	85%	99.6
		GMT	1.5	0.85	>99.9
Toddler dose	Pertussis–PRN	% vaccine response	10%	85%	99.6
		GMT	1.5	0.88	>99.9
Overall Power	All above endpoints simultaneously				92.6

Source: STN 125563/0, section 5.3.5.1: V419 Protocol 005-04, Section 9.7.2.1.1: Table 9-5, V419 Protocol 005-04, page 68 of 400.
†The pertussis vaccine response was defined as follows: (1) If pre-vaccination antibody concentration < 4X LLOQ, then the post-vaccination antibody concentration was ≥ 4X LLOQ, (2) If pre-vaccination antibody concentration ≥ 4 X LLOQ, then the post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level is defined as the antibody titer at pre-Dose 1.
‡Lower bound limit for acceptability.
Time point Post-dose 3 was one-month after the third dose; Toddler dose was one-month after the Toddler dose.
FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, GMT = Geometric mean titer of antibody titer, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, LLOQ = Lower limit of quantification, NAb = Neutralizing antibodies, PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid, SD = Standard deviation of natural logarithm of antibody titers.

For subjects whose antibody titer values were below the LLOQ, their antibody titer values, (reported as < LLOQ by the testing laboratory) were replaced by 0.5*LLOQ for calculating GMT; and were replaced by 0.5*LLOQ for a numerator and by LLOQ for a denominator for calculating a fold-rise. If both the numerator and denominator were < LLOQ, then both were to be converted in the same way. Values that were greater than the ULOQ were converted to the ULOQ. Missing and incomplete data was not replaced.

As a secondary immunogenicity hypothesis, the power to evaluate the non-inferiority of PRP endpoints regarding the proportion of subjects with an anti-PRP titer ≥ 0.15 μg/mL with the margin of 10% and the GMT at Post-dose 3 was > 99.9 for both endpoints. The assumptions for the calculation were that the expected proportion was 97% and the non-inferiority margin for the proportion endpoint was 10%, and the standard deviation (SD) of log anti-PRP titer was 1.49 and the non-inferiority margin for the GMT endpoint was 1.5-fold.

The power to evaluate the non-inferiority of anti-rotavirus IgA titers, assuming the SD of log transformed titer for anti-rotavirus IgA was 1.72, was approximately 97.5% for the non-inferiority of GMT for RotaTeq concomitant use. Please see Table 12 below for the pre-specified endpoints for the secondary hypothesis.

Table 12. STN 125636/V419-005: Secondary Endpoints and Pre-specified Non-inferiority Margins

Time Point	Antigen	Secondary Endpoint	Non-inferior Margin (δ)	Assumed True Response Rates (P) or SD
Post-dose 3	PRP	% with titer ≥ 0.15 μg/mL	10%	97%
		GMT	1.5	1.49
Post-dose 3	Anti-rotavirus IgA	GMT	1.5	1.72

Source: STN 125563/0, section 5.3.5.1: V419 Protocol 005-04, section 9.7.3.1: Table 9-9, page 72 of 400.
Time point Postdose 3 was one-month after the third dose.
GMT = Geometric mean titer of antibody titer, SD = Standard deviation of natural logarithm of antibody titers.

The All Subjects as Treated population (ASaT) was used for safety evaluations. If no serious adverse events were observed in a sample of 960 PR5I recipients, this study provided 97.5% confidence that the true rate for SAEs was < 0.38% (i.e., one out of every 261 subjects). The estimated incidence and the upper bound of the 95% CI for the underlying percentage of subjects with serious adverse events for the PR5I group are provided in Table 13 below. These calculations were based on the exact binomial method.

Table 13. STN 125636/V419-005: Estimate of Incidence of Serious Adverse Events and 95% Upper Confidence Bound Based on Hypothetical Number of Subjects with Serious Adverse Events Among 960 Subjects in the PR5I Group

Hypothetical Number of Subjects with serious adverse events	Estimate of Incidence	95% Upper Confidence Bound†
1	0.10%	0.58%
5	0.52%	1.21%
10	1.04%	1.91%
20	2.08%	3.20%
40	4.17%	5.63%
80	8.33%	10.26%
160	16.67%	19.18%
320	33.33%	36.42%

Source: STN 125563/0, section 5.3.5.1: V419 Protocol 005-04, Section 9.7.2.2: Table 9-6, page 70 of 400.
†Based on the 2-tailed exact CI of a binomial proportion (Clopper and Pearson).
CI = confidence interval.

The tertiary endpoints for the study were related to the immune responses demonstrated prior to and following the administration of the toddler dose of vaccine. They were:

- GMT for all antigens in PR5I and component vaccine Controls at Post-dose 3.
- Proportion (%) of subjects with anti-PRP≥ 0.15 μg/mL before the toddler dose of DAPTACEL.
- Proportion (%) of subjects with anti-PRP≥ 1.0 μg/mL at one-month after the toddler dose of Pedvax HIB or ActHIB.

Criteria for evaluation of the response rates, one-month following the toddler dose are given in Table 14 below.

Table 14. STN 125636/V419-005: Response Rates One-month After Toddler Dose

Antigen	Response Rate
PRP	% with titer ≥ 1.0 μg/mL
HBsAg	% with titer ≥10 mIU/mL
Diphtheria	% with titer ≥ 0.1 IU/mL
Tetanus	% with titer ≥ 0.1 IU/mL
IPV1	% with NAb ≥ 1:8 dilution
IPV2	% with NAb ≥ 1:8 dilution
IPV3	% with NAb ≥ 1:8 dilution

HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, NAb = Neutralizing antibodies, PRP = Polyribosylribitol phosphate. Source: STN 125563/0, section 5.3.5.1: V419 Protocol 005-04, Section 9.7.3.1: Table 9-10, page 72 of 400.

The All Subjects as Treated (ASaT) population was used for the safety analyses. There were no primary endpoints for safety and safety parameters were reported descriptively. Safety was monitored by the Medical Monitoring Team (including clinical research and statistics personnel) on an ongoing basis, however, there was no formal interim analysis.

For further discussion of statistical analyses and methods, please see the statistical reviewer's review.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

All subjects who received at least one dose of study vaccine and had safety follow-up in this open label study were included in the safety analysis [All Subjects as Treated (ASaT)] population.

The Per Protocol populations formed the basis for the primary immunogenicity analyses. All subjects who met the inclusion criteria, who were not protocol violators, and had serology results within the specified day ranges, were included in the PP immunogenicity analyses. The primary immunogenicity analyses included two Per Protocol populations (PP); PP-RW (per protocol revised windows) and PP-OW (per protocol original windows). Subjects included in the PP populations met all inclusion criteria and none of the exclusion criteria, had serology results within the specified day ranges, followed the protocol, and did not have any major protocol violations.

The protocol violations were identified according to the protocol and Statistical Analysis Plan and without the knowledge of subject's immunogenicity data. The definitions for these two PP populations are the same except for the allowed PP day ranges for vaccinations and blood sample draws. PP-RW was defined as the PP population using a 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. PP-OW was defined as the PP population using a vaccination window of 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. Because the day ranges for the PP-OW were nested in the PP-RW day ranges, the PP-OW was a subset of the PP-RW. [The second per protocol population

was added to account for subjects who received study vaccinations and/or blood draws outside of original protocol-defined visit windows, amendment 4 (24 January 2013) to IND 14496.]

6.1.10.1.1 Demographics

Forty investigative sites screened a total of 1587 subjects for study participation. Of these, 39 sites randomized a total of 1473 subjects, of whom 1465 received study vaccinations; 8 subjects were randomized but did not receive study vaccines.

A total of 1473 subjects were randomized such that 986 subjects were enrolled to the PR5I group and 487 subjects to the Control group. Among all randomized subjects, 53.0% were male and 47.0% were female. The PR5I and the Control group were similar in their gender distribution. The mean age of subjects was 65.6 for the PR5I group and 65.0 for the control group (range: 46 days to 89 days). The mean weight of subjects was 5.2 kg (range: 3 kg to 8 kg). Most (79.2%) subjects were White, with Black (14.1%) and Multi-racial (5.2%) as the next largest racial groups. Most subjects (91.4%) were of non-Hispanic or non-Latino ethnicity. Table 15 below gives the demographic characteristics of all randomized subjects.

Table 15. STN 125636/V419-005. Subject Demographic Characteristics for all Randomized Subjects

	PR5I	PR5I	Control	Control	Total	Total
	n	%	n	%	n	%
Subjects in population	986		487		1473	
Gender						
Male	507	(51.4)	273	(56.1)	780	(53.0)
Female	479	(48.6)	214	(43.9)	693	(47.0)
Age (days)[1]						
Mean	65.6		65.0		65.4	
SD	7.5		6.9		7.3	
Median	64.0		63.0		64.0	
Range	46 to 89		47 to 87		46 to 89	
Weight (kg)						
Mean	5.2		5.2		5.2	
SD	0.7		0.7		0.7	
Median	5.1		5.1		5.1	
Range	3 to 8		3 to 8		3 to 8	
Unknown [2]	3	(0.3)	1	(0.2)	4	(0.3)
Race						
American Indian or Alaska Native	2	(0.2)	1	(0.2)	3	(0.2)
Black	154	(15.6)	53	(10.9)	207	(14.1)
Native Hawaiian or Other Pacific Island	1	(0.1)	1	(0.2)	2	(0.1)
White	765	(77.6)	402	(82.5)	1167	(79.2)
Asian	13	(1.3)	4	(0.8)	17	(1.2)
Multi-racial	51	(5.2)	26	(5.3)	77	(5.2)
At least once race is Asian	14	(1.4)	5	(1.0)	19	(1.3)
Other	37	(3.8)	21	(4.3)	58	(3.9)
Ethnicity						
Hispanic or Latino	77	(7.8)	29	(6.0)	106	(7.2)
Not Hispanic or Latino	895	(90.8)	451	(92.6)	1346	(91.4)
Not reported	9	(0.9)	3	(0.6)	12	(0.8)
Unknown	5	(0.5)	4	(0.8)	9	(0.6)
Japanese ancestry[3]						
yes	5	(18.5)	0	(0.0)	5	(13.9)
no	22	(81.5)	9	(100.0)	31	(86.1)

Source: STN 125536/0, section 5.3.5.1: Table 10-7, V419 Protocol 005-04, section 10.5.1, page101 of 400.
[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.
[3] Only subjects with a primary race of Asian or subjects in the subcategory "at least one race is Asian" were included in this summary and the percentages under this category were based on these subjects.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.

Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
Percentages were based on the number of randomized subjects.
mos = months, n = Number of subjects in each category, SD = Standard deviation

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

As part of the inclusion criteria, subjects who enrolled in the study were to have received a birth dose of a Hepatitis B vaccine. Any monovalent Hepatitis B vaccine was acceptable as a birth dose (age of administration was at birth to approximately one-month of age). No notable differences were observed between the vaccination groups with regard to vaccine brand and timing of administration of Hepatitis B vaccine received at birth. (See Table 16 below) Overall, 42.1% (620 subjects; 42.0% [414 subjects] in the PR5I group and 42.3% [206 subjects] in the Control group) received RECOMBIVAX HB vaccine at birth while 56.4% (831 subjects; 56.4% [556 subjects] in the PR5I group and 56.5% [275 subjects] in the Control group) received other brands of Hepatitis B vaccine at birth (e.g., ENGERIX-B: GSK). The brand of Hepatitis B vaccine received at birth was unknown in 1.5% (22 subjects) (1.6% [16 subjects] in the PR5I group and 1.2% [6 subjects] in the Control group).

Table 16. STN 125636/V419-005. Randomized Subjects by Birth Dose of Hepatitis B Vaccine

	PR5I	PR5I	Control	Control	Total	Total
	n	%	n	%	n	%
Subjects randomized	986		487		1473	
Brand of Hepatitis B vaccine administered at birth						
Recombivax HB	414	(42.0)	206	(42.3)	620	(42.1)
Other	556	(56.4)	275	(56.5)	831	(56.4)
Unknown	16	(1.6)	6	(1.2)	22	(1.5)

Source: STN 125536/0, section 5.3.5.1: V419 Protocol 005-04, Table 10-8, section 10.5.2, page102 of 400.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL+ ActHIB + Prevnar 13 at 15 mos.
Other = all other brands of hepatitis B vaccine (e.g., ENGERIX-B).
Percentages were based on the number of randomized subjects.
mos = months, n = Number of subjects in each category

Previous Medical Conditions

Medical conditions which occurred prior to the initial vaccination in ≥ 5% of subjects in any vaccination group were assessed by system organ class and preferred term. The most frequent medical conditions by preferred term were circumcision, neonatal jaundice, and gastroesophageal reflux disease. No notable differences were observed between the vaccination groups with regard to the frequency and types of medical conditions documented prior to Visit 1(data not shown). Medications taken within 14 days of the initial vaccination by ≥ 1% of subjects were tabulated. The medications that had been administered most frequently were simethicone and ranitidine hydrochloride for gastrointestinal disorders. No differences were noted between the vaccination groups in the frequency of administration or type of medications administered.

Anti-pyretic/Analgesic use

An evaluation of antipyretic, analgesic and anti-inflammatory medications taken within 48 hours prior to and after each vaccination demonstrated that overall 2.3% to 4.0 % of subjects received prophylactic medication. A slightly higher percentage (5.5%) of subjects in the PR5I group (40.9% of subjects) received antipyretic, analgesic and anti-inflammatory medications within 48

hours after vaccination at Visit 2 than in the Control group (35.4% of subjects). There was also a higher percentage (5.3%) of antipyretic, analgesic and anti-inflammatory use following the Toddler dose in subjects receiving PR5I (36.3%) as compared to Control (31.0%) for the infant series. Of note, the incidence of antipyretic, analgesic and anti-inflammatory use following each infant dose (within 48 hours 34.6% to 40.9%, PR5I) was higher than the incidence of fever after an infant dose (within 48 hours 18.1% to 29.5%, PR5I), so the post-vaccination antipyretic, analgesic and anti-inflammatory may have been administered to treat non-fever related issues (e.g., pain, fussiness).

6.1.10.1.3 Subject Disposition

The disposition of subjects enrolled at 39 sites by vaccination group and vaccination received is provided below in Table 17. Subjects were randomized 2:1 to the PR5I or Control group. Screening failure was the only reason that subjects were not randomized.

There were three-time points analyzed for discontinuation of subjects from the study:

- During the three dose infant series
- Between the infant series and the Toddler dose
- After administration of the Toddler dose

All 3 doses of the infant series were received by 93.7% (924 subjects) in the PR5I group and 94.5% (460 subjects) in the Control group. A total of 5.5% (81 subjects) discontinued the infant series; 5.8% (57 subjects) in the PR5I group and 4.9% (24 subjects) in the Control group. The most frequent reasons for discontinuation from the infant series were due to protocol violations, subjects lost to follow-up, and withdrawal by subject. The most common reasons for "withdrawal by subject" were 1) parents no longer wished to participate in study, 2) parents lost insurance coverage and 3) parents did not wish to comply with study blood draws.

A total of 121 subjects (8.2%) discontinued participation in the study between the infant series and the Toddler dose; 81 subjects (8.2%) in the PR5I group and 40 subjects (8.2%) in the Control group.
The most frequent reasons for discontinuing between the infant series and the Toddler dose were: lost to follow-up, withdrawal by subject, and physician's decision.
A total of thirteen subjects discontinued the study due to "physician's decision". Four of the subjects were placed in foster care and could not complete the study, most of the other subjects were removed from the study due to parents being unable to meet study schedule and requirements.

A total of 1264 subjects (85.8%) of 1266 subjects completed the Toddler dose vaccinations; 844 of 846 subjects (85.6%) in the PR5I group and 420 subjects (86.2%) in the Control group. A total of 27 subjects (1.8%) discontinued after the Toddler dose; 14 subjects (1.4%) in the PR5I group and 13 subjects (2.7%) in the Control group.

Table 17. STN 125536/V419-005. Subject Disposition (All)

	PR5I (N=981)		Control (N=484)		Total (N=1465)	
	n	(%)	n	(%)	n	(%)
Screened					1587	
Randomized subjects	986		487		1473	
Not vaccinated	5	(0.5)	3	(0.6)	8	(0.5)
Received all 3 doses of the Infant Series (PR5I / Control) [1]	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 [2]	924	(93.7)	460	(94.5)	1384	(94.0)
Did not complete the Infant Series (PR5I / Control) Reason for Withdrawal: [3]	57	(5.8)	24	(4.9)	81	(5.5)
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: [3]						
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)
Received Toddler Dose vaccinations [4]	846	(85.8)	420	(86.2)	1266	(85.9)
Completed Toddler Dose [5]	844	(85.6)	420	(86.2)	1264	(85.8)
Discontinued after Toddler Dose	14	(1.4)	13	(2.7)	27	(1.8)
Reason for Withdrawal: [3]						
Lost to Follow-up	11	(1.1)	12	(2.5)	23	(1.6)
Protocol Violation	0	(0.0)	1	(0.2)	1	(0.1)
Withdrawal by Subject	3	(0.3)	0	(0.0)	3	(0.2)

Source: STN 125563/0, section 5.3.5.1, V419 Protocol 005-04, Table 10-1, Section 10.1, page 85/400.
[1] Received all 3 infant dose vaccinations of PR5I / Control vaccines.
[2] Received all 3 infant full dose vaccinations of PR5I / Control vaccines and all full doses of concomitant associated study vaccines. [3] Percentages were based on the number of randomized subjects who received at least 1 dose of PR5I or Control.
[4] Received Toddler Dose of DAPTACEL and monovalent Hib vaccine (including 10 subjects who received vaccines at non-study visits).
[5] 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.

PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos. mos = months, N = Number of subjects vaccinated,
n = Number of subjects in analysis. Eight subjects were randomized but were not vaccinated.
One primary reason for discontinuation per subject was reported,
Other - Other criteria specified in the protocol that is not met by the subject

Table 18. STN 125536/V419-005. Subject Disposition by Vaccination Received

	PR5I (N=981)	**PR5I (N=981)**	**Control (N=484)**	**Control (N=484)**	**Total[4] (N=1465)**	**Total[4] (N=1465)**
	n	(%)	n	(%)	n	(%)
Screened/ Randomized subjects	986		487		1587 1473	
Vaccinated at Visit 1 with[1]						
PR5I	981	100	NA		981	67.0
Pentacel	NA		484	100	484	33.0
RECOMBIVAX HB	NA		484	100	484	33.0
Prevnar 13	981	100	484	100	1465	100
RotaTeq	981	100	484	100	1465	100
Vaccinated at Visit 2 with[1]						
PR5I	950	96.8	NA		950	64.8
Pentacel	NA		472	97.5	472	32.2
Prevnar 13	950	96.8	472	97.5	1422	97.1
RotaTeq	950	96.8	472	97.5	1422	97.1
Vaccinated at Visit 3 with[1]						
PR5I	924	94.2	NA		924	63.1
Pentacel	NA		460	95.0	460	31.4
RECOMBIVAX HB	NA		460	95.0	460	31.4
Prevnar 13	924	94.2	460	95.0	1384	94.5
RotaTeq	924	94.2	460	95.0	1384	94.5
Vaccinated at Visit 6 with:[1]						
DAPTACEL	842	85.8	418	86.4	1260	86.0
PedvaxHIB	840	85.6	NA		840	57.3
ActHIB	NA		418	86.4	418	28.5
Prevnar 13	819	83.5	413	85.3	1232	84.1
Did not complete the Infant series (PR5I / Control)[2]	57	5.8	24	4.9	81	5.5
Discontinued between the Infant series and Toddler dose[2]	81	8.2	40	8.2	121	8.2

	PR5I (N=981)	PR5I (N=981)	Control (N=484)	Control (N=484)	Total[4] (N=1465)	Total[4] (N=1465)
Discontinued after Toddler dose[2]	14	1.4	13	2.7	27	1.8
Age (range), days[3]	46 to 89		47 to 87		46 to 89	
Gender[2]						
Male	507	51.4	273	56.1	780	53
Female	479	48.6	214	43.9	693	47.0

Source: Source: STN 125563/0, section 5.3.5.1: V419 Protocol 005-04, Table S2, page 6 of 400.
1 Percentages were based on the number of randomized subjects who received at least one dose of PR5I or Control.
2 Percentages were based on the number of randomized subjects.
3 Age was calculated as the integer value of (date of vaccination dose 1 – date of birth). For 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).
4 A total of 1473 subjects were randomized, of those1465 received study vaccinations; 8 subjects were randomized but did not receive study vaccination.
N = Number of subjects vaccinated, n = Number of subjects included in the analysis.

6.1.11 Immunogenicity Analyses

The primary immunogenicity analyses were based on the Per Protocol (PP) populations. Two PP populations, PP-RW and PP-OW were evaluated (see section 6.1.10.1 above for definitions). The number and percentage of subjects excluded from the PP-RW population (overall PR5I vaccination group N = 986; Control, N = 487) one-month Post-dose 3 for PR5I endpoints is provided in Table 19 below. The number of subjects that were excluded from the PP-RW population were comparable between the PR5I and Control groups. The most common reasons for exclusion were: received incomplete or incorrect study vaccine regimen, sample not collected and result not available/insufficient serum for both the PR5I and Control groups.

The number (%) of subjects excluded from the PP-OW population one-month Post-dose 3 is provided in Table 20. The PR5I and Control groups were comparable with regard to the number of subjects that were excluded from the PP-OW population. The number of subjects that were excluded from the PP-OW population was marginally higher than the number of subjects excluded from the PP-RW population for all PR5I endpoints. The most common reasons for exclusion were: vaccination out of day range and received incomplete or incorrect study vaccine regimen for the PR5I group, sample not collected and vaccination out of day range for the Control group.

Results were similar for subjects who were excluded from the PP-OW population at one-month Post-dose 3 for the PR5I endpoints (data not shown).

The number and percentage of subjects excluded from the PP-RW and PP-OW populations one-month after the Toddler dose for PR5I endpoints was similar between the groups with approximately 26-30% of subjects excluded in both groups. The most common reasons for exclusion from both the PP-RW and the PP-OW populations were “received incomplete or incorrect study vaccine regimen” and “sample not collected” for both the PR5I and Control groups.

The number and percentage of subjects excluded from the PP-RW and PP-OW populations one-month Post-dose 3 for RotaTeq endpoints showed no notable differences between the PR5I and Control groups with regard to the number of subjects that were excluded from the PP-RW or the

PP-OW populations (over 40% in both cases). The most common reasons for exclusion from the PP-RW population were “result not available/insufficient serum”, “received incomplete or incorrect study vaccine regimen”, and “sample not collected” for both the PR5I and Control groups. The most common reasons for exclusion from the PP-OW population were “result not available/insufficient serum”, “vaccination out of day range”, “received incomplete or incorrect study vaccine regimen”, and “sample not collected” for both the PR5I and Control groups. The high percentage of subjects with insufficient serum was due to the higher priority of PR5I/Control laboratory testing as compared to concomitant use vaccine testing, combined with the limited amount of serum available for this pediatric population.

Table 19. STN 125536/V419-005. Number (%) of Subjects Excluded from the PP-RW Population at One-month Post-dose 3 for PR5I Endpoints (All Randomized Subjects)

Vaccination Group = PR5I (N=986)											
	PRP n (%)	**HBsAg n (%)**	**Diphtheria Toxoid n (%)**	**Tetanus Toxoid n (%)**	**Pertussis PT n (%)**	**Pertussis FHA n (%)**	**Pertussis FIM n (%)**	**Pertussis PRN n (%)**	**Polio Type 1 n (%)**	**Polio Type 2 n (%)**	**Polio Type 3 n (%)**
Number of subjects included	765 (77.6)	688 (69.8)	786 (79.7)	787 (79.8)	810 (82.2)	810 (82.2)	809 (82.0)	808 (81.9)	806 (81.7)	801 (81.2)	790 (80.1)
Number of subjects excluded	221 (22.4)	298 (30.2)	200 (20.3)	199 (20.2)	176 (17.8)	176 (17.8)	177 (18.0)	178 (18.1)	180 (18.3)	185 (18.8)	196 (19.9)
Reason for exclusion											
Failed to meet inc/ex criteria	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Received incomplete or incorrect study vaccine regimen	62(6.3)	61 (6.2)	62 (6.3)	62 (6.3)	62 (6.3)	62 (6.3)	62 (6.3)	62 (6.3)	62(6.3)	62 (6.3)	62(6.3)
Received temperature compromised vaccine	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)
Received prohibited vaccine(s)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)
Received prohibited medication	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Sample not collected	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)
Vaccination out of day range	23 (2.3)	23 (2.3)	23 (2.3)	23 (2.3)	23 (2.3)	23 (2.3)	23 (2.3)	23 (2.3)	23 (2.3)	23 (2.3)	23 (2.3)
Sample collected out of day range	24 (2.4)	24 (2.4)	24 (2.4)	24 (2.4)	24 (2.4)	24 (2.4)	24 (2.4)	24 (2.4)	24 (2.4)	24 (2.4)	24 (2.4)
Result not available /Insufficient serum	45 (4.6)	121(12.3)	24 (2.4)	23 (2.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	4 (0.4)	9 (0.9)	20 (2.0)

Vaccination Group = Control (N=487)											
	PRP n (%)	**HBsAg n (%)**	**Diphtheria Toxoid n (%)**	**Tetanus Toxoid n (%)**	**Pertussis PT n (%)**	**Pertussis FHA n (%)**	**Pertussis FIM n (%)**	**Pertussis PRN n (%)**	**Polio Type 1 n (%)**	**Polio Type 2 n (%)**	**Polio Type 3 n (%)**
Number of subjects included	382 (78.4)	353 (72.5)	393 (80.7)	390 (80.1)	400 (82.1)	400 (82.1)	400 (82.1)	400 (82.1)	398 (81.7)	399 (81.9)	396 (81.3)
Number of subjects excluded	105 (21.6)	134 (27.5)	94 (19.3)	97 (19.9)	87 (17.9)	87 (17.9)	87 (17.9)	87 (17.9)	89 (18.3)	88 (18.1)	91 (18.7)
Reason for exclusion											
Failed to meet inc/ex criteria	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)
Received incomplete or incorrect study vaccine regimen	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)
Received temperature compromised vaccine	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)
Received prohibited vaccine(s)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)
Received prohibited medication	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Sample not collected	33(6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)
Vaccination out of day range	9 (1.8)	9 (1.8)	9 (1.8)	9 (1.8)	9 (1.8)	9 (1.8)	9 (1.8)	9 (1.8)	9 (1.8)	9 (1.8)	9 (1.8)
Sample collected out of day range	10 (2.1)	10 (2.1)	10 (2.1)	10 (2.1)	10 (2.1)	10 (2.1)	10 (2.1)	10 (2.1)	10 (2.1)	10 (2.1)	10 (2.1)
Result not available/Insufficient serum	18 (3.7)	47 (9.7)	7 (1.4)	10 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	4 (0.8)

Source: STN 125563/0, section 5.3.5.1: V419 Protocol 005-04, Table 10-3, page 93 of 400.
PR5I group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
Note: A subject was counted under one reason of exclusion in the order listed. Percentages were based on the number of randomized subjects.
FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, HBsAg = Hepatitis B surface antigen, mos = Months, N = Number of randomized subjects, n = Number of subjects included in each category, PP-RW = Per-protocol-Revised Windows (defined as 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), PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid.

Table 20. STN 125536/V419-005. Number (%) of Subjects Excluded from the PP-OW Population at One-month Post-dose 3 for PR5I Endpoints (All Randomized Subjects)

Vaccination Group Reason for exclusion	PRP n (%)	HBsAg n (%)	Diphtheria Toxoid n (%)	Tetanus Toxoid n (%)	Pertussis PT n (%)	Pertussis FHA n (%)	Pertussis FIM n (%)	Pertussis PRN n (%)	Polio Type 1 n (%)	Polio Type 2 n (%)	Polio Type 3 n (%)
PR5I(N=986) Number of subjects included	716 (72.6)	645 (65.4)	737 (74.7)	737 (74.7)	760 (77.1)	760 (77.1)	759 (77.0)	758 (76.9)	756 (76.7)	751 (76.2)	741 (75.2)
PR5I(N=986) Number of subjects excluded	270 (27.4)	341 (34.6)	249 (25.3)	249 (25.3)	226 (22.9)	226 (22.9)	227 (23.0)	228 (23.1)	230 (23.3)	235 (23.8)	245 (24.8)
PR5I(N=986) Failed to meet inclusion/exclusion criteria	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR5I(N=986) Received incomplete or incorrect study vaccine regimen	62 (6.3)	61 (6.2)	62 (6.3)	62 (6.3)	62 (6.3)	62 (6.3)	62 (6.3)	62 (6.3)	62 (6.3)	62 (6.3)	62 (6.3)
PR5I(N=986) Received temperature compromised vaccine	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)	8 (0.8)
PR5I(N=986) Received prohibited vaccine(s)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)
PR5I(N=986) Received prohibited medication(s)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
PR5I(N=986) Sample not collected	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)	54 (5.5)
PR5I(N=986) Vaccination out of day range	70 (7.1)	70 (7.1)	70 (7.1)	70 (7.1)	70 (7.1)	70 (7.1)	70 (7.1)	70 (7.1)	70 (7.1)	70 (7.1)	70 (7.1)
PR5I(N=986) Sample collected out of day range	27 (2.7)	27 (2.7)	27 (2.7)	27 (2.7)	27 (2.7)	27 (2.7)	27 (2.7)	27 (2.7)	27 (2.7)	27 (2.7)	27 (2.7)
PR5I(N=986) Result not available/Insufficient serum	44 (4.5)	114 (11.6)	23 (2.3)	23 (2.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	4 (0.4)	9 (0.9)	19 (1.9)
Control (N=487) Number of subjects included	354 (72.7)	328 (67.4)	363 (74.5)	361 (74.1)	370 (76.0)	370 (76.0)	370 (76.0)	370 (76.0)	368 (75.6)	369 (75.8)	366 (75.2)
Control (N=487) Number of subjects excluded	133 (27.3)	159 (32.6)	124 (25.5)	126 (25.9)	117 (24.0)	117 (24.0)	117 (24.0)	117 (24.0)	119 (24.4)	118 (24.2)	121 (24.8)

Vaccination Group Reason for exclusion	**PRP** n (%)	**HBsAg** n (%)	**Diphtheria Toxoid** n (%)	**Tetanus Toxoid** n (%)	**Pertussis PT** n (%)	**Pertussis FHA** n (%)	**Pertussis FIM** n (%)	**Pertussis PRN** n (%)	**Polio Type 1** n (%)	**Polio Type 2** n (%)	**Polio Type 3** n (%)
Control (N=487) Failed to meet inclusion/exclusion criteria	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)
Control (N=487) Received incomplete or incorrect study vaccine regimen	26 (5.3)	26 (5.3)	26 (5.3)	26 (5.3)	26 (5.3)	26 (5.3)	26 (5.3)	26 (5.3)	26 (5.3)	26 (5.3)	26 (5.3)
Control (N=487) Received temperature compromised vaccine	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)
Control (N=487) Received prohibited vaccine(s)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)
Control (N=487) Received prohibited medication(s)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Control (N=487) Sample not collected	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)	33 (6.8)
Control (N=487) Vaccination out of day range	29 (6.0)	29 (6.0)	29 (6.0)	29 (6.0)	29 (6.0)	29 (6.0)	29 (6.0)	29 (6.0)	29 (6.0)	29 (6.0)	29 (6.0)
Control (N=487) Sample collected out of day range	20 (4.1)	20 (4.1)	20 (4.1)	20 (4.1)	20 (4.1)	20 (4.1)	20 (4.1)	20 (4.1)	20 (4.1)	20 (4.1)	20 (4.1)
Control (N=487) Result not available/Insufficient serum	16 (3.3)	42 (8.6)	7 (1.4)	9 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	4 (0.8)

Source: STN 125563/0, section 5.3.5.1: V419 Protocol 005-04, Table 10-4, page 94-5 of 400.
PR5I group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
Note: A subject was counted under one reason of exclusion in the order listed. Percentages were based on the number of randomized subjects.
FHA = Filamentous haemagglutinin, FIM = Fimbrae types 2 and 3, HBsAg = Hepatitis B surface antigen, mos = Months, N = Number of randomized subjects, n = Number of subjects included in each category, PP-RW = Per-protocol-Revised Windows (defined as vaccination window of Days 42 to 84 after the previous vaccination and a blood draw sample window of Days 28 to 44 following Dose 3 or the Toddler dose), PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid.

6.1.11.1 Analyses of Primary Endpoint(s) Study V419-005

Post-dose 3 Immune Responses

The primary immunogenicity endpoints included the response rates for all component antigens of PR5I and the GMTs for pertussis antigens one-month after the third dose in the infant series of vaccinations and one-month after the Toddler dose at 15 months. Please see Table 10 for the primary endpoints and the pre-specified non-inferiority margins for antigens contained in PR5I (section 6.1.8).

The non-inferiority analysis of the PR5I antibody responses one-month post-dose 3 included 95% confidence intervals and were stratified by brand/type of birth dose hepatitis B vaccine (i.e., RECOMBIVAX HB or Other/Unknown).

Results and pre-specified criteria are presented below for each antigen.

Pertussis antigens

Non-inferiority analysis of PR5I antigen responses and GMTs for pertussis antibody responses one-month Post-dose 3 were based on the PP-RW population demonstrated that the lower bound of the 2-sided 95% CI for the group difference (PR5I group minus Control group) was above the pre-specified non-inferiority margin for all pre-specified endpoints for the antigens at one-month Post-dose 3, excepting the GMT for the FHA antigen. Thus, immune response to pertussis antigens contained in PR5I was shown to be non-inferior to the Control group (who received Pentacel) except for the FHA GMT.

Response to the pertussis antigens in the vaccines was defined as:
(1) if pre-vaccination antibody concentration was < 4 X LLOQ, then the post-vaccination antibody concentration should be ≥ 4 X LLOQ,
(2) if pre-vaccination antibody concentration was ≥ 4 X LLOQ, then the post-vaccination antibody concentration should be ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titer at pre-Dose 1.

- The difference (PR5I group minus Control group) regarding the proportion of subjects with a pertussis-PT vaccine response one-month Post-dose 3 was -0.33% (95% CI: -1.80% to 1.60%); the lower bound of the 2-sided 95% CI for the difference was > -10%.

  The GMT ratio (PR5I group/Control group) one-month Post-dose 3 was 1.28 (CI: 1.20 to 1.38); the lower bound of the 2-sided 95% CI of the GMT ratio was > 0.67. Thus, non-inferiority was demonstrated for the response to the PT antigen in PR5I.

- The difference (PR5I group minus Control group) regarding the proportion of subjects with a pertussis-FHA vaccine response one-month Post-dose 3 was -4.70% (95% CI: -8.14% to -0.97%); the lower bound of the 2-sided 95% CI for the difference was > -10%. Thus, non-inferiority was demonstrated.

  The GMT ratio (PR5I group/Control group) one-month Post-dose 3 was 0.64 (95% CI: 0.59 to 0.70); the lower bound of the 2-sided 95% CI of the GMT ratio was < 0.67 margin. Thus, non-inferiority was not demonstrated.

- The difference (PR5I group minus Control group) regarding the proportion of subjects with pertussis-PRN vaccine response one-month Post-dose 3 was -2.67% (95% CI: -7.27% to 2.23%); the lower bound of the 2-sided 95% CI for the difference was > -10%.

The GMT ratio (PR5I group/Control group) one-month Post-dose 3 was 0.83 (95% CI: 0.73 to 0.95); the lower bound of the 2-sided 95% CI of the GMT ratio was > 0.67. Thus, non-inferiority was demonstrated.

- The difference (PR5I group minus Control group) regarding the proportion of subjects with pertussis-FIM vaccine response one-month Post-dose 3 was 4.05% (95% CI: 0.23% to 8.28%); the lower bound of the 2-sided 95% CI for the difference was > -10%.

  The GMT ratio (PR5I group/Control group) one-month Post-dose 3 was 1.28 (95% CI: 1.15 to 1.42); the lower bound of the 2-sided 95% CI of the GMT ratio was > 0.67. Thus, non-inferiority was demonstrated.

Neutralizing Antibodies Against Poliovirus

The difference (PR5I group minus Control group) regarding the proportion of subjects with neutralizing antibodies (NAb) ≥ 1:8 dilution one-month Post-dose 3 was 1.76% (95% CI: 0.85% to 3.59%) for IPV1; 0.26% (95% CI: -0.22% to 1.42%) for IPV2; and 0.25% (95% CI: -0.24% to 1.41%) for IPV3; the lower bound of the 2-sided 95% CI for the difference was > -5% for all. Thus, non-inferiority was demonstrated.

Anti-Polyribosylribitol Phosphate (PRP)

- The difference (PR5I group minus Control group) regarding the proportion of subjects with anti-PRP ≥ 0.15 µg/mL one-month Post-dose 3 was 4.87% (95% CI: 2.23% to 8.14%); the lower bound of the 2-sided 95% CI for the difference was > -5%.

- The difference (PR5I group minus Control group) regarding the proportion of subjects with anti-PRP ≥ 1.0 µg/mL one-month Post-dose 3 was 9.68% (95% CI: 4.83% to 14.83%); the lower bound was > -10%. Thus, non-inferiority was demonstrated for PRP.

Anti-Hepatitis B Surface Antigen (HBsAg)

The difference (PR5I group minus Control group) regarding the proportion of subjects with anti-HBsAg ≥ 10 mIU/mL one-month Post-dose 3 was 0.84% (95% CI: -0.35% to 2.74%); the lower bound of the 2-sided 95% CI for the difference was > -10%. Thus, non-inferiority between the groups was demonstrated for the Hepatitis B component.

Anti-Diphtheria

The difference (PR5I group minus Control group) regarding the proportion of subjects with anti-diphtheria ≥ 0.1 IU/mL one-month Post-dose 3 was -3.84% (95% CI: -8.02% to 0.66%); the lower bound of the 2-sided 95% CI for the difference was > -10%. Thus, non-inferiority was demonstrated for immune response to diphtheria.

Anti-Tetanus

The difference (PR5I group minus Control group) regarding the proportion of subjects with anti-tetanus ≥ 0.1 IU/mL one-month Post-dose 3 was 0.39% (95% CI: -0.28% to 1.74%); the lower bound of the 2-sided 95% CI for the difference was > -5%. Thus, non-inferiority was demonstrated.

Similar non-inferiority analyses were performed based on the PP-OW population and on the FAS population which supported the conclusion that PR5I was non-inferior to the Control vaccines with regard to the pre-specified endpoints for all antigens at one-month Post-dose 3 except for the endpoint of the GMT for FHA antigen (data not shown).

Table 21. STN 125536/V419-005. Non-Inferiority Comparison of PR5I Antigen Responses One-month Post-dose 3 (PP-RW Population)

			PR5I (n=924)	PR5I (n=924)	Control (n=460)	Control (n=460)	Estimated Difference/ GMT Ratio [2] (95% CI)
Antigen	**Endpoint**	**Non-Inferiority margin (NI)**	**n**	**Estimated Response [2]**	**n**	**Estimated Response [2]**	**Estimated Difference/ GMT Ratio [2] (95% CI)**
Diphtheria	% with titer ≥ 0.1 IU/mL	-10%	786	82.44	393	86.28	-3.84 (-8.02, 0.66)
Tetanus	% with titer ≥ 0.1 IU/mL	-5%	787	99.87	390	99.48	0.39 (-0.28, 1.74)
PT	% vaccine response [1]	-10%	796	98.12	391	98.45	-0.33 (-1.80, 1.60)
PT	GMT	0.67	810	109.61	400	85.41	1.28 (1.20, 1.38)
FHA	% vaccine response [1]	-10%	796	87.33	391	92.04	-4.70 (-8.14, -0.97)
FHA	GMT	0.67	810	46.59	400	72.28	0.64 (0.59, 0.70)
PRN	% vaccine response [1]	-10%	794	79.34	390	82.01	-2.67 (-7.27, 2.23)
PRN	GMT	0.67	808	55.77	400	66.81	0.83 (0.73, 0.95)
FIM	% vaccine response [1]	-10%	796	90.20	391	86.15	4.05 (0.23, 8.28)
FIM	GMT	0.67	809	235.87	400	184.40	1.28 (1.15, 1.42)
HBsAg	% with titer ≥10 mIU/mL	-10%	688	99.42	353	98.58	0.84 (-0.35, 2.74)
PRP	% with titer ≥ 1.0 µg/mL	-10%	765	84.99	382	75.31	9.68 (4.83, 14.83)
PRP	% with titer ≥ 0.15 µg/mL	-5%	765	97.26	382	92.39	4.87 (2.23, 8.14)
IPV1	% with NAb≥1:8 dilution	-5%	806	100.00	398	98.24	1.76 (0.85, 3.59)
IPV2	% with NAb≥1:8 dilution	-5%	801	100.00	399	99.74	0.26 (-0.22, 1.42)
IPV3	% with NAb≥1:8 dilution	-5%	790	100.00	396	99.75	0.25 (-0.24, 1.41)

Source: STN 125563/0: Section 5.3.5.1: V419 Protocol 005-04, Section 11.1.1, Table 11-1, pages 117-118.

[1] The pertussis vaccine response was defined as follows: (1) if pre-vaccination antibody concentration was < 4X LLOQ, then the post-vaccination antibody concentration was ≥ 4 X LLOQ,
(2) if pre-vaccination antibody concentration was ≥ 4 X LLOQ, then the post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titer at pre-Dose 1.
[2] The estimates for the response rate, rate difference (PR5I group minus Control group), and p-value were based on the method by Miettinen and Nurminen stratified by actual brand of birth dose of hepatitis B vaccine (RECOMBIVAX HB™ or Other/Unknown). The estimates for GMT, GMT ratio (PR5I group/Control group were based on an ANCOVA model with natural log-transformed post-vaccination titer as the response variable, and vaccination group, natural log-transformed pre-vaccination titer, actual brand of birth dose of hepatitis B vaccine (RECOMBIVAX HB™ or Other/Unknown) as explanatory variables. The missing pre-vaccination titers were imputed by a multiple imputation method and used in the ANCOVA analysis.
PR5I group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13™ at 15 mos.
Control group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
CI = Confidence interval, FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, GMT = Geometric mean titer, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, mos = Months, 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),
PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid

Acceptability of IPV antigen responses in the PR5I group one-month post-dose 3 was assessed for the PP-RW population. An acceptable antigen response was defined as the lower bound of the 95% CI for the endpoints was to be > 90%. The response rate for IPV 1, 2 and 3 was 100.00% (95% CI: 99.54% [99.53% for IPV 3] to 100.00%) for subjects who had Nab ≥ 1:8 dilution; the lower bound of the 2-sided 95% CI of the point estimate was ≥ 90%, indicating the acceptability criterion was met. Results were similar when the analysis was done using the PR5I cohort in the PP-OW population (data not shown).

Of note, the poliovirus contained in PR5I is manufactured using vero cells while the poliovirus in Pentacel is manufactured using MRC5 cells. Non-inferiority was shown in the comparison of the immune responses for the poliovirus manufactured in two different cell lines.

Table 22. STN 125536/V419-005. Acceptability* of IPV Antigen Responses in the PR5I Group at One-month Post-dose 3 (PP-RW Population)

Antigen	Endpoint	N	n	Point Estimate (95% CI)
IPV1	% with Nab ≥1:8 dilution	924	806	100.00 (99.54, 100.00)
IPV2	% with Nab ≥ 1:8 dilution	924	801	100.00 (99.54, 100.00)
IPV3	% with Nab ≥1:8 dilution	924	790	100.00 (99.53, 100.00)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 11.1.3, Table 11-5, pages 124.
[1] 95% CI and p-value were calculated based on an exact binomial method by Clopper and Pearson.
PR5I group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
CI = Confidence interval, IPV = Inactivated poliovirus, mos = Months, N = Number of vaccinated subjects, n = Number of subjects included in the analysis, NAb = Neutralizing antibodies, PP-RW = Per-protocol-Revised Windows (defined as 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).
*Acceptable antigen response for each serotype was defined as the lower bound of the 95% CI for the endpoints was to be > 90%.

Pertussis Responses One-month Post-DAPTACEL Toddler Dose

The primary endpoint of the non-inferiority analysis for pertussis antigen responses and GMTs one-month after the Toddler dose following an infant series of PR5I/Control was based on the PP-RW population and is provided in Table 23 below. This fourth dose of pertussis-containing vaccine completes the primary series for pertussis vaccination. The pertussis vaccine response rates one-month after the Toddler dose of DAPTACEL demonstrated that the PR5I group was non-inferior to the Control group as the lower bound of the 2-sided 95% CI for the group difference (PR5I group minus Control group) was above the pre-specified non-inferiority margin. Results of the non-inferiority analysis of the pertussis antigen responses one-month after the Toddler dose following an infant series of PR5I/Control for the PP-OW and FAS populations were similar to those seen in the PP-RW population (data not shown). The similar results across these study populations support the conclusions that the infant series of PR5I followed by a Toddler dose of DAPTACEL was non-inferior to the Control vaccines with regard to pertussis antigen responses since the lower bound of the 2-sided 95% CI for the group difference above the pre-specified non-inferiority margins.

Table 23. STN 125536/V419-005. Non-Inferiority Comparison of PR5I Pertussis Antigen Responses One-month After the Toddler Dose of DAPTACEL (PP-RW Population)

		PR5I (N=843)	PR5I (N=843)	Control (N=420)	Control (N=420)		
Antigen	**Endpoint**	**n**	**Estimated Response [2]**	**n**	**Estimated Response [2]**	**Estimated Difference/ GMT Ratio [2] (95% CI)**	**NI Margin**
PT	**% vaccine response [1]**	701	99.28	349	97.40	1.88 (0.39, 4.18)	-10%
PT	**GMT**	713	126.90	356	90.78	1.40 (1.28, 1.52)	0.67
FHA	**% vaccine response [1]**	699	94.44	350	93.14	1.30 (-1.67, 4.78)	-10%
FHA	**GMT**	710	87.52	357	87.54	1.00 (0.91, 1.10)	0.67
PRN	**% vaccine response [1]**	701	93.00	351	93.41	-0.41 (-3.46, 3.10)	-10%
PRN	**GMT**	713	108.48	358	139.71	0.78 (0.68, 0.89)	0.67
FIM	**% vaccine response [1]**	700	97.30	351	91.12	6.18 (3.26, 9.78)	-10%
FIM	**GMT**	713	657.28	358	415.00	1.58 (1.41, 1.78)	0.67

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 11.1.2, Table 11-3, pages 122.

[1] The pertussis vaccine response was defined as follows: (1) if pre-vaccination antibody concentration was < 4X LLOQ, then the post-vaccination antibody concentration was ≥ 4 X LLOQ,

(2) if pre-vaccination antibody concentration was ≥ 4 X LLOQ, then the post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titer at pre-Dose 1.

[2] The estimates for the response rate, rate difference (PR5I group minus Control group), and p-value were based on the method by Miettinen and Nurminen stratified by actual brand of birth dose of hepatitis B vaccine (RECOMBIVAX HB or Other/Unknown). The estimates for GMT, GMT ratio (PR5I group/Control group), and p-value were based on

an ANCOVA model with natural log-transformed post-vaccination titer as the response variable, and vaccination group, natural log-transformed pre-vaccination titer, actual brand of birth dose of hepatitis B vaccine (RECOMBIVAX HB or Other/Unknown) as explanatory variables. The missing pre-vaccination titers were imputed by a multiple imputation method and used in the ANCOVA analysis.
PR5I group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos. Control group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
CI = Confidence interval, FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, GMT = Geometric mean titer, mos = Months, N = Number of subjects vaccinated, n = Number of subjects included in the analysis, 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), PP-OW = PP population using a vaccination window of 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. PRN = Pertactin, PT = Pertussis toxoid.

Summary of Primary Immunogenicity Endpoints

Although there are well accepted serological correlates of protection for Diphtheria, Tetanus, Hepatitis B virus, Haemophilus influenza PRP and the Polioviruses contained in PR5I, for the pertussis antigens there are no well-accepted serological correlates of protection. Thus, for the pertussis antigens (PT, PRN, FHA and FIM) a comparison to immune responses observed following vaccination with Pentacel (DTaP-IPV/Hep B) vaccine were used to establish non-inferiority of the pertussis antigen immune responses for PR5I.
The non-inferiority analysis for the responses to all the antigens (D, T, PT, PRN, FHA, FIM, $IPV_{1,2,3}$, HBsAg, PRP) contained in PR5I and the GMTs for the pertussis antibody responses for subjects in the PP-RW population showed that the pre-specified endpoints were met for all response rates at one-month post-dose 3 except for the FHA antigen GMT. Except for FHA, the lower bound of the 2-sided 95% CI for the group difference in response rates (PR5I group minus Control group) or GMT ratio (PR5I/Control) was above the pre-specified non-inferiority margin, thus non-inferiority to the control vaccines was shown. The non-inferiority criteria were not demonstrated for FHA GMTs post-dose 3 as the GMT ratio (PR5I group/Control group) one-month Post-dose 3 was 0.64 (95% CI: 0.59 to 0.70;) where the lower bound of the 2-sided 95% CI of the GMT ratio was to be demonstrated by a margin < 0.67.
A primary series for pertussis is four-doses for the antigens contained in PR5I and DAPTACEL/Pentacel. In study 005 the four-dose primary pertussis series was completed with DAPTACEL. The pertussis response rates one-month following the Toddler dose of DAPTACEL for infants who received the 3-dose series of PR5I/Control showed that the PR5I group was non-inferior to the Control group as the lower bound of the 2-sided 95% CI for the group difference (PR5I group minus Control group) was above the pre-specified non-inferiority margin for all pertussis antigens, including FHA. Since non-inferiority was demonstrated for FHA responses after completion of the 4-dose primary series with the Toddler dose of DAPTACEL, the missed FHA GMT endpoint post-dose 3 is considered of limited clinical significance.

Post-dose 3 acceptable immune responses to all poliovirus serotypes were demonstrated. The response rate for IPV 1, 2 and 3 was 100.00% (95% CI: 99.54% [99.53% for IPV 3] to 100.00%) for subjects who had Nab ≥ 1:8 dilution; the lower bound of the 2-sided 95% CI of the point estimate was ≥ 90%; indicating the acceptability criterion was met for all defined populations (PP-RW, PP-OW and FAS).

6.1.11.2 Analyses of Secondary Endpoints and Descriptive Tertiary Endpoints

The secondary endpoints of the study compared the immune response rates and GMTs to PRP one-month after the 6-month dose of PR5I or control vaccines when given concomitantly with Prevnar 13 and RotaTeq. The statistical criteria for non-inferior antibody response to PRP required that:

a. the lower bound of the 2-sided 95% CI for the difference in percent of subjects with anti-PRP ≥ 0.15 μg/mL (PR5I group minus Control group) be > -10%, and
b. the lower bound of the 2-sided 95% CI of the GMT ratio (PR5I group/Control group) be > 0.67.

For PRP, the difference (PR5I group minus Control group) in the proportion of subjects with anti-PRP ≥ 0.15 μg/mL at one-month Post-dose 3 was 4.87% (95% CI: 2.23% to 8.14%); indicating a non-inferior antibody response in the PR5I group compared to the Control group (97.26% vs. 92.39%).

The GMC ratio (PR5I group/Control group) one-month Post-dose 3 was 1.62 (95% CI: 1.32 to 1.98); the lower bound of the 2-sided 95% CI for the ratio was > 0.67 also indicating a non-inferior response in the PR5I group compared to the Control group (4.94 vs. 3.05). Results based on the PP-OW and FAS populations were similar to those in the PP-RW population.

Additionally, the immunogenicity of RotaTeq was assessed by a non-inferiority comparison between the groups one-month after the third dose of the infant series. The statistical criteria required that, for anti-rotavirus immunoglobulin A (IgA), the lower bound of the 2-sided 95% CI of the antibody GMT ratios (PR5I group/Control group) be > 0.67.

The antibody GMT ratio (PR5I group/Control group) one-month Post-dose 3 was 1.02 (CI: 0.83 to 1.24) for anti-rotavirus IgA; the lower bound of the 2- sided 95% CI of the GMT ratio was > 0.67 indicating a non-inferior response in the PR5I group compared to the Control group (282.54 vs. 277.95). Results based on the PP-OW and FAS populations were similar to results in the PP-RW population.

Descriptive Tertiary Endpoints
As part of the tertiary objectives of the study, a descriptive analysis of the GMT/GMC (with 95% CI) concentrations for all antigens in PR5I and the component control vaccines were to be presented for the one-month post-dose 3-time point.

Two additional descriptive analyses were:
- the proportion of subjects with anti-PRP ≥ 0.15 μg/mL before the Toddler dose of PedvaxHIB or ActHIB and the proportion of subjects with anti-PRP ≥ 1.0 μg/mL at one-month after the Toddler dose of PedvaxHIB or ActHIB and
- the response rates to all antigens, except pertussis (i.e., diphtheria, tetanus, and Hib) at one-month after the Toddler dose with 95% CI.

The antibody responses to the mono-valent PRP-OMPC HIB vaccines (contained in PR5I) and those of PRP-T HIB vaccines (contained in Pentacel) are well described in previous clinical studies. The descriptive analyses from study V419-005, showed that one-month Post-dose 3, Hib responses for PR5I, as measured by GMCs, were higher [5.11 (4.55, 5.73)] compared to the Control group [3.18 (2.66, 3.81)]; post-Toddler dose, Hib GMCs were also higher [8.44 (7.68, 9.28)] in the PR5I group compared to the Control group [17.21(14.755, 20.09)]. Similar findings were seen in the PP-OW and FAS populations.

The GMT/GMCs for most antigens were similar between the PR5I group and Control group, except for HBsAg. Subjects who received PR5I had more than a 2-fold higher GMT, which was expected given the difference in total number of hepatitis B doses (4 doses for infants receiving PR5I: birth, 2, 4, 6-month doses versus 3 doses for infants in the control group: birth, 2 and 6 months).

6.1.11.3 Subpopulation Analyses

A summary of the immune responses by time, vaccination group and hepatitis B vaccine birth dose stratum based on the PP-RW population for anti-HBsAg is provided in Table 24, below. The summary by hepatitis B vaccine birth dose stratum indicated no significant difference in immune responses between the 2 strata, and comparability between the 2 vaccination groups within each stratum, indicating that the brand of hepatitis B vaccine at birth did not impact the GMT or seroprotection rates at one-month Post-dose 3, pre-Toddler dose, and one-month after the Toddler dose. This information must be assessed in the context of differing number of doses of Hepatitis B vaccine. Subjects who received PR5I, received 4 doses of Hepatitis B vaccine, while those subjects in the control group received a total of 3 doses of Hepatitis B vaccine.

Table 24. STN 125536/V419-005. Summary of Anti-HBsAg Response by Time, Vaccination Group and Hepatitis B Vaccine Birth Dose Stratum (PP-RW Population)

Brand of Hepatitis B vaccine at birth	**RECOMBIVAX-HB**					**Other/Unknown**			
		PR5I		**Control**		**PR5I**		**Control**	
Timepoint	**Endpoint**	**n**	**Observed response**	**n**	**Observed response**	**n**	**Observed response**	**n**	**Observed response**
One-month Post dose 3	% with titer ≥ 10 mIU/mL (s/n)	270	99.63 (269/270) (97.95, 99.99)	139	98.56 (137/139) (94.90, 99.83)	418	99.28 (415/418) (97.92, 99.85)	214	98.60 (211/214) (95.96, 99.71)
	GMT	270	1114.16 (961.08, 1291.62)	139	423.13 (336.81, 531.59)	418	1055.85 (939.61, 1186.47)	214	464.58 (385.36, 560.09)
Pre-Toddler dose	% with titer ≥ 10 mIU/mL (s/n)	290	93.79 (272/290) (90.37, 96.28)	145	84.14 (122/145) (77.16, 89.67)	401	93.52 (375/401) (90.64, 95.72)	207	86.47 (179/207) (81.05, 90.82)
	GMT	290	114.61 (97.14, 135.22)	145	58.30 (44.81, 75.84)	401	97.88 (84.46, 113.44)	207	62.09 (49.86, 77.31)
One-month post Toddler dose	% with titer ≥ 10 mIU/mL (s/n)	298	93.29 (278/298) (89.82, 95.85)	145	85.52 (124/145) (78.72, 90.81)	389	91.00 (354/389) (87.71, 93.65)	201	84.58 (170/20) (78.83, 89.27)
	GMT	298	99.89 (85.01, 117.36)	145	48.59 (37.56, 62.85)	389	81.95 (70.20, 95.65)	201	55.15 (43.81, 69.42)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 14, Table 14-35, pages 241.
[1] The 95% CI for response rate was based on the exact binomial method by Clopper and Pearson. The 95% CI for GMT was based on the t-distribution of the natural log-transformed antibody titer.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL+ PedvaxHIB+ Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL+ ActHIB + Prevnar 13 at 15 mos.
CI = Confidence interval, GMT = Geometric mean titer, HBsAg = Hepatitis B surface antigen, n = Number of subjects included in the analysis, PP-RW = Per-protocol-Revised Windows (defined as 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), s = Number of responders.

6.1.11.4 Missing Data

All antibody titer values below the LLOQ values were replaced by 0.5*LLOQ for calculating GMTs; and were replaced by 0.5*LLOQ for a numerator and by LLOQ for a denominator for calculating a fold-rise. Missing and incomplete data were not replaced. Subjects with missing or incomplete data for a particular endpoint were not included in the primary analyses of the endpoint.

6.1.11.5 Exploratory and Post Hoc Analyses

Summaries of immune responses by time, vaccination group and intake of antipyretic, analgesic and anti-inflammatory medications within 48 hours after any infant dose based on the PP-RW population were provided (data not shown). Use of anti-pyretics / analgesics and anti-inflammatory medications was similar between the groups. There were no notable differences to suggest that analgesic, antipyretic and anti-inflammatory use within 48 hours after infant doses of PR5I or Control vaccines affected the immune responses to antigens in PR5I and Control vaccines.

6.1.12 Safety Analyses

6.1.12.1 Methods

Subjects were monitored for adverse events from Days 1 to 15 after each vaccine administration time point. The occurrences of immediate reactions were assessed for 30 minutes following each vaccination. Solicited injection site adverse events, solicited systemic adverse events, and temperatures were collected from Day 1 to Day 5. Adverse events were recorded on a subject diary card from Day 1 to Day 15 following each visit by parents or guardians. Serious adverse events and deaths were collected throughout the study and up to 181 days after Dose 3.

Safety evaluations were based on All Subjects as Treated (ASaT) populations, defined as all randomized subjects who received at least one vaccination and who had a safety follow up. Statistical evaluation of the safety data followed a tiered approach, as described below.

Analyses of adverse events compared solicited adverse events and unsolicited adverse events after any infant vaccination, following each infant vaccination and following the toddler dose of vaccines.

6.1.12.2 Overview of Adverse Events

The ASaT population included 981 and 484 subjects in PR5I and Control groups, respectively, who received the infant series of vaccinations, and 846 and 420 subjects, respectively, were administered the Toddler dose of vaccine(s).

Adverse Events During the Infant Vaccination Series

Table 25 below presents a summary of adverse events following any of the three doses in the infant vaccination series. The majority of subjects (> 90%) in each vaccine group reported one or more adverse events during the surveillance period. One subject from each group discontinued study participation due to a non-serious adverse event. (see section 6.1.12.7)

The rate and type of adverse events for each group following vaccination were similar between the PR5I group and the Control group, with a trend toward higher rates of adverse reactions in those subjects who received PR5I.

Table 25. STN 125536/V419-005. Summary of Adverse Events Following Any Infant Dose Vaccination (All Subjects as Treated Population- ASaT)

	PR5I (N=981)		Control (N=484)	
	n	(%)	n	(%)
Subjects in population	980		483	
Number of subjects:				
With no adverse event	41	(4.2)	29	(6.0)
With one or more adverse events (Day 1 to Day 15)	936	(95.5)	451	(93.4)
Injection-site adverse events (Day 1 to Day 15)	824	(84.1)	390	(80.7)
Solicited injection-site adverse events (Day 1 to Day 5)	821	(83.8)	389	(80.5)
Systemic adverse events (Day 1 to Day 15)	918	(93.7)	439	(90.9)
Solicited systemic adverse events (Day 1 to Day 5)	905	(92.3)	432	(89.4)
Unsolicited systemic adverse events (Day 1 to Day 15)	403	(41.1)	182	(37.7)
With vaccine-related adverse events (Day 1 to Day 15) [1]	926	(94.5)	446	(92.3)
Injection-site adverse events (Day 1 to Day 15)	824	(84.1)	390	(80.7)
Solicited injection-site adverse events (Day 1 to Day 5)	821	(83.8)	389	(80.5)
Systemic adverse events (Day 1 to Day 15)	873	(89.1)	415	(85.9)
Solicited systemic adverse events (Day 1 to Day 5)	872	(89.0)	415	(85.9)
Unsolicited systemic adverse events (Day 1 to Day 15)	90	(9.2)	41	(8.5)
With serious adverse events (Day 1 to Day 15)	21	(2.1)	8	(1.7)
With serious adverse events (Day 1 after Dose 1 to Day 181 after Dose 3)	53	(5.4)	31	(6.4)
With serious vaccine-related adverse events [1, 2]	1	(0.1)	0	(0.0)
Who died [2]	1	(0.1)	1	(0.2)
Discontinued due to an adverse event [2]	1	(0.1)	1	(0.2)
Discontinued due to a vaccine-related adverse event [1]	1	(0.1)	1	(0.2)
Discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
Discontinued due to a serious vaccine-related adverse event [1]	0	(0.0)	0	(0.0)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 12.2.1, Table 12-1, pages 137.
[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.
PR5I group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL+ PedvaxHIB + Prevnar 13 at 15 mos.
Control group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
All serious adverse events were collected up to 181 days after Dose 3. Vaccine-related serious adverse events and deaths were collected for the duration of the study. Solicited adverse events were collected Day 1 to Day 5 after each vaccination. Other adverse events were collected from Day 1 to Day 15 after vaccination.
Number of subjects in the All Subjects as Treated population i.e., all vaccinated subjects with safety follow-up.
Percentages were based on the number of subjects in the population.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

Local Injection Site Adverse Events

Table 26 below shows the rate of solicited injection site adverse events which occurred Day 1-5 following any infant dose of PR5I or the Control vaccine. The incidence of solicited injection site pain was similar between the groups overall, the rate of injection site swelling, and erythema is

slightly greater in the PR5I group versus the Control group, with the rate differences of 5.3% (0.0, 10.5) and 6.5% (1.11, 11.9), respectively.

Table 26. STN 125536/V419-005. Analysis of Solicited Injection-Site Adverse Events Related to PR5I or Control (Incidence > 0% in One or More Vaccination Groups) Day 1 to Day 5 Following Any Infant Dose Vaccination (All Subjects as Treated Population)

	PR5I (N=981)		Control (N=484)		Difference [1]	
	n	(%)	n	(%)	Estimate	(95% CI) [2]
Subjects in population	980		483			
With one or more solicited injection-site adverse events	796	(81.2)	378	(78.3)		
With no solicited injection-site adverse event	184	(18.8)	105	(21.7)		
Subjects reporting:						
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)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 12.2.3, Table 12-3, pages 142.
[1] Difference was PR5I group minus Control group (Pentacel and/or RECOMBIVAX HB).
[2] Based on un-stratified Miettinen & Nurminen method.
PR5I group received PR5I + Prevnar 13+ RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control group received Pentacel+ Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Solicited injection-site adverse events included injection-site erythema, injection-site pain and injection-site swelling.
Percentages were based on the number of subjects in the population.
CI = Confidence interval, mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

Analysis of the occurrence of solicited injection site reactions following each of the infant vaccinations is presented in Table 27 below. It is noted that there was increase erythema and pain following the second vaccination with PR5I when compared to the Control group. This difference in incidence was not noted following the third dose of vaccine. Of note, one of the two subjects that withdrew secondary to a non-serious adverse event was an infant who withdrew after the second dose of PR5I with severe injection site pain, moderate swelling and mild erythema.

Table 27. STN 125536/V419-005. Number (%) of Subjects with Any Solicited Injection-Site Adverse Events Related to PR5I or Control (Incidence > 0% in One or More Vaccination Groups) by Vaccination Day 1 to Day 5 Following Each Infant Dose Vaccination (ASaT)

Vaccination Group	PR5I (N=980)		Control (N=483)					
Injection-site	PR5I		Pentacel or RECOMBIVAX HB		Pentacel		RECOMBIVAX HB	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	980		483		483		483	
After Any Infant Dose Vaccination [1]	980		483		483		483	
Injection site erythema	478	(48.8)	204	(42.2)	200	(41.4)	144	(29.8)
Injection site pain	719	(73.4)	347	(71.8)	337	(69.8)	283	(58.6)
Injection site swelling	393	(40.1)	168	(34.8)	161	(33.3)	108	(22.4)
After Vaccination Visit 1 [1]	980		483		483		483	
Injection site erythema	270	(27.6)	125	(25.9)	118	(24.4)	87	(18.0)
Injection site pain	513	(52.3)	258	(53.4)	249	(51.6)	226	(46.8)
Injection site swelling	194	(19.8)	102	(21.1)	93	(19.3)	72	(14.9)
After Vaccination Visit 2 [1]	948		469		469		469	
Injection site erythema	321	(33.9)	126	(26.9)	126	(26.9)	0	(0.0)
Injection site pain	485	(51.2)	196	(41.8)	196	(41.8)	0	(0.0)
Injection site swelling	242	(25.5)	100	(21.3)	100	(21.3)	0	(0.0)
After Vaccination Visit 3 [1]	920		457		457		457	
Injection site erythema	301	(32.7)	146	(31.9)	136	(29.8)	108	(23.6)
Injection site pain	409	(44.5)	197	(43.1)	183	(40.0)	158	(34.6)
Injection site swelling	237	(25.8)	107	(23.4)	100	(21.9)	67	(14.7)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 14, Table 14-49, pages 305-6.
[1] Number of subjects in the All Subjects as Treated population at the considered visit(s) i.e. all vaccinated subjects with safety follow-up for the considered visit(s).
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Solicited injection-site adverse events included injection-site erythema, injection-site pain and injection-site swelling.
Percentages were based on the number of subjects in the population at each vaccination.
N = Number of vaccinated subjects, n = Number of subjects in each category

Table 28 below shows the overall number of subjects with solicited local injection site AEs by maximum size or intensity for the Days 1-5 following any vaccination during the three-dose infant series. Most local adverse reactions were mild or moderate in severity. The rates of mild to moderate injection site erythema and mild swelling were greater for PR5I when compared to the control vaccines. Rates of severe injection site erythema and swelling were similar between the groups. Severe pain occurred in 5.9% of the subjects who received PR5I compared to 4.6% subjects who received the Control vaccinations.

Table 28. STN 125536/V419-005. Number (%) of Subjects with Any Solicited Injection-Site Adverse Events Related to PR5I or Control (Incidence > 0% in One or More Vaccination Groups) by Maximum Size / Intensity Day 1 to Day 5 Following Any Infant Dose Vaccination (All Subjects as Treated Population)

Vaccination Group		PR5I (N=981)		Control (N=484)					
	Intensity /	PR5I		Pentacel and/or RECOMBIVAX HB		Pentacel		RECOMBIVAX HB	
Injection-Site	Size Rating (cm)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population		980		483		483		483	
Injection-site erythema	Total	478	(48.8)	204	(42.2)	200	(41.4)	144	(29.8)
	< 2.5 cm	451	(46.0)	194	(40.2)	190	(39.3)	140	(29.0)
	≥ 2.5 to ≤ 5.0 cm	25	(2.6)	7	(1.4)	7	(1.4)	3	(0.6)
	> 5.0 cm	2	(0.2)	3	(0.6)	3	(0.6)	1	(0.2)
Injection-site pain	Total	719	(73.4)	347	(71.8)	337	(69.8)	283	(58.6)
	Mild	421	(43.0)	205	(42.4)	203	(42.0)	192	(39.8)
	Moderate	240	(24.5)	120	(24.8)	113	(23.4)	80	(16.6)
	Severe	58	(5.9)	22	(4.6)	21	(4.3)	11	(2.3)
Injection-site swelling	Total	393	(40.1)	168	(34.8)	161	(33.3)	108	(22.4)
	< 2.5 cm	348	(35.5)	149	(30.8)	143	(29.6)	102	(21.1)
	≥ 2.5 to ≤ 5.0 cm	42	(4.3)	17	(3.5)	16	(3.3)	6	(1.2)
	> 5.0 cm	3	(0.3)	2	(0.4)	2	(0.4)	0	(0.0)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 12.2.3.1, Table 12-4, pages 144.
PR5I group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event. A subject with multiple injection-site adverse events within a preferred term was counted once for that preferred term and was classified according to the highest intensity grading recorded.
Solicited injection-site adverse events included injection-site erythema, injection site pain and injection-site swelling.
Subjects = the number of subjects in the All Subjects as Treated population i.e., all vaccinated subjects with safety follow-up.
Percentages were based on the number of subjects in the population.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

An analysis of the incidence of solicited local adverse events following each vaccination is presented in Table 29. PR5I was more reactogenic following the second dose compared to the control vaccine. Most reactions were mild-to-moderate in intensity. The rates and intensity of

adverse events following the first and third doses of PR5I were similar to those seen after receipt of the Control vaccine.

Table 29. STN 125536/V419-005. Number (%) of Subjects with Any Solicited Injection-Site Adverse Events Related to PR5I or Control (Incidence > 0% in One or More Vaccination Groups) by Vaccination and Maximum Size / Intensity Day 1 to Day 5 Following Any Infant Dose Vaccination (All Subjects as Treated Population)

		Vaccination Visit 1				Vaccination Visit 2				Vaccination Visit 3			
		PR5I (N=981)		Control (N=484)		PR5I (N=950)		Control (N=472)		PR5I (N=924)		Control (N=460)	
Vaccination Group	Intensity / Size Rating (cm)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population		980		483		948		469		920		457	
Injection site erythema	Total	270	(27.6)	125	(25.9)	321	(33.9)	126	(26.9)	301	(32.7)	146	(31.9)
	< 2.5 cm	264	(26.9)	121	(25.1)	311	(32.8)	123	(26.2)	286	(31.1)	141	(30.9)
	≥ 2.5 to ≤ 5.0 cm	6	(0.6)	2	(0.4)	9	(0.9)	2	(0.4)	14	(1.5)	5	(1.1)
	> 5.0 cm	0	(0.0)	2	(0.4)	1	(0.1)	1	(0.2)	1	(0.1)	0	(0.0)
Injection site pain	Total	513	(52.3)	258	(53.4)	485	(51.2)	196	(41.8)	409	(44.5)	197	(43.1)
	Mild	346	(35.3)	168	(34.8)	337	(35.5)	143	(30.5)	294	(32.0)	145	(31.7)
	Moderate	149	(15.2)	80	(16.6)	115	(12.1)	42	(9.0)	99	(10.8)	44	(9.6)
	Severe	18	(1.8)	10	(2.1)	33	(3.5)	11	(2.3)	16	(1.7)	8	(1.8)
Injection site swelling	Total	194	(19.8)	102	(21.1)	242	(25.5)	100	(21.3)	237	(25.8)	107	(23.4)
	< 2.5 cm	167	(17.0)	89	(18.4)	226	(23.8)	96	(20.5)	222	(24.1)	101	(22.1)
	≥ 2.5 to ≤ 5.0 cm	27	(2.8)	12	(2.5)	15	(1.6)	3	(0.6)	13	(1.4)	6	(1.3)
	> 5.0 cm	0	(0.0)	1	(0.2)	1	(0.1)	1	(0.2)	2	(0.2)	0	(0.0)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 14, Table 14-50, pages 307.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB+ Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + P revnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event. A subject with multiple injection-site adverse events within a preferred term was counted once for that preferred term and was classified according to the highest intensity grading recorded.
Solicited injection-site adverse events included injection-site erythema, injection-site pain and injection-site swelling.
Subjects in population is the number of subjects in the All Subjects as Treated population at the considered visit i.e. all vaccinated subj ects with safety follow-up for the considered visit.
Percentages were based on the number of subjects in the population at the corresponding visit.
N = Number of vaccinated subjects, n = Number of subjects in each category.

Unsolicited injection site adverse events were collected Day 1-15 after each vaccination via subject diary card. Unsolicited injection-site adverse events related to PR5I or Control vaccines following any infant vaccination were reported by 8.5% of subjects (83/980) in the PR5I group and 6.6% of subjects (32/483). Those events with an incidence of ≥ 1 % included injection site included bruising, injection site induration and injection site nodule. The intensity of most unsolicited adverse events was mild.

Systemic Adverse Events

Solicited Systemic Adverse Events were assessed Days 1-5 following each infant dose of vaccine. One or more solicited systemic adverse events (crying, decreased appetite, irritability, pyrexia, somnolence and vomiting) were reported by 92.3% of subjects (905/980) in the PR5I group and 89.4% of subjects (432/483) in the Control group during Day 1 to Day 5 following any infant dose vaccination.

During the infant vaccination series, pyrexia was reported by 47.4% of subjects (465/980) in the PR5I group and 34.4% of subjects (166/483) in the Control group during Day 1 to Day 5 following any infant dose vaccination. The difference (PR5I group minus Control group) in the percentage of subjects who had pyrexia was 13.1% (95% CI: 7.7% to 18.3%). The occurrence of all other adverse events was similar between the groups. Table 30 below summarizes the incidence of solicited systemic adverse events following any dose of vaccine in the infant vaccination series.

Table 30. STN 125536/V419-005. Solicited Systemic Adverse Events (Incidence > 0% in One or More Vaccination Groups) Day 1 to Day 5 Following Any Infant Dose Vaccination (ASaT)

	PR5I (N=981)		Control (N=484)		Difference [1]	
	n	(%)	n	(%)	Estimate	(95% CI) [2]
Subjects in population	980		483			
with one or more solicited systemic adverse events	905	(92.3)	432	(89.4)		
with no solicited systemic adverse event	75	(7.7)	51	(10.6)		
Crying	733	(74.8)	349	(72.3)	2.5	(-2.2, 7.5)
Decreased appetite	479	(48.9)	209	(43.3)	5.6	(0.2, 11.0)
Irritability	814	(83.1)	395	(81.8)	1.3	(-2.8, 5.6)
Pyrexia	465	(47.4)	166	(34.4)	13.1	(7.7, 18.3)
Somnolence	726	(74.1)	346	(71.6)	2.4	(-2.3, 7.4)
Vomiting	252	(25.7)	104	(21.5)	4.2	(-0.5, 8.7)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 12.2.4, Table 12-6, pages 148.
[1] Difference was PR5I group minus Control group.
[2] Based on un-stratified Miettinen & Nurminen method.
PR5I group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Solicited systemic adverse events included crying, decreased appetite, irritability, pyrexia, somnolence and vomiting.
Subjects in population is the number of subjects in the All Subjects as Treated population i.e., all vaccinated subjects with safety follow-up.
Percentages were based on the number of subjects in the population.
CI = Confidence interval, mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

Most of solicited systemic adverse events following any infant vaccination were mild to moderate in nature. The occurrences of severe solicited adverse events were reported by 15.5% of subjects (152/980) in the PR5I group and 13.7% of subjects (66/483) in the Control group. The greatest difference was seen in reports of severe irritability and decreased appetite in the PR5I group. The occurrence of severe pyrexia was similar between the groups. The most frequently reported severe solicited systemic adverse events were as follows:

- Crying: 7.9% of subjects (77/980) in the PR5I group and 8.3% of subjects (40/483) in the Control group.
- Irritability: 7.7% of subjects (75/980) in the PR5I group and 5.8% of subjects (28/483) in the Control group.
- Somnolence 3.5% of subjects (34/980) in the PR5I group and 2.9% of subjects (14/483) in the Control group.

An analysis of the solicited systemic adverse events Day 1-5 following each infant vaccination demonstrated that there was an increase the rate of pyrexia following the second and third vaccination with PR5I. There also appeared to be a trend toward an increasing incidence of vomiting after each dose of PR5I when compared to the control vaccines regardless of dose. The incidence of solicited systemic adverse events following each vaccination is presented below in Table 31.

Table 31. STN 125536/V419-005. Number (%) of Subjects with Any Solicited Systemic Adverse Events Related to PR5I or Control (Incidence > 0% in One or More Vaccination Groups) by Vaccination Day 1 to Day 5 Following Each Infant Dose Vaccination (All Subjects as Treated Population)

	Vaccination Visit 1				Vaccination Visit 2				Vaccination Visit 3			
	PR5I (N= 981)		Control (N= 484)		PR5I (N= 950)		Control (N= 472)		PR5I (N= 924)		Control (N= 460)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	980		483		948		469		920		457	
With one or more solicited systemic adverse events	772	(78.8)	362	(74.9)	684	(72.2)	316	(67.4)	626	(68.0)	284	(62.1)
With no solicited systemic adverse event	208	(21.2)	121	(25.1)	264	(27.8)	153	(32.6)	294	(32.0)	173	(37.9)
Crying	499	(50.9)	235	(48.7)	459	(48.4)	201	(42.9)	386	(42.0)	165	(36.1)
Decreased appetite	269	(27.4)	116	(24.0)	228	(24.1)	93	(19.8)	192	(20.9)	79	(17.3)
Irritability	619	(63.2)	292	(60.5)	537	(56.6)	247	(52.7)	485	(52.7)	223	(48.8)
Pyrexia	158	(16.1)	61	(12.6)	252	(26.6)	77	(16.4)	245	(26.6)	74	(16.2)
Somnolence	535	(54.6)	261	(54.0)	407	(42.9)	194	(41.4)	352	(38.3)	160	(35.0)
Vomiting	110	(11.2)	38	(7.9)	97	(10.2)	40	(8.5)	74	(8.0)	21	(4.6)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 12.2.4.2, Table 12-9, pages 152.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Solicited systemic adverse events included crying, decreased appetite, irritability, pyrexia, somnolence and vomiting.

Subjects in population is the number of subjects in the All Subjects as Treated population at the considered visit i.e. all vaccinated subjects with safety follow-up for the considered visit.
Percentages were based on the number of subjects in the population at the corresponding visit.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

Evaluation of Fever/Pyrexia with and without Seizures

Although the overall adverse events, any adverse event and solicited local and systemic events, were similar between the groups, an analysis of the solicited systemic adverse events Day 1-5 following any dose of infant vaccine demonstrated a difference in the rate of pyrexia (fever) between the groups. [See Table 32 below]

Overall, approximately 97% of subjects provided temperature data for Days 1-5 following any vaccination. The route of temperature measurement was comparable between the groups, with the majority of subjects reporting temperatures measured rectally (89.4% in PR5I group and 88.9% in Control group). Axillary temperatures were reported by 10.4% PR5I and 11.1% of control subjects. An analysis of subjects exhibiting fever ≥ 38.0°C by severity during Days 1-5 following any vaccination is presented below in Table 32. Of note, the differences (PR5I group minus Control group) by all routes of temperature measurement were 5.1% (95% CI: 0.5% to 9.5%) for mild fever and 7.1% (95% CI: 2.8% to 11.2%) for moderate fever. Differences observed when analyzed for those subjects who had temperature measurements by rectal method, 6.5% (95% CI: 1.9% to 10.8%) for mild fever and 6.7% (95% CI: 2.4% to 10.7%) for moderate fever. There is a difference of approximately 13% higher temperatures in the PR5I group as for mild and moderate fevers. The rates of severe fever regardless of route of measurement, were higher in the PR5I group.

Table 32. STN 125536/V419-005. Analysis of Subjects with Elevated Temperatures by Severity Day 1 to Day 5 Following Any Infant Dose Vaccination (All Subjects as Treated Population)

	PR5I (N=981)		**Control (N=484)**		**Difference [6]**	
	n	**(%)**	**n**	**(%)**	**Estimate**	**(95% CI) [7]**
Subjects in analysis population [1]	980		483			
Subjects with temperature data [2]	949	(96.8)	470	(97.3)		
Subjects with no temperature data	31	(3.2)	13	(2.7)		
Maximum Temperature (All routes [3, 4])						
< 38.0ºC	485	(51.1)	302	(64.3)	-13.1	(-18.4, -7.7)
≥ 38.0ºC and < 38.5ºC (Mild)	230	(24.2)	90	(19.1)	5.1	(0.5, 9.5)
≥ 38.5ºC and < 39.5ºC (Moderate)	215	(22.7)	73	(15.5)	7.1	(2.8, 11.2)
≥ 39.5ºC (Severe)	19	(2.0)	5	(1.1)	0.9	(-0.6, 2.2)
Maximum Temperature (Rectal [4, 5])						
< 38.0ºC	422	(44.5)	271	(57.7)	-13.2	(-18.6, -7.7)
≥ 38.0ºC and < 38.5ºC (Mild)	231	(24.3)	84	(17.9)	6.5	(1.9, 10.8)
≥ 38.5ºC and < 39.5ºC (Moderate)	205	(21.6)	70	(14.9)	6.7	(2.4, 10.7)
≥ 39.5ºC (Severe)	19	(2.0)	4	(0.9)	1.2	(-0.3, 2.4)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 12.2.5.1, Table 12-11, pages 153.
[1] Percentages were based on the number of subjects in the population with safety follow-up.
[2] Included subjects whose temperature methods were not reported for Day 1 to Day 5.

[3] Temperatures were based on actual temperatures recorded with no adjustments to the measurement route.
[4] Percentages were based on the number of subjects in the population with safety follow-up and temperature data.
[5] All subjects were required to take a rectal temperature if the reading by another method is ≥ 38.0°C.
[6] Difference was PR5I group minus Control group.
[7] Based on unstratified Miettinen & Nurminen method.
PR5I group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13™ at 15 mos.
Subjects in population is the number of subjects in the All Subjects as Treated population i.e., all vaccinated subjects with safety follow-up.
CI = Confidence interval, mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

An analysis of temperatures by vaccination dose demonstrated that following the second and third infant doses of vaccine, fevers were higher after administration of PRI5 when compared to the Control vaccines. Severe fevers were comparable between the vaccination groups regardless of dose. For all time points, the majority of subjects did not demonstrate an elevation in temperature following vaccination. For those subjects experiencing fever following vaccination, most of the fevers were mild-to-moderate in intensity with duration of 48 hours or less.

Table 33. STN 125536/V419-005. Number (%) of Subjects with Elevated Temperatures by Severity Day 1 to Day 5 Following Any Infant Dose and After Each Vaccination (All Subjects as Treated Population)

	PR5I (N=981)		**Control (N=484)**	
After Vaccination 1	n	(%)	n	(%)
Subjects in analysis population [1]	980		483	
Subjects with temperature data [2]	930	(94.9)	464	(96.1)
Subjects with no temperature data	50	(5.1)	19	(3.9)
Maximum Temperature (All Routes [3, 4])				
< 38.0 °C	762	(81.9)	393	(84.7)
≥ 38.0 °C and < 38.5 °C (Mild)	123	(13.2)	53	(11.4)
≥ 38.5 °C and < 39.5 °C (Moderate)	42	(4.5)	17	(3.7)
≥ 39.5 °C (Severe)	3	(0.3)	1	(0.2)
Maximum Temperature (Rectal [4, 5])				
< 38.0 °C	643	(69.1)	342	(73.7)
≥ 38.0 °C and < 38.5 °C (Mild)	121	(13.0)	53	(11.4)
≥ 38.5 °C and < 39.5 °C (Moderate)	40	(4.3)	17	(3.7)
≥ 39.5 °C (Severe)	3	(0.3)	0	(0.0)
	PR5I (N=950)		Control (N=472)	
After Vaccination 2	n	(%)	n	(%)
Subjects in analysis population [1]	948		469	
Subjects with temperature data [2]	901	(95.0)	448	(95.5)
Subjects with no temperature data	47	(5.0)	21	(4.5)
Maximum Temperature (All Routes [3, 4])				

	PR5I (N=981)		**Control (N=484)**	
After Vaccination 1	n	(%)	n	(%)
< 38.0 °C	639	(70.9)	366	(81.7)
≥ 38.0 °C and < 38.5 °C (Mild)	147	(16.3)	49	(10.9)
≥ 38.5 °C and < 39.5 °C (Moderate)	113	(12.5)	33	(7.4)
≥ 39.5 °C (Severe)	2	(0.2)	0	(0.0)
Maximum Temperature (Rectal [4, 5])				
< 38.0 °C	534	(59.3)	320	(71.4)
≥ 38.0 °C and < 38.5 °C (Mild)	145	(16.1)	46	(10.3)
≥ 38.5 °C and < 39.5 °C (Moderate)	109	(12.1)	32	(7.1)
≥ 39.5 °C (Severe)	2	(0.2)	0	(0.0)
	PR5I (N=924)		Control (N=460)	
After Vaccination 3	n	(%)	n	(%)
Subjects in analysis population [1]	920		457	
Subjects with temperature data [2]	871	(94.7)	430	(94.1)
Subjects with no temperature data	49	(5.3)	27	(5.9)
Maximum Temperature (All Routes [3, 4])				
< 38.0 °C	614	(70.5)	350	(81.4)
≥ 38.0 °C and < 38.5 °C (Mild)	127	(14.6)	43	(10.0)
≥ 38.5 °C and < 39.5 °C (Moderate)	116	(13.3)	33	(7.7)
≥ 39.5 °C (Severe)	14	(1.6)	4	(0.9)
Maximum Temperature (Rectal [4, 5])				
< 38.0 °C	527	(60.5)	311	(72.3)
≥ 38.0 °C and < 38.5 °C (Mild)	124	(14.2)	39	(9.1)
≥ 38.5 °C and < 39.5 °C (Moderate)	110	(12.6)	31	(7.2)
≥ 39.5 °C (Severe)	14	(1.6)	4	(0.9)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 005-04, Section 14, Table 14-63, pages 338-340. (Reviewer modified table)
[1] Percentages were based on the number of subjects in the population with safety follow-up.
[2] Included subjects whose temperature methods were not reported for Day 1 to Day 5.
[3] Temperatures were based on actual temperatures recorded with no adjustments to the measurement route.
[4] Percentages were based on the number of subjects in the population with safety follow-up and temperature data.
[5] All subjects were required to take a rectal temperature if the reading by another method was ≥ 38° C.
PR5I Group received PR5I + Prevnar 13+ RotaTeq at 2, 4, 6 mos; DAPTACEL + PedvaxHIB + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; DAPTACEL + ActHIB + Prevnar 13 at 15 mos.
Subjects in population is the number of subjects in the All Subjects as Treated population at the considered visit(s) i.e. all vaccinated subjects with safety follow-up for the considered visit(s).
N = Number of vaccinated subjects, n = Number of subjects in each category.

Children rarely develop febrile seizures prior to 6 months of age, however, an analysis of the occurrence of increased temperature and febrile seizure during Day 1-15 following any vaccination of the infant dose of vaccine was performed. No febrile seizures were noted during this time period.

During the conduct of the study (Days 1-181), there were 6 serious adverse events related to fever and/or febrile convulsion. (The timing of the events in relation to vaccination is provided below.) One subject in the Control experienced an episode of pyrexia considered to be a serious adverse event. Two subjects who received PR5I had a febrile convulsion regarded as a serious adverse event during Day 1-180 following the infant vaccination series. In the same time frame, 3 subjects (1 PR5I and 2 Control vaccines) experienced seizures. Further discussion of SAE following vaccination can be found in section 6.1.12.4 Nonfatal Serious Adverse Events, but these SAEs related to fever/febrile convulsion or convulsion will be discussed here. None of the reported occurrences of febrile seizure or seizure appears to be related to vaccination.

SAE	Vaccine dose	Action	Concomitant event	Outcome
Febrile Convulsions (complex)	**PR5I-** 111 days post dose 3, Tmax 101.6F	Hospitalized with continuing seizure activity, treated with phenobarbital	RSV infection, OM	Recovered and stable at discharge. Lost to care
Febrile Convulsion (complex)	**PR5I**-66 days post dose 3	Hospitalized	Diarrhea (negative stool cultures, vomiting	Discharged to home
Convulsion*	**PR5I**- 33 days post dose 2	Hospitalized	Vomiting, diarrhea (reported as severe gastroenteritis), cardiac arrest required resuscitation, hypovolemic shock	Discharged with continuing seizure disorder; discontinued from study
Pyrexia	**Control vaccines (Pentacel)**-77 days post dose 3	Hospitalized with fever, T. max 103◦F, treated with IV antibiotics	Leukocytosis	Discharged to home
Convulsion (Tonic, multiple episodes)	**Control vaccines (Pentacel)-** 48 days post dose 3	Hospitalized for anticonvulsant therapy, outpatient KEPPRA	Vomiting, diarrhea (initial)	Normal EEG, discharged to home
Convulsion	**Control vaccines (Pentacel)**-29 days post dose 1	Hospitalized for evaluation	EEG with focal slowing R parietal and post temporal regions	Discharged to home, no follow-up

*Seizures were evident after cardiac/respiratory arrest not as a presenting symptom
None of these serious adverse events were assessed by the investigators as related to vaccination.

Unsolicited systemic adverse events
Unsolicited systemic adverse events were reported by 41.1% of subjects (403/980) in the PR5I group and 37.7% of subjects (182/483) in the Control group during Day 1 to Day 15 following any infant dose vaccination. The most frequent unsolicited systemic reactions described by preferred term were upper respiratory tract infection, otitis media, and diarrhea as would be expected in this age group. The frequency and types of unsolicited adverse events were generally similar between the PR5I and Control groups. The intensity of the unsolicited systemic adverse events between the groups was similar.

A comparison of the most frequently occurring unsolicited adverse events (Day 1-15 following vaccination) which were documented as severe presented below:

- Diarrhea was reported by 0.7% of subjects (7/980) in the PR5I group and 0.4% of subjects (2/483) in the Control group.
- Upper respiratory tract infection was reported by 0.4% of subjects (4/980) in the PR5I group and 0.2% of subjects (1/483) in the Control group
- Pneumonia and acute otitis media were both reported by 0.3% of subjects (3/980) in the PR5I group and by no subjects in the Control group.

Adverse Events Related to Concomitant Vaccination
Solicited injection-site adverse events related to receipt of Prevnar 13 which occurred during Day 1 to Day 5 following any infant dose vaccination were assessed by maximum size / intensity. Most injection-site adverse events following Prevnar 13 were mild to moderate in nature. Moderate injection site pain at the Prevnar 13 injection site was reported by more of subjects in the PR5I group than in the control vaccine group (24.0% versus 20.1%). Mild swelling at the injection site was reported by 35.3% of subjects in the PR5I group compared to 30.4% of subjects in the control vaccine group. The occurrence of severe injection site reactions was similar between the groups. (Data not shown)

Adverse Events after the Toddler Dose of Vaccine
As part of the study a Toddler dose of DAPTACEL and PedvaxHIB was administered at 15 months of age concomitantly with Prevnar 13 (standard of care). No notable differences were observed between vaccination groups with regard to the solicited injection-site adverse events or the maximum size and intensity of AEs related to DAPTACEL occurring Day 1 to Day 5 following the Toddler dose vaccination. Unsolicited injections-site adverse events were comparable between the two study groups.

Solicited systemic adverse events that occurred during Day 1 to Day 5 and unsolicited systemic adverse events during Day 1 to Day 15 following the Toddler dose of vaccines were overall similar between the groups except for fever. Despite both groups receiving the same vaccines, moderate fever was higher in subjects in the PR5I group (11.2% versus 4.5%) (Data not shown).

6.1.12.3 Deaths

There were two deaths during the conduct of the study, one in the PR5I vaccination group and one in the Control group. Neither death was considered to be related to vaccination. A summary of each event follows below.

- Subject (b) (6), a 23-week old multi-racial male with no reported medical history, was randomized into Study 005 and received PR5I, Prevnar 13, and RotaTeq on (b) (6) (Dose 1) and (b) (6) (Dose 2). A birth dose of monovalent hepatitis B vaccine (ENGERIX-B) had been administered on (b) (6), prior to study entry. (b) (6) days post-dose 2, the subject died from positional asphyxia. The infant was found unresponsive, wedged between a mattress and a wall with his face against the mattress. Resuscitation attempts were unsuccessful by emergency personnel who responded to the scene and by medical personnel in hospital. Post-mortem concluded cause of death as asphyxia.

- Subject (b) (6), a 12-week old white female with a history of premature birth (born at 31 weeks), was randomized to Study 005 and received Pentacel, Recombivax HB, Prevnar 13, and RotaTeq on (b) (6) (Dose 1). The subject had also received a dose of monovalent hepatitis B vaccine (ENGERIX B) on (b) (6), prior to study entry. Subject exhibited rhinorrhea beginning on 14-Oct-2011, then on (b) (6) ((b) (6) days post-dose 1), the subject

was diagnosed with bilateral pneumonia and was hospitalized with symptoms including: vomiting, fever, hypoxia, difficulty breathing, and mild tachycardia. Antibiotic treatment with IV ceftriaxone was begun and after three days the subject was discharged to home on oral antibiotics (Amoxicillin). Later, following a nap, the infant was found unresponsive in crib. Resuscitation attempts were unsuccessful by responding emergency personnel at the scene. No autopsy was performed but cause of death is noted in report as aspiration, cardiac arrest, and respiratory arrest. Investigator determined that the bilateral pneumonia and subsequent events were not related to vaccination.

6.1.12.4 Nonfatal Serious Adverse Events

The most frequent serious adverse events during the entire study period by preferred term are presented below. These events reported are age appropriate for the study population.

- Bronchiolitis was reported by 0.6% of subjects (6/980) in the PR5I group and 1.0% of subjects (5/483) in the Control group.
- Dehydration was reported by 1.2% of subjects (12/980) in the PR5I group and 0.4% of subjects (2/483) in the Control group.
- Respiratory syncytial virus bronchiolitis was reported by 0.5% of subjects (5/980) in the PR5I group and 0.8% of subjects (4/483) in the Control group.
- Croup infectious was reported by 0.3% of subjects (3/980) in the PR5I group and 0.6% of subjects (3/483) in the Control group.

One nonfatal serious adverse event was reported in a subject in the PR5I group. Subject (b) (6) had two 'apparent life-threatening events' (ATLE) on Day 1 and Day 3 after the first dose of PR5I and other concomitant vaccinations and was hospitalized after the first event. The second ATLE occurred following discharge from the hospital on Day 3 post-vaccination, which led to re-hospitalization. At the time of the event the subject presented with hypotonia and "rolling eyes" following an episode of emesis. The subject was afebrile, and a respiratory culture was found to be positive for parainfluenza virus. The subject was discharged from the hospital after three days (6 days post-vaccination). The subject's parent withdrew consent and the subject was withdrawn from the study.

6.1.12.5 Adverse Events of Special Interest (AESI)

There were no pre-specified adverse events of special interest for this study.

However, subject (b) (6) who was randomized to the PR5I group, was reported as developing pertussis disease due to vaccination failure, 165 days post dose three of PR5I. Pertussis was diagnosed by PCR and culture. This event was not considered to be a serious adverse event. The subjects was excluded from the per-protocol immunogenicity analyses at the toddler time points.

6.1.12.6 Clinical Test Results

Not applicable.

6.1.12.7 Dropouts and/or Discontinuations

Two subjects, one who received PR5I and one who received the control vaccines, withdrew from the study due to adverse events.

One subject (b) (6), who received two doses of PR5I according to protocol along with the concomitant vaccinations, experienced injection site erythema (< 2.5 cm), severe injection site pain and severe injection site swelling (≥2.5 cm-< 5.0 cm) on the day of receipt of the second

dose of PR5I. The AEs were considered to be related to vaccination and the parent withdrew consent for further participation in the study. All adverse events resolved within 48 hours of vaccinations.

The second subject (b) (6) , was vaccinated with the first dose of Pentacel, Recombivax HB, Prevnar 13 and RotaTeq as prescribed in the study protocol. One day following vaccination the subjects experienced moderate irritability. No treatment was sought for the adverse event, which the investigator felt was related to the vaccinations. The parent withdrew consent and discontinued the subject from further treatment in the study. The adverse event resolved within 24 hours of onset and within 72 hours of vaccinations.

Another subject in the PR5I group withdrew following two 'apparent life-threatening event' beginning on the first day following vaccination. See section 6.1.12.4 for narrative of this SAE.

6.1.13 Study V419-005 Summary and Conclusions

This randomized, active comparator-controlled, open-label, multicenter study evaluated the safety, tolerability, and immunogenicity of PR5I in healthy infants who had previously received a birth dose of a mono-valent Hepatitis vaccine outside of and prior to the study conduct.

Subjects in the PR5I group received a dose of PR5I concomitantly with Prevnar 13 and RotaTeq at 2, 4, and 6 months to complete three doses of the four dose primary immunization series for the pertussis antigens. Vaccination with DAPTACEL, Prevnar 13, and PedvaxHIB vaccines at 15 months completed the primary pertussis series. Subjects in the Control group received one of the current standard of care vaccine regimes; Pentacel concomitantly with Prevnar 13 and RotaTeq vaccines at 2, 4, and 6 months and with doses of RECOMBIVAX HB at 2 and 6 months followed by DAPTACEL, Prevnar 13, and ActHIB vaccines at 15 months.

Immunogenicity of PR5I was assessed by measuring the Post-dose 3 antibody responses to each of the components in PR5I vaccine and comparing them to the corresponding responses of the Control group. Antibody responses for all antigens except the pertussis antigens were defined based on accepted antibody thresholds that correlate with, or are associated with, protection from disease.

There are no well accepted immunologic correlates of protection for pertussis antigens. Evaluation of the effectiveness of the pertussis components of PR5I following three doses was the same as that defined for the licensed control vaccine, Pentacel. Previously the effectiveness of Pentacel was based, in part, on a study conducted among US children comparing immune responses following administration of Pentacel vaccine to responses following DAPTACEL vaccine. The efficacy of DAPTACEL was demonstrated in a clinical endpoint efficacy study conducted in Sweden (Sweden I Efficacy Trial) which enrolled infants who received DAPTACEL at 2, 4, and 6 months of age. [See DAPTACEL and Pentacel package inserts].

The non-inferiority analysis for the responses to all the antigens (D, T, PT, PRN, FHA, FIM, IPV1,2,3 , HBsAg, PRP) contained in PR5I and the GMTs for the pertussis antibody responses for subjects in the PP-RW population showed that the pre-specified primary endpoints were met for all response rates at one-month post-dose 3 except for the FHA antigen GMT. The failure of PR5I to demonstrate non-inferiority of FHA GMTs post-dose 3 is considered of limited significance as a primary series for pertussis is four-doses for the antigens contained in PR5I and Pentacel.

Upon completion of the primary pertussis series with administration of a Toddler dose of DAPTACEL, the pertussis response rates one-month following the Toddler dose of DAPTACEL for infants who received the 3-dose series of PR5I or Control vaccines showed that the PR5I group was non-inferior to the Control group as the lower bound of the 2-sided 95% CI for the group difference (PR5I group minus Control group) was above the pre-specified non-inferiority margin for all pertussis antigens, including FHA.

Other immune response endpoints of note:
The polio response rate was 100% for all three serotypes of poliovirus following the third dose of the infant series of PR5I.

Immune responses to RotaTeq were non-inferior in subjects who received it concomitantly either with a 3-dose infant series of PR5I or with a licensed Control vaccine regimen

An analysis of the effect of the brand of the Hepatitis B vaccine administered at birth, demonstrated no significant difference on the seroprotection rates or the GMTs for the Hepatitis B antibodies post-vaccination with PR5I or the control vaccine. Acceptability of immune responses to all three serotypes of poliovirus was met.

Anti-PRP responses after the third dose of PR5I or Control vaccines was higher for subjects in the PR5I group (PRP-OMPC HIB) as compared to subjects who received Pentacel (PRP-T Hib). Following the Toddler dose of vaccine, when all subjects received DAPTACEL concomitantly with ActHIB, higher GMTs were observed in the Control group. This result was as expected based on the known kinetics of antibody responses to PRP-OMPC HIB and PRP-T Hib vaccines.

Immunogenicity of RotaTeq concomitantly administered with PR5I was non-inferior to RotaTeq concomitantly administered with Control.

Safety was evaluated by assessments of solicited injection site adverse events and temperatures Day 1 to Day 5 after each vaccination and systemic adverse events Day 1 to Day 15 after each vaccination. Serious adverse events were monitored up to 180 days following completion of the infant series, and vaccine-related serious adverse events and deaths were monitored throughout the study.

The safety profile of PR5I was consistent with the expected solicited local and systemic events seen following vaccination with other similar licensed combination vaccines. A statistically significant higher incidence of mild-to-moderate fever was noted after receipt of PR5I when compared to the control vaccines. Following any infant dose of vaccine during days 1-5 post-vaccination, pyrexia was reported by 47.4% of subjects who received PR5I and 34.4% of subjects administered the Control vaccines. The difference (PR5I group minus Control group) in the percentage of subjects who had pyrexia was 13.1% (95% CI: 7.7% to 18.3%). The rates of severe fever were similar between the groups and the incidence of medically attended fever or febrile convulsions were similar between the investigational and the control group in the study.

6.2 Study V419-006 (PR506): Phase 3 Lot Consistency Study

Protocol No.: 006-02. “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™”

The purpose of study V419-006 was to demonstrate the consistency of the manufacturing process of 3 different lots of PR5I by evaluating the consistency of the immune responses in healthy infants who had previously received a dose of monovalent hepatitis B vaccine, administered at birth or up to one-month of age.

6.2.1 Objectives

Primary Objective:

1. To evaluate the consistency of the Post-dose 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).

Secondary Objectives:

1. To evaluate the consistency of the Post-dose 3 immune response to 3 manufactured lots of PR5I when given at 2, 4, and 6 months of age with respect to response rates.
2. To compare the immunogenicity of pertussis responses at one-month after the Toddler dose of Pentacel after receiving an infant series of either 3 doses of PR5I or Pentacel.
3. To compare the immunogenicity of PR5I with the component vaccine Control at one-month after the third dose.
4. To evaluate the immunogenicity of Prevnar 13 (at Post-dose 3) when administered concomitantly with PR5I.
5. 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. To describe the fever profile after the administration of each dose of PR5I or the component vaccine Control when given concomitantly with Prevnar 13 and RotaTeq.
7. To describe the percentage of subjects with solicited injection-site adverse events (i.e., pain, erythema, and swelling), and solicited systemic adverse events (i.e., vomiting, crying abnormal, drowsiness, appetite lost, and irritability) within 5 days after each and any doses of PR5I or the component vaccine Control when co-administered with other recommended vaccines.
8. To describe the incidence of serious adverse events that occurs up to 6 months following the last dose of PR5I/Control (i.e., the 6-month dose).

Tertiary Objectives:

1. To describe the response rates and GMTs to all antigens in PR5I and the component vaccine Control at one-month post dose 3 with 95% confidence interval (CI).
2. To describe the response rates and GMTs to all antigens one-month after the Toddler dose with 95% CI.

6.2.2 Design Overview

This randomized, active comparator-controlled, multicenter, partially double blinded lot-to-lot consistency study enrolling healthy infants 46-89 days of age assessed the safety and immune responses following administration of PR5I (and concomitant vaccines) when administered as a 3-dose infant series, followed by the recommended licensed vaccines in the second year of life. A total of 2808 healthy infants who had received a dose of monovalent hepatitis B vaccine outside the conduct of the study (birth dose) were randomized into one of 4 vaccination groups (ratio 2:2:2:1). The brand of Hepatitis B vaccine administered at birth (up to one-month of age) was recorded upon enrollment. Subjects were randomized to either the PR5I or Control group stratified by the brand of hepatitis B vaccine used at birth (RECOMBIVAX HB vs. all other hepatitis B vaccines, including those for which the brand of hepatitis B vaccine was unknown).

In this partially blinded study, the investigators, applicant representatives, site personnel and parents/guardians were blinded only to the lot of vaccine received, not to the identity of the vaccine(s) administered. This open-label design was agreed upon with CBER at the end of the

Phase 2 meeting in 2008. Laboratory personnel were blinded to vaccination group to avoid introducing bias for the immunogenicity results.

Subjects who were randomized to the PR5I groups (3 different lots to measure lot consistency, approximately 800 subjects per group) received PR5I, Prevnar 13 and RotaTeq at 2, 4, and 6 months followed by Pentacel and Prevnar 13 at 15 months (toddler dose). Subjects randomized to the Control group (402 subjects) 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.

Study Initiation Date (First Patient Entered [FPE]): 11-May-2011
Study Completion Date (Last Patient Last Visit [LPLV]): 26-Jul-2013

Table 34. STN 125663/V419-006. Study Design and Schedule

Group	**Infant Series†**				**Toddler Dose**	**Close-Out Visit**
	Visit 1 Age: 2 months	**Visit 2 Age: 4 months**	**Visit 3 Age: 6 months**	**Visit 4 Age: ~7 months**	**Visit 6 Age: ~15 months**	**Visit 7 Age: ~16 months**
Group 1 n=800	Blood Draw† **PR5I**, Lot A Prevnar 13	**PR5I**, Lot A Prevnar 13 RotaTeq	**PR5I**, Lot A Prevnar 13 RotaTeq	Blood draw†	Blood draw† **Pentacel** Prevnar 13	Blood draw†
Group 2 n=797	Blood Draw† **PR5I**, Lot B Prevnar 13 RotaTeq	**PR5I**, Lot B Prevnar 13 RotaTeq	**PR5I**, Lot B Prevnar 13 RotaTeq	Blood draw†	Blood draw† **Pentacel** Prevnar 13	Blood draw†
Group 3 n=809	Blood Draw† **PR5I**, Lot C Prevnar 13	**PR5I**, Lot C Prevnar 13 RotaTeq	**PR5I**, Lot C Prevnar 13 RotaTeq	Blood draw†	Blood draw† **Pentacel** Prevnar 13	Blood draw†
Control n=402	Blood Draw† **Pentacel** RECOMBIVAX HB Prevnar 13	**Pentacel** Prevnar 13 RotaTeq	**Pentacel** RECOMBIVAX HB Prevnar 13 RotaTeq	Blood draw†	Blood draw† **Pentacel** Prevnar 13	Blood draw†

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 9.1, Table 9-1, pages 49.
All subjects received 1 dose of monovalent hepatitis B vaccine at birth (outside of study).
† A blood sample used to assess immunogenicity was taken immediately prior to administration of Dose 1, Postdose 3 (28 to 37 days), immediately prior to administration of the Toddler Dose, and after the Toddler Dose (28 to 37 days). The method of blood draw was by venipuncture (by vein).

PR5I, Pentacel, Prevnar 13, and RECOMBIVAX HB vaccines were supplied in vials containing 0.5 mL sterile suspension for intramuscular injection. RotaTeq was supplied in a tube containing 2 mL of dose solution for oral administration. All licensed vaccines were administered as approved in respective current package inserts.

There were two protocol amendments which followed the finalization of the original protocol on 30 June 2010. In protocol amendment 1 (07 Mar 2011) a revision of the primary and secondary objective and hypotheses was presented to include the following:

1. The evaluation of lot consistency (primary Objective and Hypothesis #1) was revised to be based on GMTs, rather than response rates, at one-month after the third dose of PR5I/Control.
2. The analysis of lot consistency based on response rates has been moved from a conditional primary hypothesis to Secondary Hypothesis #1.
3. A non-inferiority analysis of PR5I to Control was added as Secondary Hypothesis #3.
4. The statistical criterion for the evaluation of the immunogenicity of Prevnar 13 was revised.
5. Objectives and Hypotheses were renumbered accordingly.

Protocol amendment 2 (24 Jan 2013) was revised the study to include the following:

1. Added a new primary statistical analysis method for all GMT analyses (i.e., ANCOVA with multiple imputation for missing baseline titers [MI ANCOVA]) to account for missing baseline titers due to limited serum volumes obtained from 2-month old infant subjects at study entry.
2. Added a second PP population (referred to as PP-RW) in addition to the existing PP population (referred to as PP-OW) to account for subjects who received study vaccinations and/or blood draws outside of narrow protocol-defined visit windows. The success of the hypothesis test will be based on the results from the PP-RW population. PP-RW is defined as the PP population using a 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. PP-OW is defined as the PP population using a vaccination window of 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.
3. The Statistical Analysis Plan (SAP) was revised such that 2 sensitivity analyses were added:
   - An analysis of GMT endpoints with no baseline adjustment and
   - An analysis of GMT endpoints based on data from subjects with both baseline and post-vaccination titers to support the MI ANCOVA primary analysis for GMT endpoints.

Of note, study management, site monitoring, medical affairs, data management, biostatistics, and medical writing services were provided by the Contract Research Organization, (b) (4) (hereafter referred to as (b) (4) (medical writing); (b) (4) (biostatistics); and (b) (4) (study management, site monitoring, medical affairs, and data management).

6.2.3 Population

Inclusion Criteria

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

1. Subject is a healthy infant and is greater than or equal to 46 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 as per subject's medical history.
3. Subject's parent/legal guardian understands the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agrees to the subject's participation 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
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, splenectomy, etc.).
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, cyclosporin, 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 (exceeding 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, or inhaled) were eligible for vaccination.
6. Subject has a history of leukemia, lymphoma, malignant melanoma, or myeloproliferative disease.
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 (PnPs), rotavirus, measles, mumps, rubella, or varicella vaccines or combination thereof.
12. *Subject has had a febrile illness within 24 hours prior to enrollment or a rectal temperature ≥ 38.0ºC [≥ 100.4ºF] at Visit 1.
13. *Subject had 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 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).

6.2.4 Study Treatments or Agents Mandated by the Protocol

Groups 1, 2, and 3 received a 0.5-mL dose each of PR5I (Lot A, B, or C), Prevnar 13, and RotaTeq at 2, 4, and 6 months followed by Pentacel and Prevnar 13 at 15 months. Subjects in the Control group received a 0.5-mL dose of Pentacel along with Prevnar 13, and RotaTeq at 2, 4, and 6 months, and a 0.5-mL dose of RECOMBIVAX HB at 2 and 6 months followed by Pentacel and Prevnar 13 at 15 months. All vaccines except RotaTeq were administered as IM vaccinations, preferably in the anterolateral thigh. RotaTeq was administered orally.

All vaccines administered during the course of the study were provided by the Applicant in un-blinded single dose units. Identification of the individual lots of PR5I was, however, blinded.

RotaTeq and RECOMBIVAX HB were manufactured by Merck Sharp & Dohme Corp. Prevnar 13 was manufactured by Wyeth Pharmaceuticals, a subsidiary of Pfizer, Inc. PR5I and Pentacel were manufactured by Sanofi Pasteur Limited.

Please see section 6.1.4 Study Treatments or Agents Mandated by the Protocol for a description of the study products.

Table 35. STN 125536/V419-006. Study Treatments, Dosage Forms and Routes of Administration

Clinical Material	Packaging Lot Number	Batch Number (Formulation number)	Dosage Form/Packaging	Route of Administration
PR5I[1, 2]	WL00041788, WL00043027	(b) (4)	0.5 mL single dose glass vial	IM
RotaTeq[3]	WL00041679 WL00042295 WL00044317	(b) (4)	2 mL single dose plastic tube	Oral
Pentacel[4]	WL00041485 WL00041487 WL00047178	(b) (4)	0.5 mL single dose glass vial	IM
RECOMBIVAX HB[5]	WL00041808	(b) (4)	0.5 mL single dose glass vial	IM
Prevnar 13[6]	WL00041540, WL00043329 WL00044536 WL00046309 WL00051619	(b) (4)	0.5 mL dose sterile suspension for intramuscular injection, pre-filled syringe	IM

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 12.2.4.2, Table S-3, page 7.
1 PR5I = V419 = DTaP-IPV-Hib-HepB.
2 The PR5I was packaged twice during the study, which is the reason for the 2 packaging lot numbers. Each packaging lot number contained all 3 batch numbers.
3 RotaTeq = Rotavirus Vaccine, Live, Oral, Pentavalent.
4 Pentacel = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, IPV, and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine.
5 RECOMBIVAX HB = Recombinant hepatitis B vaccine.
6 Prevnar 13= Pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein].
DTaP = Diphtheria, tetanus, and acellular pertussis, HepB = Hepatitis B, Hib = Haemophilus influenzae type b, IPV = Inactivated poliovirus.

Concomitant Treatments
Administration of non-study licensed pediatric vaccines (e.g., influenza vaccine, measles, mumps, rubella, and varicella vaccines) was permitted during this study provided the following criteria were met:

1. Inactivated influenza vaccine was not administered within 14 days before or within 14 days after any dose of study vaccine.
2. Other inactivated, conjugated, or live non-study licensed pediatric vaccines were not administered within 30 days before or within 30 days after any dose of study vaccine.
3. It was preferred that the toddler vaccines (e.g., measles, mumps, rubella, and varicella vaccines, etc) were given after the completion of the 6-month safety follow-up period for PR5I (i.e., ~12 months of age or later), if possible.

Vaccination with additional doses of any vaccine component of PR5I or the concomitant vaccines administered during the study was not permitted.

Prophylactic antipyretic, analgesics and NSAIDs were not to be administered within 48 hours prior to vaccination. These medications could however be given in response to fever (temperature ≥ 38.0°C [100.4°F]) following vaccination.

All medications and vaccinations were documented in the vaccine record for Day 1-15 after each study vaccination. All non-study vaccines administered within 30 days of vaccination in the study or within Day 1-31 after any vaccination were recorded. [See section 6.2.3 of this review for inclusion/exclusion criteria]

6.2.5 Directions for Use
See Table 35 in section 6.2.4 of this review.

6.2.6 Sites and Centers
There were 73 investigative sites in the U.S. evaluated and considered eligible to screen 3019 subjects for study participation. These 73 sites randomized a total of 2808 subjects, of which 2800 received study vaccinations.

6.2.7 Surveillance/Monitoring
A subject had completed the study when (1) all scheduled vaccinations had been received; (2) the safety data after each vaccination had been collected (Day 1 through Day 15 after each vaccine dose); and (3) all blood samples had been collected. (See section 6.2 Study Design for the timing of vaccinations and blood draws.) Safety data were monitored by a Medical Monitoring team, which included clinical, statistical, and data management representatives to assess not only safety, but also the integrity of the study. Any serious adverse event, including death due to any cause, which occurred following consent through 6 months (~180 days) after last vaccination of PR5I/component vaccine Control(s) (i.e., the 6 month dose), and through 14 days following administration of vaccines at the Toddler dose whether or not related to the investigational product, was reported within 24 hours to the Applicant or their representative. Standard definitions for serious adverse events (SAE) were applied.

Safety Surveillance
- Immediate reactions for 30 minutes following each set of vaccinations

- Daily measurement of temperatures in the evening from Day 1 (day of vaccination) through Day 5 following each vaccination. Rectal temperature was preferred and recommended. Alternative routes were allowed per local practice, but if fever of ≥ 38.0°C (≥ 100.4°F) was noted by alternative route, it was to be confirmed by a rectal temperature measurement.
- Daily collection of solicited injection-site adverse events (i.e., injection-site pain/tenderness, injection-site redness [erythema], and injection-site swelling) from Day 1 through Day 5 following each vaccination
- Daily collection of solicited systemic adverse events (i.e., fever, vomiting, crying abnormal, drowsiness, appetite loss, and irritability) from Day 1 through Day 5 following each vaccination
- Daily collection of unsolicited adverse events (including injection-site and systemic) from Day 1 through Day 15 following each vaccination.
- Collection of serious adverse events regardless of causality, that occurred from study entry up to 6 months (~180 days) after the last vaccination of PR5I/component vaccine Control(s) (i.e., the 6-month dose).
- Collection of serious adverse events that occurred from Day 1 through Day 15 following administration of vaccines at the Toddler dose.
- Deaths, irrespective of the Investigator's assessment of causality, occurring at any time during the study.

Assessment of intensity of adverse events was assessed as outlined in Table 36 below.

Table 36. STN 125563/V419-006: Solicited Injection-Site Reactions: Definitions, Terminology and Severity Scales

VRC term†	Injection-Site Pain or Tenderness‡	Injection-Site Erythema (redness)	Injection-Site Swelling
Definition	See severity scale	Presence of redness around the approximate point of needle entry	Swelling at or near the injection site
Severity scale	Mild = minor reaction when injection site is touched Moderate = cries and protests when injection site is touched Severe = cries when injected limb is moved or the movement of the injected limb is reduced	Mild: < 2.5 cm Moderate: ≥ 2.5 to ≤ 5 cm Severe: > 5 cm	Mild: < 2.5 cm Moderate: ≥ 2.5 to ≤ 5 cm Severe: > 5 cm

Source: Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 9.5.1.2, Table 9-3, page 62.
† These terms appeared in the VRC.
‡ The severity scale listed here was specific for injection-site pain or tenderness. VRC = Vaccination report card.

Table 37. STN 125563/ V419-006: Solicited Systemic Adverse Events: Definitions, Terminology and Severity Scales.

	Fever	Vomiting	Crying Abnormal	Drowsiness	Appetite Lost	Irritability
VRC term	**Temperature**	**Vomiting**	**Abnormal crying**	**Drowsiness**	**Loss of appetite**	**Irritability**
Definition	Elevation of temperature to ≥ 38ºC	Vomiting does not include spitting up.	Inconsolable crying without a resolution.	Reduced interest in surroundings or increased sleepiness.	See severity scale.	An excessive response to stimuli; increased fussiness; whining, and fretfulness despite attempts to comfort the infant and despite parental responses that would normally be soothing.
Severity scale	Mild: ≥ 38ºC to ≤ 38.4ºC Moderate: ≥ 38.5ºC to ≤ 39.4ºC Severe: ≥ 39.5ºC Rectal	Mild: 1 episode per 24 hours Moderate: 2-5 episodes per 24 hours Severe: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Mild: < 1 hour Moderate: 1-3 hours Severe: > 3 hours	Mild: Sleepier than usual or less interested in surroundings Moderate: not interested in surroundings or did not wake up for a meal Severe: Sleeping most of the time or difficult to wake up	Mild: eating less than normal Moderate: missed 1 or 2 feeds/meals completely Severe: refuses ≥ 3 feeds or refuses most feeds	Mild: easily consolable Moderate: requiring increased attention Severe: inconsolable

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 9.5.1.2, Table 9-4, page 63.
VRC = Vaccination report card.

Immunogenicity Assessments

Blood specimens (~3 mL whole blood at Visit 1 and ~5 mL whole blood at Visits 4, 6, and 7) used to assess immunogenicity were collected immediately prior to administration of Dose 1 (Visit 1), Post-dose 3 (28 to 37 days) (Visit 4), immediately prior to administration of the Toddler dose (Visit 6), and after the Toddler dose (28 to 37 days) (Visit 7).

All subject serum specimens were tested for PR5I antigens (anti-PRP, anti-HBsAg, anti-diphtheria, anti-tetanus, anti-pertussis [PT, FHA, PRN, FIM] and anti-polio Type 1, 2, and 3).
Testing was performed for each serotype of Prevnar 13. Remaining serum was available for use for additional immune response testing for the antigens contained within the vaccines administered in the study, including PR5I/Control and concomitant vaccines.

Limited serum volume and the number of antigens to be tested, required that samples were prioritized in accordance with the priority of study hypotheses and based on antigen assay variability (primary hypotheses and more variable antigens were prioritized higher).
The assays used to assess immune response are provided below.

Table 38. STN 125563/ V419-006: Laboratory Assays

(b) (4)				

Reviewer generated table based upon information provided in section 9.5.2 PR506 page 65-68/552

6.2.8 Endpoints and Criteria for Study Success

Immunogenicity Endpoints:
Primary Immunogenicity Analysis

- The endpoints for the primary hypothesis of lot consistency were the GMTs for all antigens contained in PR5I one-month after the third dose of PR5I.

Secondary Immunogenicity Analyses

- Lot consistency: response rate at one-month after the third dose;
- Non-inferiority of pertussis responses: GMTs and response rates for pertussis components after the Toddler dose;
- Non-inferiority of PR5I responses: GMTs and response rates at Post-dose 3
- Concomitant use of PR5I and Prevnar 13: GMTs for Prevnar 13 antigens.

Safety Endpoints:
The safety endpoints included:

- Daily measurement of rectal temperatures Day 1 through Day 5 following each vaccination.
- Solicited injection-site complaints (e.g., redness, swelling, and pain/tenderness) and solicited systemic adverse events (fever, vomiting, crying abnormal, drowsiness, appetite lost, and irritability) reported from Day 1 through Day 5 following each vaccination.
  Unsolicited adverse events from Day 1 through Day 15 following each vaccination. Serious adverse events were recorded without regard to causality within 7 days, within 14 days, within30 days, and within 180 days after Dose 1 to 3 of PR5I/component vaccine Control(s); serious adverse events were recorded from Day 1 through Day 15 following administration of vaccines at the Toddler dose.
- Vaccine-related serious adverse events and deaths, without regard to causality, were reported at any time throughout the study.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Hypotheses to be tested
Primary Hypothesis
1. For the three manufacturing lots (Lots A, B, and C) of PR5I similar GMTs to all antigens contained in PR5I will be induced at one-month after the third dose of PR5I, when given concomitantly with Prevnar 13 and RotaTeq.

For each of the PR5I antigens, the 2-sided 95% confidence intervals (CIs) of the GMT ratios between any 2 lots are within the equivalence margin (0.67 to 1.5).

Secondary Hypotheses
1. Three manufacturing lots (Lots A, B, and C) of PR5I induce similar response rates to all antigens contained in PR5I one-month after the third dose of PR5I, when given concomitantly with Prevnar 13 and RotaTeq. The statistical criteria require that, for each of the PR5I antigens, the 2-sided 95% CIs of the response rate difference between any 2 lots are within the equivalence margin.

2. Compared to subjects who receive Pentacel at 2, 4, and 6 months followed by
Pentacel at 15 months, the subjects who receive PR5I at 2, 4, and 6 months followed by Pentacel at 15 months will have a non-inferior response rate and non-inferior GMTs for pertussis antibody responses at one-month after the Toddler dose of Pentacel.

The statistical criteria for non-inferior responses to pertussis require that for pertussis-pertussis toxoid (PT), pertussis-filamentous hemagglutinin (FHA), pertussis-pertactin (PRN), and pertussis-fimbriae types 2 and 3 (FIM), both:

- the lower limit of the 2-sided 95% CI of the difference in response rates (PR5I group minus Control group) is > -10%, and
- the lower limit of the 2-sided 95% CI of the GMT ratios (PR5I group/Control group) is > 0.67.

3. Compared with subjects who receive licensed component vaccine Control(s) at 2, 4, and 6 months, the subjects who receive PR5I as an infant series at 2, 4, and 6 months have a non-inferior response rate to each antigen contained in PR5I and non-inferior GMTs for anti-PRP and pertussis antibody responses at one-month after the third dose of PR5I/component vaccine Control(s), when given concomitantly with Prevnar 13 and RotaTeq.

The statistical criteria for non-inferior response rate require that, for each of the PR5I antigens, the lower limit of the 2-sided 95% CI of the difference in rates (PR5I group minus Control group) is greater than the pre-specified margin.

The statistical criteria for non-inferior antibody response to pertussis also require that, for pertussis-PT, pertussis-FHA, pertussis-PRN and pertussis-FIM the lower limit of the 2-sided 95% CI of the GMT ratios (PR5I group/Control group) is > 0.67.

The statistical criteria for non-inferior antibody response to PRP require that:
i. the difference in percent of subjects with anti-PRP ≥ 1.0 mcg/mL (PR5I group minus Control group) is greater than -10%.
ii. the difference in percent of subjects with anti-PRP ≥ 0.15 μg/mL (PR5I group minus Control group) is greater than -5%.
iii. the lower limit of the 2-sided 95% CI of the GMT ratios (PR5I group/Control group) is > 0.67.

4. The immunogenicity of Prevnar 13 in subjects who receive it concomitantly with the PR5I as an infant series at 2, 4, and 6 months is non-inferior to the immunogenicity observed in subjects who receive Prevnar 13 concomitantly with the component vaccine Control at one-month after the third dose of PR5I/Control.

The statistical criteria for non-inferior antibody response require that, for each of the Prevnar 13 antigens, the lower limit of the 2-sided 95% CI of the GMT ratios (PR5I group/Control group) is > 0.67.

Immunogenicity and safety endpoints were to be evaluated within treatment groups and between treatment differences as described below in Table 39.

Table 39. STN 125563/ V419-006: Summary of Immunogenicity Analyses Performed

Analysis/Endpoint	Type of Analysis	Method	Population	
			Main Analysis‡	Supportive Analysis
Primary Immunogenicity Analyses				
Lot consistency—GMTs for all antigens contained in PR5I at Post-dose 3	95% CI for GMT Ratio	MI ANCOVA†	PP-RW, PP-OW	FAS
		cLDA model	N/A	PP-RW
Secondary Immunogenicity Analyses				
Lot consistency—response rates for all antigens contained in PR5I at Post-dose 3	95% CI for response rate difference	Miettinen and Nurminen method	PP-RW, PP-OW	FAS
Non-inferiority—Response rates for pertussis components at Toddler dose	95% CI for response rate difference	Miettinen and Nurminen method	PP-RW, PP-OW	FAS
Non-inferiority —GMTs for pertussis components contained in PR5I at Toddler dose	95% CI for GMT Ratio	MI ANCOVA†	PP-RW, PP-OW	FAS
		cLDA model	N/A	PP-RW
Non-inferiority—Response rates at Post-dose 3 for all PR5I Antigens	95% CI for response rate difference	Miettinen and Nurminen method	PP-RW, PP-OW	FAS
Non-inferiority—GMTs for pertussis components at Post-dose 3	95% CI for GMT ratio	MI ANCOVA†	PP-RW, PP-OW	FAS
		cLDA model	N/A	PP-RW
Non-inferiority—GMTs for all antigens contained in Prevnar 13™ at Post-dose 3	95% CI for response rate difference	MI ANCOVA†	PP-RW, PP-OW	FAS
		cLDA model	N/A	PP-RW

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 2 Synopsis, Table S4, page 9.
† MI ANCOVA was the primary analysis method used; cLDA was a supportive analysis method.
‡ The success of the hypothesis test was based on the results from the PP-RW population.
MI ANCOVA = Analysis of covariance with multiple imputation for missing baseline titers, CI = Confidence interval, cLDA = Constrained longitudinal data analysis, FAS = Full analysis set, GMT = Geometric mean titer, IPV = Inactivated poliovirus, N/A = Not applicable, PP-OW = Per-protocol-Original Windows (defined as vaccination window of 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), PP-RW = Per-protocol-Revised Window (defined as 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 Toddlerdose).

Safety

The Safety endpoints included the incidence of the following events.

1. Daily measurement of rectal temperatures Day 1 (day of vaccination) through Day 5 following each vaccination.
2. Solicited injection-site complaints (e.g., redness, swelling, and pain/tenderness) from Day 1 to Day 5 following each vaccination.
3. Solicited systemic adverse events that are prompted for on the VRC (including fever, vomiting, crying abnormal, drowsiness, appetite lost, and irritability) from Day 1 through Day 5 following each vaccination.
4. Unsolicited adverse events (including injection-site and systemic) from Day 1 through Day 15 following each vaccination.
5. Serious adverse events observed within 7 days, within 14 days, within 30 days, and within 180 days after Dose 1 to 3 of PR5I/component vaccine Control(s).

The use of antipyretics/analgesics and NSAIDs in response to fever following vaccination was also assessed.

All Subjects as Treated population was used for the safety data evaluation. The probability of observing at least one serious adverse event in this study depended on the number of subjects enrolled and the incidence rate of serious adverse events in the general population. If no serious adverse events were observed in a sample of 2400 PR5I recipients, this study provided 97.5% confidence that the true rate was < 0.15% (i.e., one out of every 651 subjects).

Immunogenicity

To achieve a power of 85% to evaluate subjects following the third dose of PR5I and 80% following the Toddler dose, approximately 2400 subjects were to be enrolled in the PR5I group (800 subjects in each lot group) and 400 subjects in the Control group. It was expected that the number of evaluable subjects would be approximately 2040 in the PR5I group (680 in each lot group) and 340 in the Control group at Post-dose 3, and 1920 in the PR5I group (640 in each lot group) and 320 in the Control group after the Toddler dose.

Given 680 evaluable subjects in each PR5I lot group, the power for the immunogenicity hypothesis based on GMTs was ~92% at the one-sided 2.5% alpha level if the 3 lots of PR5I are equivalent, post-dose 3. The power for each antigen contained in pR5I is presented below in Table 40.

Table 40. STN 125563/ V419-006: Power, for All PR5I Antigens Regarding GMT at Post-dose 3 (Non-inferiority Margin is 1.5-fold)

Antigen	Power for each Antigen (%)
PRP	99.4
HBsAg	99.0
Diphtheria	> 99.9
Tetanus	> 99.9
PT	> 99.9
FHA	> 99.9
PRN	> 99.9
FIM	> 99.9
IPV1	96.8
IPV2	99.0
IPV3	97.8
Overall Power	92.1

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 9.7.2.1.1, Table 9-5, page 72.
Assumed true standard deviations dependent on antigen ranging from 0.69 to 1.67.
FHA = Filamentous hemagglutinin; FIM = Fimbriae types 2 and 3; GMT = Geometric mean titer; HBsAg = Hepatitis B surface antigen; IPV = Inactivated poliovirus; PRN = Pertactin; PRP = Polyribosylribitol phosphate; PT = Pertussis toxoid; SD = Standard deviation.

The power to assess the secondary immunogenicity hypotheses is presented below in Table 41. The overall power was 89.9% for the secondary consistency hypothesis based on response rates at one-sided 2.5% alpha level if the 3 lots of PR5I were equivalent.

Table 41. STN 125563/ V419-006: Powers, Pre-specified Endpoints and Lot Consistency Margins for All PR5I Antigens Post-dose 3

Antigen	Endpoint	Assumed True Response Rates (P)	Non-inferior Margin (δ)	Power for each Antigen (%)
PRP	% with titer ≥ 1.0 µg/mL	85%	10%	99.6
HBsAg	% with titer ≥ 10 mIU/mL	95%	10%	> 99.9
Diphtheria	% with titer ≥ 0.1 IU/mL	90%	10%	> 99.9
Tetanus	% with titer ≥ 0.1 IU/mL	97%	5%	99.7
Pertussis–PT	% seroresponse†	85%	10%	99.6
Pertussis–FHA	% seroresponse	80%	10%	97.8
Pertussis–FIM	% seroresponse	85%	10%	99.6
Pertussis–PRN	% seroresponse	75%	10%	93.4
IPV1	% with NAb ≥ 1:8 dilution	97%	5%	99.7
IPV2	% with NAb ≥ 1:8 dilution	97%	5%	99.7
IPV3	% with NAb ≥ 1:8 dilution	97%	5%	99.7
Overall Power				89.9

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 9.7.2.1.2, Table 9-6, page 73.
† Pertussis seroresponse was defined as follows: (1) If pre-vaccination antibody concentration < 4xLLOQ, then the post-vaccination antibody concentration was ≥ 4xLLOQ, (2) If pre-vaccination antibody concentration ≥ 4xLLOQ, then the post-vaccination antibody concentration was ≥ pre-vaccination levels.
FHA = Filamentous hemagglutinin; FIM = Fimbriae types 2 and 3; HBsAg = Hepatitis B surface antigen; IPV = Inactivated poliovirus; LLOQ = Lower limit of quantification; NAb = Neutralizing antibodies; PRN = Pertactin; PRP = Polyribosylribitol phosphate; PT = Pertussis toxoid.

The study was to have > 99% power for the secondary hypothesis of non-inferiority (10% margin) for the response rate and GMTs for pertussis components of PR5I one-month following the Toddler dose of vaccine if the PR5I group was equivalent to the control group.

The study had 97.5% power for the secondary hypothesis of non-inferiority of PR5I endpoints with a one-sided 2.5% alpha level if the PR5I group was equivalent to the Control group based on response rates and GMTs post-dose 3. See Table 42 below.

Table 42. STN 125563/ V419-006: Power, Assumed Response Rate, Standard Deviation, and Non-Inferiority Margin for Testing Non-inferiority of PR5I at Post-dose 3 (PR5I vs. Control)

Time Point	Antigen	Endpoint	Non-inferior Margin (δ)	Assumed True Response Rates (P) or SD	Power (%)
Post-dose 3	PRP	% with titer ≥ 1.0 µg/mL	10%	85%	> 99.9
		% with titer ≥ 0.15 µg/mL	5%	97%	> 99.9
		GMT	1.5	1.49	99.6
Post-dose 3	HBsAg	% with titer ≥ 10 mIU/mL	10%	95%	> 99.9
Post-dose 3	Diphtheria	% with titer ≥ 0.1 IU/mL	10%	90%	> 99.9
Post-dose 3	Tetanus	% with titer ≥ 0.1 IU/mL	5%	97%	> 99.9
Post-dose 3	Pertussis–PT	% vaccine response†	10%	85%	> 99.9
		GMT	1.5	0.69	> 99.9
Post-dose 3	Pertussis–FHA	% vaccine response	10%	80%	99.5
		GMT	1.5	0.76	> 99.9
Post-dose 3	Pertussis–FIM	% vaccine response	10%	85%	> 99.9
		GMT	1.5	0.93	> 99.9
Post-dose 3	Pertussis–PRN	% vaccine response	10%	75%	98.6
		GMT	1.5	1.18	> 99.9
Post-dose 3	IPV1	% with NAb ≥ 1:8 dilution	5%	97%	> 99.9
Post-dose 3	IPV2	% with NAb ≥ 1:8 dilution	5%	97%	> 99.9
Post-dose 3	IPV3	% with NAb ≥ 1:8 dilution	5%	97%	> 99.9
Overall Power					97.5

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 9.7.2.1.2, Table 9-9, page 75.
† The pertussis vaccine response was defined as follows: (1) If pre-vaccination antibody concentration < 4 X LLOQ, then the post-vaccination antibody concentration was ≥ 4 X LLOQ, (2) If pre-vaccination antibody concentration was ≥ 4 X LLOQ, then the post-vaccination antibody concentration was ≥ preimmunization levels. The preimmunization level was defined as the antibody titer at pre-Dose 1.
FHA = Filamentous hemagglutinin; FIM = Fimbriae types 2 and 3; GMT = Geometric mean titer; HBsAg = Hepatitis B surface antigen; IPV = Inactivated poliovirus; LLOQ = Lower limit of quantification; NAb = Neutralizing antibodies; PRN = Pertactin; PRP = Polyribosylribitol phosphate; PT = Pertussis toxoid; SD = Standard deviation of natural logarithm of antibody titers.

For concomitant use of Prevnar 13 during the infant series, the study had an overall power of ~97.9% for the secondary concomitant hypothesis tests at a one sided, 2.5% alpha-level, if the PR5I group was equivalent to the Control group for each of the pneumococcal antigens

6.2.10 Study Population and Disposition

A total of 2802 subjects were randomized and enrolled at 73 study sites in the U.S. The study period was 11-May-2011 (First Patient Entered) to 26-Jul-2013 (Last Patient Last Visit).

6.2.10.1 Populations Enrolled/Analyzed

A subject had completed the study when (1) all scheduled vaccinations had been received; (2) the safety data after each vaccination had been collected (Day 1 through Day 15 after each vaccine dose); and (3) all blood samples had been collected.

Per-Protocol (PP)

Immunogenicity analyses were based on PP populations. All subjects who met the inclusion criteria, were not protocol violators, and had serology results within the specified day ranges, were included in the PP analysis.

Two PP populations, PP-Revised Windows (PP-RW) and PP-Original Windows (PP-OW), were used in this study. Hypothesis testing will be based on results on the results from the PP-RW population. PP-RW was defined as the PP population using a 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.

PP-OW was defined as the PP population using a vaccination window of 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 revised windows were based upon previously conducted Phase II studies of PR5I which allowed for inclusion of immunogenicity data from more vaccinated subjects in the PP analysis.]

Full Analysis Set
Supportive immunogenicity summary and analysis were also provided for all endpoints associated with the primary hypothesis based on the Full Analysis Set (FAS) population that included all randomized subjects with available serology data.

Safety Analysis Population
The All Subjects as Treated (ASaT) population was used for the analysis of safety data. The All Subjects as Treated population consisted of all randomized subjects who received at least one dose of study vaccine and had any safety follow-up. For the safety analyses, the subjects from the 3 PR5I lots were combined. Subjects were included and analyzed in a vaccination group corresponding to the study vaccines actually received. Subjects who received incorrect study vaccines only part of the vaccination period were included in the group to which they were randomized for the summary tables and analyses. [Nine subjects were cross-treated with differing lots of PR5I during the conduct of the study. There was no cross treatment between the PR5I and the Control Groups.]

6.2.10.1.1 Demographics

No statistical analysis was performed to assess the demographic characteristics of the vaccination groups. All results were descriptive.

For all randomized subjects, 52.4% were male and 47.6% were female with a mean age of 64.5 days (range: 46-89 days). The majority of subjects overall were white (67.8%) and non-Hispanic (76.8%). See Table 43 below for gender, racial and ethnic characteristics. The groups were comparable between PR5I groups and to the control group for age, gender, race and ethnicity.

Table 43. STN 125563/ V419-006: Summary of Characteristics for All Randomized Subjects

	PR5I Lot A		PR5I Lot B		PR5I Lot C		Overall PR5I		Control		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	800		797		809		2406		402		2808	
Gender												
Male	423	(52.9)	431	(54.1)	429	(53.0)	1283	(53.3)	187	(46.5)	1470	(52.4)
Female	377	(47.1)	366	(45.9)	380	(47.0)	1123	(46.7)	215	(53.5)	1338	(47.6)
Age (days) [1]												
Mean	64.6		64.4		64.7		64.6		64.3		64.5	
SD	6.7		6.2		6.6		6.5		6.6		6.5	
Median	63.0		63.0		63.0		63.0		63.0		63.0	
Range	46 to 89		46 to 89		46 to 89		46 to 89		46 to 86		46 to 89	
Weight (kg)												
Mean	5.3		5.3		5.3		5.3		5.2		5.3	
SD	0.7		0.7		0.7		0.7		0.7		0.7	
Median	5.3		5.2		5.2		5.2		5.1		5.2	
Range	3 to 7		3 to 9		3 to 8		3 to 9		4 to 8		3 to 9	
Unknown [2]	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)	1	(0.2)	3	(0.1)
Race												
American Indian or Alaska Native	58	(7.3)	55	(6.9)	47	(5.8)	160	(6.7)	29	(7.2)	189	(6.7)
Black or African American	68	(8.5)	80	(10.0)	78	(9.6)	226	(9.4)	38	(9.5)	264	(9.4)
Native Hawaiian or Other Pacific Island	6	(0.8)	7	(0.9)	8	(1.0)	21	(0.9)	7	(1.7)	28	(1.0)
White	539	(67.4)	546	(68.5)	550	(68.0)	1635	(68.0)	269	(66.9)	1904	(67.8)
Asian	35	(4.4)	34	(4.3)	39	(4.8)	108	(4.5)	23	(5.7)	131	(4.7)
Multi-Racial [4]	94	(11.8)	75	(9.4)	87	(10.8)	256	(10.6)	36	(9.0)	292	(10.4)
At Least One Race is Asian	28	(3.5)	22	(2.8)	23	(2.8)	73	(3.0)	10	(2.5)	83	(3.0)
Other	66	(8.3)	53	(6.6)	63	(7.8)	182	(7.6)	25	(6.2)	207	(7.4)
Ethnicity												
Hispanic or Latino	182	(22.8)	184	(23.1)	180	(22.2)	546	(22.7)	98	(24.4)	644	(22.9)
Not Hispanic or Latino	617	(77.1)	610	(76.5)	627	(77.5)	1854	(77.1)	302	(75.1)	2156	(76.8)
Not Reported	0	(0.0)	3	(0.4)	2	(0.2)	5	(0.2)	2	(0.5)	7	(0.2)
Unknown	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Japanese Ancestry [3]												
Yes	5	(7.9)	7	(12.5)	4	(6.5)	16	(8.8)	0	(0.0)	16	(7.5)
No	58	(92.1)	49	(87.5)	58	(93.5)	165	(91.2)	33	(100.0)	198	(92.5)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 10.5.1, Table 10-7, page 113-114.
[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.
[3] Only subjects with a primary race of Asian or subjects in the subcategory “at least one race is Asian” were included in this summary and the percentages under this category were based on these subjects.
[4] Two (2) subjects reported Multi-Racial but no specified race was provided for inclusion in this table.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.

Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos. Percentages were based on the number of randomized subjects. mos = Months, SD = Standard deviation.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

As part of the inclusion criteria, subjects who enrolled in the study were to have received a birth dose of Hepatitis B vaccine. Any monovalent Hepatitis B vaccine was acceptable as a birth dose (age of administration birth to approximately one-month). Overall, 29.2% (820 subjects; 29.1% [699 subjects] in the PR5I group and 30.1% [121 subjects] in the Control group) received RECOMBIVAX HB vaccine at birth while 66.6% (1871 subjects; 67.0% [1611 subjects] in the PR5I group and 64.7% [260 subjects] in the Control group) received other brands of hepatitis B vaccine at birth (e.g., ENGERIX-B). The brand of hepatitis B vaccine received at birth was unknown in 4.2% (117 subjects; 4.0% [96 subjects] in the PR5I group and 5.2% [21 subjects] in the Control group). No notable differences were observed between the vaccination groups with regard to frequency and types of Hepatitis B vaccine received at birth. (See Table 44 below)

Table 44. STN 125563/V419-006: Brand of Hepatitis B Vaccine Received at Birth (All Randomized Subjects)

	PR5I Lot A		PR5I Lot B		PR5I Lot C		Overall PR5I		Control		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects randomized	800		797		809		2406		402		2808	
Brand of hepatitis B vaccine at birth												
RECOMBIVAX HB	233	(29.1)	234	(29.4)	232	(28.7)	699	(29.1)	121	(30.1)	820	(29.2)
Other	532	(66.5)	529	(66.4)	550	(68.0)	1611	(67.0)	260	(64.7)	1871	(66.6)
Unknown	35	(4.4)	34	(4.3)	27	(3.3)	96	(4.0)	21	(5.2)	117	(4.2)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 11.5.2, Table 10-8, page 116.
Subjects (b) (6) (PR5I Lot B) and (b) (6) (PR5I Lot A) had not received Hepatitis B vaccine at birth.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Other = all other brands of hepatitis B vaccine (e.g., ENGERIX-B).
Percentages were based on the number of randomized subjects. mos = Months, n = Number of subjects in each category.

A comparison between the PR5I groups and the control groups of infants with medical conditions present prior to receipt of the first vaccination (occurring in the randomized population in ≥ 2% of subjects) showed similar rates . The most frequent medical conditions by preferred term were jaundice neonatal, circumcision, and gastroesophageal reflux disease

Medications taken within 14 days of the initial vaccination were similar between the group and age appropriate. The most frequent prior medications by overall drug category were vitamins, drugs for acid related disorders, and drugs for functional gastrointestinal disorders and analgesics

Treatment with and use of prophylactic anti-pyretic/ anti-inflammatory medications was not permitted within the 48 hours prior to vaccination by the protocol. Use of these medications was allowed for the treatment of fever following vaccinations. Overall, 3.5% to 5.0% of subjects received antipyretics prior to vaccination prophylactically. A slightly higher percentage of subjects in the PR5I group (40.1%) received antipyretic, analgesic and anti-inflammatory medications within 48 hours after vaccination Visit 2 than in the Control group (35.9%). There was also a slightly higher percentage of antipyretic, analgesic and anti-inflammatory use within

48 hours following the Toddler dose in subjects receiving PR5I (35.7%) as compared to Control (33.1%) for the infant series. Of note, the incidence of antipyretic, analgesic and anti-inflammatory use following each infant vaccination (39.3% to 42.6% in the PR5I group), was higher than the incidence of fever by infant dose (19.7% to 29.3% in the PR5I group), suggesting that some medication usage may have been in response to non-fever related conditions.

The administration of specific concomitant non-study vaccines was permitted within 14 days of vaccination with the study products (pre- or post-vaccination). The most frequent concomitant non-study vaccination administered was inactivated influenza virus vaccine. Overall, only 6.8% of subjects received any concomitant vaccinations during the course of the study (6.5% of which were influenza vaccines).

6.2.10.1.3 Subject Disposition

Subjects were randomized 2:2:2:1 to the PR5I group (to 3 different lots of the investigational product) or the Control group at 73 centers in the US. Of the 3019 subjects screened, 2808 subjects were randomized; 2406 subjects to the PR5I group (800, 797, and 809 subjects to Lots A, B, and C, respectively), and 402 subjects to the Control group. Screening failure was the main reason that consented subjects were not randomized (1 subject not randomized due to "technical reasons", 2 subjects withdrew, and the reason was unknown for 2 additional subjects).

There were three-time points analyzed for discontinuation of subjects from the study:

- During the three dose infant series
- Between the infant series and the Toddler dose
- After receipt of the Toddler dose

Of randomized subjects, a total of 92.7% (2602 subjects) received all 3 doses of the infant series; 92.8% (2232 subjects) in the PR5I group and 92.0% (370 subjects), in the Control group. Toddler vaccinations were received by 83.3% (2003 subjects) in the PR5I group and 81.3% (327 subjects) in the Control group. The number of subjects not completing the three-dose series in the PR5I groups and the Control group were similar; 6.9% and 7.7% respectively. The two vaccination groups were comparable with respect to discontinuations during the infant series, with the most common reason for discontinuation given as lost to follow-up and subject withdrawal.

A total of 271 subjects (9.7%) discontinued between the infant series and the Toddler dose; 230 subjects (9.6%) in the PR5I group and 41 subjects (10.2%) in the Control group; with the most frequent reasons for discontinuations recorded as subjects lost to follow up and withdrawal by subject. A total of 196 subjects (168 in the PR5I groups and 28 in the Control group) discontinued due to withdrawal by subject. When the information was available; the most common reason for subject withdrawal were: (1) parents no longer wished to participate in study, (2) loss of insurance coverage and (3) parents did not wish to comply with blood draws. In the PR5I groups, 0.1% of subjects withdrew due to an adverse event, and no subject withdrew for the same reason from the Control group.

A total of 2329 subjects (82.9%) completed the Toddler dose vaccinations; 2002 subjects (83.2%) in the PR5I group and 327 subjects (81.3%) in the Control group. A total of 45 subjects (1.6%) discontinued after the Toddler dose; 35 subjects (1.5%) in the PR5I group and 10 subjects (2.5%) in the Control group. The most frequent reason for discontinuation was "lost to follow-up".

Nine subjects were cross-treated with differing lots of PR5I, receiving a mixed regime of vaccine from their assigned randomization group and other lots. There was no cross treatment between the PR5I and Control groups.

Table 45 shows overall vaccine compliance by the number and percentage of subjects vaccinated at each study visit for all vaccinated subjects.

Table 45. STN 125563/ V419-006: Number (%) of Subjects Vaccinated at Each Visit (All Vaccinated Subjects)

	PR5I Lot A (N=800)		PR5I Lot B (N=792)		PR5I Lot C (N=807)		Overall PR5I (N=2399)		Control (N=401)		Total (N=2800)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vaccinated at Visit 1 with:												
PR5I	800	(100.0)	792	(100.0)	807	(100.0)	2399	(100.0)	N/A		2399	(85.7)
Pentacel	N/A		N/A		N/A		N/A		401	(100.0)	401	(14.3)
RECOMBIVAX HB	N/A		N/A		N/A		N/A		401	(100.0)	401	(14.3)
Prevnar 13	800	(100.0)	792	(100.0)	807	(100.0)	2399	(100.0)	401	(100.0)	2800	(100.0)
RotaTeq	800	(100.0)	792	(100.0)	807	(100.0)	2399	(100.0)	401	(100.0)	2800	(100.0)
Vaccinated at Visit 2 with:												
PR5I	762	(95.3)	753	(95.1)	769	(95.3)	2284	(95.2)	N/A		2284	(81.6)
Pentacel	N/A		N/A		N/A		N/A		382	(95.3)	382	(13.6)
Prevnar 13	762	(95.3)	753	(95.1)	769	(95.3)	2284	(95.2)	382	(95.3)	2666	(95.2)
RotaTeq	762	(95.3)	753	(95.1)	769	(95.3)	2284	(95.2)	382	(95.3)	2666	(95.2)
Vaccinated at Visit 3 with:												
PR5I	742	(92.8)	737	(93.1)	753	(93.3)	2232	(93.0)	N/A		2232	(79.7)
Pentacel	N/A		N/A		N/A		N/A		370	(92.3)	370	(13.2)
RECOMBIVAX HB	N/A		N/A		N/A		N/A		370	(92.3)	370	(13.2)
Prevnar 13	742	(92.8)	737	(93.1)	753	(93.3)	2232	(93.0)	370	(92.3)	2602	(92.9)
RotaTeq	741	(92.6)	737	(93.1)	753	(93.3)	2231	(93.0)	370	(92.3)	2601	(92.9)
Vaccinated at Visit 6 with:												
Pentacel	670	(83.8)	655	(82.7)	665	(82.4)	1990	(83.0)	324	(80.8)	2314	(82.6)
Prevnar 13	666	(83.3)	656	(82.8)	666	(82.5)	1988	(82.9)	321	(80.0)	2309	(82.5)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 10.6, Table 10-15, page 136-7.
All Vaccinated Subjects = Subjects randomized who had at least 1 vaccination.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Subjects were classified by the actual vaccine received.
Percentages were based on the number of randomized subjects who received at least 1 dose of PR5I / Control.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in analysis, N/A = Not applicable by the study design

Table 46 below presents a summary of subject disposition with regard to the safety evaluations for the study period.

Table 46. STN 125563/V419-006: Subject Disposition (All Subjects)

	PR5I Lot A		PR5I Lot B		PR5I Lot C		Overall PR5I		Control		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Screened											3019	
Randomized subjects	800		797		809		2406		402		2808	
Not vaccinated	0	(0.0)	5	(0.6)	2	(0.2)	7	(0.3)	1	(0.2)	8	(0.3)
Received all 3 doses of the Infant Series (PR5I/Control) [1]	742	(92.8)	737	(92.5)	753	(93.1)	2232	(92.8)	370	(92.0)	2602	(92.7)
Received all 3 doses of the Infant Series (PR5I/Control) and all doses of concomitant study vaccines [2]	741	(92.6)	737	(92.5)	752	(93.0)	2230	(92.7)	370	(92.0)	2600	(92.6)
Did not complete the Infant Series (PR5I/Control)	58	(7.3)	55	(6.9)	54	(6.7)	167	(6.9)	31	(7.7)	198	(7.1)
Reason for Withdrawal: [3]												
Adverse Event	0	(0.0)	1	(0.1)	4	(0.5)	5	(0.2)	0	(0.0)	5	(0.2)
Death	2	(0.2)	0	(0.0)	2	(0.2)	4	(0.2)	0	(0.0)	4	(0.1)
Lost to Follow-up	20	(2.5)	14	(1.8)	12	(1.5)	46	(1.9)	13	(3.2)	59	(2.1)
Physician Decision	2	(0.2)	3	(0.4)	1	(0.1)	6	(0.3)	0	(0.0)	6	(0.2)
Protocol Violation	1	(0.1)	4	(0.5)	4	(0.5)	9	(0.4)	3	(0.7)	12	(0.4)
Withdrawal by Subject	33	(4.1)	32	(4.0)	30	(3.7)	95	(4.0)	15	(3.7)	110	(3.9)
Other	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)	0	(0.0)	2	(0.1)
Discontinued between the Infant Series and Toddler Dose	67	(8.4)	79	(9.9)	84	(10.4)	230	(9.6)	41	(10.2)	271	(9.7)
Reason for Withdrawal: [3]												
Adverse Event	1	(0.1)	0	(0.0)	1	(0.1)	2	(0.1)	0	(0.0)	2	(0.1)
Lost to Follow-up	29	(3.6)	48	(6.1)	53	(6.6)	130	(5.4)	23	(5.7)	153	(5.5)
Physician Decision	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)	0	(0.0)	2	(0.1)
Protocol Violation	5	(0.6)	3	(0.4)	6	(0.7)	14	(0.6)	3	(0.7)	17	(0.6)
Technical Problems	4	(0.5)	4	(0.5)	6	(0.7)	14	(0.6)	3	(0.7)	17	(0.6)
Withdrawal by Subject	28	(3.5)	23	(2.9)	17	(2.1)	68	(2.8)	12	(3.0)	80	(2.9)
Received Toddler Dose Vaccinations [4]	675	(84.4)	659	(82.7)	669	(82.7)	2003	(83.3)	327	(81.3)	2330	(83.0)
Completed Toddler Dose [5]	674	(84.3)	659	(82.7)	669	(82.7)	2002	(83.2)	327	(81.3)	2329	(82.9)
Discontinued after Toddler Dose	9	(1.1)	17	(2.1)	9	(1.1)	35	(1.5)	10	(2.5)	45	(1.6)
Reason for Withdrawal: [3]												
Lost to Follow-up	6	(0.7)	14	(1.8)	7	(0.9)	27	(1.1)	8	(2.0)	35	(1.3)
Protocol Violation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Technical Problems	1	(0.1)	1	(0.1)	1	(0.1)	3	(0.1)	0	(0.0)	3	(0.1)
Withdrawal by Subject	2	(0.2)	2	(0.3)	1	(0.1)	5	(0.2)	1	(0.2)	6	(0.2)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 10.1, Table 10-1, page 91-92.
[1] Received all 3 infant dose vaccinations of PR5I / Control.
[2] Received all 3 infant full dose vaccinations of PR5I / Control and all full doses of concomitant associated study vaccines.
[3] Percentages were based on the number of randomized subjects who received at least 1 dose of PR5I or Control.
[4] Received Toddler Dose of Pentacel (including 16 subjects who received vaccines at non-study visits).
[5] Received Toddler Dose of Pentacel and concomitant study vaccines (including subjects who received vaccines at non-study visits).

PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
One primary reason for discontinuation per subject was reported.
Percentages were based on the number of randomized subjects.
mos = Months, n = Number of subjects in analysis.

For immunogenicity analyses there were two per-protocol populations, PP-RW (Per-Protocol based on Revised Windows) and PP-OW (Per-Protocol based on Original Windows) are used in this study. All subjects who met the inclusion criteria, who were not protocol violators, and had serology results within the specified day ranges, were included in the PP immunogenicity analyses. The two PP populations are the same except their allowable day windows for the vaccination and blood draws. A comparison of the two study populations is provided below:

(a) Received study vaccine(s) outside the pre-specified day range below:

Vaccination	**Population PP-RW**	**Population PP-OW**
Dose 1	46-89 days of age	46-89 days of age
Dose 2	42 to 84 days after Dose 1	46 to 74 days after Dose 1
Dose 3	42 to 84 days after Dose 2	46 to 74 days after Dose 2
Toddler Dose	436 to 493 days of age	436 to 493 days of age

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 16.2, un-numbered table, Appendix 16 page 3/402.

(b) Serology samples collected outside the pre-specified day range below:

Serology Sample	**Population PP-RW**	**Population PP-OW**
Prior to Dose 1	within 5 days of vaccination	within 5 days of vaccination
Post-dose 3 (Visit 4)	28 to 51 days	28 to 44 days
Prior to Toddler Dose	within 5 days of vaccination	within 5 days of vaccination
Toddler Dose	28 to 51 days	28 to 44 days

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 16.2, un-numbered table, Appendix 16 page 3/402.

Subjects excluded from the PP-RW population are, by definition, also excluded from the PP-OW population.

Five subjects were excluded from all PP populations for analyses of hepatitis responses (2 subjects did not receive the Hepatitis B vaccine at birth and 30 days prior to enrollment and 3 subjects received the Hepatitis vaccine within 30 days of vaccination with the first dose of PR5I.)

A summary of subjects with protocol violations is provided in Table 47 below and reflects the reasons and timing of the protocol violations. The most frequent reasons for protocol violation were recorded as: “Received incomplete or incorrect study vaccine regimen”, “Sample not collected”, “Result not available/Insufficient serum”, “Vaccination out of day range”, and “Sample collected out of day range”. The occurrence of and reasons for protocol violations were similar across treatment groups. Not all protocol violations resulted in discontinuation from the study.

A summary of subjects excluded from the PP-RW population one-month Post-dose 3 for the PR5I endpoints is presented below.

Table 47. STN 125563/V419-006: Number (%) of Subjects Excluded from the PP-RW Population at One-month Post-dose 3 for PR5I Endpoints (All Randomized Subjects)

	PRP n (%)	HBsAg n (%)	Diphtheria Toxoid n (%)	Tetanus Toxoid n (%)	Pertussis PT n (%)	Pertussis FHA n (%)	Pertussis FIM n (%)	Pertussis PRN n (%)	Polio Type 1 n (%)	Polio Type 2 n (%)	Polio Type 3 n (%)
Vaccination Group PR5I Lot A (N=800)											
Number of subjects included	604 (75.5)	588 (73.5)	622 (77.8)	622 (77.8)	647 (80.9)	644 (80.5)	641 (80.1)	632 (79.0)	630 (78.8)	630 (78.8)	624 (78.0)
Number of subjects excluded	196 (24.5)	212 (26.5)	178 (22.3)	178 (22.3)	153 (19.1)	156 (19.5)	159 (19.9)	168 (21.0)	170 (21.3)	170 (21.3)	176 (22.0)
Reason for exclusion											
Failed to meet inclusion/exclusion criteria	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Received incomplete or incorrect study vaccine regimen	60 (7.5)	60 (7.5)	60 (7.5)	60 (7.5)	60 (7.5)	60 (7.5)	60(7.5)	60 (7.5)	60 (7.5)	60 (7.5)	60 (7.5)
Received temperature compromised vaccine	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Received incomplete or incorrect concomitant vaccine regimen	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Received prohibited vaccine(s)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1(0.1)	1 (0.1)	1 (0.1)
Received prohibited medication(s)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Sample not collected	43 (5.4)	43 (5.4)	43 (5.4)	43 (5.4)	43 (5.4)	43 (5.4)	43 (5.4)	43 (5.4)	43 (5.4)	43 (5.4)	43 (5.4)
Vaccination out of day range	15 (1.9)	15 (1.9)	15 (1.9)	15 (1.9)	15 (1.9)	15 (1.9)	15 (1.9)	15 (1.9)	15 (1.9)	15 (1.9)	15 (1.9)
Sample collected out of day range	26 (3.3)	26 (3.3)	26 (3.3)	26 (3.3)	26 (3.3)	26 (3.3)	26 (3.3)	26 (3.3)	26 (3.3)	26 (3.3)	26 (3.3)
Result not available/ Insufficient serum	48 (6.0)	63 (7.9)	30 (3.8)	30 (3.8)	5 (0.6)	8 (1.0)	11 (1.4)	20 (2.5)	22 (2.8)	22 (2.8)	28 (3.5)
Vaccination Group PR5I Lot B (N=797)											
Number of subjects included	596 (74.8)	599 (75.2)	625 (78.4)	609 (76.4)	634 (79.5)	631 (79.2)	632 (79.3)	616 (77.3)	632 (79.3)	632 (79.3)	625 (78.4)
Number of subjects excluded	201 (25.2)	198 (24.8)	172 (21.6)	188 (23.6)	163 (20.5)	166 (20.8)	165 (20.7)	181 (22.7)	165 (20.7)	165 (20.7)	172 (21.6)
Reason for exclusion											
Failed to meet inclusion/exclusion criteria	2 (0.3)	3 (0.4)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Received incomplete or incorrect study vaccine regimen	63 (7.9)	63 (7.9)	63 (7.9)	63 (7.9)	63 (7.9)	63 (7.9)	63 (7.9)	63 (7.9)	63 (7.9)	63 (7.9)	63 (7.9)
Received temperature compromised vaccine	4 (0.5)	4 (0.5)	4 (0.5)	4 (0.5)	4 (0.5)	4 (0.5)	4 (0.5)	4 (0.5)	4 (0.5)	4 (0.5)	4 (0.5)

	PRP n (%)	HBsAg n (%)	Diphtheria Toxoid n (%)	Tetanus Toxoid n (%)	Pertussis PT n (%)	Pertussis FHA n (%)	Pertussis FIM n (%)	Pertussis PRN n (%)	Polio Type 1 n (%)	Polio Type 2 n (%)	Polio Type 3 n (%)
Received prohibited vaccine(s)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Sample not collected	46 (5.8)	45 (5.6)	46 (5.8)	46 (5.8)	46 (5.8)	46 (5.8)	46 (5.8)	46 (5.8)	46 (5.8)	46 (5.8)	46 (5.8)
Vaccination out of day range	19 (2.4)	19 (2.4)	19 (2.4)	19 (2.4)	19 (2.4)	19 (2.4)	19 (2.4)	19 (2.4)	19 (2.4)	19 (2.4)	19 (2.4)
Sample collected out of day range	20 (2.5)	20 (2.5)	20 (2.5)	20 (2.5)	20 (2.5)	20 (2.5)	20 (2.5)	20 (2.5)	20 (2.5)	20 (2.5)	20 (2.5)
Result not available/Insufficient serum	45 (5.6)	42 (5.3)	16 (2.0)	32 (4.0)	7 (0.9)	10 (1.3)	9 (1.1)	25 (3.1)	9 (1.1)	9 (1.1)	16 (2.0)
Vaccination Group PR5I Lot C (N=809)											
Number of subjects included	595 (73.5)	580 (71.7)	618 (76.4)	612 (75.6)	622 (76.9)	628 (77.6)	623 (77.0)	611 (75.5)	628 (77.6)	633 (78.2)	625 (77.3)
Number of subjects excluded	214 (26.5)	229 (28.3)	191 (23.6)	197 (24.4)	187 (23.1)	181 (22.4)	186 (23.0)	198 (24.5)	181 (22.4)	176 (21.8)	184 (22.7)
Reason for exclusion											
Failed to meet inclusion/exclusion criteria	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)
Received incomplete or incorrect study vaccine regimen	59 (7.3)	59 (7.3)	59 (7.3)	59 (7.3)	59 (7.3)	59 (7.3)	59 (7.3)	59 (7.3)	59 (7.3)	59 (7.3)	59 (7.3)
Received temperature compromised vaccine	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)
Received prohibited vaccine(s)	5 (0.6)	5 (0.6)	5 (0.6)	5 (0.6)	5 (0.6)	5 (0.6)	5 (0.6)	5 (0.6)	5 (0.6)	5 (0.6)	5 (0.6)
Sample not collected	53 (6.6)	53 (6.6)	53 (6.6)	53 (6.6)	53 (6.6)	53 (6.6)	53 (6.6)	53 (6.6)	53 (6.6)	53 (6.6)	53 (6.6)
Vaccination out of day range	28 (3.5)	28 (3.5)	28 (3.5)	28 (3.5)	28 (3.5)	28 (3.5)	28 (3.5)	28 (3.5)	28 (3.5)	28 (3.5)	28 (3.5)
Sample collected out of day range	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)
Result not available/Insufficient serum	42 (5.2)	57 (7.0)	19 (2.3)	25 (3.1)	15 (1.9)	9 (1.1)	14 (1.7)	26 (3.2)	9 (1.1)	4 (0.5)	12 (1.5)
Vaccination Group = Overall PR5I (N=2406)											
Number of subjects included	1795 (74.6)	1767 (73.4)	1865 (77.5)	1843 (76.6)	1903 (79.1)	1903 (79.1)	1896 (78.8)	1859 (77.3)	1890 (78.6)	1895 (78.8)	1874 (77.9)

	PRP n (%)	**HBsAg n (%)**	**Diphtheria Toxoid n (%)**	**Tetanus Toxoid n (%)**	**Pertussis PT n (%)**	**Pertussis FHA n (%)**	**Pertussis FIM n (%)**	**Pertussis PRN n (%)**	**Polio Type 1 n (%)**	**Polio Type 2 n (%)**	**Polio Type 3 n (%)**
Number of subjects excluded	611 (25.4)	639 (26.6)	541 (22.5)	563 (23.4)	503 (20.9)	503 (20.9)	510 (21.2)	547 (22.7)	516 (21.4)	511 (21.2)	532 (22.1)
Reason for exclusion											
Failed to meet inclusion/exclusion criteria	4 (0.2)	6 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)
Received incomplete or incorrect study vaccine regimen	182 (7.6)	182 (7.6)	182 (7.6)	182 (7.6)	182 (7.6)	182 (7.6)	182 (7.6)	182 (7.6)	182 (7.6)	182 (7.6)	182 (7.6)
Received temperature compromised vaccine	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)
Received incomplete or incorrect concomitant vaccine regimen	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)
Received prohibited vaccine(s)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)	8 (0.3)
Received prohibited medication(s)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)	1 (0.04)
Sample not collected	142 (5.9)	141 (5.9)	142 (5.9)	142 (5.9)	142 (5.9)	142 (5.9)	142 (5.9)	142 (5.9)	142 (5.9)	142 (5.9)	142 (5.9)
Vaccination out of day range	62 (2.6)	62 (2.6)	62 (2.6)	62 (2.6)	62 (2.6)	62 (2.6)	62 (2.6)	62 (2.6)	62 (2.6)	62 (2.6)	62 (2.6)
Sample collected out of day range	68 (2.8)	68 (2.8)	68 (2.8)	68 (2.8)	68 (2.8)	68 (2.8)	68 (2.8)	68 (2.8)	68 (2.8)	68 (2.8)	68 (2.8)
Result not available/Insufficient serum	135 (5.6)	162 (6.7)	65 (2.7)	87 (3.6)	27 (1.1)	27 (1.1)	34 (1.4)	71 (3.0)	40 (1.7)	35 (1.5)	56 (2.3)
	PRP n (%)	HBsAg n (%)	Diphtheria Toxoid n (%)	Tetanus Toxoid n (%)	Pertussis PT n (%)	Pertussis FHA n (%)	Pertussis FIM n (%)	Pertussis PRN n (%)	Polio Type 1 n (%)	Polio Type 2 n (%)	Polio Type 3 n (%)
Vaccination Group Control (N=402)											
Number of subjects included	288 (71.6)	286 (71.1)	301 (74.9)	300 (74.6)	309 (76.9)	312 (77.6)	309 (76.9)	303 (75.4)	307 (76.4)	307 (76.4)	304 (75.6)
Number of subjects excluded	114 (28.4)	116 (28.9)	101 (25.1)	102 (25.4)	93 (23.1)	90 (22.4)	93 (23.1)	99 (24.6)	95 (23.6)	95 (23.6)	98 (24.4)
Reason for exclusion											

	PRP n (%)	HBsAg n (%)	Diphtheria Toxoid n (%)	Tetanus Toxoid n (%)	Pertussis PT n (%)	Pertussis FHA n (%)	Pertussis FIM n (%)	Pertussis PRN n (%)	Polio Type 1 n (%)	Polio Type 2 n (%)	Polio Type 3 n (%)
Failed to meet inclusion/exclusion criteria	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Received incomplete or incorrect study vaccine regimen	32 (8.0)	32 (8.0)	32 (8.0)	32 (8.0)	32 (8.0)	32 (8.0)	32 (8.0)	32 (8.0)	32 (8.0)	32 (8.0)	32 (8.0)
Received temperature compromised vaccine	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Received prohibited vaccine(s)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Sample not collected	30 (7.5)	30 (7.5)	30 (7.5)	30 (7.5)	30 (7.5)	30 (7.5)	30 (7.5)	30 (7.5)	30 (7.5)	30 (7.5)	30 (7.5)
Vaccination out of day range	12 (3.0)	12 (3.0)	12 (3.0)	12 (3.0)	12 (3.0)	12 (3.0)	12 (3.0)	12 (3.0)	12 (3.0)	12 (3.0)	12 (3.0)
Sample collected out of day range	7 (1.7)	7 (1.7)	7 (1.7)	7 (1.7)	7 (1.7)	7 (1.7)	7 (1.7)	7 (1.7)	7 (1.7)	7 (1.7)	7 (1.7)
Result not available/Insufficient serum	29 (7.2)	31 (7.7)	16 (4.0)	17 (4.2)	8 (2.0)	5 (1.2)	8 (2.0)	14 (3.5)	10 (2.5)	10 (2.5)	13 (3.2)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 10.4, Table 10-3, page 99-104.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, HBsAg = Hepatitis B surface antigen, mos = Months, N = Number of randomized subjects, n = Number of subjects included in each category, PP RW = Per protocol Revised Windows (defined as 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), PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid.
Note: A subject was counted under one reason of exclusion in the order listed. Percentages were based on the number of randomized subjects.

The number (%) of subjects excluded from the PP-OW population one-month Post-dose 3 was also summarized (data not shown) with no notable differences observed between the PR5I and Control groups or among the 3 lot groups with respect to individual antigens. The most frequent reasons for exclusion were Incomplete or incorrect study vaccine regimen and Vaccination out of date range for both the PR5I and Control groups.

As noted earlier, by definition, the subjects in the PP-OW population were also in the PP-RW population. More than 90% of subjects in the PP-RW population were also in the PP-OW population. The percentage of subjects (27.6% for PR5I overall) that were excluded from the PP-OW population was numerically higher than the percentage of subjects (22.1%) excluded from the PP-RW population for all PR5I antigens due to a higher percentage of subjects with protocol violations for Vaccination out of day range and Sample collected out of day range, as would be expected. (Data not shown)

The number (%) of subjects excluded from the PP-RW and PP-OW populations one-month after the Toddler dose for PR5I endpoints is provided in Table 48 below. There were no notable

differences were observed between the PR5I and Control groups or among the 3 PR5I lot groups with regard to the number of subjects that were excluded from the PP-RW compared with the PP-OW populations with respect to individual antigens. The most frequent reason for exclusion was 'Received an incomplete or incorrect study vaccine regimen'.

Table 48. STN 125563/V419-006: Number (%) of Subjects Excluded from the PP-RW Population at One-month After the Toddler Dose for PR5I Endpoints (All Randomized Subjects)

	PRP n (%)	HBsAg n (%)	Diphtheria Toxoid n (%)	Tetanus Toxoid n (%)	Pertussis PT n (%)	Pertussis FHA n (%)	Pertussis FIM n (%)	Pertussis PRN n (%)	Polio Type 1 n (%)	Polio Type 2 n (%)	Polio Type 3 n (%)
Vaccination Group PR5I Lot A (N=800)											
Number of subjects included	530 (66.3)	561 (70.1)	580 (72.5)	577 (72.1)	584 (73.0)	583 (72.9)	584 (73.0)	584 (73.0)	582 (72.8)	582 (72.8)	565 (70.6)
Number of subjects excluded	270 (33.8)	239 (29.9)	220 (27.5)	223 (27.9)	216 (27.0)	217 (27.1)	216 (27.0)	216 (27.0)	218 (27.3)	218 (27.3)	235 (29.4)
Reason for exclusion											
Failed to meet inclusion/exclusion criteria	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Received incomplete or incorrect study vaccine regimen	132 (16.5)	131 (16.4)	132 (16.5)	132 (16.5)	132 (16.5)	132 (16.5)	132 (16.5)	132 (16.5)	132 (16.5)	132 (16.5)	132 (16.5)
Received temperature compromised vaccine	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Received incomplete or incorrect concomitant vaccine regimen	9 (1.1)	9 (1.1)	9 (1.1)	9 (1.1)	9 (1.1)	9 (1.1)	9 (1.1)	9 (1.1)	9 (1.1)	9 (1.1)	9 (1.1)
Received prohibited vaccine(s)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)
Sample not collected	27 (3.4)	27 (3.4)	27 (3.4)	27 (3.4)	27 (3.4)	27 (3.4)	27 (3.4)	27 (3.4)	27 (3.4)	27 (3.4)	27 (3.4)
Vaccination out of day range	22 (2.8)	22 (2.8)	22 (2.8)	22 (2.8)	22 (2.8)	22 (2.8)	22 (2.8)	22 (2.8)	22 (2.8)	22 (2.8)	22 (2.8)
Sample collected out of day range	16 (2.0)	16 (2.0)	16 (2.0)	16 (2.0)	16 (2.0)	16 (2.0)	16 (2.0)	16 (2.0)	16 (2.0)	16 (2.0)	16 (2.0)
Result not available/Insufficient serum	54 (6.8)	23 (2.9)	4 (0.5)	7 (0.9)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.3)	19 (2.4)
Vaccination Group PR5I Lot B (N=797)											
Number of subjects included	520 (65.2)	550 (69.0)	569 (71.4)	567 (71.1)	572 (71.8)	572 (71.8)	573 (71.9)	573 (71.9)	569 (71.4)	571 (71.6)	543 (68.1)
Number of subjects excluded	277 (34.8)	247 (31.0)	228 (28.6)	230 (28.9)	225 (28.2)	225 (28.2)	224 (28.1)	224 (28.1)	228 (28.6)	226 (28.4)	254 (31.9)
Reason for exclusion											

	PRP n (%)	HBsAg n (%)	Diphtheria Toxoid n (%)	Tetanus Toxoid n (%)	Pertussis PT n (%)	Pertussis FHA n (%)	Pertussis FIM n (%)	Pertussis PRN n (%)	Polio Type 1 n (%)	Polio Type 2 n (%)	Polio Type 3 n (%)
Failed to meet inclusion/exclusion criteria	2 (0.3)	3 (0.4)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Received incomplete or incorrect study vaccine regimen	145 (18.2)	145 (18.2)	145 (18.2)	145 (18.2)	145 (18.2)	145 (18.2)	145 (18.2)	145 (18.2)	145 (18.2)	145 (18.2)	145 (18.2)
Received temperature compromised vaccine	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Received incomplete or incorrect concomitant vaccine regimen	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Received prohibited vaccine(s)	6 (0.8)	6 (0.8)	6 (0.8)	6 (0.8)	6 (0.8)	6 (0.8)	6 (0.8)	6 (0.8)	6 (0.8)	6 (0.8)	6 (0.8)
Sample not collected	37 (4.6)	37 (4.6)	37 (4.6)	37 (4.6)	37 (4.6)	37 (4.6)	37 (4.6)	37 (4.6)	37 (4.6)	37 (4.6)	37 (4.6)
Vaccination out of day range	18 (2.3)	18 (2.3)	18 (2.3)	18 (2.3)	18 (2.3)	18 (2.3)	18 (2.3)	18 (2.3)	18 (2.3)	18 (2.3)	18 (2.3)
Sample collected out of day range	12 (1.5)	12 (1.5)	12 (1.5)	12 (1.5)	12 (1.5)	12 (1.5)	12 (1.5)	12 (1.5)	12 (1.5)	12 (1.5)	12 (1.5)
Result not available/Insufficient serum	53 (6.6)	22 (2.8)	4 (0.5)	6 (0.8)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.5)	2 (0.3)	30 (3.8)
Vaccination Group PR5I Lot C (N=809)											
Number of subjects included	527 (65.1)	558 (69.0)	579 (71.6)	577 (71.3)	588 (72.7)	587 (72.6)	589 (72.8)	589 (72.8)	583 (72.1)	585 (72.3)	565 (69.8)
Number of subjects excluded	282 (34.9)	251 (31.0)	230 (28.4)	232 (28.7)	221 (27.3)	222 (27.4)	220 (27.2)	220 (27.2)	226 (27.9)	224 (27.7)	244 (30.2)
Reason for exclusion											
Failed to meet inclusion/exclusion criteria	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)
Received incomplete or incorrect study vaccine regimen	146 (18.0)	146 (18.0)	146 (18.0)	146 (18.0)	146 (18.0)	146 (18.0)	146 (18.0)	146 (18.0)	146 (18.0)	146 (18.0)	146 (18.0)
Received temperature compromised vaccine	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)
Received incomplete or incorrect concomitant vaccine regimen	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)
Received prohibited vaccine(s)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)	3 (0.4)

	PRP n (%)	HBsAg n (%)	Diphtheria Toxoid n (%)	Tetanus Toxoid n (%)	Pertussis PT n (%)	Pertussis FHA n (%)	Pertussis FIM n (%)	Pertussis PRN n (%)	Polio Type 1 n (%)	Polio Type 2 n (%)	Polio Type 3 n (%)
Sample not collected	22 (2.7)	22(2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22 (2.7)	22(2.7)	22(2.7)	22(2.7)
Vaccination out of day range	33 (4.1)	33(4.1)	33 (4.1)	33 (4.1)	33 (4.1)	33 (4.1)	33 (4.1)	33 (4.1)	33(4.1)	33(4.1)	33(4.1)
Sample collected out of day range	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)	8 (1.0)
Result not available/Insufficient serum	62 (7.7)	31(3.8)	10 (1.2)	12 (1.5)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	6 (0.7)	4 (0.5)	24(3.0)
Vaccination Group Overall PR5I (N=2406)											
Number of subjects included	1577 (65.5)	1669 (69.4)	1728 (71.8)	1721 (71.5)	1744 (72.5)	1742 (72.4)	1746 (72.6)	1746 (72.6)	1734 (72.1)	1738 (72.2)	1673 (69.5)
Number of subjects excluded	829 (34.5)	737 (30.6)	678 (28.2)	685 (28.5)	662 (27.5)	664 (27.6)	660 (27.4)	660 (27.4)	672 (27.9)	668 (27.8)	733 (30.5)
Reason for exclusion											
Failed to meet inclusion/exclusion criteria	4 (0.2)	6 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)
Received incomplete or incorrect study vaccine regimen	423 (17.6)	422 (17.5)	423 (17.6)	423 (17.6)	423 (17.6)	423 (17.6)	423 (17.6)	423 (17.6)	423 (17.6)	423 (17.6)	423 (17.6)
Received temperature compromised vaccine	7 (0.3)	7 (0.3)	7 (0.3)	7 (0.3)	7 (0.3)	7 (0.3)	7 (0.3)	7 (0.3)	7 (0.3)	7 (0.3)	7 (0.3)
Received incomplete or incorrect concomitant vaccine regimen	14 (0.6)	14 (0.6)	14 (0.6)	14 (0.6)	14 (0.6)	14 (0.6)	14 (0.6)	14 (0.6)	14 (0.6)	14 (0.6)	14 (0.6)
Received prohibited vaccine(s)	17 (0.7)	17(0.7)	17 (0.7)	17 (0.7)	17 (0.7)	17 (0.7)	17 (0.7)	17 (0.7)	17(0.7)	17(0.7)	17(0.7)
Sample not collected	86 (3.6)	86(3.6)	86 (3.6)	86 (3.6)	86 (3.6)	86 (3.6)	86 (3.6)	86 (3.6)	86(3.6)	86(3.6)	86(3.6)
Vaccination out of day range	73 (3.0)	73(3.0)	73 (3.0)	73 (3.0)	73 (3.0)	73 (3.0)	73 (3.0)	73 (3.0)	73(3.0)	73(3.0)	73(3.0)
Sample collected out of day range	36 (1.5)	36(1.5)	36 (1.5)	36 (1.5)	36 (1.5)	36 (1.5)	36 (1.5)	36 (1.5)	36(1.5)	36(1.5)	36(1.5)
Result not available/Insufficient serum	169(7.0)	76(3.2)	18 (0.7)	25 (1.0)	2 (0.1)	4 (0.2)	0 (0.0)	0 (0.0)	12(0.5)	8 (0.3)	73(3.0)
Vaccination Group Control (N=402)											
Number of subjects included	241 (60.0)	261 (64.9)	267 (66.4)	266 (66.2)	271 (67.4)	271 (67.4)	271 (67.4)	271 (67.4)	270 (67.2)	270 (67.2)	256 (63.7)
Number of subjects excluded	161 (40.0)	141 (35.1)	135 (33.6)	136 (33.8)	131 (32.6)	131 (32.6)	131 (32.6)	131 (32.6)	132 (32.8)	132 (32.8)	146 (36.3)
Reason for exclusion											

	PRP n (%)	HBsAg n (%)	Diphtheria Toxoid n (%)	Tetanus Toxoid n (%)	Pertussis PT n (%)	Pertussis FHA n (%)	Pertussis FIM n (%)	Pertussis PRN n (%)	Polio Type 1 n (%)	Polio Type 2 n (%)	Polio Type 3 n (%)
Failed to meet inclusion/exclusion criteria	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Received incomplete or incorrect study vaccine regimen	78 (19.4)	78 (19.4)	78 (19.4)	78 (19.4)	78 (19.4)	78 (19.4)	78 (19.4)	78 (19.4)	78 (19.4)	78 (19.4)	78 (19.4)
Received temperature compromised vaccine	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Received incomplete or incorrect concomitant vaccine regimen	5 (1.2)	5 (1.2)	5 (1.2)	5 (1.2)	5 (1.2)	5 (1.2)	5 (1.2)	5 (1.2)	5 (1.2)	5 (1.2)	5 (1.2)
Received prohibited vaccine(s)	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)
Sample not collected	21(5.2)	21(5.2)	21 (5.2)	21 (5.2)	21 (5.2)	21 (5.2)	21 (5.2)	21 (5.2)	21(5.2)	21(5.2)	21(5.2)
Vaccination out of day range	13(3.2)	13(3.2)	13 (3.2)	13 (3.2)	13 (3.2)	13 (3.2)	13 (3.2)	13 (3.2)	13(3.2)	13(3.2)	13(3.2)
Sample collected out of day range	8 (2.0)	8 (2.0)	8 (2.0)	8 (2.0)	8 (2.0)	8 (2.0)	8 (2.0)	8 (2.0)	8(2.0)	8(2.0)	8 (2.0)
Result not available/Insufficient serum	30(7.5)	10(2.5)	4 (1.0)	5 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(0.2)	1(0.2)	15(3.7)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 10-4., Table 10-5, page 106-108.
PR5I Group received PR5I + Prevnar 13™ + RotaTeq™ at 2, 4, 6 mos; Pentacel™ + Prevnar 13™ at 15 mos.
Control Group received Pentacel™ + Prevnar 13™ + RotaTeq™ at 2, 4, 6 mos, RECOMBIVAX HB™ at 2, 6 mos; Pentacel™ + Prevnar 13™ at 15 mos.
FHA = Filamentous haemagglutinin, FIM = Fimbrae types 2 and 3, HBsAg = Hepatitis B surface antigen, mos = Months, N = Number of randomized subjects, n = Number of subjects included in each category, PP RW = Per protocol Revised Windows (defined as 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), PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid.
Note: A subject was counted under one reason of exclusion in the order listed. Percentages were based on the number of randomized subjects.

An assessment of the number (%) of subjects excluded from the PP-RW and PP-OW populations one-month Post-dose 3 for Prevnar 13 endpoints showed that > 47% of subjects in each of the PR5I lot cohorts and the control group were excluded (data not shown). No notable differences were observed between the PR5I and Control groups or among the 3 lot groups with regard to the number of subjects that were excluded from the PP-RW and PP-OW populations with respect to individual antigens. The most frequent reasons for exclusion were 'Received an incomplete or incorrect study vaccine regimen' and 'Results not available/Insufficient serum'. Insufficient serum was the reason for exclusion for 26.5- 31.3% of subjects in the PP-RW population. The high percentage of subjects with insufficient serum was due to the higher priority of PR5I/Control antigen testing as compared to concomitant use vaccine testing, combined with the limited amount of serum available for this pediatric population.

6.2.11 Primary Immunogenicity Analyses

The endpoints for the primary hypothesis of lot consistency were the GMTs for all antigens contained in PR5I one-month after the third dose of PR5I (see Section 6.2.8 and Section 6.2.9 of this review).

6.2.11.1 Analyses of Primary Immunogenicity Endpoint

One-month following the third dose of PR51 administered from one of the 3 manufacturing lots (Lots A, B, or C), the GMTs demonstrated by subjects using the PP-RW population to all the antigens contained in PR5I were similar when given concomitantly with Prevnar 13 and RotaTeq. The lower and upper limits of the 2-sided 95% CI of the GMT ratios between any 2 lots were within the equivalence margin (0.67 to 1.5), indicating lot consistency among the 3 manufacturing lots. The findings based on the PP-OW population and FAS were consistent with those based on the PP-RW population (data not shown).

Analyses evaluating the GMTs to all antigens contained in PR5I for the PP-OW and FAS populations demonstrated lot consistency with the lower and upper limits of the 2-sided 95% CI of the GMT ratios between any 2 lots were within the equivalence margin (0.67 to 1.5) [data not shown].

Table 49. STN 125563/V419-006: Lot Consistency Analysis Regarding GMT at One-month Post-dose 3 PR5I with Concomitant Vaccinations (PP-RW Population)

Antigen	Lot A n GMT [1]	Lot B n GMT [1]	Lot C n GMT [1]	Lot A/Lot B Ratio (95% CI)[2]	Lot A/Lot C Ratio (95% CI)[2]	Lot B/Lot C Ratio (95% CI)[2]	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

Antigen	Lot A n GMT [1]	Lot B n GMT [1]	Lot C n GMT [1]	Lot A/Lot B Ratio (95% CI)[2]	Lot A/Lot C Ratio (95% CI)[2]	Lot B/Lot C Ratio (95% CI)[2]	Lot Consistency Criteria Met
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

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 11.1.1., Table 11-1, page 139-140.
[1] Observed GMT.
[2] The estimates for GMT ratios are based on an ANCOVA model with natural log-transformed post-vaccination titer as the response variable, and vaccination group, natural log-transformed
Pre-vaccination titer, actual brand of birth dose Hep B vaccine (RECOMBIVAX or Other/Unknown) as explanatory variables. The missing pre-vaccination titers are imputed by a multiple imputation method and used in the ANCOVA analysis. Margin for GMT ratio was between 0.67 and 1.15.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
ANCOVA = Analysis of covariance, CI = Confidence interval, FHA = Pertussis-filamentous haemagglutinin, FIM = Pertussis-fimbriae types 2 and 3, GMT = Geometric mean titer, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, mos = Months, n = Number of subjects included in the analysis, PP-RW = Per-protocol-Revised Windows (defined as 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), PRN = Pertussis-pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid

6.2.11.2 Analyses of Immunogenicity Secondary and Tertiary Endpoints

Multiple secondary analyses were for PR5I responses and responses to Prevnar as a concomitant vaccine were evaluated as part of this study. Tertiary endpoints for the evaluation of anti-PRP levels pre- and post-the Toddler dose of PR5I were also analyzed. [see section 6.2.8 of this review]

For the PP-RW population, the responses rate at one-month post-dose 3 demonstrated similar responses to all antigens contained in PR5I, for each of the 3 manufacturing lots. The lower and upper limits of the 2-sided 95% CI of the response rate difference between any 2 lots were within the equivalence margin (-5% and 5% for the response rate for tetanus, IPV1, IPV2, and IPV3; and -10% and 10% for all other antigens), indicating lot consistency among the 3 manufacturing lots, as evaluated by response rates. The findings for the PP-OW and FAS populations were similar for the demonstration of response rates for PR5I and Prevnar (data not shown).

Table 50. STN 125563/V419-006: Lot Consistency Analysis Regarding Response Rates at One-month Post-dose 3 (PP-RW Population)

Antigen	Lot A n Response Rate [1]	Lot B n Response Rate [1]	Lot C n Response Rate [1]	Lot A minus Lot B (Rate Difference) (95% CI) [2]	Lot A minus Lot C (Rate Difference) (95% CI) [2]	Lot B minus Lot C (Rate Difference) (95% CI) [2]	Lot Consistency Criteria Met
PRP	604 86.75	596 87.25	595 88.40	-0.48 (-4.31, 3.35)	-1.62 (-5.38, 2.12)	-1.16 (-4.89, 2.58)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
HBsAg	588 99.66	599 100.00	580 100.00	-0.34 (-1.23, 0.30)	-0.34 (-1.23, 0.32)	0.00 (-0.64, 0.66)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
Diphtheria	622 85.05	625 84.80	618 86.41	0.25 (-3.74, 4.24)	-1.35 (-5.26, 2.57)	-1.64 (-5.56, 2.28)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
Tetanus	622 99.84	609 100.00	612 100.00	-0.16 (-0.91, 0.47)	-0.16 (-0.90, 0.47)	0.00 (-0.63, 0.62)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
PT	596 99.33	585 97.61	580 98.97	1.73 (0.37, 3.40)	0.36 (-0.77, 1.63)	-1.36 (-3.03, 0.15)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
FHA	620 85.97	615 87.32	601 89.02	-1.35 (-5.17, 2.47)	-3.06 (-6.79, 0.67)	-1.71 (-5.37, 1.94)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
PRN	590 81.19	574 78.40	560 78.75	2.77 (-1.83, 7.39)	2.41 (-2.21, 7.06)	-0.36 (-5.14, 4.42)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
FIM	613 86.95	611 91.00	594 91.08	-4.12 (-7.69, -0.63)	-4.17 (-7.75, -0.66)	-0.07 (-3.32, 3.20)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
IPV1	630 100.00	632 100.00	628 100.00	0.00 (-0.61, 0.61)	0.00 (-0.61, 0.61)	0.00 (-0.61, 0.61)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
IPV2	630 100.00	632 100.00	633 100.00	0.00 (-0.61, 0.61)	0.00 (-0.61, 0.60)	0.00 (-0.61, 0.60)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes
IPV3	624 100.00	625 100.00	625 100.00	0.00 (-0.61, 0.61)	0.00 (-0.61, 0.61)	0.00 (-0.61, 0.61)	Lot A vs. Lot B: Yes Lot A vs. Lot C: Yes Lot B vs. Lot C: Yes

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 11.2.1., Table 11-3, page 144-145.
[1] Observed response rate. Pertussis seroresponse was defined as follows: (1) If pre-vaccination antibody concentration was < 4xLLOQ, then the post-vaccination antibody concentration was ≥ 4xLLOQ, (2) If pre-vaccination antibody concentration was ≥ 4xLLOQ, then the post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titer at pre-Dose 1.
[2] The estimates for the response rate difference and p-value were based on the method by Miettinen and Nurminen stratified by actual brand of birth dose of hepatitis B vaccine (RECOMBIVAX HB™ or Other/Unknown). The prespecified lower and upper bounds were -5% and 5% respectively for the response rate for Tetanus, IPV1, IPV2, and IPV3. For all other antigens, the lower and upper bounds were -10% and 10% respectively.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
CI = Confidence interval, FHA = Pertussis-filamentous haemagglutinin, FIM = Pertussis-fimbriae types 2 and 3, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, LLOQ = Lower limit of quantification, mos = Months, n = Number of subjects included in the analysis, PP-RW = Per-protocol-Revised Windows (defined as 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), PRN = Pertussis-pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid

As a secondary endpoint, non-inferiority of PR5I antigen responses in comparison to responses in the control group one-month post dose 3 was evaluated. The results were presented for each of the antigens contained in PR5I. Results are not available for all antigens at all-time points, per study design due to the priority of testing and the limited blood samples available. The lower limit of the 2 sided 95% CI for the group difference was above the pre-specified non-inferiority margin regarding all pre-specified endpoints for all antigens at one-month Post-dose 3, except the GMT for the FHA antigen for all populations (Data not shown for the PP-OW and FAS populations).

This data supports the conclusions based on the PP-RW population that PR5I was non-inferior to the Control vaccines with regard to pre-specified endpoints for all antigens at one-month Post-dose 3 except for the endpoint of the GMT for FHA antigen.
See Table 51 below for the results of the non-inferiority comparisons for the antigens in PR5I for the PP-RW population one-month post-dose 3.

Table 51. STN 125563/V419-006: Non-Inferiority Analysis of PR5I Antigen Responses at One-month Post-dose 3 (PP-RW Population)

		PR5I (N=2232)		Control (N=370)				
Antigen	**Endpoint**	**n**	**Estimated Response [2]**	**n**	**Estimated Response [2]**	**Estimated Difference/ GMT Ratio [2] (95% CI)**	**NI Margin**	**Non-inferiority Criterion Met/Not Met**
PRP	% with titer ≥ 1.0 µg/mL	1795	87.46	288	79.53	7.93 (3.38, 13.17)	-10%	Met
	% with titer ≥ 0.15 µg/mL	1795	98.38	288	96.19	2.20 (0.39, 5.12)	-5%	Met
	GMT	1795	5.59	288	3.42	1.63 (1.35, 1.98)	0.67	Met
HBsAg	% with titer ≥ 10 mIU/mL	1767	99.89	286	98.97	0.92 (0.20, 2.90)	-10%	Met
Diphtheria	% with titer ≥ 0.1 IU/mL	1865	85.42	301	87.77	-2.35 (-6.02, 2.09)	-10%	Met
Tetanus	% with titer ≥ 0.1 IU/mL	1843	99.95	300	98.66	1.28 (0.46, 3.33)	-5%	Met
PT	% vaccine response [1]	1761	98.64	289	97.92	0.72 (-0.59, 3.14)	-10%	Met
	GMT	1903	95.60	309	79.89	1.20 (1.11, 1.29)	0.67	Met
FHA	% vaccine response [1]	1836	87.42	304	92.12	-4.70 (-7.73, -0.86)	-10%	Met
	GMT	1903	46.45	312	69.10	0.67 (0.62, 0.73)	0.67	Not Met
PRN	% vaccine response [1]	1724	79.48	286	76.19	3.28 (-1.70, 8.85)	-10%	Met
	GMT	1859	52.84	303	51.49	1.03 (0.90, 1.17)	0.67	Met
FIM	% vaccine response [1]	1818	89.67	298	86.82	2.85 (-0.85, 7.36)	-10%	Met
	GMT	1896	255.32	309	168.97	1.51 (1.37, 1.66)	0.67	Met
IPV1	% with NAb ≥ 1:8 dilution	1890	100.00	307	99.34	0.66 (0.18, 2.36)	-5%	Met
IPV2	% with NAb ≥ 1:8 dilution	1895	100.00	307	100.00	0.00 (-0.20, 1.24)	-5%	Met
IPV3	% with NAb ≥ 1:8 dilution	1874	100.00	304	99.67	0.33 (0.05, 1.85)	-5%	Met

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 11.2.2., Table 11-5, page 151-152.
[1] The pertussis vaccine response was defined as follows: (1) if pre-vaccination antibody concentration was < 4X LLOQ, then the post-vaccination antibody concentration was ≥ 4X LLOQ, (2) if pre-vaccination antibody concentration was ≥ 4X LLOQ, then the post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titer at pre-Dose 1.
[2] The estimates for the response rate, rate difference (PR5I Group minus Control Group), and p-value were based on the method by Miettinen and Nurminen stratified by actual brand of birth dose of hepatitis B vaccine (RECOMBIVAX HB or Other/Unknown). The estimates for GMT, GMT ratio (PR5I Group/Control Group), are based on an ANCOVA model with natural log-transformed post-vaccination titer as the response variable, and vaccination group, natural log-transformed pre-vaccination titer, actual brand of birth dose Hep B vaccine (RECOMBIVAX HB or Other/Unknown) as explanatory variables. The missing pre-vaccination titers are imputed by a multiple imputation method and used in the ANCOVA analysis.PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
ANCOVA = Analysis of covariance, CI = Confidence interval, FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, GMT = Geometric mean titer, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, LLOQ = Lower limit of quantification, mos = Months, N = Number of vaccinated subjects, n = Number of subjects included in the analysis, Nab = Neutralizing antibodies, NI = Non-inferiority, PP-RW = Per-protocol-Revised Windows (defined as 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), PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid.

Although not a co-primary endpoint, the analysis of non-inferiority regarding GMTs for Prevnar 13 administered concomitantly with PR5I was analyzed at one-month Post-dose 3 for the PP-RW population and is provided in Table 52 below. Antibodies to the pneumococcal polysaccharides (PnPs) were assessed by a (b) (4) assay which detects serum IgG antibody to PnPs serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F. The PnPs(b) (4) assay was performed by (b) (4) .

The difference in the response for 12 out of 13 of the Prevnar 13 antigens, showed that the lower limit of the 2 sided 95% CI of the GMT ratios (PR5I group/Control group) was > 0.67, indicating a non-inferior response in the PR5I group compared to the Control group. Only, the PN 6B antigen of Prevnar 13 did not meet the pre-specified non-inferiority margin with a PR5I/Control GMT ratio of 0.79 (95% CI: 0.64 to 0.96). Similar findings were observed for the PP-OW population (data not shown). The non-inferiority criterion was met for all 13 antigens in the FAS population (data not shown).

Table 52. STN 125563/ V419-006: Non-Inferiority Analysis of Prevnar 13 Antigens for GMTs at One-month Post-dose 3 (PP-RW population) *

	PR5I (N=2232)		Control (N=370)				
Antigen	n	Estimated GMT [1]	n	Estimated GMT [1]	Estimated Difference/ GMT Ratio [1] (95% CI)	NI Margin	Non-inferiority Criterion Met/Not Met
PN 1	1256	1.38	191	1.50	0.92 (0.82, 1.04)	0.67	Met
PN 3	1255	0.48	191	0.51	0.95 (0.84, 1.06)	0.67	Met
PN 4	1255	1.19	189	1.19	1.00 (0.89, 1.12)	0.67	Met
PN 5	1256	1.42	191	1.53	0.93 (0.80, 1.07)	0.67	Met
PN 6A	1251	2.52	191	2.89	0.87 (0.77, 0.99)	0.67	Met
PN 6B	1255	0.96	190	1.22	0.79 (0.64, 0.96)	0.67	Not Met
PN 7F	1256	2.68	191	3.02	0.89 (0.80, 0.99)	0.67	Met
PN 9V	1256	1.31	189	1.31	1.00 (0.88, 1.13)	0.67	Met
PN 14	1256	4.66	191	4.90	0.95 (0.82, 1.10)	0.67	Met
PN 18C	1253	1.57	191	1.78	0.89 (0.79, 1.00)	0.67	Met
PN 19A	1254	1.56	191	1.71	0.91 (0.80, 1.03)	0.67	Met
PN 19F	1256	2.14	191	2.21	0.97 (0.87, 1.08)	0.67	Met
PN 23F	1254	1.05	190	1.16	0.90 (0.77, 1.06)	0.67	Met

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 11.2.3., Table 11-7, page 155.
[1] The estimates for GMT, GMT ratio (PR5I Group/Control Group), and p-value are based on an ANCOVA model with natural log-transformed post-vaccination titer as the response variable, and vaccination group, natural log-transformed pre-vaccination titer, actual brand of birth dose Hep B vaccine (RECOMBIVAX or Other/Unknown) as explanatory variables. The missing pre-vaccination titers are imputed by a multiple imputation method and used in the ANCOVA analysis.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13™at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
ANCOVA = Analysis of covariance, CI = Confidence interval, GMT = Geometric mean titer, mos = Months, N = Number of vaccinated subjects, n = Number of subjects included in the analysis, NI = Non-inferiority, PP-RW = Per-protocol-Revised Windows (defined as 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).
* Antibody responses (IgG) measured by (b) (4)

Non-inferiority with respect to pertussis responses one-month after the Toddler dose of Pentacel were assessed for the study populations. For the PP-RW population the lower bound of the 2-sided 95% CI of the difference was above the pre-specified noninferiority margin regarding all pre-specified endpoints, except for the endpoint of the GMT for the PRN antigen. The GMT ratio (PR5I group/Control group) for pertussis PRN one-month Post-dose 3 was 0.74 (95% CI: 0.66 to

0.83); thus, the lower bound of the 2 sided 95% CI of the GMT ratio which was to be < 0.67 was marginally missed and non-inferiority criteria were not demonstrated for pertussis PRN GMT.

The same analysis for the PP-OW population demonstrated similar results as the PP-RW population, while the FAS populations demonstrated non-inferiority of for all pertussis antigens one-month after the Toddler dose.

Table 53. STN 125563/ V419-006: Non-Inferiority Analysis of Pertussis Responses one-month after the Toddler dose of Pentacel (PP-RW population)

		PR5I (N=2002)		Control (N=326)				
Antigen	**Endpoint**	**n**	**Estimated Response [2]**	**n**	**Estimated Response [2]**	**Estimated Difference/ GMT Ratio [2] (95% CI)**	**NI Margin**	**Non-inferiority Criterion Met/Not Met**
PT	% vaccine response [1]	1616	98.51	254	98.40	0.12 (-1.11, 2.58)	-10%	Met
	GMT	1744	104.94	271	98.26	1.07 (0.98, 1.17)	0.67	Met
FHA	% vaccine response [1]	1669	95.32	261	95.48	-0.16 (-2.41, 3.22)	-10%	Met
	GMT	1742	98.98	271	114.65	0.86 (0.79, 0.95)	0.67	Met
PRN	% vaccine response [1]	1608	92.18	258	91.03	1.15 (-2.13, 5.47)	-10%	Met
	GMT	1746	105.33	271	141.88	0.74 (0.66, 0.83)	0.67	Not Met
FIM	% vaccine response [1]	1664	93.00	264	90.00	3.00 (-0.39, 7.40)	-10%	Met
	GMT	1746	426.42	271	325.86	1.31 (1.17, 1.46)	0.67	Met

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 11.2.4., Table 11-9, page 159.
[1] The pertussis vaccine response was defined as follows: (1) if pre-vaccination antibody concentration was < 4X LLOQ, then the post-vaccination antibody concentration was ≥ 4X LLOQ, (2) if pre-vaccination antibody concentration was ≥ 4X LLOQ, then the post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titer at pre-Dose 1.
[2] The estimates for the response rate, rate difference (PR5I Group minus Control Group), and p-value were based on the method by Miettinen and Nurminen stratified by actual brand of birth dose of hepatitis B vaccine (RECOMBIVAX HB or Other/Unknown). The estimates for GMT, GMT ratio (PR5I Group/Control Group), are based on an ANCOVA model with natural log-transformed post-vaccination titer as the response variable, and vaccination group, natural log-transformed pre-vaccination titer, actual brand of birth dose Hep B vaccine (RECOMBIVAX HB or Other/Unknown) as explanatory variables. The missing pre-vaccination titers are imputed by a multiple imputation method and used in the ANCOVA analysis.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
ANCOVA = Analysis of covariance, CI = Confidence interval, FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, GMT = Geometric mean titer, LLOQ = Lower limit of quantification, mos = Months, N = Number of vaccinated subjects, n = Number of subjects included in the analysis, NI = Non-inferiority, PP-RW = Per-protocol-Revised Windows (defined as 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), PRN = Pertactin, PT = Pertussis toxoid.

6.2.11.3 Subpopulation Analyses

A summary of the immune response by time, vaccination group and hepatitis B vaccine birth dose stratum for the PP-RW population is provided below for anti-HBsAg.

Table 54. STN 125563/ V419-006: Anti-HBsAg Response by Time, Vaccination Group and Hepatitis B Vaccine Birth Dose Stratum (PP-RW Population)

Brand of Hepatitis B Vaccine at Birth		**RECOMBIVAX-HB**				**Other / Unknown**			
		PR5I		**Control**		**PR5I**		**Control**	
Time Point	Endpoint	n	Observed Response % (95% CI) [1]	n	Observed Response% (95% CI) [1]	n	Observed Response% (95% CI) [1]	n	Observed Response% (95% CI) [1]
Pre-Vaccination 1	% with titer ≥ 10 mIU/mL (s/n)	563	40.85 (230/563)	102	44.12 (45/102)	1431	39.62 (567/1431)	235	46.38 (109/235)
			(36.76,45.04)		(34.29,54.29)		(37.08,42.21)		(39.88,52.98)
	GMT	563	11.31	102	12.82	1431	10.47	235	12.09
			(9.61, 13.30)		(8.74, 18.83)		(9.50, 11.53)		(9.48, 15.41)
One-month Post-dose 3	% with titer ≥ 10 mIU/mL (s/n)	495	100.00 (495/495)	83	97.59 (81/83)	1272	99.84 (1270/1272)	203	99.51 (202/203)
			(99.26, 100.00)		(91.57, 99.71)		(99.43, 99.98)		(97.29, 99.99)
	GMT	495	1432.68	83	526.97	1272	1285.99	203	646.23
			(1313.73, 1562.40)		(373.74, 743.03)		(1205.57, 1371.78)		(534.14, 781.83)
Pre-Toddler Dose	% with titer ≥ 10 mIU/mL (s/n)	482	95.85 (462/482)	82	86.59 (71/82)	1191	94.21 (1122/1191)	179	87.71 (157/179)
			(93.66, 97.45)		(77.26, 93.11)		(92.72, 95.46)		(81.99, 92.13)
	GMT	482	124.52	82	56.37	1191	123.97	179	74.91
			(110.57, 140.23)		(39.86, 79.73)		(113.59, 135.30)		(59.14, 94.87)
One-month After the Toddler Dose	% with titer ≥ 10 mIU/mL (s/n)	474	95.99 (455/474)	90	82.22 (74/90)	1195	92.97 (1111/1195)	171	85.96 (147/171)
			(93.81,97.57)		(72.74,89.48)		(91.37,94.35)		(79.84, 90.80)
	GMT	474	114.59	90	42.89	1195	119.05	171	70.06
			(101.52, 129.34)		(30.84, 59.65)		(108.87, 130.18)		(55.20, 88.92)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 14.2, Table 14-41, page 341.
[1] The 95% CI for response rate was based on the exact binomial method by Clopper and Pearson. The 95% CI for GMT was based on the t-distribution of the natural log-transformed antibody titer.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq™ at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.

CI = Confidence interval, GMT = Geometric mean titer, HBsAg = Hepatitis B surface antigen, n = Number of subjects included in the analysis, PP-RW = Per-protocol-Revised Windows (defined as 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), s = Number of responders.

Immune response pre- and one-month post the Toddler dose did not demonstrate a change in the percentage of subjects with titers ≥ 10 mIU/mL regardless of brand of previous Hepatitis B vaccines received.

6.2.11.4 Dropouts and/or Discontinuations

For GMTs, antibody values reported as < LLOQ were replaced by 0.5*LLOQ. For calculating a fold-rise, values< LLOQ were replaced by 0.5*LLOQ for a numerator and by LLOQ for a denominator. If both the numerator and denominator were < LLOQ, then both were converted in the same way. Values that were greater than the ULOQ were converted to the ULOQ.
Subjects with missing or incomplete data for any unique endpoint were not included in the primary analyses for that endpoint. Missing and incomplete data were not replaced.

6.2.11.5 Exploratory and Post Hoc Analyses

See section 6.2.11.3 Subpopulation Analyses in this review.

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety was evaluated as a secondary objective for this study. The safety and tolerability of PR5I was compared to that of the Control vaccine(s) when given concomitantly with Prevnar 13 and RotaTeq to healthy infants. Subjects were observed for all adverse events from Day 1 to Day 15 after each vaccine administration. Solicited injection-site adverse events, solicited systemic adverse events, and temperature were observed from Day 1 to Day 5. Adverse events were recorded on the VRC from Day 1 to Day 15 following each visit. All serious adverse events were collected up to Day 181 after Dose 3. All serious adverse events and deaths were to be recorded throughout the study. There were no AESI defined for this study. The safety evaluation was based on the ASaT population, which included all randomized subjects who received at least one vaccination and who had safety follow-up. (Please see section 6.2.7 of this review for further information on safety surveillance.)
The adverse events following vaccination were characterized as those events during and following the three dose infant series at 2, 4, and 6 months of age and those events following the Toddler dose of vaccines at 12 months of age. The safety evaluations of the ASaT population i.e. all vaccinated subjects with safety follow-up, included 2390 subjects in the PR5I group and 397 subjects in the Control group. The PR5I groups (different lots) were pooled for safety evaluations.

6.2.12.2 Overview of Adverse Events

Summary of Adverse events after any Infant Dose of Vaccine

Overall adverse events were reported by 94.5% of subjects (2259/2390) in the PR5I groups and 92.4% of subjects (367/397) in the Control group during Day 1 to Day 15 following any infant dose vaccination. Most subjects, 93.4% of subjects (2232/2390) in the PR5I group and 89.7% of subjects (356/397), reported systemic adverse events during Day 1 to Day 15 following any infant vaccination. For Days 1-5 following any infant vaccination, solicited systemic adverse events (i.e., crying, decreased appetite, irritability, pyrexia, somnolence, and vomiting) were reported by 91.4% of subjects (2185/2390) in the PR5I groups and 88.2% of subjects (350/397) in the Control

group. Unsolicited systemic adverse events were reported during this time period by 43.9% of subjects (1049/2390) in the PR5I groups and 41.8% of subjects (166/397) in the Control group.

Injection-site adverse events were reported by 81.2% of subjects (1940/2390) in the pooled PR5I group and 80.9% of subjects (321/397) in the Control group during Day 1 to Day 15. During Days 1-5 following vaccination, solicited injection site adverse events (i.e., injection-site erythema, injection-site pain, and injection-site swelling) were reported by 80.7% of subjects (1928/2390) in the PR5I group and 80.6% of subjects (320/397) in the Control group.

Solicited injection-site adverse events and temperature were observed from Day 1 to Day 5 were considered to be vaccine related by the investigators with the overall percentage of vaccine-related adverse events assessed as 92.8% for subjects (2219/2390) in the PR5I group and 91.2% for subjects (362/397) in the Control group during Day 1 to Day 15. A majority of subjects reported solicited systemic vaccine-related adverse events (i.e., crying, decreased appetite, irritability, pyrexia, somnolence, and vomiting); 90.5% of subjects (2163/2390) in the PR5I group and 86.9% of subjects (345/397) in the Control group during Day 1 to Day 5. Unsolicited systemic vaccine-related adverse events were reported by 10.7% of subjects (256/2390) in the PR5I group and 9.3% of subjects (37/397) in the Control group during Day 1 to Day 15.

All injection site reactions were considered to be related to vaccination and were reported by 81.2% of subjects (1940/2390) in the PR5I group and 80.9% of subjects (320/397) in the Control group during Day 1 to Day 15. Most of the reported injection site reactions were solicited injection-site adverse events (i.e., injection-site erythema, injection site pain, and injection-site swelling) and were reported by 80.7% of subjects (1928/2390) in the PR5I group and 80.6% of subjects (320/397) in the Control group during Day 1 to Day 5.

Serious adverse events were reported by 0.9% of subjects (21/2390) in the PR5I group and 0.8% of subjects (3/401) in the Control group during the vaccination period (Day 1 to Day 15); and by 3.8% of subjects (90/2390) in the PR5I group and 3.5% of subjects (14/397) in the Control group from Day 1 (after Dose 1) to Day 181 Post-dose 3. Serious vaccine-related adverse events that occurred after any infant dose vaccination and up to the day prior to the Toddler vaccination were observed in 0.2% of subjects [5/2390] in the PR5I group and by no [0/401] subjects in the Control group. The 5 SAEs considered to be related to administered vaccinations were three cases of fever, intussusception and diarrhea. The case of intussusception occurred after the third dose of RotaTeq and the case of diarrhea followed the first dose of RotaTeq.

Discontinuations due to adverse events were reported by 0.3% of subjects (7/2390) in the PR5I group and by no subjects (0/401) in the Control group for events that occurred after any infant dose vaccination, and up to before the Toddler vaccination. Of the 7 subjects who discontinued due to adverse events, one subject was discontinued due to vaccine-related non-serious adverse events (injection site pain/severe) and 3 subjects were discontinued due to serious adverse events (hydrocephalus, ITP and colitis) that were not considered as vaccine-related by the investigator. The other three subjects were discontinued secondary to gastrointestinal disorder, myoclonus, somnolence/irritability and injection site reactions (mild to moderate in intensity).

Five subjects (0.2%) died during the entire study duration. A single subject was deceased due to each of the following: hydrocephalus (b) (6) Post-dose 2, death unknown cause (suspected roll-over with asphyxiation) (b) (6) days Post-dose 1, sepsis (b) days Post-dose 1. Two subjects suffered sudden infant death syndrome [SIDS] at (b) (6) days Post-dose 2 and (b) (6) days Post-dose 1, respectively. All subjects were in the PR5I groups. No death was assessed by the investigators to be related to the study vaccinations.

Table 55 below shows that analysis of clinical adverse events for all subjects treated after any infant dose of vaccine. More subjects (93.4%; 2232/2390) in the PR5I group experienced any systemic adverse events during Day 1 to Day 15 after any infant dose vaccination compared to the Control group (89.7%; 356/397) (95% CI: 0.9% to 7.2%). Solicited systemic adverse events occurred more frequently in subjects who had received one of the lots of PR5I (91.4%; 2185/2390) than subjects who received the control vaccines (88.2%; 350/397) (95% CI: 0.2% to 7.0%), Days 1-5 following vaccination. The occurrence of Serious Adverse events during Day 1-15 following any dose of infant vaccination and from Day 1 after the initial dose of vaccine to 6 months post-dose 3 was similar.

Table 55. STN 125563/PR506: Analysis of Adverse Event Summary Following Any Infant Dose Vaccination (All Subjects as Treated Population)

	PR5I (N=2399)		Control (N=401)		Difference [3]	
	n	(%)	n	(%)	Estimate	(95% CI) [4]
Subjects in population	2390		397			
Number of subjects:						
With no adverse event	117	(4.9)	30	(7.6)	-2.7	(-5.8, -0.3)
With one or more adverse events (Day 1 to Day 15)	2259	(94.5)	367	(92.4)	2.1	(-0.4, 5.2)
Injection-site adverse events (Day 1 to Day 15)	1940	(81.2)	321	(80.9)	0.3	(-3.6, 4.7)
Solicited injection-site adverse events (Day 1 to Day 5)	1928	(80.7)	320	(80.6)	0.1	(-3.9, 4.5)
Systemic adverse events (Day 1 to Day 15)	2232	(93.4)	356	(89.7)	3.7	(0.9, 7.2)
Solicited systemic adverse events (Day 1 to Day 5)	2185	(91.4)	350	(88.2)	3.3	(0.2, 7.0)
Unsolicited systemic adverse events (Day 1 to Day 15)	1049	(43.9)	166	(41.8)	2.1	(-3.2, 7.2)
With vaccine-related adverse events (Day 1 to Day 15) [1]	2219	(92.8)	362	(91.2)	1.7	(-1.0, 5.0)
Injection-site adverse events (Day 1 to Day 15)	1940	(81.2)	321	(80.9)	0.3	(-3.6, 4.7)
Solicited injection-site adverse events (Day 1 to Day 5)	1928	(80.7)	320	(80.6)	0.1	(-3.9, 4.5)
Systemic adverse events (Day 1 to Day 15)	2167	(90.7)	346	(87.2)	3.5	(0.3, 7.3)
Solicited systemic adverse events (Day 1 to Day 5)	2163	(90.5)	345	(86.9)	3.6	(0.4, 7.4)
Unsolicited systemic adverse events (Day 1 to Day 15)	256	(10.7)	37	(9.3)	1.4	(-2.1, 4.2)
With serious adverse events (Day 1 to Day 15)	21	(0.9)	3	(0.8)	0.1	(-1.3, 0.8)
With serious adverse events (Day 1 after Dose 1 to Day 181 after Dose 3)	90	(3.8)	14	(3.5)	0.2	(-2.2, 1.9)
With serious vaccine-related adverse events [1] [2]	5	(0.2)	0	(0.0)	0.2	(-0.7, 0.5)
Who died [2]	5	(0.2)	0	(0.0)	0.2	(-0.7, 0.5)
Discontinued due to an adverse event [2]	7	(0.3)	0	(0.0)	0.3	(-0.7, 0.6)
Discontinued due to a vaccine-related adverse event [1]	1	(0.0)	0	(0.0)	0.0	(-0.9, 0.2)
Discontinued due to a serious adverse event	3	(0.1)	0	(0.0)	0.1	(-0.8, 0.4)
Discontinued due to a serious vaccine-related adverse event [1]	0	(0.0)	0	(0.0)	0.0	(-1.0, 0.2)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 12.2.2, Table 12-2, page 171.
[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.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel+ Prevnar 13 at 15 mos.
All serious adverse events were collected up to Day 181 after Dose 3. Vaccine related serious adverse events and deaths were collected for the duration of the study. Solicited adverse events were collected Day 1 to Day 5 after each vaccination. Other adverse events were collected from Day 1 to Day 15 after vaccination.
Subjects in population is the number of subjects in the All Subjects as Treated population i.e. all vaccinated subjects with safety follow-up.
Percentages were based on the number of subjects in the population.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

Solicited Local Adverse Events Following Any Infant Vaccination

Solicited injection-site or local adverse events related to vaccination with PR5I or Control vaccines were assessed during Day 1 to Day 5 following any infant dose vaccination. Solicited injection-site adverse events related to PR5I or Control were reported by 78.4% of subjects

(1874/2390) in the PR5I group and 78.1% of subjects (310/397) in the Control group. Table 56 below shows that the occurrence of injection site pain, erythema and swelling was comparable between the vaccine groups.

Table 56. STN 125563/V419-006: Analysis of Solicited Injection-Site Adverse Events Related to PR5I or Control (Incidence > 0% in One or More Vaccination Groups) Day 1 to Day 5 Following Any Infant Dose Vaccination (All Subjects as Treated Population)

	PR5I (N=2399)		Control (N=401)		Difference [1]	
	n	(%)	n	(%)	Estimate	(95% CI) [2]
Subjects in population	2390		397			
With one or more solicited injection-site adverse events	1874	(78.4)	310	(78.1)		
With no solicited injection-site adverse event	516	(21.6)	87	(21.9)		
Injection site erythema	1065	(44.6)	162	(40.8)	3.8	(-1.5, 8.9)
Injection site pain	1674	(70.0)	286	(72.0)	-2.0	(-6.6, 2.9)
Injection site swelling	825	(34.5)	137	(34.5)	0.0	(-5.1, 4.9)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 12.2.3, Table 12-3, page 173.
[1] Difference was PR5I group minus Control group.
[2] Based on unstratified Miettinen & Nurminen method.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Solicited injection-site adverse events included injection-site erythema, injection-site pain and injection-site swelling.
Subjects in population is the number of subjects in the All Subjects as Treated population i.e. all vaccinated subjects with safety follow-up. Percentages were based on the number of subjects in the population.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

Table 57 below presents the percentage of subjects reporting solicited injection site adverse events during Days 1-5 following any infant vaccination. The frequency and intensity of solicited local injection site adverse reactions (erythema, pain and swelling) were similar between the two vaccine groups.

Table 57. STN 125563/V419-006: Number (%) of Subjects with Any Solicited Injection-Site Adverse Events Related to PR5I or Control (Incidence > 0% in One or More Vaccination Groups) by Maximum Size / Intensity Day 1 to Day 5 Following Any Infant Dose Vaccination (All Subjects as Treated Population)

Vaccination Group		PR5I (N=2399)		Control (N=401)					
		PR5I		Pentacel and/or RECOMBIVAX HB		Pentacel		RECOMBIVAX HB	
Injection-Site	Intensity /Size Rating (cm)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population		2390		397		397		397	
Injection site erythema	Total	1065	(44.6)	162	(40.8)	155	(39.0)	108	(27.2)
	< 2.5 cm	989	(41.4)	146	(36.8)	139	(35.0)	101	(25.4)
	≥ 2.5 to ≤ 5.0 cm	61	(2.6)	11	(2.8)	11	(2.8)	4	(1.0)
	> 5.0 cm	7	(0.3)	3	(0.8)	3	(0.8)	2	(0.5)
	Unknown	8	(0.3)	2	(0.5)	2	(0.5)	1	(0.3)
Injection site pain	Total	1674	(70.0)	286	(72.0)	283	(71.3)	242	(61.0)
	Mild	977	(40.9)	168	(42.3)	166	(41.8)	164	(41.3)
	Moderate	554	(23.2)	96	(24.2)	95	(23.9)	62	(15.6)
	Severe	143	(6.0)	22	(5.5)	22	(5.5)	16	(4.0)
Injection site swelling	Total	825	(34.5)	137	(34.5)	133	(33.5)	85	(21.4)
	< 2.5 cm	711	(29.7)	117	(29.5)	113	(28.5)	79	(19.9)
	≥ 2.5 to ≤ 5.0 cm	96	(4.0)	16	(4.0)	16	(4.0)	6	(1.5)
	> 5.0 cm	11	(0.5)	2	(0.5)	2	(0.5)	0	(0.0)
	Unknown	7	(0.3)	2	(0.5)	2	(0.5)	0	(0.0)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 12.2.3, Table 12-4, page 175-6.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Solicited injection-site adverse events included injection-site erythema, injection-site pain and injection-site swelling.
Subjects in population is the number of subjects in the All Subjects as Treated population i.e. all vaccinated subjects with safety follow-up. Percentages were based on the number of subjects in the population.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

An evaluation of the systemic adverse reactions following any vaccination is shown in Table 58 below. The incidence of solicited adverse events Day 1-5 following vaccination was similar between the subjects who received PR5I or the control vaccines, with the exception of pyrexia. Pyrexia was reported by 47.1% of subjects (1125/2390) in the PR5I group and 33.2% of subjects (132/397) in the Control group during Day 1 to Day 5 following any infant dose vaccination. The difference (PR5I group minus Control group) in the percentage of subjects who had pyrexia was 13.8% (95% CI: 8.7% to 18.7%). [see Table 62 for gradation of pyrexia by body temperature increments]

Table 58. STN 125563/V419-006: Analysis of 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)

	PR5I (N=2399)		Control (N=401)		Difference [1]	
	n	(%)	n	(%)	Estimate	(95% CI) [2]
Subjects in population	2390		397			
With one or more solicited systemic adverse events	2185	(91.4)	350	(88.2)		
With no solicited systemic adverse event	205	(8.6)	47	(11.8)		
Crying	1787	(74.8)	288	(72.5)	2.2	(-2.3, 7.1)
Decreased appetite	1159	(48.5)	188	(47.4)	1.1	(-4.2, 6.4)
Irritability	1929	(80.7)	317	(79.8)	0.9	(-3.1, 5.4)
Pyrexia	1125	(47.1)	132	(33.2)	13.8	(8.7, 18.7)
Somnolence	1749	(73.2)	291	(73.3)	-0.1	(-4.6, 4.8)
Vomiting	637	(26.7)	99	(24.9)	1.7	(-3.1, 6.1)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 12.2.4, Table 12-6, page 179.
[1] Difference was PR5I group minus Control group.
[2] Based on unstratified Miettinen & Nurminen method.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Solicited systemic adverse events included crying, decreased appetite, irritability, pyrexia, somnolence and vomiting.
Subjects in population is the number of subjects in the All Subjects as Treated population i.e. all vaccinated subjects with safety follow-up.
Percentages were based on the number of subjects in the population.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

An evaluation of fever following each dose of PR5I compared to the control vaccines is presented in Table 59 below. The rate of pyrexia was higher following vaccination with PR5I regardless of dose. The highest incidence of fever when compared to the control vaccine was seen after the second and third vaccination with PR5I [26.7% versus 16.1% and 27.4% versus 15.8% respectively].

Table 59. STN 125563/V419-006: Number (%) of Subjects With Any Solicited Systemic Adverse Events Related to PR5I or Control (Incidence > 0% in One or More Vaccination Groups) by Vaccination Day 1 to Day 5 Following Each Infant Dose Vaccination (All Subjects as Treated Population)

	Vaccination Visit 1				Vaccination Visit 2				Vaccination Visit 3			
	PR5I (N=2399)		Control (N=401)		PR5I (N=2284)		Control (N=382)		PR5I (N=2232)		Control (N=370)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	2390		397		2273		380		2214		368	
With one or more solicited systemic adverse events	1915	(80.1)	314	(79.1)	1747	(76.9)	279	(73.4)	1610	(72.7)	252	(68.5)
With no solicited systemic adverse event	475	(19.9)	83	(20.9)	526	(23.1)	101	(26.6)	604	(27.3)	116	(31.5)
Crying	1249	(52.3)	209	(52.6)	1128	(49.6)	191	(50.3)	1026	(46.3)	168	(45.7)
Decreased appetite	693	(29.0)	110	(27.7)	546	(24.0)	79	(20.8)	529	(23.9)	86	(23.4)
Irritability	1458	(61.0)	251	(63.2)	1348	(59.3)	224	(58.9)	1239	(56.0)	201	(54.6)
Pyrexia	431	(18.0)	51	(12.8)	606	(26.7)	61	(16.1)	607	(27.4)	58	(15.8)
Somnolence	1355	(56.7)	222	(55.9)	1130	(49.7)	176	(46.3)	922	(41.6)	156	(42.4)
Vomiting	303	(12.7)	54	(13.6)	247	(10.9)	36	(9.5)	194	(8.8)	31	(8.4)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 12.2.4.2, Table 12-9, page 184.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel+ Prevnar 13 at 15 mos.
Control Group received Pentacel+ Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel+ Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Solicited systemic adverse events included crying, decreased appetite, irritability, pyrexia, somnolence and vomiting.
Subjects in population is the number of subjects in the All Subjects as Treated population i.e. all vaccinated subjects with safety follow-up.
Percentages were based on the number of subjects in the population.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

The maximum intensity of the solicited systemic adverse events after any dose of infant vaccine are presented below in Table 60. Most solicited systemic adverse events were mild to moderate in intensity and the percentage of subjects reporting severe solicited systemic adverse events was similar between the groups. More subjects reported mild to moderate fever in the PR5I vaccination group than in the control vaccine group.

Table 60. STN 125563/V419-006: Number (%) of Subjects With Any Solicited Systemic Adverse Events (Incidence > 0% in One or More Vaccination Groups) by Maximum Intensity Day 1 to Day 5 Following Any Infant Dose Vaccination (All Subjects as Treated Population)

		PR5I (N=2399)		Control (N=401)	
	Intensity Grading	**n**	**(%)**	**n**	**(%)**
Subjects in population		2390		397	
All Solicited Systemic Adverse Events	Total	2185	(91.4)	350	(88.2)
	Mild	721	(30.2)	101	(25.4)
	Moderate	1079	(45.1)	182	(45.8)
	Severe	385	(16.1)	67	(16.9)
Crying	Total	1787	(74.8)	288	(72.5)
	Mild	881	(36.9)	127	(32.0)
	Moderate	680	(28.5)	111	(28.0)
	Severe	226	(9.5)	50	(12.6)
Decreased appetite	Total	1159	(48.5)	188	(47.4)
	Mild	793	(33.2)	134	(33.8)
	Moderate	332	(13.9)	49	(12.3)
	Severe	34	(1.4)	5	(1.3)
Irritability	Total	1929	(80.7)	317	(79.8)
	Mild	886	(37.1)	142	(35.8)
	Moderate	856	(35.8)	149	(37.5)
	Severe	187	(7.8)	26	(6.5)
Pyrexia	Total	1125	(47.1)	132	(33.2)
	Mild	771	(32.3)	102	(25.7)
	Moderate	321	(13.4)	25	(6.3)
	Severe	33	(1.4)	5	(1.3)
Somnolence	Total	1749	(73.2)	291	(73.3)
	Mild	1109	(46.4)	186	(46.9)
	Moderate	556	(23.3)	93	(23.4)
	Severe	84	(3.5)	12	(3.0)

		PR5I (N=2399)		Control (N=401)	
	Intensity Grading	**n**	**(%)**	**n**	**(%)**
Vomiting	Total	637	(26.7)	99	(24.9)
	Mild	449	(18.8)	64	(16.1)
	Moderate	169	(7.1)	29	(7.3)
	Severe	19	(0.8)	6	(1.5)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 12.2.4.1, Table 12-7, page 181-2.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel+ Prevnar 13 at 15 mos.
Control Group received Pentacel+ Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel+ Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Solicited systemic adverse events included crying, decreased appetite, irritability, pyrexia, somnolence and vomiting.
Subjects in population is the number of subjects in the All Subjects as Treated population i.e. all vaccinated subjects with safety follow-up.
Percentages were based on the number of subjects in the population.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

The number of subjects reporting a solicited adverse event following each infant vaccination is shown below in Table 61.

Table 61. STN 125563/V419-006: Number (%) of Subjects With Any Solicited Systemic Adverse Events Related to PR5I or Control (Incidence > 0% in One or More Vaccination Groups) by Vaccination Day 1 to Day 5 Following Each Infant Dose Vaccination (All Subjects as Treated Population)

	Vaccination Visit 1				Vaccination Visit 2				Vaccination Visit 3			
	PR5I (N=2399)		Control (N=401)		PR5I (N=2284)		Control (N=382)		PR5I (N=2232)		Control (N=370)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects in population	2390		397		2273		380		2214		368	
With one or more solicited systemic adverse events	1915	(80.1)	314	(79.1)	1747	(76.9)	279	(73.4)	1610	(72.7)	252	(68.5)
With no solicited systemic adverse event	475	(19.9)	83	(20.9)	526	(23.1)	101	(26.6)	604	(27.3)	116	(31.5)
Crying	1249	(52.3)	209	(52.6)	1128	(49.6)	191	(50.3)	1026	(46.3)	168	(45.7)
Decreased appetite	693	(29.0)	110	(27.7)	546	(24.0)	79	(20.8)	529	(23.9)	86	(23.4)
Irritability	1458	(61.0)	251	(63.2)	1348	(59.3)	224	(58.9)	1239	(56.0)	201	(54.6)
Pyrexia	431	(18.0)	51	(12.8)	606	(26.7)	61	(16.1)	607	(27.4)	58	(15.8)
Somnolence	1355	(56.7)	222	(55.9)	1130	(49.7)	176	(46.3)	922	(41.6)	156	(42.4)
Vomiting	303	(12.7)	54	(13.6)	247	(10.9)	36	(9.5)	194	(8.8)	31	(8.4)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 12.2.4.2, Table 12-8, page 183.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Solicited systemic adverse events included crying, decreased appetite, irritability, pyrexia, somnolence and vomiting.

Subjects in population is the number of subjects in the All Subjects as Treated population at the considered visit i.e. all vaccinated subjects with safety follow-up for the considered visit.
Percentages were based on the number of subjects in the population.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category.

Analysis of Fever/Pyrexia

Temperatures were recorded mostly by rectal method/route (92.7% in the PR5I group and 92.1% in the Control group). The analysis of subjects with elevated temperatures by severity from Day 1 to Day 5 following any infant dose vaccination is shown below in Table 62.

More subjects in the PR5I group reported fever of any intensity during Day 1 to Day 5 following any infant dose vaccination when compared to the Control group. The differences (PR5I group minus Control group) for temperatures obtained by any route of measurement were not considered to be statistically significant.

- 3.9% (95% CI: -0.9% to 8.3%) for mild fever
- 8.7% (95% CI: 4.8% to 11.9%) for moderate fever (statistically significant)
- 1.1% (95% CI: -0.7% to 2.2%) for severe fever

Most episodes of pyrexia/fever lasted ≤ 48 hours. As seen in the previous study V419-005, there was an increase in incidence of fever/pyrexia following the second infant vaccination. Additionally, there was more temperatures ≥ 39.5ºC following vaccination in the PR5I group (2.1%) versus the Control (1.3%).

Table 62. STN 125563/V419-006: Analysis of Subjects with Elevated Temperatures by Severity Day 1 to Day 5 Following Any Infant Dose Vaccination (All Subjects as Treated Population)

	PR5I (N=2399)		Control (N=401)		Difference [6]	
	n	(%)	n	(%)	Estimate	(95% CI) [7]
Subjects in analysis population [1]	2390		397			
Subjects with temperature data [2]	2308	(96.6)	378	(95.2)		
Subjects with no temperature data	82	(3.4)	19	(4.8)		
Maximum Temperature (All Routes [3, 4])						
< 38.0°C	1173	(50.8)	244	(64.6)	-13.7	(-18.8, -8.4)
≥ 38.0°C and < 38.5°C (Mild)	628	(27.2)	88	(23.3)	3.9	(-0.9, 8.3)
≥ 38.5°C and < 39.5°C (Moderate)	451	(19.5)	41	(10.8)	8.7	(4.8, 11.9)
≥ 39.5°C (Severe)	56	(2.4)	5	(1.3)	1.1	(-0.7, 2.2)
Maximum Temperature (Rectal [4, 5])						
< 38.0°C	1100	(47.7)	223	(59.0)	-11.3	(-16.6, -5.9)
≥ 38.0°C and < 38.5°C (Mild)	611	(26.5)	87	(23.0)	3.5	(-1.4, 7.8)
≥ 38.5°C and < 39.5°C (Moderate)	438	(19.0)	40	(10.6)	8.4	(4.6, 11.6)
≥ 39.5°C (Severe)	55	(2.4)	5	(1.3)	1.1	(-0.7, 2.1)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 12.2.5.1, Table 12-11, page 187.
[1] Percentages were based on the number of subjects in the population with safety follow-up.
[2] Included subjects whose temperature methods were not reported for Day 1 to Day 5.
[3] Temperatures were based on actual temperatures recorded with no adjustments to the measurement route.
[4] Percentages were based on the number of subjects in the population with safety follow-up and temperature data.
[5] All subjects were required to take a rectal temperature if the reading by another method was ≥38° C.
[6] Difference was PR5I group minus Control group.
[7] Based on un-stratified Miettinen & Nurminen method.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.

Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Subjects in population is the number of subjects in the All Subjects as Treated population i.e. all vaccinated subjects with safety follow-up.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category. [1] Percentages were based on the number of subjects in the population with safety follow-up.

Fever and Seizure

During Days 1 through 15 following any infant vaccination there was an increased incidence in fever reported as an adverse event for subjects in the investigational vaccine groups. In the PR5I group, 47.9% of subjects (1144/2390) reported fever as compared to 34.8% of subjects (138/397) in the Control group. There were no reports of a convulsion or a febrile convulsion in either group during that time period.

Fever/pyrexia was reported as a serious adverse event in the PR5I group (0.1% of subjects [3/2390]) and in none of the subjects in the Control group (0/397) during Day 1-15 following any infant vaccination.

An analysis of serious adverse events over Day 1 through Day 181 demonstrated that pyrexia/fever was reported in 0.2% of subjects (4/2390) in the PR5I group and in no subjects in the Control group (0/397); febrile convulsion was reported in 0.1% of subjects (3/2390) in the PR5I group and in none of the subjects in the Control group (0/397). The reported febrile convulsions occurred 120,146, 163 days following the third dose of PR5I.Three subjects (0.1%) reported fever as a vaccine-related serious adverse event in the PR5I groups. No subjects in the Control group reported a vaccine-related serious adverse event of fever.

Table 63. STN 125563/V419-006: Number (%) of Subjects with Pyrexia, Febrile Convulsion, Convulsion (Incidence > 0% in One or More Vaccination Groups) Day 1 to Day 15 Following Any Infant Dose Vaccination (All Subjects as Treated Population)

	PR5I (N=2399)		Control (N=401)		Total (N=2800)	
	n	(%)	n	(%)	n	(%)
Subjects in population	2390		397		2787	
Adverse Events (Days 1 to 15):						
Pyrexia	1144	(47.9)	138	(34.8)	1282	(46.0)
Febrile Convulsion	0	(0.0)	0	(0.0)	0	(0.0)
Convulsion	0	(0.0)	0	(0.0)	0	(0.0)
Serious Adverse Events (Days 1 to 15):						
Pyrexia	3	(0.1)	0	(0.0)	3	(0.1)
Febrile Convulsion	0	(0.0)	0	(0.0)	0	(0.0)
Convulsion	0	(0.0)	0	(0.0)	0	(0.0)
Serious Adverse Events (Days 1 to 181):						
Pyrexia	4	(0.2)	0	(0.0)	4	(0.1)
Febrile Convulsion	3	(0.1)	0	(0.0)	3	(0.1)
Convulsion	0	(0.0)	0	(0.0)	0	(0.0)
Vaccine-related Serious Adverse Events (Days 1 to 181):						
Pyrexia	3	(0.1)	0	(0.0)	3	(0.1)
Febrile Convulsion	0	(0.0)	0	(0.0)	0	(0.0)
Convulsion	0	(0.0)	0	(0.0)	0	(0.0)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 006-02, Section 12.2.5.2, Table 12-12, page 189.
PR5I Group received PR5I + Prevnar 13 + RotaTeq at 2, 4, 6 mos; Pentacel + Prevnar 13 at 15 mos.
Control Group received Pentacel + Prevnar 13 + RotaTeq at 2, 4, 6 mos, RECOMBIVAX HB at 2, 6 mos; Pentacel + Prevnar 13 at 15 mos.
A subject was counted once for each applicable specific adverse event.
Subjects in population is the number of subjects in the All Subjects as Treated population i.e. all vaccinated subjects with safety follow-up.
Percentages were based on the number of subjects in the population.
mos = Months, N = Number of vaccinated subjects, n = Number of subjects in each category

Unsolicited Adverse Events Following Any Infant Dose of Vaccine

Unsolicited systemic adverse events were reported by 43.9% of subjects (1049/2390) in the PR5I group and 41.8% of subjects (166/483) in the Control group during Day 1 to Day 15 following any infant dose vaccination. The most frequent unsolicited systemic adverse events by preferred term were upper respiratory tract infection, diarrhea and otitis media and were similar between the groups. Most unsolicited adverse events were mild to moderate in intensity. The most frequently reported unsolicited adverse events of severe intensity were:

- Diarrhea and vomiting both reported by 0.3% of subjects (6/2390) in the PR5I group and 0.3% of subjects (1/397) in the Control group.
- Bronchiolitis reported by 0.3% of subjects (6/2390) in the PR5I group and none of

subjects in the Control group.
- Upper respiratory tract infection reported by 0.2% of subjects (5/2390) in the PR5I group and by no subjects in the Control group.

Unsolicited adverse events occurring Day 1-15 after any infant dose were similar to those seen within five days of vaccination and were generally similar between the groups except for the report of increased body temperature. Pyrexia occurred in 0.6% of subjects who received PR5I compared to an occurrence rate of 0.3% in subjects in the Control group. Of note, the parameter of "body temperature increased" as separate from pyrexia was reported by 1.6% of subjects in the PR5I group and in 0.5% of subjects in the control group.

Adverse Events after Concomitant Vaccination
Solicited, unsolicited injection site reactions after administration of Prevnar 13 for Days 1-5 or Days 1-15 was similar between the PR5I group and the Control group.

Adverse Events Following the Licensed Toddler Dose Vaccine
Solicited and unsolicited adverse events following administration of the Toddler dose of Pentacel and concomitant vaccines was similar in type and intensity between the study groups for Day 1 to 5 and Day 1-15 following vaccination. One subject experienced a febrile convulsion one day after vaccination, who had previously received three doses of PR5I.

6.2.12.3 Deaths

Five subjects (0.2%) in the PR5I group died during the conduct of the study. Cause of death is presented as: hydrocephalus secondary to Alexander disease[one subject] (b) (6) Post-dose 2, death, cause unknown, possibly due to "roll-over" co-sleeping event [one subject] (b) (6) days Post-dose 1, sepsis [one subject] (b) (6) days Post-dose 1, and SIDS [2 subjects] (b) (6) days Post-dose 2 and (b) (6) days Post-dose 1, respectively.

6.2.12.4 Nonfatal Serious Adverse Events

The events reported after the infant doses (Day 1 until the Toddler dose) in the PR5I group were:
- Subject (b) (6) , experienced ileocolic intussusception 6 days post-dose 3 PR5I, which was considered by the investigator as related to the third dose of RotaTeq and not related to the other study vaccines.
- Subjects (b) (6) (Day 1 post-dose, moderate intensity), and (b) (6) (Day 1 post-dose 1, moderate intensity) experienced fever, which was considered by the investigator as related to the study vaccines
- Subject (b) (6) , experienced diarrhea, which was considered by the investigator as related to the first dose of RotaTeq and not related to the other study vaccines.

Two subjects reported serious vaccine-related adverse events after the Toddler dose;
Subject (b) (6) in the PR5I group experienced febrile seizure, which was consider by the investigator as related to the fourth dose of Prevnar 13 and the Toddler dose of Pentacel and
Subject (b) (6) in the Control group reported fever, which was considered by the investigator as related to the fourth dose of Pentacel and the fourth dose of Prevnar 13.

6.2.12.5 Adverse Events of Special Interest (AESI)

No Adverse Events of Special Interest were pre-specified for Study V419-006.

6.2.12.6 Clinical Test Results

Not applicable for this study as no additional laboratory tests were obtained.

6.2.12.7 Dropouts and/or Discontinuations

Seven subjects who received PR5I discontinued participation in the clinical study due to adverse events identified below:

- Hydrocephalus with fatal outcome
- Failure to thrive
- Injection site erythema, injection site pain and injection site swelling were considered to be related to Dose 1 of PR5I.
- Gastrointestinal disorder (following Dose 3, unrelated)
- ITP (unrelated to vaccination)
- Colitis (unrelated to vaccination)
- Myoclonus

The discontinuation of these subjects is not thought to affect the overall safety evaluation of PR5I in Study V419-006.

6.2.13 Study Summary and Conclusions

V419-006 was a randomized, partially double-blind, active comparator-controlled, multicenter, lot-to-lot consistency study in healthy infants to assess the safety, tolerability, and immunogenicity of PR5I as compared to component vaccine Control(s) (standard-of-care) when given as an infant series. Subjects randomized to the PR5I groups (3 different lots to measure lot consistency) received PR5I, Prevnar 13 and RotaTeq at 2, 4, and 6 months followed by Pentacel and Prevnar 13 at 15 months. Subjects randomized to the Control group 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.

Immunogenicity was assessed, as a secondary endpoint, by measuring the Post-dose 3 antibody response to each of the antigens in the vaccine. A non-inferiority comparison was performed to the licensed control vaccines, with the antibody responses defined based on accepted antibody thresholds that correlated or are associated with protection from disease, when applicable. For the pertussis antibody response, which does not have a well-accepted correlate of protection, the non-inferiority comparison to Pentacel based on GMTs was accepted on the basis of immunologic bridging to an approved pertussis vaccine evaluated in efficacy trials. GMTs also served as a basis for comparison of immunogenicity for anti PRP and anti-pertussis components.

The criteria for lot consistency of GMTs (primary endpoint) were satisfied for all antigens across the 3 lots of PR5I.

The secondary endpoints for lot consistency of response rates at one-month Post-dose 3 were met for all antigens across the lots. Non-inferiority of PR5I antigens one-month Post-dose 3 to licensed Control vaccines was demonstrated for all antigens except for the FHA GMT at one-month Post-dose 3. Failure to meet non-inferiority success criteria for the FHA response post dose 3 should be considered in the context of other information. After completion of the 4-dose series with a Toddler dose of Pentacel, non-inferiority was demonstrated for FHA.

After the Toddler dose of Pentacel, non-inferiority was demonstrated for all pertussis antigens except for the GMT for PRN, which narrowly missed the non-inferiority margin of 0.67 for the lower bound of the 95% CI (GMT ratio: 0.74 [95% CI: 0.66 to 0.83]).

The anti-PRP responses for each immunogenicity time-point during the study for both PR5I and Control demonstrate an acceptable antibody response. Of note, the post-Toddler anti-PRP GMT

was higher in the PR5I group (49.41; 95% CI: 46.78 to 52.19) as compared to Control (19.17; 95% CI: 16.11 to 22.82). This result may be related to "mixed" regimes of vaccination using different PRP-conjugates. Subjects in the PR5I group of V419-006 received PRP-OMPC for 3 infant doses, and a Toddler dose of PRP-T as contained in Pentacel.
Antibody responses (measured by (b) (4) assay) to Prevnar 13 antigens when administered concomitantly with PR5I were non-inferior to Prevnar 13 administered with Control vaccines, for all of the antigens, except the PN 6B antigen, mirroring the results seen in the pivotal non-inferiority study of Prevnar 13.
The primary and secondary immunogenicity results support the administration of PR5I as a 3-dose infant series at 2, 4, and 6 months of age as part of the four dose DTaP primary vaccination series.

Safety was evaluated by pre-specified safety assessments, including solicited injection site adverse events and temperature Day 1 to Day 5 after each vaccination and systemic adverse events Day 1 to Day 15 after each vaccination. Serious adverse events were monitored for up to 180 days following completion of the infant series, and vaccine-related serious adverse events and deaths were monitored throughout the study.

The safety profile of PR5I was consistent with the known safety profile of the licensed component vaccines, and similar to the Control vaccines. A higher incidence of fever was noted following any vaccination with PR5I when compared to Control vaccinations. For subjects with fever, most subjects experienced mild to moderate fever. Severe fever ($\geq$ 39.5 °C) occurred in 2.4% of subjects who received PR5I as compared to 1.3% of subjects administered the Control vaccines. There were no febrile convulsions temporally related to the infant vaccination series (Day 1-15).

6.3 Study V419-003 (PR503): Supportive Phase 2 Trial (Dose/Formulation Finding)

V419-003: Multicenter Phase 2 Study (Canada): Safety Tolerability and Immunogenicity of 3 Different Formulations of a Liquid Hexavalent Combination Vaccine, HR5I (*Haemophilus influenza* Type b Conjugate, Recombinant Hepatitis B Surface Antigen, Diphtheria Toxoid, Tetanus Toxoid, 5-Component Acellular Pertussis Vaccine, and Inactivated Poliovirus Type 1, 2, and 3), When Administered to Healthy Hepatitis B Vaccine-Naive Infants at 2, 4, 6, and 12 to 14 Months of Age

This study administered HR5I vaccines, one formulation which would later be identified as the investigational vaccine PR5I, presented for licensure in this application. Each investigational vaccine administered during the study PR503 contained *Haemophilus influenzae* type b conjugate, recombinant hepatitis B surface antigen, diphtheria, tetanus, 5-component acellular pertussis, and inactivated poliovirus Types 1, 2, and 3. The vaccines were preservative-free, liquid, hexavalent vaccines to provide active immunization against disease caused by Hib, hepatitis B virus (HBV), *Corynebacterium diphtheria*, *Clostridium tetani, Bordetella pertussis*, and poliovirus Type 1, 2, and 3.

The study was a partially double-blind, randomized, multicenter clinical study that evaluated the safety, tolerability, and immunogenicity of 3 different formulations of HR5I [AR5I ((b) (4)), PR5I (3,10), and PR5I ((b) (4))]. The selected vaccine or control vaccines were administered to 756 healthy, hepatitis B vaccine-naïve infants by intramuscular injection as a 3-dose series at 2, 4, and 6 months of age plus a booster dose at 12 to 14 months of age.

This study included an open-label control arm. Infants randomized to the control arm received Pentacel, licensed in the United States in 2008: Sanofi Pasteur, Ltd., but not licensed in the US at the time the study was conducted. Children in the control arm also received concomitant immunization with Recombivax HB.

This study provides additional safety data related to the administration of PR5I in infants and toddlers.

Prior to submittal of the application for licensure, it was agreed that the immunogenicity results would not be evaluated as part of the licensure package. As part of the overall clinical development of PR5I, the primary hypothesis of this study was that at least one of the 3 formulations of HR5I administered as a primary series at 2, 4, and 6 months of age would be acceptable based on pre-specified response rates with respect to Post-dose 3 antibody response for all antigens. [Of note, during the conduct of the study there were several issues related to the assays used to assess the immune responses to the pertussis antigens. The procedure for the FHA and pertussis toxin (b) (4) were found to be out of compliance with the original planned assay. Results from the corrected assay procedures are presented in the final study report. Following the completion of the validated testing, the initial results of the PRN and FIM (b) (4) performed in the U.S. (using methodology transferred from Sanofi Pasteur Limited), were investigated due to unusually high results. A further investigation retested all available samples for PRN and FIM at Sanofi Pasteur Limited (Toronto, Ontario, CA). The original assay methodology (performed at Sanofi Pasteur Inc.) was found to be in compliance with proper procedures and data obtained from the original assay are considered to be valid.]

6.3.1 Objectives

Primary Objective

- To show that at least 1 of the 3 formulations of HR5I administered as a primary series at 2, 4, and 6 months of age is acceptable with respect to Post-dose 3 antibody response to all antigens.

Secondary Objectives

1. To assess the safety and tolerability of all 3 formulations of HR5I.
2. To show that at least 1 of the 3 formulations of HR5I administered as a primary series at 2, 4, and 6 months of age is acceptable with respect to Post-dose 2 antibody response to all antigens.
3. To evaluate the Pre-booster and Post-booster antibody response to all antigens from all 3 HR5I formulations.
4. To evaluate the Post-dose 2, Post-dose 3, Pre-booster, and Post-booster antibody response to all antigens from the control vaccination group.

6.3.2 Design Overview

This study partially double-blinded (the HR5I vaccination groups were blinded to investigator, study site personnel, subject/parent/legal guardian, and laboratory personnel, while the control vaccination group was open-label), randomized, controlled, dose-ranging, multicenter Canadian Phase II clinical trial was conducted to evaluate the safety, tolerability, and immunogenicity of 3 different formulations of HR5I when administered as an IM injection.

HR5I vaccines were administered as a primary series followed by a Toddler dose on a 2, 4, 6, and 12 to 14 months of age vaccination schedule. The open-label control group received the standard of care in Canada; receiving four doses of Pentacel* (at 2, 4, 6, and 12 to 14 months of age) and 3 doses of RECOMBIVAX HB (at 2, 4, and 6 months of age) as IM injections.

Enrollment was planned to be approximately 708 infants, 2 months of age. Subjects were randomized to one of four vaccination groups as described below. Subjects were to be naïve to previous hepatitis B vaccination.
*At the time of this study, Pentacel was not licensed in the U.S.

Study Initiation Date (FPI): 10-May-2001
Study Completion Date (LPO): 04-Jan-2003

Table 64. STN 125563/PR503: Study Sample Size, Vaccination Schedule, and Formulations of Vaccines Administered

Vaccination Group	n	Vaccination Schedule	Vaccine(s) Administered
1	177	2, 4, 6, and 12 to 14 months	AR5I ((b) (4))
2	177	2, 4, 6, and 12 to 14 months	PR5I* (3,10)
3	177	2, 4, 6, and 12 to 14 months	PR5I ((b) (4))
4	177	2, 4, and 6 months 12 to 14 months	Pentacel Pentacel

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 003, Section 9.1 , Table 9-1, page 35.
* PR5I (3, 10) is the same formulation as the product for licensure

Blood samples were obtained at 5-time points during the study: age 2 months (Pre-vaccination), 6 months (2 months Post-dose 2), 7 months (1 month Post-dose 3), 12 to 14 months (Pre-booster), and 13 to 16.5 months (3 to 6 weeks Post-booster).

6.3.3 Population
Inclusion Criteria
Healthy infants 2 months of age (14 days before 2-month birthday to 1 day before 3-month birthday) who have not received a single dose of any *Haemophilus influenza* type b (Hib); hepatitis B; diphtheria, tetanus and whole cell pertussis (DTwP); diphtheria, tetanus and acellular pertussis (DTaP), or poliovirus vaccine.

Exclusion Criteria
1. Documented HIV infection in the child or his/her mother.
2. Documented HBsAg seropositivity in the child or his/her mother.
3. Recent (72 hours) history of febrile illness (axillary temperature 37.8 C[100.0 F]).
4. History of invasive Hib disease, hepatitis B, diphtheria, tetanus, pertussis, or poliovirus infection.
5. History of seizure disorder, developmental delay, or any other neurologic disorder.
6. Underlying medical conditions such as inborn errors of metabolism, failure to thrive, or any major congenital abnormalities requiring surgery.
7. Prior or anticipated receipt of immune globulin, blood, or blood products.
8. Known hypersensitivity to any component of the investigational or marketed vaccines being administered in this protocol.
9. Any history or condition that would exclude the child from receiving any vaccine administered under this protocol based on the contraindications that appear in the package circulars for each component of these vaccines.
10. Any condition that, in the opinion of the investigator, is not stable or may interfere with the evaluation of the study objectives.

6.3.4 Study Treatments or Agents Mandated by the Protocol

The HR5I vaccines varied by formulation with respect to the PRP component of the vaccine; with the formulation containing (b) (4) designated as AR5I; the formulations containing PRP-OMPC designated as PR5I. The PR5I formulations differ with respect to the amount of their Hib component contained in each vaccine.

The numbers following a formulation name refer to the amounts (µg) of PRP and HBsAg in each formulation as follows:

- PRP-T ((b) (4) µg per dose); designated AR5I ((b) (4))
- PRP-OMPC (3 µg per dose); designated PR5I (3,10) *
- PRP-OMPC ((b) (4) µg per dose); designated PR5I ((b) (4))

* PR5I (3, 10) is the same formulation as the product for licensure.

The doses of the HBsAg, DTaP and IPV components are identical in all of the HR5I formulations in this study. All HR5I formulations were administered as 0.5-mL intramuscular (IM) injections.

Subjects in the control arm received Pentacel and RECOMBIVAX HB, the components of which are similar to those found in the AR5I formulation. The purpose of the control arm was to provide additional data for the comparison of the PRP-T versus PRP-OMPC components.

Table 65. STN 125563/PR503: Vaccine Formulations (0.5 mL per dose)

Vaccine	**AR51** (b) (4)	**PR5I (3,10)***	**PR5I** (b) (4)	**Pentacel**	**RECOMBIVAX HB**
Final Container .	(b) (4)			--	--
Labeled Final Container No.	(b) (4)			--	--
Final Formulated Bulk No.	(b) (4)				
Packaged Batch No	--	--	--	(b) (4)	
VACCINE COMPONENTS Per 0.5 mL dose					
PRP-T	(b) (4)	--	(b) (	10 mcg	--
PRP-OMPC	(b) (	3 mcg	(b) (4)	--	--
HBsAg	(b) (4)	10 mcg	(b) (4)	--	10 mcg
Diphtheria toxoid	(b) (4)	(b) (4) (15 Lf/dose)	(b) (4)	(b) (4) (15 Lf/dose)	--
Tetanus toxoid	(b) (4)	(b) (4) (5 Lf/dose)	(b) (4)	(b) (4) (5 Lf/dose)	--
PT	(b) (4)	20 µg	(b) (4)	20 µg	--
FHA	(b) (4)	20 µg	(b) (4)	20 µg	--
PRN	(b) (4)	3 µg	(b) (4)	3 µg	
FIM 2,3	(b) (4)	5 µg	(b) (4)	5 µg	
Poliovirus Type 1	(b) (4)	29 DU	(b) (4)	40 DU	
Poliovirus Type 2	(b) (4)	7 DU	(b) (4)	8DU	
Poliovirus Type 3	(b) (4)	26 DU	(b) (4)	32 DU	
Aluminum	(b) (4)	(b) (4)	(b) (4)	1.5 mg	0.25 mg

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 003, Synopsis, un-numbered table, page 4.
IU = International Units Lf = Limit of Flocculation
DU = D-Antigen Units PRP-T = polyribosylribitol phosphate conjugates to tetanus toxoid

PRP-OMPC = polyribosylribitol phosphate conjugated to the outer membrane protein complex of Neisseria meningitidis HBsAg = hepatitis B surface antigen
PT = pertussis toxoid FHA = filamentous haemagglutinin PRN = pertactin FIM = fimbriae agglutinogens 2 & 3
* PR5I (3,10) is the same formulation as the product for licensure

Laboratory assays were performed by Merck & Co., Inc. Research Laboratories (Wayne, Pennsylvania, USA), Sanofi Pasteur, Inc. (Swiftwater, Pennsylvania, USA) and Sanofi Pasteur Limited (Toronto, Ontario, Canada).

6.3.5 Directions for Use

Each vaccine was administered as a 0.5 mL IM dose.

6.3.6 Sites and Centers

Seven centers in Canada (Ontario, Nova Scotia, Quebec, British Columbia).

6.3.7 Surveillance/Monitoring

The primary safety objective for this study was to assess the safety and tolerability of all formulations of HR5I in infants 2 months to 14 months of age. All subjects who received at least 1 vaccination were included in the safety analysis.

All subjects were assessed for 15 minutes following each vaccination. Parents or legal guardians were to record daily temperatures (axillary temperatures ≥ 37.8C were considered as AEs) for Day 1 to Day 5 following each vaccination, and to record injection-site reactions (pain/redness/swelling) and systemic reactions for Day 1 to Day 15 following each vaccination using a vaccination report card (VRC). Vaccine-related serious adverse experiences and deaths that occurred at any time during the study were also reported.

6.3.8 Endpoints and Criteria for Study Success

Although immunogenicity responses will not be reviewed for this trial, the criteria for evaluation are given below and are consistent with the criteria that were used in the pivotal licensure studies.

Presented in Table 66 below are the pre-specified endpoints for Study PR503.

Table 66. STN 125563/PR503: Post-dose 3 and Post-dose 2 Endpoint Criteria

Antigen	Primary Endpoint	Targeted Response Rates (P)	Lower Bound Limit (P_0)
PRP	% with titer > 1.0 g/mL	85%	70%
HBsAg	% with titer 10 mIU/mL	95%	80%
Diphtheria	% with titer 0.01 IU/mL	95%	80%
Tetanus	% with titer 0.01 IU/mL	97%	85%
Pertussis - PT	% with 4-fold rise	85%	70%
Pertussis - FHA	% with 4-fold rise	85%	70%
Pertussis - FIM	% with 4-fold rise	85%	70%
Pertussis - PRN	% with 4-fold rise	85%	70%
Poliovirus Type 1	% with NA 1:8 dilution	97%	85%
Poliovirus Type 2	% with NA 1:8 dilution	97%	85%
Poliovirus Type 3	% with NA 1:8 dilution	97%	85%

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 003,

SAFETY MEASUREMENTS: Safety and tolerability were assessed by statistical and clinical review of all safety data as secondary endpoints. All subjects who received at least one injection of vaccine and had safety follow-up data were included in the safety and tolerability analysis.

6.3.9 Statistical Considerations & Statistical Analysis Plan
Prior to submission of the BLA it was agreed that this study would provide supportive safety data only. As such, the immunogenicity results for V419-003/PR503will not be presented in this review.

6.3.10 Study Population and Disposition
6.3.10.1 Populations Enrolled/Analyzed
A subject was considered to have completed the study if the following criteria were met: (1) all scheduled vaccinations were received; (2) the safety data for the follow-up period through Day 14 after the booster injection were completed; and (3) the subject returned to have the final blood sample obtained 4 to 6 weeks after the booster injection was given.

Primary immunogenicity summaries and analyses will be done on a per protocol population. All subjects who meet the inclusion criteria, were not protocol violators, and have serology and vaccinations within the pre-specified day ranges were included in the per-protocol analysis. Immunogenicity analyses will also be provided for "All Subjects with Serology." This analysis will include all subjects with serology, regardless of whether they are protocol violators or not.

All subjects who receive at least one injection and have follow-up data were included in the safety and tolerability summaries.

6.3.10.1.1 Demographics
There were 756 healthy subjects approximately 2 months of age enrolled and vaccinated at 7 investigator sites in Canada. Subjects were screened and randomized to 1 of 4 vaccination groups. Overall of the enrolled subjects, 54.4% were male. The mean age, standard deviation, and median age were similar across all vaccination groups. Median age at enrollment in each of the vaccination groups was 10 weeks. The majority of the subjects (87.6%) were white.

Table 67. STN 125563/PR503: Summary of Randomized Subjects' Characteristics by Vaccination Group

	AR5I (b) (4) (N=192) n (%)	PR5I (3,10) (N=188) n (%)	PR5I (b) (4) (N=189) n (%)	Pentacel + RECOMBIVAX HB (N=187) n (%)
Gender				
Male	109 (56.8)	100 (53.2)	102 (54.0)	100 (53.5)
Female	83 (43.2)	88 (46.8)	87 (46.0)	87 (46.5)
Age (weeks)				
6 And Under	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
7 to 8	25 (13.0)	21 (11.2)	20 (10.6)	21 (11.2)
9 to 10	95 (49.5)	106 (56.4)	100 (52.9)	113 (60.4)
11 to 12	59 (30.7)	52 (27.7)	56 (29.6)	41 (21.9)
Over 12	13 (6.8)	9 (4.8)	13 (6.9)	12 (6.4)
Mean	10.1	10.1	10.2	10.0
SD	1.43	1.33	1.41	1.42
Median	10.0	10.0	10.0	10.0
Range	7 to 13	7 to 13	7 to 14	7 to 14
Male	7 to 13	7 to 13	8 to 13	7 to 14
Female	7 to 13	7 to 13	7 to 14	7 to 14
Race				
Asian	4 (2.1)	1 (0.5)	6 (3.2)	8 (4.3)
Black	4 (2.1)	4 (2.1)	5 (2.6)	6 (3.2)
European	2 (1.0)	2 (1.1)	0 (0.0)	1 (0.5)
Indian	5 (2.6)	2 (1.1)	0 (0.0)	3 (1.6)
Multi-racial	8 (4.2)	16 (8.5)	10 (5.3)	5 (2.7)
Native American	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)
White	169 (88.0)	162 (86.2)	168 (88.9)	163 (87.2)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 003, Section 10.5.1, Table 10-5, page 87.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Medical conditions which were reported at the time of study entry were age appropriate for the population. The percent of subjects with at least one medical condition was similar between vaccination groups ranging from 73.9% to 79.4%. The most common medical conditions were skin and subcutaneous tissue disorders (35.5%), such as acne infantile and gastrointestinal disorders (28.5%), such as infantile colic.

The most common concomitant drug therapies administered (incidence ≥5% in one or more vaccination group) on Day 1 of vaccination to Day 15 post-vaccination were analgesics (81.3%) such as acetaminophen and vitamins (28.3%) such as vitamin D. The rates of concomitant therapy use were very similar across vaccination groups, ranging from 94.2 to 96.8%. Drugs with anti-pyretic properties were not prohibited and were used as prophylaxis and for the treatment of fever, injection site pain and other general disorders. Use of anti-pyretic/analgesic drugs was similar between the vaccination groups at approximately 80%.
Overall, 5.8% of subjects received a concomitant vaccination. The most common concomitant vaccine across all vaccination groups was meningococcal C conjugate vaccine (4.9%).

6.3.10.1.3 Subject Disposition

Of the 756 subjects who met inclusion criteria and were randomly allocated to the four vaccination groups, 36 (4.8%) subjects discontinued from the study with the most common reason for discontinuation was withdrawal of subject's consent (2.5%). The control group had the largest number of subjects discontinue at 7.5%. One subject ((b) (6)) discontinued from the study due to a clinical adverse experience. This subject was from the control vaccination group and this subject died during the study (see section 6.3.12.3 of this review).
Four (0.5%) subjects, enrolled in this study, were discontinued from the study early due to protocol deviations.
- (b) (6), allocated to the AR5I (b) (4) vaccine group, received the booster dose labeled for (b) (6), who was allocated to the PR5I (b) (4) vaccine group.
- Subject (b) (6) allocated to the PR5I (b) (4) vaccine group, received an unknown vaccine prohibited by the protocol.
- Subject (b) (6), allocated to the control vaccination group, received only one vaccination at Visit 1; however, it could not be determined which vaccine the subject received, and thus this subject was discontinued from the study.
- Subject (b) (6), randomized to the control vaccination group, received an additional dose of Pentacel 16 days after having received the initial vaccination.

These four subjects have been excluded from the serology analyses but were included in the safety analyses.

Two subjects ((b) (6)) were un-blinded early for unknown reasons but were included in both the immunogenicity and safety analyses.

Table 68. STN 125563/PR503: Subject Disposition

	AR5I (b) (4)		**PR5I (3, 10)***		**PR5I** (b) (4)		**Pentacel + RECOMBIVAX HB**		**Total**	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Randomized (N)	192		188		189		187		756	
Vaccinated at:										
Visit 1	192	(100)	188	(100)	189	(100)	187	(100)	756	(100)
Visit 2	190	(99.0)	187	(99.5)	186	(98.4)	180	(96.3)	743	(98.3)
Visit 3	187	(97.4)	185	(98.4)	185	(97.9)	178	(95.2)	735	(97.2)
Visit 5	185	(96.4)	182	(96.8)	183	(96.8)	175	(93.6)	725	(95.9)
Completed	184	(95.8)	182	(96.8)	181	(95.8)	173	(92.5)	720	(95.2)
Discontinued	8	(4.2)	6	(3.2)	8	(4.2)	14	(7.5)	36	(4.8)
Clinical AE	0	(0.0)	0	(0.0)	0	(0.0)	1†	(0.5)	1†	(0.5)
Lost to FU	1	(0.5)	1	(0.5)	2	(1.1)	2	(1.1)	6	(0.8)
Other reason	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.1)
Subject moved	1	(0.5)	3	(1.6)	0	(0.0)	1	(0.5)	5	(0.7)

	AR5I (b) (4)		**PR5I (3, 10)***		**PR5I** (b) (4)		**Pentacel + RECOMBIVAX HB**		**Total**	
Withdrew consent	5	(2.6)	2	(1.1)	4	(2.1)	8	(4.3)	19	(2.5)
Protocol deviation	1	(0.5)	0	(0.0)	1	(0.5)	2	(1.1)	4	(0.5)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 003, Section 10.1, Table 10-1, page 80.
† One subject ((b) (6)) discontinued the study due to a clinical AE outside the 14-day follow-up period following vaccination. This subject died on Study Day (b) (6) Post-dose 2. The death was determined by the investigator to be probably not related to study vaccine.
*Formulation for licensure

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Since the determination of which vaccine formulation would be used in later studies was dependent upon the immunogenicity findings in this study, a brief overview of the immunogenicity results are presented here. The final per-protocol immunogenicity analyses included subjects whose immune responses were evaluated at post-dose 2 and post-dose 3 time points. Due to the methodology for evaluating fold-rise, more subjects were excluded from evaluation of response to the pertussis antigens, due to missing values. The number of subjects included in the pertussis PT and FHA categories for all vaccination groups represents the samples that were tested by the corrected assay, as previously described. The number of subjects included in the pertussis FIM and PRN categories represents the original set of samples tested for these antigens. Due to the priority of testing there were lower numbers of subjects with adequate sera to assess the immune response to polioviruses. Subjects were excluded from analysis due to: subject outside of age range at enrollment, sample inadequate for serology testing, subject vaccinated outside of day range, subject bled outside of day range and missed baseline serology.

1) The primary hypothesis of the study was met for at least one of the formulations of HR5I administered as a primary series at 2, 4 and 6 months of age with respect to Post-dose 3 antibody responses to all antigens. The formulations containing PRP-OMPC [PR5I (3,10) and PR5I (b) (4) were found to be acceptable with respect to all antigens tested based on pre-specified criteria. The AR5I (b) (4) formulation was not found to be acceptable due to the PRP responses.
2) None of the 3 formulations of HR5I administered as a primary series at 2, 4 and 6 months of age were acceptable (met predefined lower bound limits of the response) with respect to Post-dose 2 antibody responses to antigens.

6.3.11.2 Analyses of Secondary Endpoints

Not applicable

6.3.11.3 Subpopulation Analyses

Not applicable.

6.3.11.4 Dropouts and/or Discontinuations

Not applicable.

6.3.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.3.12 Safety Analyses

6.3.12.1 Methods

All subjects were observed for 15 minutes after each vaccine injection for any adverse reactions. The subject parent/legal guardian were to record daily temperatures for Day 1 to Day 5 following each vaccination using a Vaccination Report Card (VRC) and record any injection-site reactions and systemic reactions for Day 1 to Day 15 following each vaccination. All adverse experiences (AEs) that occurred from the time the consent form was signed to Day 15 after the first vaccination, and from the time of any subsequent vaccination(s) through Day 15, were recorded.

Safety measurements of interest included: (1) incidence of any SAEs; (2) incidence of any injection-site AEs; (3) incidence of any systemic AEs; and (4) incidence of any vaccine related AEs.

The primary safety objective for this study was to assess the safety and tolerability of all formulations of HR5I in infants 2 months to 14 months of age. Safety was evaluated as a secondary endpoint without criteria or pre-specified solicited adverse events except for fever. Data was collected on any injection site adverse event and any systemic adverse event. Only fever was queried for specifically during the study.

6.3.12.2 Overview of Adverse Events

Although safety in the supportive studies was to be assessed primarily for serious adverse events, in light of the increase in mild to moderate fever seen in the pivotal studies and the concerns related to the (b) (4), further analyses were reviewed.

Table 69. STN 125563/PR503: Summary of Adverse Events Days 1 to 15 Following Any Vaccination

	AR5I (b) (4) (N=192)		**PR5I* (3,10) (N=188)**		**PR5I (b) (4) (N=189)**		**Pentacel + RECOMBIVAX HB (N=186)**	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	192		188		189		186	
Subjects without follow-up	0		0		1		2	
Subjects with follow-up	192		188		188		184	
Number (%) of subjects:								
-with no adverse experience	11	(5.7)	5	(2.7)	4	(2.1)	11	(6.0)
- with one or more adverse experiences	181	(94.3)	183	(97.3)	184	(97.9)	173	(94.0)
- injection-site adverse experiences	135	(70.3)	152	(80.9)	165	(87.8)	151	(82.1)
- systemic adverse experiences	163	(84.9)	163	(86.7)	172	(91.5)	161	(87.5)
- with vaccine-related adverse experiences	168	(87.5)	178	(94.7)	178	(94.7)	170	(92.4)
- injection-site adverse experiences	135	(70.3)	152	(80.9)	165	(87.8)	151	(82.1)
- systemic adverse experiences	133	(69.3)	145	(77.1)	151	(80.3)	138	(75.0)
- with serious adverse experiences	0	(0.0)	2	(1.1)	2	(1.1)	4	(2.2)
- with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 003, Section 12.1.2.1, Table 12-1, page 143.
*Formulation for licensure

In general, for the investigational products, the occurrence of injections site and systemic adverse events were highest in subjects who received PR5I (b) (4) and lowest in subjects who were administered AR5I (b) (4) The rates of adverse events in the control group (Pentacel + Recombivax HB) were similar to those seen in subjects who received PR5I (3, 10) [formulation for licensure].

Eight subjects reported experiencing at least 1 serious adverse experience Day 1 through Day 15 following any vaccination visit. One of these subjects (in the control group) had a serious AE that was determined by the investigator to be related to the study vaccine. No deaths occurred Day 1 through Day 15 following any vaccination visit.

One death was reported during the conduct of the study (see section 6.3.12.3 below).

No subjects were discontinued from the study due to an adverse experience Day 1 to Day 15 following any vaccination visit.

For overall systemic adverse events collected Day 1-15 regardless of dose/age, the proportion of subjects reporting systemic events was higher in the PR5I (b) (4) group. The most commonly reported adverse events were fever and irritability. The occurrence of pyrexia was higher in the PR5I (3, 10) and PR5I (b) (4) vaccination groups compared to the AR5I (b) (4) and control vaccination groups. The occurrence of irritability was similar among the groups.

Analysis of systemic adverse events for Day 1 through Day 15 following each vaccination visit ((Vaccination Visit 1, Vaccination Visit 2, Vaccination Visit 3 and Booster Visit, respectively) demonstrated that AEs were lower following Vaccination Visit 2 and Vaccination Visit 3 compared to Vaccination Visit 1 and Booster Visit for all vaccination groups. (Data not shown)

An analysis of the difference in the rate of fever/pyrexia showed a statistically significant greater proportion of subjects with the systemic clinical AEs of pyrexia and decreased appetite (data not shown) in the PR5I (3, 10) and PR5I (b) (4) vaccination groups than in the AR5I (b) (4) and control vaccination groups **(**Table 70). This mirrors the findings for fever rates in the clinical studies conducted under Protocols V419-005 (PR5) andV419-006 (PR506).

Table 70. STN 125563/PR503: Pairwise Differences Between Vaccination Groups for Systemic Clinical Adverse Experiences/Pyrexia Days 1 to 15 Following Any Vaccination Visit

Endpoint	Comparison Vaccines	Estimated Difference	95% CI	AR5I (b) (4) (n=192)	PR5I (3,10) (n=188)	PR5I (b) (4) (n=189)	Pentacel + RECOMBIVAX HB (n=187)
Pyrexia^				n %	n %	n %	n %
	AR5I (b) (4) – PR5I(3,10)	-14.8%	(-23.5, -5.9)	37 (19.3%)	64 (34.0%)	---	---
	AR5I (b) (4) - PR5I (b) (4)	-22.5%	(-31.4, -13.4)	37 (19.3%)	---	79 (41.8%)	----
	AR5I (b) (4) - Pentacel+ Recombivax HB	-1.1%	(-9.2, 7.0)	37 (19.3%)	---	---	38 (20.3%)

Endpoint	Comparison Vaccines	Estimated Difference	95% CI	AR5I (b) (4) (n=192)	PR5I (3,10) (n=188)	PR5I (b) (4) (n=189)	Pentacel + RECOMBIVAX HB (n=187)
	PR5I(3,10) - PR5I(b) (4)	-7.8%	(-17.4, 2.1)	---	64 (34.0%)	79 (41.8%)	---
	PR5I(3,10) - Pentacel+ Recombivax HB	13.7%	(4.7, 22.6)	---	64 (34.0%)	---	38 (20.3%)
	PR5I(b) (4) - Pentacel+ Recombivax HB	21.5%	(12.2, 30.4)	---	---	79 (41.8%)	38 (20.3%)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 003, Reviewer modified table, Section 12.2.2.2, Table 12-4, page 154.
^ Pyrexia defined as axillary temperatures ≥ 37.80° C (100.0° F)

The majority of subjects (> 70% across the vaccine groups) did not report fever during days 1-5 following vaccination where was fever defined as axillary or axillary temperature equivalents ≥ 37.80° C (100.0° F). For subjects with reported fever, temperatures were mild to moderate in intensity. More subjects in the PR5I vaccine groups reported the occurrence of fever when compared to subjects in the ARI5 and control groups. There were no reports of severe fever in any vaccination group (≥ 40.0° C (104.0° F). It should be noted; however, that the axillary route of fever measurement may result in the reporting of lower fever rates overall. (Data not shown) One convulsion (graded as severe) occurred in the PR5I (3,10) study group and one febrile convulsion (graded as mild) occurred in the control vaccine group within 15 days of vaccination. The investigators did not assess these events as serious adverse events related to vaccination. [PR5I (3,10) is the same formulation administered during the Phase 3 studies V419-005 and V419-006.]

Parents or legal guardians were asked to record any injection site reaction occurring Day 1-5 following each vaccination. All injection-site AEs are considered to be vaccine related. The numbers (%) of subjects with injection-site AEs (incidence ≥1 %) for Day 1 through Day 5 following any vaccination visit for selected AEs are in Table 71 below. The overall number (%) of subjects with one or more injection-site AEs was slightly higher in the PR5I (b) (4) vaccination group as compared to the other vaccination groups. The percentage of subjects with at least one injection-site AE was lowest in the AR5I (b) (4) vaccination group. The most commonly reported injection-site AEs were pain, redness and swelling. Severe pain occurred in all vaccine groups, occurring in 4.2 to 7.4% of subjects. Subjects who received PR5I (b) (4) reported the highest incidence of severe pain and subjects in the AR5I and Pentacel (only) reported the lowest incidence of pain following any vaccination. No cases of severe swelling were reported after any vaccination in any vaccination group.

Table 71. STN 125563/PR503: Number (%) of Subjects With Injection-Site Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) Days 1 to 5 Following Any Vaccination Visit

Endpoint	AR5I (b) (4) (n=191)	PR5I(3,10) (n=187)	PR5I (b) (4) (n=189)	Pentacel + RECOMBIVAX HB (Pentacel Injection Site) (n=186)
	n %	n %	n %	n %
n (%) with one or more injection site AEs	133 (69.6)	151 (80.7)	165 (87.8)	145 (78.8)
Redness/Erythema	83 (43.5)	117 (62.6)	129 (68.6)	100 (54.3)
Pain	103 (53.9)	118 (63.1)	139 (73.9)	118 (64.1)
Swelling	73 (38.2)	91 (48.7)	113 (60.1)	78 (42.4)
Induration	6 (3.1)	12 (6.4)	9 (4.8)	9 (4.9)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 003, Reviewer modified table, Section 12.2.4.1, Table 12-8, page 161.
Pain was graded as mild, moderate or severe based upon limitations in activities.
Redness, swelling and induration were measured by size using a measuring device and scale provided by the investigator.

Most injection site reactions were reported as mild to moderate intensity in the five days following any vaccination. The incidence of AEs decreased following the second and third vaccination but was slightly increased following the booster dose vaccines.

Serious Adverse Events (SAE)
There were a total of 15 serious adverse experiences reported during the course of the entire study in 9 (0.01%) subjects for the enrolled population of 756 subjects. One subject in the control group was assessed as having a SAE related to vaccination (lymphadenitis/neutropenia) within twelve days of the second dose of control vaccines. Other SAEs included pneumonia, UTI, bronchiolitis, sudden infant death syndrome, bacteremia and pyrexia. The occurrence of pyrexia was 11 days following Dose 1 of the control vaccine. One convulsion (graded as severe) which occurred in the PR5I (3,10) study group and one febrile convulsion (graded as mild) occurred in the control vaccine group within 15 days of vaccination and were not considered by the investigators as serious adverse events.

6.3.12.3 Deaths

One death occurred during the clinical trial. Subject (b) (6), randomized to the Control group, died on Study Day (b) (6) Post-dose 2. The cause of death was reported as sudden infant death syndrome (autopsy performed).

6.3.12.4 Non-fatal Serious Adverse Events

See "Serious Adverse Events" in section 6.3.12.2 Overview of Adverse Events above.

6.3.12.5 Adverse Events of Special Interest (AESI)

Not applicable.

6.3.12.6 Clinical Test Results

Not applicable.

6.3.12.7 Dropouts and/or Discontinuations

One subject was discontinued from the study due to a clinical adverse experience; subject (b) (6) (deceased).See section 6.3.12.3 of this review.

6.3.13 Study Summary and Conclusions

In general, PR5I (b) (4) was more reactogenic than PR5I (3, 10) * and both the PR5I vaccines were more reactogenic than the AR5I formulations. [* PR5I formulation used in subsequent Phase 3 studies]
1) All formulations used in this study had safety profiles similar to those seen with previously licensed component vaccines when administered as a primary series at 2, 4, and 6 months of age, and as a booster dose at 12 to 14 months of age.
2) Systemic clinical adverse experiences and injection-site adverse experiences were highest with the PR5I (b) (4) formulation as compared to AR5I (b) (4), PR5I (3,10), and Pentacel and RECOMBIVAX HB.
Although most subjects who experienced fever had mild to moderate fevers, there was a greater proportion of subjects with the pyrexia and decreased appetite (data not shown) in the PR5I (3,10) and PR5I (b) (4) vaccination groups than in the AR5I (b) (4) and control vaccination groups. There were no reports of severe fever in any vaccination group (≥ 40.0° C (104.0° F).
The rates and types of adverse events following vaccination with the HR5I vaccines was similar to those seen following control component vaccines.

In general, there were no unexpected solicited, unsolicited or unexpected serious adverse events were noted for the population, however two seizure events were reported in the 15-day post-vaccination period, one in the PR5I (3,10) group and one in the Control group, which were not considered to be serious adverse events by the investigators.

6.4 Study V419-004 (PR504): Supportive Phase 2 Study (Four-dose series)

V419-004: "A randomized trial to assess the immunogenicity and safety of (b) (4) to the Hepatitis B component and when given concomitantly with Prevnar"

Date of FVFS: 10 August 2006
Date of LVLS: 10 April 2008

6.4.1 Objectives

Primary Objective

- To assess the immunogenicity of PR5I with the (b) (4) composition change to the hepatitis B component using predetermined lower limits of response rates as reference when administered concomitantly with Prevnar

Secondary Objectives

- To assess the safety of PR5I administered concomitantly with Prevnar (Group A).
- To assess the immunogenicity and safety of PR5I administered 1 month apart from Prevnar Group B).
- To assess the immunogenicity and safety of separately administered licensed vaccines used for routine infant vaccination in Canada (with a modified hepatitis B schedule Group C).

6.4.2 Design Overview

For this Phase 2 study, the manufacturing process for the (b) (4) in the HBsAg bulk intermediate was modified. Study V419-004 was conducted (1) to confirm that the immunogenicity and safety profile of PR5I had not been adversely affected by this change and (2) to obtain descriptive concomitant use data with pneumococcal conjugate vaccine (Prevnar, 7-valent). This study will be evaluated for safety responses only.

Randomized, open-label, multi-center trial conducted at 8 sites in Canada.
Subjects were randomly allocated to the following 3 study groups using a 1:1:1 ratio:

Group A	**PR5I** (0.5 mL) and concomitant Prevnar (0.5 mL) at 2, 4, 6 and 15 months
Group B	**PR5I** (0.5 mL) at 2, 4, 6, and 15 months and Prevnar (0.5 mL) at 3, 5, 7 and 16 months
Group C	**Pentacel** (0.5 mL) and concomitant ENGERIX B (0.5 mL) and Prevnar (0.5 mL) at 2, 4 and 6 months, and **Pentacel** (0.5 mL) and concomitant Prevnar (0.5 mL) at 15 months

Antibody levels were assayed at baseline (prior to Dose 1) for pertussis only, 28-42 days post-Dose 3, prior to and 28-42 days post-Dose 4, for all PR5I antigens. Participants were monitored for safety until 30 days after Dose 4. (Immunogenicity will not be assessed for this study as part of this application)

6.4.3 Population

Inclusion Criteria:
1) Infants aged 42 to 89 days inclusive on the day of inclusion.
2) Born at full term of pregnancy (>37 weeks).
3) Informed consent form signed by the parent(s) or legally authorized representative.
4) Able to attend all scheduled visits and to comply with the study procedures.
5) Parent or legally authorized representative has access to a telephone.
6) Parent or legally authorized representative able to read and write in English or French.

Exclusion Criteria:
1) Participation in another clinical trial in the 4 weeks preceding the first trial vaccination.
2) Planned participation in another clinical trial during the present trial period.
3) Personal or immediate family history of congenital or acquired immunodeficiency, immunosuppressive therapy such as long-term systemic corticosteroid therapy.
4) Known or suspected systemic hypersensitivity to any of the vaccine components or history of a life-threatening reaction to a vaccine containing the same substances as the trial vaccine(s).
5) Chronic illness that could interfere with trial conduct or completion.
6) Received blood or blood-derived products since birth.
7) Any vaccination preceding the first trial vaccination or planned in the 4 weeks after any trial vaccination (influenza vaccine may be given a minimum of 4 weeks prior to the first study vaccination).
8) Previous vaccination with any acellular pertussis- (DTaP) or whole cell pertussis- (DTwP) based combination vaccines, *Haemophilus influenzae* type b (Hib)- conjugate, poliovirus, hepatitis B, or pneumococcal conjugate vaccines.
9) Coagulation disorder contraindicating IM vaccination.
10) Clinically significant findings on review of systems (determined by investigator or sub-investigator to be sufficient for exclusion).

11) Developmental delay or neurological disorder.
12) Any condition which, in the opinion of the investigator, would interfere with the evaluation of the vaccine or pose a health risk to the subject.
13) Documented HBsAg seropositivity in the child or his/her mother.
14) History of Hib, hepatitis B, diphtheria, tetanus, pertussis or poliovirus disease.

6.4.4 Study Treatments or Agents Mandated by the Protocol
Investigational Product:
PR5I vaccine (Sanofi Pasteur, Swiftwater, PA, USA and Merck & Co., Inc., Whitehouse Station, NJ, USA) is composed of DTaP (HCPDT, Hybrid Component Pertussis Vaccine in combination with Diphtheria and Tetanus Toxoids, Sanofi Pasteur), IPV (Imovax Polio, Inactivated Poliovirus Vaccine, Sanofi Pasteur), Hepatitis B vaccine (RECOMBIVAX HB, Merck) and Haemophilus influenzae type b vaccine (PedvaxHIB, Merck), in a liquid formulation.

Form: Liquid

Composition of PR5I, each 0.5 mL dose contains:

Antigen	Amount
PT	20 µg
FHA	20 µg
FIM	5 µg
PRN	3 µg
Diphtheria	15 Lf
Tetanus	5 Lf
Vero-derived IPV – Type 1	29 D-antigen Units
Vero-derived IPV – Type 2	7 D-antigen Units
Vero-derived IPV – Type 3	26 D-antigen Units
HBsAg	10 µg
PRP-OMPC	3 µg
Aluminum	(b) (4) µg

Route: Intramuscular (IM)

Batch Number: UD08135

Control Products:

Pentacel (Sanofi Pasteur, Toronto, ON, Canada)
Form: Liquid Quadracel (HCPDT-IPV) used to reconstitute lyophilized ActHIB (PRP-T)

Composition: Each 0.5 mL dose contains:

Antigen	Amount
PT	20 µg
FHA	20 µg
FIM	5 µg
PRN	3 µg
Diphtheria	15 Lf
Tetanus	5 Lf
MRC5-derived IPV – Type 1	40 D-antigen Units
MRC5-derived IPV – Type 2	8 D-antigen Units
MRC5-derived IPV – Type 3	32 D-antigen Units
PRP-T	10 µg purified PRP capsular polysaccharide of Haemophilus influenzae type b covalently bound to 24 µg of Tetanus Toxoid

Route: IM

Batch Number: Various (marketed product was supplied by sites)

ENGERIX-B (GlaxoSmithKline, Research Triangle Park, NC, USA)
Form: Liquid
Composition: Each 0.5 mL dose contains:
HBsAg = 10 µg
Route: IM
Batch Number: Various (marketed product was supplied by sites)

Other Product(s): Prevnar 7 (Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA)
Form: Liquid
Composition: Each 0.5 mL dose contains:
Serotypes 4, 9V, 14, 18C, 19F, 23F = 2 µg
Serotype 6B = 4 µg
Route: IM
Batch Number: Various (marketed product was supplied by sites)

6.4.5 Directions for Use
As described in approved package inserts and per protocol.

6.4.6 Sites and Centers
This was a multi-center study conducted at 8 sites in Canada.

6.4.7 Surveillance/Monitoring
Safety was assessed as a secondary endpoint. Monitoring included the following evaluations:
- Immediate reactions were assessed for 30 minutes following each vaccination
- Occurrence of solicited injection site reactions (tenderness, erythema, swelling) Day 0-7 following each vaccination

- Occurrence of solicited systemic reactions (fever, vomiting, crying, drowsiness, appetite loss, irritability) Days0-7 following each vaccination
- Unsolicited adverse events Day 0- 30 following each vaccination
- SAEs throughout the trial, up to 30 days after the last vaccination

Table 72. STN 125563/V419-004 (PR504): Solicited Injection Site Reactions: Definitions, Terminology and Intensity Scales

	Injection site tenderness	Injection site erythema	Injection site swelling
Term Used in the Diary Card	Tenderness	Redness	Swelling
Definition	See intensity scale	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity. Depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch, and can be best described by looking at the size of the swelling.
Intensity scale[1]	**Mild**: shows minor reaction when injection site is touched **Moderate**: cries and protests when injection site is touched **Severe**: cries when injected limb is moved or the movement of the injected limb is reduced	**Mild**: <2.5 cm **Moderate**: ≥ 2.5 to <5 cm **Severe**: ≥ 5 cm	**Mild**: <2.5 cm **Moderate**: ≥ 2.5 to <5 cm **Severe**: ≥ 5 cm

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 004, Section 3.5.2.3.3.2 , Table 3.9, page 72/644.
1- Parents were asked to record just the maximum daily measurement

Table 73. STN 125563/V419-004 (PR504): Solicited Systemic Reactions: Definitions, Terminology and Intensity Scales

	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Term Used in the Diary Card	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥ 38°C (rectal)	Vomiting does not include spitting up	Inconsolable crying without a reason	Reduced interest in surroundings or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the infant and despite parental responses that would normally be soothing
Intensity scale[1]	**Mild**: ≥ 38.0°C – ≤38.5°C **Moderate**: >38.5°C – ≤39.5°C **Severe**: >39.5°C	**Mild**: 1 episode per 24 hours **Moderate**: 2 – 5 episodes per 24 hours **Severe**: ≥ 6 episodes per 24 hours or requiring parenteral hydration	**Mild**: < 1 hour **Moderate**: 1 – 3 hours **Severe**: >3 hours	**Mild**: Sleepier than usual or less interested in surroundings **Moderate**: not interested in surroundings or did not wake up for a feed/meal Severe: Sleeping most of the time or difficult to wake up	**Mild**: Eating less than normal **Moderate**: Missed 1 or 2 feeds/meals completely, **Severe**: Refuses ≥3 feeds/meals or refuses most feeds/meals	**Mild**: Easily consolable **Moderate**: **Moderate:** Requiring increased attention **Severe**: Inconsolable

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 004, Section 3.5.2.3.3.2 , Table 3.10, page 73/644.
1- Parents were asked to record just the maximum daily measurement

6.4.8 Endpoints and Criteria for Study Success

For purposes of this application only safety will be assessed descriptively as described in section 6.4.7 of this review.

6.4.9 Statistical Considerations & Statistical Analysis Plan

Safety will be assessed descriptively as a secondary endpoint of the study.

6.4.10 Study Population and Disposition

Table 74. STN 125563/V419-004 (PR504): Summary of Subject Disposition

	Group A n (%)	Group B n (%)	Group C n (%)	Total n (%)
Randomized Subjects	157	150	153	460
Received All 3 Doses of the Infant Series as Randomized [1,2]	153 (97.5)	149 (99.3)	150 (98.0)	452 (98.3)
Completed the Infant Series [1,3]	152 (96.8)	147 (98.0)	151 (98.7)	450 (97.8)
Did Not Complete the Infant Series [1]	5 (3.2)	3 (2.0)	2 (1.3)	10 (2.2)
Terminated Between the Infant Series and 4th Dose [1]	3 (1.9)	2 (1.3)	7 (4.5)	12 (2.6)
Received the 4th Dose [1,2]	149 (94.9)	145 (96.7)	144 (94.1)	438 (95.2)
Completed the 4th Dose [1]	148 (94.3)	144 (96.0)	142 (92.8)	434 (94.3)
Did Not Complete the 4th Dose [1]	1 (0.6)	1 (0.7)	2 (1.3)	4 (0.9)
ITTS Population for Infant Series [1,4]	156 (99.4)	150 (100.0)	153 (100.0)	459 (99.8)
ITTS Population for 4th Dose [1,4]	156 (99.4)	150 (100.0)	153 (100.0)	459 (99.8)
Subject Disposition for Immunogenicity:				
ITTI Population for Infant Series [1,5]	146 (93.0)	141 (94.0)	147 (96.1)	434 (94.3)
Per-Protocol (PP) Analysis Set for Infant Series [1,6]	116 (73.9)	95 (63.3)	116 (75.8)	327 (71.1)
ITTI Population for 4th Dose [1,5]	148 (94.3)	140 (93.3)	139 (90.8)	427 (92.8)
Per-Protocol (PP) Analysis Set for 4th Dose [1,6]	118 (75.2)	102 (68.0)	111 (72.5)	331 (72.0)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 004, Synopsis, Table S1, page 21/644.
n (%): Number and percentage of subjects.
[1] Percentages are based on the number of randomized subjects who received at least one dose of PR5I or Pentacel.
[2] Subjects are classified by the actual vaccine received.
[3] One subject received a dose of Pentacel outside the study but was not withdrawn and completed the study.
[4] ITTS Population = subjects who received at least one dose of PR5I or Pentacel according to the vaccination schedule and who contributed at least one post-vaccination safety measurement.
[5] ITTI Population = subjects who received at least one dose of PR5I or Pentacel, had at least one blood sample drawn, and had a valid serology test result for at least one antigen.
[6] PP Population = ITTI subjects who did not have a protocol violation affecting immunogenicity results.
Group A: Received PR5I and Prevnar at 2, 4, 6, and 15 months.
Group B: Received PR5I at 2, 4, 6, and 15 months; Prevnar at 3, 5, 7, and 16 months.
Group C: Received Pentacel, ENGERIX-B and Prevnar at 2, 4, and 6 months; Pentacel and Prevnar at 15 months.

6.4.10.1 Populations Enrolled/Analyzed

Intent-to-Treat Safety (ITTS) Population = subjects who received at least one dose of PR5I or Pentacel according to the vaccination schedule and who contributed at least one post-vaccination safety measurement.

Intent-to-treat Immunogenicity (ITTI) Population = subjects who received at least one dose of PR5I or Pentacel, had at least one blood sample drawn, and had a valid serology test result for at least one antigen.

Per-protocol (PP Population) = ITTI subjects who did not have a protocol violation affecting immunogenicity results.

6.4.10.1.1 Demographics

Overall, the total number of male (50.5%) and female (49.5%) subjects was similar between groups. Group A and Group C had a higher number of males than females, compared to Group B. The mean age at Dose 1 was similar between the three groups. The mean ages, in days, of

subjects in Group A, Group B, and Group C were 62.6, 63.1, and 63.3, respectively. The majority of subjects were Caucasian (78.2% in Group A, 81.3% in Group B, and 80.4% in Group C).

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Not applicable.

6.4.10.1.3 Subject Disposition

The disposition of the 460 randomized subjects is presented below in Table 75. A total of 452 (98.3%) subjects received all 3 doses of the Infant Series as randomized (153/157 [97.5%] subjects in Group A, 149/150 [99.3%] subjects in Group B and 150/153 [98.0%] subjects in Group C]. Greater than 94% (n=438) subjects received the 4th Dose of vaccine (149/157 [94.9%] subjects in Group A, 145/150 [96.7%] subjects in Group B and 144/153 [94.1%] subjects in Group C) and 434 infants completed the study (148/167 [94.3%] subjects in Group A, 144/150 [96.0%] subjects in Group B and 142/153 [92.8%] subjects in Group C). The most common reason for not completing the study during the Infant Series was voluntary withdrawal not due to an AE. The most common reason for not completing the 4th Dose was lost to follow up. There was 1/157 (0.6%) subject in Group A and 1/153 (0.7%) subject in Group C who withdrew from the Infant Series due to an SAE [hypotonia and fibrosarcoma].

Table 75. STN 125563/V419-004 (PR504): Summary of Subject Disposition

	Group A n (%)	Group B n (%)	Group C n (%)	Total n (%)
Randomized Subjects	157	150	153	460
Received All 3 Doses of the Infant Series as Randomized [1,2]	153 (97.5)	149 (99.3)	150 (98.0)	452 (98.3)
Completed the Infant Series [1, 3]	152 (96.8)	147 (98.0)	151 (98.7)	450 (97.8)
Did Not Complete the Infant Series [1]	5 (3.2)	3 (2.0)	2 (1.3)	10 (2.2)
Reason for Withdrawal:				
Serious Adverse Event [1,4]	1 (0.6)	0 (0.0)	1 (0.7)	2 (0.4)
Other Adverse Event [1,4]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Compliance with the Protocol [1,4]	2 (1.3)	1 (0.7)	0 (0.0)	3 (0.7)
Lost to Follow-Up [1,4]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Voluntary Withdrawal Not Due to Adverse Event [1,4]	2 (1.3)	2 (1.3)	1 (0.7)	5 (1.1)
Terminated Between the Infant Series and 4th Dose [1]	3 (1.9)	2 (1.3)	7 (4.5)	12 (2.6)
Reason for Withdrawal:				
Serious Adverse Event [1,4]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other Adverse Event [1,4]	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.4)
Non-Compliance with the Protocol [1,4]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-Up [1,4]	1 (0.6)	0 (0.0)	3 (2.0)	4 (0.9)
Voluntary Withdrawal Not Due to Adverse Event [1,4]	2 (1.3)	0 (0.0)	4 (2.6)	6 (1.3)
Received the 4th Dose [1,2]	149 (94.9)	145 (96.7)	144 (94.1)	438 (95.2)
Completed the 4th Dose [1]	148 (94.3)	144 (96.0)	142 (92.8)	434 (94.3)
Did Not Complete the 4th Dose [1]	1 (0.6)	1 (0.7)	2 (1.3)	4 (0.9)

	Group A n (%)	Group B n (%)	Group C n (%)	Total n (%)
Reason for Withdrawal:				
Serious Adverse Event [1,4]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other Adverse Event [1,4]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Compliance with the Protocol [1,4]	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
Lost to Follow-Up [1,4]	0 (0.0)	1 (0.7)	1 (0.7)	2 (0.4)
Voluntary Withdrawal Not Due to Adverse Event [1,4]	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 004, Section 4.1, Table 4.1, page 91/644.
n (%): Number and percentage of subjects.
[1] Percentages are based on the number of randomized subjects who received at least one dose of PR5I or Pentacel.
[2] Subjects are classified by the actual vaccine received.
[3] One subject received a dose of Pentacel outside the study but was not withdrawn and completed the study.
[4] One primary reason for termination per subject is collected.
Group A: Received PR5I and Prevnar at 2, 4, 6, and 15 months.
Group B: Received PR5I at 2, 4, 6, and 15 months; Prevnar at 3, 5, 7, and 16 months.
Group C: Received Pentacel, ENGERIX-B and Prevnar at 2, 4, and 6 months; Pentacel and Prevnar at 15 months.

6.4.11 Safety Analyses

Safety was assessed by observation for immediate reactions within thirty minutes of each vaccination. All solicited injections site and systemic reactions were recorded for Day 0-7 following each vaccination. Unsolicited AEs were collected from Day 0 through Day 30 after any vaccination. SAEs were collected for the duration of the study.

Two immediate reactions in the PR5I concomitant with Prevnar (Group A): neither of the reactions were serious in nature (diaper dermatitis and diarrhea), both resolved without sequelae.

Table 76. STN 125563/V419-004 (PR504): Safety Overview After Any Vaccination – ITTS Population

	Group A (N=156)		Group B (N=150)		Group C (N=153)	
	Infant Series	**4th Dose**	**Infant Series**	**4th Dose**	**Infant Series**	**4th Dose**
Subjects with at least one:	**n/M (%) (95% CI)**	**n/M (%) (95% CI)**	**n/M (%) (95% CI)**	**n/M (%) (95% CI)**	**n/M (%) (95% CI)**	**n/M (%) (95% CI)**
Immediate Reaction	2/156 (1.3) (0.2; 4.6)	0/156 (0.0) (0.0; 2.3)	0/150 (0.0) (0.0; 2.4)	0/150 (0.0) (0.0; 2.4)	0/153 (0.0) (0.0; 2.4)	0/153 (0.0) (0.0; 2.4)
Solicited Reaction	151/156 (96.8) (92.7; 99.0)	126/149 (84.6) (77.7; 90.0)	147/150 (98.0) (94.3; 99.6)	116/145 (80.0) (72.6; 86.2)	148/153 (96.7) (92.5; 98.9)	105/142 (73.9) (65.9; 80.9)
Solicited Injection Site	112/156 (71.8)	89/148 (60.1)	108/150 (72.0)	75/145 (51.7)	103/153 (67.3)	72/142 (50.7)
Solicited Injection Site Reaction	112/156 (71.8) (64.0; 78.7)	89/148 (60.1) (51.8; 68.1)	108/150 (72.0) (64.1; 79.0)	75/145 (51.7) (43.3; 60.1)	103/153 (67.3) (59.3; 74.7)	72/142 (50.7) (42.2; 59.2)
Solicited Systemic Reaction	150/156 (96.2) (91.8; 98.6)	112/149 (75.2) (67.4; 81.9)	143/150 (95.3) (90.6; 98.1)	103/145 (71.0) (62.9; 78.3)	146/153 (95.4) (90.8; 98.1)	85/142 (59.9) (51.3; 68.0)
Unsolicited Adverse Event (AE)	117/156 (75.0) (67.4; 81.6)	58/156 (37.2) (29.6; 45.3)	108/150 (72.0) (64.1; 79.0)	62/150 (41.3) (33.4; 49.7)	112/153 (73.2) (65.5; 80.0)	54/153 (35.3) (27.7; 43.4)
Unsolicited Adverse Reaction	32/156 (20.5) (14.5; 27.7)	5/156 (3.2) (1.0; 7.3)	29/150 (19.3) (13.3; 26.6)	6/150 (4.0) (1.5; 8.5)	27/153 (17.6) (12.0; 24.6)	9/153 (5.9) (2.7; 10.9)
Unsolicited Injection Site Reaction	5/156 (3.2) (1.0; 7.3)	0/156 (0.0) (0.0; 2.3)	5/150 (3.3) (1.1; 7.6)	2/150 (1.3) (0.2; 4.7)	10/153 (6.5) (3.2; 11.7)	2/153 (1.3) (0.2; 4.6)
Unsolicited Systemic	27/156 (17.3)	5/156 (3.2)	24/150 (16.0)	4/150 (2.7)	17/153 (11.1)	7/153 (4.6)

	Group A (N=156)		Group B (N=150)		Group C (N=153)	
	Infant Series	**4th Dose**	**Infant Series**	**4th Dose**	**Infant Series**	**4th Dose**
Reaction	(11.7; 24.2)	(1.0; 7.3)	(10.5; 22.9)	(0.7; 6.7)	(6.6; 17.2)	(1.9; 9.2)
Serious Adverse Event (SAE)	8/156 (5.1)	1/156 (0.6)	10/150 (6.7)	0/150 (0.0)	6/153 (3.9)	1/153 (0.7)
	(2.2; 9.9)	(0.0; 3.5)	(3.2; 11.9)	(0.0; 2.4)	(1.5; 8.3)	(0.0; 3.6)
Discontinued due to SAE or AE	1/156 (0.6)	0/156 (0.0)	2/150 (1.3)	0/150 (0.0)	1/153 (0.7)	0/153 (0.0)
	(0.0; 3.5)	(0.0; 2.3)	(0.2; 4.7)	(0.0; 2.4)	(0.0; 3.6)	(0.0; 2.4)
Death	0/156 (0.0) (0.0; 2.3)	0/156 (0.0) (0.0; 2.3)	0/150 (0.0) (0.0; 2.4)	0/150 (0.0) (0.0; 2.4)	0/153 (0.0) (0.0; 2.4)	0/153 (0.0) (0.0; 2.4)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 004, Section 6.1 , Table 6.1, page 112/644.
Group A: Received PR5I and Prevnar at 2, 4, 6, and 15 months.
Group B: Received PR5I at 2, 4, 6, and 15 months; Prevnar at 3, 5, 7, and 16 months.
Group C: Received Pentacel, ENGERIX-B and Prevnar at 2, 4, and 6 months; Pentacel and Prevnar at 15 months.
Notes: Reactions are events identified by the investigator in the CRF as related to the vaccines PR5I or Pentacel.
N= Number of subjects in the ITTS analysis set; n= any reaction/ event after 2, 4, 6, and 15 months of vaccination.
For solicited reactions, (M) is the number of vaccinated subjects with at least one available safety record for this solicited reaction.
For unsolicited events and immediate events, (M) is the number of vaccinated subjects where safety data is available (ITTS Analysis Set).

Solicited injection site reactions (Tenderness, Erythema, and Swelling) were reported at similar rates in all groups and were mostly Mild to Moderate at all vaccination time-points. The majority of the reactions resolved within 3 days of vaccination. The most frequently reported injection site reaction in Group A [PR5I + Prevnar] was Tenderness, followed by Erythema and Swelling. Severe Tenderness after any dose was reported by (< 5.1%) and similar across groups. Rates of erythema was similar across all 3 groups following any dose of vaccine. Severe Erythema was reported by (<6.0%) across all groups after any dose.

For solicited systemic reaction of fever, in majority of cases temperature was measured rectally. Rectal temperature was the preferred and recommended route for temperature measurement. If an alternative route (e.g., oral or axillary) was used, no mathematical adjustments were performed to convert temperatures. Fever was reported by 57.7%, 40.0%, and 41.2% of subjects in Groups A, B, and C, respectively during the Infant Series. The intensity of the Fever was Mild, with a very low number of participants (< 5%) reporting Severe Fever (>38.5°C). Post-Dose 4 Fever rates were 38.5%, 35.9% and 28.2% in Groups A, B and C, respectively, with Severe Fever after any dose being reported by 4.5%, 6.0% and 2% subjects in Groups A, B and C, respectively.

There appears to have been a trend toward more severe adverse events following the toddler dose for those in the PR5I groups as compared to subjects who received Pentacel. See Table 77 below.

Table 77. STN 125563/V419-004 (PR504): Summary of Severe Solicited Reactions Within 7 Days After Each Vaccination (ITTS Analysis Set)

	Group A (N=156)	Group A (N=156)	Group A (N=156)	Group B (N= 150)	Group B (N= 150)	Group B (N= 150)	Group C (N= 153)	Group C (N=153)	Group C (N= 153)
Subjects with at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Severe solicited injection site reaction									
Post-Dose 1	1/156	0.6	(0.0; 3.5)	2/150	1.3	(0.2; 4.7)	6/153	3.9	(1.5; 8.3)
Post-Dose 2	3/155	1.9	(0.4; 5.6)	4/149	2.7	(0.7; 6.7)	3/151	2.0	(0.4; 5.7)
Post-Dose 3	1/153	0.7	(0.0; 3.6)	2/150	1.3	(0.2; 4.8)	2/151	1.3	(0.2; 4.7)
Post-Dose 4	8/148	5.4	(2.4; 10.4)	11/145	7.6	(3.8; 13.2)	4/142	2.8	(0.8; 7.1)
Severe solicited systemic reaction									
Post-Dose1	5/156	3.2	(1.0; 7.3)	5/150	3.3	(1.1; 7.6)	8/153	5.2	(2.3; 10.0)
Post-Dose2	7/154	4.5	(1.8; 9.1)	4/149	2.7	(0.7; 6.7)	6/151	4.0	(1.5; 8.4)
Post-Dose3	5/153	3.3	(1.1; 7.5)	6/149	4.0	(1.5; 8.6)	4/151	2.6	(0.7; 6.6)
Post-Dose 4	14/149	9.4	(5.2; 15.3)	11/145	7.6	(3.8; 13.2)	6/142	4.2	(1.6; 9.0)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 004, Section 6.2.1 , Table 6.2, page 113/644.
Group A: Received PR5I and Prevnar at 2, 4, 6, and 15 months.
Group B: Received PR5I at 2, 4, 6, and 15 months; Prevnar at 3, 5, 7, and 16 months.
Group C: Received Pentacel, ENGERIX-B and Prevnar at 2, 4, and 6 months; Pentacel and Prevnar at 15 months.

A total of 30 SAEs were reported during the study. During the Infant Series, 5.1% (8/156) subjects in Group A, 6.7% (10/150) subjects in Groups B, and 3.9 % (6/153) subjects in Group C experienced at least 1 SAE. During the 4th Dose, 0.6% (1/156) subjects in Group A and 0.7% (1/153) subjects in Group C experienced at least one SAE. Most SAEs were due to infections common in this age group, with bronchiolitis being the most commonly reported. Three SAEs of interest occurred in 1 subject each: hypotonia (Group A, second infant dose), febrile convulsion (Group C, fourth dose) and bronchospasm (Group A, fourth dose).

Narrative summaries for these SAEs are presented below:
- Subject (b) (6) who received PR5I (15.5 months of age) presented with bronchospasms, 15 days post-vaccination with Dose 4. The event lasted 15 days. The subject recovered fully and continued in the trial.
- Subject (b) (6) who received PR5I (4.6 months of age) presented with hypotonia, 0 days post-vaccination with Dose 2. The event lasted 2 days. The investigator deemed that the event was related to vaccine administration. The subject recovered fully but did not continue in the trial.
- Subject (b) (6) who received Pentacel (15.5 months of age) presented with febrile convulsion, 4 days post-vaccination with Dose 4. The event lasted 1 day. The investigator deemed that the event was not related to vaccine administration. The subject recovered fully and continued in the trial.

One subject in Group A who received PR5I (case of hypotonia noted above) and one subject in Group C, Pentacel group, was diagnosed with fibrosarcoma. Both subjects discontinued the study due to nature of the reported SAE.

Table 78. STN 125563/V419-004: All SAEs Occurring During the Study by System Organ Class and Preferred Term - Safety Analysis Set for All Doses

	Group A (N=156)			Group B (N=150)			Group C (N=153)		
	n/N	%	95% CI	n/N	%	95% CI	n/N	%	95% CI
After Any Infant Series Vaccination									
Subjects With At least One SAE	8/156	5.1	2.2; 9.9	10/150	6.7	3.2; 11.9	6/153	3.9	1.5; 8.3
Blood and lymphatic system disorders	0/156	0.0	0.0; 2.3	0/150	0.0	0.0; 2.4	1/153	0.7	0.0; 3.6
Lymphadenitis	0/156	0.0	0.0; 2.3	0/150	0.0	0.0; 2.4	1/153	0.7	0.0; 3.6
Infections and infestations	7/156	4.5	1.8; 9.0	10/150	6.7	3.2; 11.9	3/153	2.0	0.4; 5.6
Bacterial pyelonephritis	0/156	0.0	0.0; 2.3	1/150	0.7	0.0; 3.7	0/153	0.0	0.0; 2.4
Bronchiolitis	3/156	1.9	0.4; 5.5	4/150	2.7	0.7; 6.7	2/153	1.3	0.2; 4.6
Croup infections	0/156	0.0	0.0; 2.3	1/150	0.7	0.0; 3.7	0/153	0.0	0.0; 2.4
Ear infection	1/156	0.6	0.0; 3.5	0/150	0.0	0.0; 2.4	0/153	0.0	0.0; 2.4
Gastroenteritis	0/156	0.0	0.0; 2.3	0/150	0.0	0.0; 2.4	1/153	0.7	0.0; 3.6
Influenza	1/156	0.6	0.0; 3.5	0/150	0.0	0.0; 2.4	0/153	0.0	0.0; 2.4
Laryngitis	0/156	0.0	0.0; 2.3	0/150	0.0	0.0; 2.4	1/153	0.7	0.0; 3.6
Pneumococcal bacteremia	1/156	0.6	0.0; 3.5	0/150	0.0	0.0; 2.4	0/153	0.0	0.0; 2.4
Pneumonia	0/156	0.0	0.0; 2.3	1/150	0.7	0.0; 3.7	0/153	0.0	0.0; 2.4
Respiratory syncytial virus infection	0/156	0.0	0.0; 2.3	2/150	1.3	0.2; 4.7	0/153	0.0	0.0; 2.4
Urinary tract infection	1/156	0.6	0.0; 3.5	1/150	0.7	0.0; 3.7	0/153	0.0	0.0; 2.4
Viremia	1/156	0.6	0.0; 3.5	0/150	0.0	0.0; 2.4	0/153	0.0	0.0; 2.4
Musculoskeletal and connective tissue disorders	0/156	0.0	0.0; 2.3	0/150	0.0	0.0; 2.4	1/153	0.7	0.0; 3.6
Synovitis	0/156	0.0	0.0; 2.3	0/150	0.0	0.0; 2.4	1/153	0.7	0.0; 3.6
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0/156	0.0	0.0; 2.3	0/150	0.0	0.0; 2.4	1/153	0.7	0.0; 3.6
Fibrosarcoma	0/156	0.0	0.0; 2.3	0/150	0.0	0.0; 2.4	1/153	0.7	0.0; 3.6
Nervous system Disorders	1/156	0.6	0.0; 3.5	0/150	0.0	0.0; 2.4	0/153	0.0	0.0; 2.4
Hypotonia	1/156	0.6	0.0; 3.5	0/150	0.0	0.0; 2.4	0/153	0.0	0.0; 2.4
After the 4th Dose Vaccination									
Subjects With At least One SAE	1/156	0.6	(0.0; 3.5)	0/150	0.0	(0.0; 2.4)	1/153	0.7	(0.0; 3.6)
Infections and infestations	1/156	0.6	(0.0; 3.5)	0/150	0.0	(0.0; 2.4)	0/153	0.0	(0.0; 2.4)
Gastroenteritis	1/156	0.6	(0.0; 3.5)	0/150	0.0	(0.0; 2.4)	0/153	0.0	(0.0; 2.4)
Nervous system Disorders	0/156	0.0	(0.0; 2.3)	0/150	0.0	(0.0; 2.4)	1/153	0.7	(0.0; 3.6)
Febrile convulsion	0/156	0.0	(0.0; 2.3)	0/150	0.0	(0.0; 2.4)	1/153	0.7	(0.0; 3.6)
Respiratory, thoracic and mediastinal disorders	1/156	0.6	(0.0; 3.5)	0/150	0.0	(0.0; 2.4)	0/153	0.0	(0.0; 2.4)
Bronchospasm	1/156	0.6	(0.0; 3.5)	0/150	0.0	(0.0; 2.4)	0/153	0.0	(0.0; 2.4)

Source: STN 125563/0: m 5.3.5.1: V419 Protocol 004, Section 6.3.2 , Table 6.6, page 123/644.
Group A: Received PR5I and Prevnar at 2, 4, 6, and 15 months.
Group B: Received PR5I at 2, 4, 6, and 15 months; Prevnar at 3, 5, 7, and 16 months.
Group C: Received Pentacel, ENGERIX-B and Prevnar at 2, 4, and 6 months; Pentacel and Prevnar at 15 months.

No deaths occurred during the conduct of the study.

6.4.12 Study Summary and Conclusions

This was a randomized open-labeled, multi-center trial conducted at 8 centers in Canada. A total of 460 subjects were randomized to 3 groups, of whom 450 (97.8%) completed the Infant Series and 438 (95.2%) completed the 4th Dose of PR5I or Pentacel. The rate of compliance with the protocol was similar across all the 3 groups, with a total of 327 (71.1%) subjects in the Infant

Series and 331 (72%) subjects in the 4th Dose being included in the PP analysis set. There were similar safety profiles observed in the PR5I cohorts (Groups A and B) when PR5I was administered concomitantly with Prevnar or one-month previous. There was a trend toward increasing severe solicited local and systemic events in the PR5I groups following the Toddler dose. No unexpected solicited, unsolicited or serious adverse events were noted for the populations in any study cohort. There was one febrile seizure reported with 7 days following the Toddler vaccination in the group C (Control vaccines).

6.5 Additional Phase 3 Studies

Two additional Phase 3 studies. Protocols V419-007 and V419-008 were conducted in the EU, for which full analysis was not completed at the time of licensure application. However, un-blinded safety data (SAEs) were available. Although these studies are not considered as supportive of the licensing application, due to the differing schedule and concomitant vaccinations, a brief description of the study design and a listing of serious adverse events are provided here for completeness.

Protocol 007 was designed to evaluate the safety, tolerability and immunogenicity of PR5I when administered at 2, 3, 4, and 12 months of age concomitantly with licensed pediatric vaccines (Prevnar 13, RotaTeq, and ProQuad). The comparator vaccine Infanrix-hexa (GSK) is not licensed in the US. This was a double-blind, randomized, active-comparator controlled Phase III study conducted in 1250 healthy infants (46 to 74days of age at enrollment) at 40 study centers across Finland, Germany, and Belgium. Serious adverse events were collected from day of vaccination through Day 14 post-vaccination (Day 1-15) Deaths and vaccine-related serious adverse events that occurred at any time during the study. Any serious adverse event occurring through 28 days following the first and second doses of ProQuad at Visits 5 and 6 were to be reported.

Seventeen subjects in the PR5I group reported serious adverse events during Day 1-15 compared to 13 subjects in the INFANRIX hexa group during the same time period. Two subjects in the PR5I group suffered convulsions/febrile convulsions.
- Subject (b) (6) (F) experienced a severe convulsion 15 days following the first dose of vaccine at 2 months of age.
- Subject (b) (6) (M) reported a febrile convulsion six days post-dose 3 (at ~ 4 months of age)

One subject in the INFANRIX hexa group developed benign familial neonatal convulsions 13 days following the second dose of INFANRIX hexa and was discontinued from the clinical study. This condition is not thought to be related to vaccination but is most likely a heritable chronic condition.
No subjects reported pyrexia as a serious adverse event.

Protocol 008 was designed to assess the safety, tolerability, and immunogenicity of PR5I when administered at 2, 4, and 11 to 12 months of age concomitantly with licensed pediatric vaccines (Prevnar 13 and RotaTeq/ Rotarix). This was a double-blind, randomized, active-comparator (INFANRIX hexa) controlled Phase III study conducted in 1315 healthy infants (46 to 89 days of age at enrollment) at 23 study centers located in Finland, Italy, and Sweden. Any serious adverse event, which occurred from the time of consent was signed through 14 days following each hexavalent vaccination was to be reported. Serious adverse events were reported Day 1 to Day 15 post-vaccination by 5 subjects in the PR5I group and 7 subjects in the INFANRIX hexa group. No seizures /convulsions were reported in either study group. One subject in the PR5I group

reported severe pyrexia 40 days after the second dose of PR5I given concomitantly with RotaTeq. One subject in the INFANRIX hexa group reported a "mild" convulsion 3 days following Dose 2.

7. INTEGRATED OVERVIEW OF IMMUNOGENICITY OF PR5I (VAXELIS)

7.1 Indication

The proposed indication for PR5I (VAXELIS) is: "vaccine for active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* type b (Hib)." To be administered as a three-dose series in children from 6 weeks through 4 years of age (up to the 5th birthday).

7.1.1 Methods of Integration

Two randomized, active-comparator controlled clinical trials conducted in the US to evaluate immunogenicity and effectiveness of PR5I (VAXELIS), studies V419-005 and V419-006, enrolled approximately 4200 subjects who had received a mono-valent birth dose of Hepatitis B vaccine outside of the context of the study. (These studies are reviewed in detail in sections 6.1 and 6.2 of this review.) The two studies were similar in design and study populations, administering an infant series of PR5I or Control vaccines (i.e., Pentacel and RECOMBIVAX HB), at 2, 4, and 6 months of age. This infant series was followed by the administration of a Toddler dose of a DTaP vaccine (DAPTACEL or Pentacel) at 15 months of age. Serum samples were obtained from study participants at 4-time points in the Phase III studies: prior to the first vaccination, 4 to 6 weeks after the third dose (i.e., after completion of the infant series), prior to the toddler vaccination, and 4 to 6 weeks after the toddler dose. Approximately 3300 subjects received PR5I as part of Studies V419-005 and V419-006. (see section 7.1.11 below)

7.1.2 Demographics and Baseline Characteristics

Please see sections 6.1.10 and 6.2.10 of this review of demographic and baseline characteristics of subjects enrolled in V419-005 and V419-006. The study populations were similar in age, gender and weight. The majority of subjects were white/Caucasian.

7.1.3 Subject Disposition

In the pivotal studies, 4606 subjects were screened, 4281 subjects were randomized [3392 subjects to the PR5I group(s) and 889 subjects to the Control group]. Of the enrolled and randomized subjects, 3380 subjects were vaccinated with at least one dose of PR5I and 885 were vaccinated with at least one dose of the Control vaccine. A total of 3986 subjects (93.1%) completed the infant series (defined as 3 doses of PR5I or Control administered at 2, 4, and 6 months of age) and ~84% of subjects completed their Toddler dose study vaccinations.
There were 279 subjects (6.5%) who did not complete the infant series of PR5I or Control vaccine. Of those subjects, 224 subjects (6.6%) were in the PR5I group and 55 subjects (6.2%) were in the Control group. The most frequent reasons for study withdrawal before completion of the infant series were Withdrawal by Subject (subject's parent/guardian), Lost to Follow-up, and Protocol Violation. Few subjects in either group discontinued the study due to an adverse event. Of the 7 subjects discontinued due to an adverse event, 6 subjects (0.2%) were in the PR5I group and 1 subject (0.1%) was in the Control group.
For 392 subjects (9.2%) who discontinued between the infant series and Toddler dose, 311 subjects (9.2%) were in the PR5I group and 81 subjects (9.1%) in the Control group. The most frequent reasons for discontinuations occurring between the infant series and the Toddler dose were: Lost to Follow-up, Withdrawal by Subject (subject's parent/guardian) and Protocol Violation. Overall, 2 subjects in the PR5I group and none in the Control group discontinued due to an adverse event.

The analyses of immunogenicity were based upon two subject populations, PP-RW and PP-OW, consistent with the populations, similarly defined for each study. Similar results were demonstrated in each population for each study. The number (%) of subjects excluded from the PP- RW and the PP-OW population at one-month Post-dose 3 for the PR5I endpoints is similar between the studies. There were no notable differences observed with respect to individual antigens within the PR5I or Control groups. The most common reasons for exclusion were 'Received incomplete or incorrect study vaccine regimen', 'Sample not collected' and 'Result not available/insufficient serum for both the PR5I and Control groups'.

7.1.4 Analysis of Primary Endpoint(s)

The immunologic endpoints evaluated in Studies V419-005 and V419-006 are in alignment with guidance from CBER during the clinical development of PR5I and comparable to the endpoints used in the licensure of the component vaccines which are contained in PR5I post-dose 3. Response criteria for the vaccine antigens are presented in Table 79 below:

Table 79. STN 125563: Response Criteria for Antigens Contained in PR5I (Study V419-005 and Study V419-006)

Antigen	Assay	Definition of Post-vaccination response
PRP	(b) (4)	≥0.15 μg/mL ≥1.0 μg/mL
HBsAg	(b) (4)	≥10 mIU/mL
Diphtheria	(b) (4)	≥ 0.1mIU/mL
Tetanus	(b) (4)	≥0.1mIU/mL
PT, FHA, PRN, FIM	(b) (4)	Vaccine response *
IPV1, IPV2, IPV3	(b) (4)	Nab ≥ 1:8 dilution

Source: STN 125563/0: m 5.3.5.3: ISE, Section 2.1, Table 5.3.5.3.2-1(modified), page 16/171.
*The pertussis vaccine response was defined as follows: (1) if pre-vaccination antibody concentration was < 4X LLOQ, then the post-vaccination antibody concentration was ≥ 4 X LLOQ, (2) if pre-vaccination antibody concentration was ≥ 4 X LLOQ, then the post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titer at pre-Dose 1.
(b) (4), FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, (b) (4), NAb = Neutralizing antibodies, NI = Non-inferiority, PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid., (b) (4)

7.1.5 Analysis of Secondary Endpoint(s)

In Study V419-005 the pre-specified secondary endpoints (with criteria) evaluated the immune response to PRP (Hib component) and to the concomitant vaccination with RotaTeq (see section 6.1.8 of this review). Non-inferiority of antibody responses was observed for in the PR5I group compared to the Control group (97.26% vs. 92.39%), with the difference (PR5I group minus Control group) regarding the proportion of subjects with anti-PRP ≥ 0.15 μg/mL at one-month post-dose 3 was 4.87% (95% CI: 2.23% to 8.14%). One-month post-dose 3 of RotaTeq, the anti-rotavirus IgA response in the PR5I group was non-inferior to the Control group as the lower bound of the 2-sided 95% CI for the GMT ratio was above the prespecified non-inferiority margin.

In the lot consistency study V419-006, the pre-specified secondary endpoints (with criteria) assessed the immune responses to the antigens contained in PR5I post-dose 3 for the three manufacturing lots of PR5I. The non-inferiority of immune responses to Prevnar 13 when administered concomitantly at 2,4, and 6 months were evaluated for each serotype one-month after the third dose for subjects in PR5I and the Control vaccine groups. Non-inferiority of

immune response (response rate and GMTs) to the Toddler dose of Pentacel after three previous doses of PR5I was also evaluated. (see section 6.2.11.2 of this review)

The subjects in the PR5I group received PRP-OMPC for 3 infant doses as contained in PR5I, and a Toddler dose of PRP-T as contained in PENTACEL, whereas the Control group received PRP-T at each vaccination time point. As has been seen in other studies with monovalent Hib vaccines, higher titers following a fourth dose were observed for "mixed" regimens in which a different PRP-conjugate were used for the booster as compared to the primary series vaccination. Results for the anti-PRP comparisons in Study 006 demonstrated that the post-Toddler anti-PRP GMT was higher in the PR5I group (49.41; 95% CI: 46.78 to 52.19) as compared to Control (19.17; 95% CI: 16.11 to 22.82), with non-overlapping confidence intervals

Immunogenicity of Prevnar 13™ antigens when administered concomitantly with PR5I was non-inferior to Prevnar 13™ concomitantly administered with Control, for all of the Prevnar 13™ antigens, except for the PN 6B antigen.

7.1.6 Other Endpoints
Not applicable.

7.1.7 Subpopulations
Prior to enrollment in V419-005 and V419-006, each subject was to have received a mono-valent dose if a Hepatitis vaccine at birth or in the one-month after birth. No significant differences were observed between the vaccination groups with regard to type of hepatitis B vaccine received at birth. Overall, 1440 subjects (32.8% in the PR5I group and 36.8% in the Control group) received RECOMBIVAX HB, while 2702 subjects (63.9% in the PR5I group and 60.2% in the Control group) received other brands of hepatitis B vaccine at birth. The brand of hepatitis B vaccine given at birth was unknown in 139 subjects (3.3% in the PR5I group and 3.0% in the control group).

7.1.8 Persistence of Efficacy
Not applicable.

7.1.9 Product-Product Interactions
The immune responses demonstrated following concomitant vaccination with Prevnar 13 and RotaTeq when administered with PR5I were comparable to those seen when administered concomitantly with the licensed Control vaccines.
There were no notable differences in immune responses to PR5I compared to the licensed Control vaccines when analyzed by gender, race or ethnicity.

7.1.10 Additional Issues/Analyses
None.

7.1.11 Immunogenicity Conclusions
A summary of the study design and immunogenicity endpoints is provided below.

Table 80. STN 125563: Study Summary of Pivotal Studies for Immunogenicity Administering PR5I

Protocol	Study Design and Treatment Duration	Vaccination Groups and Numbers of Subjects Vaccinated	Subject Gender, Number of Subjects, Mean Age, and Age Range	Immunogenicity Results
Study V419-005 (Phase III) Non-inferiority study	Open-label, multicenter, randomized, active comparator-controlled study (US) to evaluate the safety and immunogenicity of PR5I All subjects received a dose of monovalent hepatitis B vaccine at birth (outside of the study). Subjects in the PR5I group received a 0.5 mL dose of PR5I at 2, 4, and 6 months followed by DAPTACEL and PedvaxHIB at 15 months. Subjects in the Control group received a 0.5 mL dose of Pentacel at 2, 4, and 6 months and a 0.5 mL dose of RECOMBIVAX HB at 2 and 6 months followed by DAPTACEL and ActHIB at 15 months. Subjects in both groups received the concomitant vaccines (RotaTeq and Prevnar 13). Blood samples, collected at 4 time points (i.e., pre-dose 1, ~4 to 6 weeks Post-dose 3, pre-toddler dose, and ~4 to 6 weeks post-toddler dose).	Randomized: 1473 PR5I: 986 Control: 487 Vaccinated: 1465 PR5I: 981 Control: 484	Male: 780 Female: 693 Mean age (days): 65.4 Age range (days): 46 to 89	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, the following results were shown: 1. PR5I induced immune responses against all antigens. The immune response to a 3-dose infant series of PR5I was non-inferior to that of vaccination with a licensed Control regimen for all pre-specified endpoints, except for the GMT of the FHA antigen one-month Post-dose 3. 2. After the fourth dose, the pertussis responses and GMTs in subjects who received a 3-dose infant series of PR5I was non-inferior to that of subjects who received an infant series of a licensed Control vaccine. 3. The IPV response rate was 100% following the 3-dose infant series of PR5I.

				4. The immune response to RotaTeq was non-inferior in subjects who received it concomitantly either with a 3-dose infant series of PR5I or with a licensed Control vaccine regimen.
Study V419-006 (Phase III) Lot Consistency study	Partially double-blind, multicenter, randomized, active comparator controlled, lot-to-lot consistency study (U.S.) to evaluate the safety, and immunogenicity of PR5I All subjects received a dose of monovalent hepatitis B vaccine at birth (outside the study). Subjects in each of the PR5I groups received a 0.5-mL dose of PR5I (3 different lots to assess lot consistency) at 2, 4, and 6 months and a 0.5-mL dose of Pentacel at 15 months. Subjects in the Control group received a 0.5-mL dose of Pentacel at 2, 4, 6, and 15 months and a 0.5-mL dose of RECOMBIVAX HB at 2 and 6 months. Subjects in both groups received concomitant vaccines (RotaTeq and Prevnar 13). Blood samples, were collected at 4 time points (i.e., pre-dose 1, ~4 to 6 weeks Post-dose 3, pre-toddler dose, and ~4 to 6 weeks post-toddler dose).	Randomized: 2808 PR5I: 2406 Control: 402 Vaccinated: 2800 PR5I: 2399 Control: 401	Male: 1470 Female: 1338 Mean age (days): 64.5 Age range (days): 46 to 89	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 results were shown: 1. Lot consistency was demonstrated with respect to GMTs and response rates for all antigens contained in PR5I. 2. PR5I induced a immune responses against all antigens contained in PR5I. The immune response to a 3-dose infant series of PR5I was comparable to vaccination with a licensed Control regimen for all pre-specified endpoints, except for the GMT of the FHA antigen. 3. After the Toddler dose, the pertussis responses and GMTs in subjects who received a 3-dose infant series of PR5I were comparable to subjects who received an infant series of a licensed Control vaccine, except for the GMT for PRN antigen

				(marginal miss of non-inferiority margin). 4. The concomitant use of Prevnar 13 with PR5I was non-inferior to its concomitant use with the Control vaccines regarding 12 out of the 13 antigens in Prevnar 13. One endpoint, GMT for PCV 6B, missed the non-inferiority criterion.

Source: STN 125563/0: m 5.3.5.3: ISE, Section 3.2, Table 5.3.5.3.2-2 (modified), page 25/171.

Overall, the immunogenicity data presented for the pivotal studies demonstrated that a 3-dose infant series of PR5I was comparable to licensed control vaccines for all pre-specified endpoints, except for the GMT of the pertussis FHA antigen at one-month Post-dose 3. Following a Toddler dose of a pertussis-containing vaccine, the pertussis responses in subjects who received a 3-dose infant series of PR5I was comparable to subjects who received an infant series of a licensed control vaccine regimen for all pertussis antigens, except post-toddler PRN result, which marginally missed the pre-specified non-inferiority criterion in Protocol V419-006 [GMT ratio: 0.74 (95% CI: 0.66, 0.83)].

The failure to meet non-inferiority of the immune response to the pertussis FHA antigen following the three-dose infant vaccinations series in both Phase 3 studies is not thought to affect the effectiveness of PR5I to provide protection against pertussis disease. Since non-inferiority was demonstrated for FHA responses after completion of the 4-dose series (primary series) with the Toddler dose of Pentacel/DAPTACEL, the missed FHA GMT endpoint post-dose 3 is considered of limited clinical significance.
Regarding PRN responses after the Toddler dose in study V419-006, integrated results from the combined studies V419-005 and V419-006 met non-inferiority criteria for PRN prespecified for the individual studies. Therefore, the narrow miss in Study V419-006 for the non-inferiority comparison of PRN responses is also considered of little clinical significance.

It was noted that the response to PRP was higher in subjects who received PR5I as compared to subjects who received the licensed control vaccines [estimated difference in response rates (PR5I group minus Control group) for subjects with an anti-PRP titer ≥ 1.0 μg/mL was 8.55 (95% CI: 5.07, 12.36)]. A similar trend was seen in subjects with an anti-PRP titer ≥0.15 μg/mL.

The IPV response rate was 100% to all IPV antigens following a 3-dose infant series of PR5I.

The immune responses to RotaTeq were non-inferior in subjects who received it concomitantly either with a 3-dose infant series of PR5I or with licensed control vaccines. The immune responses to Prevnar 13 were non-inferior in subjects who received it concomitantly with a 3-dose infant series of PR5I or with a 3-dose series of licensed control vaccines, except for the GMT of serotype 6B, which missed (marginally) the pre-specified non-inferiority criterion at one-month Post-dose 3.

The results for the primary immunogenicity endpoints for the integrated populations in studies V419-005 and V419-006, to support the non-inferiority of PR5I compared to the Control vaccines are presented below:

Table 81. STN 125563: Analysis of PR5I Antigen Responses at One Month Post-dose 3 (PP-RW) Integrated Population (Protocols V419-005 andV419-006)

		PR5I (N=3156)	PR5I (N=3156)	Control (N=830)	Control (N=830)	Estimated Diff./ GMT
Antigen	Endpoint	n	Estimated Response	n	Estimated Response	(95% CI)
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)

Source: STN 125563/0: m 5.3.5.3: ISE, Table 5.3.5.3.2-prophylaxis: 26, page 80/171.
From Committee member Statistical Review memo dated May 2015. N = Number of subjects vaccinated, n = Number of subjects included in the analysis
Adapted from Integrated Analysis of Efficacy,. By statistical reviewer
[1] The pertussis vaccine response was defined as follows: (1) if pre-vaccination antibody concentration was < 4X LLOQ, then the Post-vaccination antibody concentration was ≥ 4X LLOQ, (2) if pre-vaccination antibody concentration was ≥ 4X LLOQ, then the Post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titer at pre-Dose 1.
[2] The estimates for the response rate and rate difference (PR5I group minus Control group) are based on the method by Miettinen and Nurminen stratified by studies and actual brand of birth dose of hepatitis B vaccine (RECOMBIVAX HB™ or Other/Unknown). The estimates for GMT and GMT ratio (PR5I/Control) were based on an ANCOVA model with natural log-transformed post vaccination titer as the response variable, vaccination group, natural log-transformed pre-vaccination titer, actual brand of birth dose Hep B vaccine (RECOMBIVAX HB™ or Other/Unknown) and studies as explanatory variables. The missing pre-vaccination tite are imputed by a multiple imputation method and used in the ANCOVA analysis.
PR5I Group received PR5I + Prevnar 13™ + RotaTeq™ at 2, 4, 6 mos; (DAPTACEL™ + PedvaxHIB™ in V419-005 study) or (PENTACEL™ in V419-006 study) + Prevnar 13™ at 15 mos.
Control Group received PENTACEL™ + Prevnar 13™ + RotaTeq™ at 2, 4, 6 mos, RECOMBIVAX HB™ at 2, 6 mos; (DAPTACEL™ + ActHIB™ in V419-005 study) or (PENTACEL™ in V419-006 study) + Prevnar 13™ at 15 mos.

CI = Confidence interval, FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, GMT = Geometric mean titer, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, N = Number of subjects vaccinated, n = Number of subjects included in the analysis, NAb = Neutralizing antibodies, PP-RW = Per-protocol-Revised Windows (defined as 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); PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid.

Table 82. STN 125563: Analysis of Pertussis Antigen Responses at One Month after Toddler Dose (PP-RW) Integrated Population (Protocols V419-005 and V419-006)

		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)

Source: STN 125563/0: m 5.3.5.3: ISE, Table 5.3.5.3.2-prophylaxis: 28, page 85/171.
From Committee member Statistical Review memo dated May 2015. N = Number of subjects vaccinated, n = Number of subjects included in the analysis
Adapted from Integrated Analysis of Efficacy,. By statistical reviewer
[1] The pertussis vaccine response was defined as follows: (1) if pre-vaccination antibody concentration was < 4X LLOQ, then the Post-vaccination antibody concentration was ≥ 4X LLOQ, (2) if pre-vaccination antibody concentration was ≥ 4X LLOQ, then the Post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titer at pre-Dose 1.
[2] The estimates for the response rate and rate difference (PR5I group minus Control group) are based on the method by Miettinen and Nurminen stratified by studies and actual brand of birth dose of hepatitis B vaccine (RECOMBIVAX HB™ or Other/Unknown). The estimates for GMT and GMT ratio (PR5I/Control) were based on an ANCOVA model with natural log-transformed post vaccination titer as the response variable, vaccination group, natural log-transformed pre-vaccination titer, actual brand of birth dose Hep B vaccine (RECOMBIVAX HB™ or Other/Unknown) and studies as explanatory variables. The missing pre-vaccination titers are imputed by a multiple imputation method and used in the ANCOVA analysis.
PR5I Group received PR5I + Prevnar 13™ + RotaTeq™ at 2, 4, 6 mos; (DAPTACEL™ + PedvaxHIB™ in V419-005 study) or (PENTACEL™ in V419-006 study) + Prevnar 13™ at 15 mos.
Control Group received PENTACEL™ + Prevnar 13™ + RotaTeq™ at 2, 4, 6 mos, RECOMBIVAX HB™ at 2, 6 mos; (DAPTACEL™ + ActHIB™ in V419-005 study) or (PENTACEL™ in V419-006 study) + Prevnar 13™ at 15 mos.
CI = Confidence interval, FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, GMT = Geometric mean titer, N = Number of subjects vaccinated, n = Number of subjects included in the analysis, PP-RW = Per-protocol-Revised Windows (defined as 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); PRN = Pertactin, PT = Pertussis toxoid.

8. INTEGRATED OVERVIEW OF SAFETY PR5I (VAXELIS)

8.1 Safety Assessment Methods

The methods for safety monitoring were the same across the pivotal safety studies of PR5I. The supportive safety studies used different monitoring time points, but similar definitions for describing adverse events. The safety analyses were observational, without formal statistical comparisons. Analyses of adverse events across doses were performed according to randomized group assignment at enrollment.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Two Phase 3 studies conducted in the US and two phase 2 studies conducted in Canada will provide the safety database for PR5I. Only serious adverse events were evaluated for the Phase 2 supportive safety studies (V419-003 and V419-004). See section 8.2.2 below.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 3875 subjects received at least one dose of PR5I in the pivotal and supportive studies to evaluate PR5I. In the two Phase 3 studies (V419-005 and V419-006) conducted in the US, 3380 subjects received PR5I and 885 subjects received Control vaccines (Pentacel + RECOMBIVAX HB). Across the two studies, 3234 subjects completed the three dose infant series. The total number of doses of PR5I administered during the Phase 3 studies was 9468.

For studies V419-005 and V419-006, 3986 subjects (93.1%) completed the infant series (defined as a total of 3 doses of PR5I or Control administered at 2, 4, and 6 months of age) and 3593 (83.9%) subjects completed their Toddler dose study vaccinations.

In the Phase 2 studies (V419-003 and V419-004) conducted in Canada, 495 subjects received the investigational formulation of PR5I and 340 subjects received Control vaccines (153 Pentacel + Engerix B and 187 Pentacel +RECOMBIVAX HB). For Study V419-004: 302 subjects completed the infant series (906 doses) and 294 subjects received a Toddler dose (at 15 or 16 months of age) of PR5I, to give a total of 1200 doses of PR5I administered in this Phase 2 study. During the conduct of V419-003, 182 subjects received four doses of PR5I (fourth dose administered at 15 months of age), for a total 728 doses administered.

Table 83. STN 125563: Summary of Pivotal Studies and Supportive Studies for Safety of PR5I

Protocol	Study Design and Treatment Duration	Vaccination Groups and Numbers of Subjects Vaccinated	Subject Gender, Number of Subjects, Mean Age, and Age Range	Safety Results
Study V419-005 (Phase III) [Non-inferiority Study]	Open-label, multicenter, randomized, active comparator-controlled study (US) to evaluate the safety and	Randomized: 1473 PR5I: 986 Control: 487 Vaccinated: 1465 PR5I: 981 Control: 484	Male: 780 Female: 693 Mean age (days): 65.4	In healthy infants who received 3 doses of PR5I at 2, 4, and 6 (concomitantly with Prevnar and RotaTeq) months followed by

	immunogenicity of PR5I All subjects received a dose of monovalent hepatitis B vaccine at birth (outside of the study). Subjects in the PR5I group received a 0.5 mL dose of PR5I at 2, 4, and 6 months followed by DAPTACEL and PedvaxHIB at 15 months. Subjects in the Control group received a 0.5 mL dose of Pentacel at 2, 4, and 6 months and a 0.5 mL dose of RECOMBIVAX HB at 2 and 6 months followed by DAPTACEL and ActHIB at 15 months. Subjects in both groups received the concomitant vaccines (RotaTeq and Prevnar 13). Daily measurement of temperature Day 1-5. Solicited AEs Day 1-5 Unsolicited AEs Day 1-15 SAE through 180 dats after the 3rd dose in the infant series		Age range (days): 46 to 89	DAPTACEL and PedvaxHIB at 15 months of age, the following results were shown: The safety profile of PR5I was consistent with that of its licensed component vaccines and generally similar to the Control vaccines. A statistically significant increase in mild and moderate fever was noted for PR5I, as compared to Control vaccines. There was a similar low incidence of fever-related hospitalizations and other events such as febrile seizures. The incidence of severe adverse events, vaccine-related serious adverse events, and adverse events leading to discontinuation following vaccination with PR5I was low. No unexpected or new serious adverse events were noted.
Study V419-006 (Phase III)	Partially double-blind, multicenter, randomized, active comparator controlled, lot-to-lot consistency study (U.S.) to evaluate the safety, and immunogenicity of PR5I All subjects received a dose of monovalent hepatitis B vaccine at birth (outside the study).	Randomized: 2808 PR5I: 2406 Control: 402 Vaccinated: 2800 PR5I: 2399 Control: 401	Male: 1470 Female: 1338 Mean age (days): 64.5 Age range (days): 46 to 89	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 safety profile of PR5I was consistent with that of its licensed

	Subjects in each of the PR5I groups received a 0.5-mL dose of PR5I (3 different lots to assess lot consistency) at 2, 4, and 6 months and a 0.5-mL dose of Pentacel at 15 months. Subjects in the Control group received a 0.5-mL dose of Pentacel at 2, 4, 6, and 15 months and a 0.5-mL dose of RECOMBIVAX HB at 2 and 6 months. Subjects in both groups received concomitant vaccines (RotaTeq and Prevnar 13). Daily measurement of temperature Day 1-5. Solicited AEs Day 1-5 Unsolicited AEs Day 1-15 SAE through 180 days after the 3rd dose in the infant series			component vaccines and similar to the Control vaccines. A statistically significant increase of moderate fever was noted for PR5I as compared to Control vaccines. The incidence of hospitalization and febrile seizures was similar to that seen in the Control group. There was a low incidence of severe adverse events, vaccine-related serious adverse events, and adverse events leading to discontinuation was observed following vaccination with PR5I.
Study V419-003 (Phase II) **Canada**	Partially double-blind; randomized, controlled, dose-ranging, multicenter study. The HR5I vaccination groups were AR5I (b) (4), PR5I (3,10)* and PR5I (b) (4) at . Subjects in each of the PR5I groups received a 0.5-mL dose of PR5I (3 different formulations) at 2, 4, and 6 months and a Toddler dose at 12-14 months of age. The control vaccination group received Pentacel + Recombivax HB for the infant series and Pentacel alone for the Toddler dose.	Randomized and vaccinated: 756 PR5I(investigational product): 188 Control: 186	PR5I (3,10) Male: 100 Female: 88 Study overall: Mean age (days): 70.7 Age range (days): 49 to 91	The safety was consistent with licensed component vaccines in subjects who received 4 doses of PR5I (3,10) at 2, 4, 6, and 12-14 months. There were no deaths or related SAEs in the PR5I (3,10) cohort.

	Daily temperatures for Day 1 to Day 5 following each vaccination and solicited injection-site reactions and systemic reactions for Day 1 to Day 15 following each vaccination. SAEs were reported during the 14 days after any vaccination and throughout the study			
Study V419-004 (Phase II) **Canada**	Open-label, multicenter, randomized, active comparator controlled Phase II study to evaluate the immunogenicity and safety of PR5I when given concomitantly with Prevnar Subjects were randomized into one of three vaccination groups as follows: Group A: Received PR5I (3, 10) * and Prevnar at 2, 4, 6, and 15 months. Group B: Received PR5I (3, 10) * at 2, 4, 6, and 15 months; Prevnar at 3, 5, 7, and 16 months. Group C: Received Pentacel, ENGERIX B and Prevnar at 2, 4, and 6 months; Pentacel and Prevnar at 15	Total Randomized subjects: 460 PR5I (A): 157 PR5I (B): 150 Control: 153	Male: 232 Female: 227 Mean age (days): 63.2 Age range (days): 42 to 99	There were no significant differences in rates of solicited injection-site and solicited systemic reactions when Prevnar was given concomitantly with PR5I or given 30 days later. There was 1 reported serious adverse event (hypotonia) assessed as related to PR5I administration and no deaths occurred during the study. There appeared to be a trend toward an increase incidence of severe solicited local and systemic events following a 4th dose of PR5I at 15 months of age.

Source: STN 125563/0: m 5.3.5.3: ISE
*PR5I (3,10) is the investigational product studied in V419-005 and V419-006

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The Phase 3 studies V419-005 and V419-006 conducted in the US used the same criteria for enrollment and assessments for safety, and thus may be pooled for safety. The Phase 2 Studies V419-003 and V419-004 used similar, but not same criteria for safety assessment. Only the occurrence of serious adverse events (same definitions as the Phase 3 studies but over differing time periods) will be assessed for these studies.

8.4 Safety Results

V419-005 and V419-006
In the pivotal Phase 3 studies, serious adverse events were reported by 42 subjects (1.2%) in the PR5I groups and 11 subjects (1.3%) in the Control groups (Day 1 to Day 15). There was a higher incidence of adverse events in the PR5I group. This increase was related to the increase in pyrexia (solicited AE) in the PR5I groups (47.2%) versus the control group (33.6%). Most fevers were mild to moderate in intensity. The majority of fevers were assessed by rectal temperature. The incidence of severe fever in the PR5I groups and the Control groups was similar across the pivotal studies [1.4% PR5I compared to 1.3% Control]. Evaluation of severe pyrexia occurring in Day 1-5 following any infant vaccination was not statistically significant (2.3% PR5I compared to 1.2 % Control). There were no reports of febrile convulsion or convulsion within Days 1 to 15 after any dose of PR5I or Control in either study.

Unsolicited adverse events during the fifteen days following infant vaccination were similar. The most frequent vaccine-related unsolicited systemic adverse event reported was diarrhea (3.0% in the PR5I group and 1.7% in the Control group). Most occurrences of diarrhea were considered mild to moderate in intensity and no subject withdrew from the study due to diarrhea.

Adverse events leading to study vaccine discontinuation were comparable; reported by 8 subjects (0.2%) in the PR5I groups and 1 (0.1%) in the Control group.

8.4.1 Deaths

V419-005 and V419-006
Death was reported in 6 subjects (0.2%) in the PR5I groups (Studies V419-005 and V419-006) and 1 subject (0.1%) in the Control group. No deaths were considered to be related to the study vaccinations [asphyxia, hydrocephalus secondary to Alexander's Disease, suspected roll-over event, sepsis, SIDS (2), pneumonia]. The difference (PR5I group minus Control group) in the percentage of subjects who died was 0.1 (95% CI: -0.5 to 0.3).

V419-003 and V419-004
One death occurred during the conduct of V419-003. The cause of death was reported as SIDS (autopsy performed) and occurred (b) (6) days post-dose 2 in the Control group.
There were no deaths during study V419-004.

8.4.2 Nonfatal Serious Adverse Events

V419-005 and V419-006
The number of subjects reporting one or more serious adverse events Days 1 to 8, Days 1 to 15 or Days 1 to 31 after any infant dose vaccination was ≤2.0% in the PR5I group and ≤2.2% in the Control group. For Days 1 to 181, the incidence of SAEs was 4.2% in the PR5I group and 5.1% in the Control group.

The most frequent serious adverse event reported Days 1 to 8, Days 1 to 15 and Days 1 to 31 was respiratory syncytial virus bronchiolitis. The most frequent serious adverse events reported Day 1 to 181 were respiratory syncytial virus bronchiolitis, bronchiolitis and dehydration.

Pyrexia

In the Protocol V419-006 there were 3 reports of pyrexia (0.1% incidence) as a serious adverse event (SAE) within Days 1 to 15 after any dose of PR5I or Control. All 3 events occurred after the first dose of study vaccines (PR5I, Prevnar 13, and RotaTeq). All subjects were evaluated for possible infectious etiology; one subject was found to have Group A streptococcus bacteremia. No subjects in V419-005 reported pyrexia as a serious adverse event.

Serious adverse events related to vaccination by investigators, after any infant dose vaccination were reported in 6 subjects (0.2%) in the PR5I group and none in the Control group. Of these 6 subjects, 2 had serious adverse events that were determined by the Investigator as related to RotaTeq (i.e., intussusception, diarrhea) only. The difference (PR5I group minus Control group) in the percentage of subjects who had vaccine-related serious adverse events was 0.2 (95% CI: -0.4 to 0.4).

Table 84. STN 125563: Serious Adverse Events Related to Infant Vaccination V419-005 and V419-006 (All vaccination subjects)

Vaccine/Study	Dose Number	Day relative to Dose	Adverse Event
PR5I/005	1	1	ALTE
PR5I/006	1	1	Pyrexia
PR5I/006	1	1	Pyrexia
PR5I/006	3	6	Intussusception
PR5I/006	1	6	Diarrhea
PR5I/006	1	2	Pyrexia
PR5I/	Toddler dose Pentacel/Prevnar	1	Febrile Convulsion
Control	Toddler dose Pentacel/Prevnar	1	Pyrexia

Source: STN 125563/0: m 5.3.5.3: ISS, Section 2.1.5.2.1, Table 5.3.5.3.3-30, Reviewer modified page 73/278.

V419-003 and V419-004

In study V419-003, there were a total of 15 SAEs which occurred during the conduct of the study. Most SAEs were related to infectious diseases. One subject had an SAE felt to be related to vaccination; lymphadenitis with neutropenia, within 12 days of receipt of the control vaccine.

SAEs were reported by 30 subjects in study V419-004, who received a total of ~ 1800 doses of vaccine (PR5I and Control) during the study to give an incidence of ~1.6% for the study overall. (Please see table 78 in section 6.4.11 of this review). Most SAEs were due to infections common in this age group, with bronchiolitis being the most commonly reported infection. Three SAEs of interest occurred: hypotonia [PR5I, on day of vaccination second dose], febrile convulsion [Pentacel, 14 days post-dose 4] and bronchospasm [PR5I, 15 days post-dose 4]. None of these SAEs led to discontinuation from the study.

8.4.3 Study Dropouts/Discontinuations

V419-005 and V419-006

In Studies V419-005 and V419-006 discontinuations from the studies due to an adverse event was uncommon (9 subjects [0.2%]) in the PR5I studies.

Table 85. STN 125563: Adverse Events Leading to Discontinuation Studies V419-005 and V419-006 (All Vaccination Subjects)

Vaccine/Study	Dose Number	Day relative to Dose	Adverse Event
PR5I/005	1	1	Injection site erythema, pain (severe) and swelling.
PR5I/006	3	284	GI disorder
PR5I/006	2	22	ITP
PR5I/006	3	66	Colitis
PR5I/006	1	21	Myoclonus
PR5I/006	2	50	Hydrocephalus
PR5I/006	1	37	Failure to thrive
PR5I/006	1	1	Crying/decrease appetite, injection site erythema, constipation
PR5I/006	1	1	Injection site erythema, pain (severe) and swelling, irritability
Control	1	1	Irritability

Source: STN 125563/0: m 5.3.5.3: ISS, Section 2.1.6.1, Table 5.3.5.3.3-33, (Reviewer modified) page 87/278.

8.5 Additional Safety Evaluations

None

8.6 Safety Conclusions

In the pivotal studies for PR5I (VAXELIS), V419-005 and V419-006, the safety evaluations were similar. A total of 3380 subjects were vaccinated with at least one dose of PR5I and 885 were vaccinated with at least one dose of the Control vaccines. In total, 3986 subjects (93.1%) completed the infant series (defined as a total of 3 doses of PR5I or Control administered at 2, 4, and 6 months of age) and 3593 (83.9%) subjects completed their Toddler dose study vaccinations. A total of 279 subjects (6.5%) did not complete the infant series of PR5I or Control vaccine. Of those subjects, 224 subjects (6.6%) were in the PR5I group and 55 subjects (6.2%) were in the Control group. The most frequent reasons for study withdrawal before completion of the infant series were 'Withdrawal by Subject (subject's parent/guardian)', 'Lost to Follow-up', and 'Protocol Violation'. Overall, 7 subjects discontinued due to an adverse event, 6 subjects (0.2%) were in the PR5I group and 1 subject (0.1%) was in the Control group. The most frequent reasons for discontinuations that occurred between the infant series and the

Toddler dose were 'Lost to Follow-up', 'Withdrawal by Subject (subject's parent/guardian)' and 'Protocol Violation'. Overall, 2 subjects (0.1%) in the PR5I group and none in the Control group discontinued due to an adverse event. Most discontinuations were not related to vaccination, were non-serious in nature and resolved without sequelae.
The safety profile of PR5I administered as a three-dose infant series at 2,4, and 6 months of age with concomitant vaccination with Prevnar 13 and RotaTeq was consistent with the safety profile observed with the component and combinations vaccines of the same antigens.
For both studies, the nature of adverse events following any vaccination with PR5I were similar to what has been seen following administration of the licensed component vaccines and combination vaccines containing the antigens in PR5I. In the Phase 3 studies, V419-005 and V419-006, no imbalances for solicited local injection site reactions (i.e., pain/tenderness, erythema, and swelling) or systemic AEs (i.e., crying, decreased appetite, irritability, somnolence and vomiting) were identified between groups for days 1-5 after each vaccination. There was an increase in the rates of pyrexia after any dose of PR5I in both studies. In the combined Phase 3 studies, rates of fever (defined as ≥38◦C) were increased for PR5I (47.2%) as compared to the Control vaccines (33.6%); [difference 13.6% (95%CI: 9.7, 17.3)]. Of note, the rates of febrile seizures were similar between the groups for Day 0-181 (0.2 study 005 and 0.1 study 006) ; no seizures occurred within 15 days post-vaccination.
There was a low rate of fever related hospitalizations and no febrile seizures observed in the 15 days following the infant vaccinations. However, it should be noted that febrile seizures are rare before the age of 6 months. In general, the observed serious adverse events were related to infectious etiologies common in this age group. No deaths appear to be associated with receipt of the study vaccines.
The available safety data did not raise any particular concerns regarding the adverse events following the administration of PR5I relative to the administered Control vaccines with exception of fever. There were no other concerning safety signals identified in the clinical studies or in the post-marketing data available following approval in other countries. Given the total number of subjects evaluated in the pivotal studies, however, the ability to detect a rare adverse event is limited.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations: Pediatrics

The applicant requested approval of use of VAXELIS in children ages 6 weeks through 4 years (before the 5th birthday). In the clinical development of VAXELIS, the rationale for the lower age limit of 6 weeks for administration of VAXELIS was based on current immunization practices and the limitations of the neonatal immune response. With the exception of Hepatitis B vaccine, which is routinely administered shortly after birth, in part, to prevent unrecognized perinatal transmission of hepatitis B virus, the infant immunization program in the U.S. is initiated at a minimum of 6 weeks of age. In general, limitations of the neonatal immune response (e.g., weak and short-lived antibody response and inhibitory influence of maternal antibodies) have been significant barriers to effective immunization earlier in life.
For the age group 7 months through 4 years of age, use of VAXELIS would be for catch-up immunization in unvaccinated children and those with delayed vaccinations. The requested upper age limit for administration of VAXELIS, 4 years (prior to the fifth birthday), coincides with the age beyond which Hib conjugate vaccines are no longer recommended for routine use.

The BLA includes safety data on VAXELIS administered to children ages 6 weeks to 16 months of age and immunogenicity data for VAXELIS administered to children ages 6 weeks through 7 months. Use of VAXELIS in children 19 months through 4 years of age is supported by clinical

evidence of the safety in children 6 weeks to 16 months of age. Extrapolation of immunogenicity data from children 6 weeks to 16 months of age to older children 17 months through 4 years of age is supported by the generally mature, robust immune response to inactivated vaccines observed in children during and beyond the second year of life.

In two Phase 2 clinical studies, the safety of VAXELIS was evaluated at each of four consecutive doses, administered at 2, 4, 6, and 15-18 months of age, respectively. Although rates of severe local and systemic reactions following VAXELIS were generally higher in children 15-18 months of age compared with infants in one study, this finding is thought to represent a higher risk of reactions with increasing dose number, rather than an age effect. Rates of severe fever following VAXELIS were higher in children 15-18 months of age compared with infants in one Phase 2 study (V419-004). However, the overall rate of solicited adverse events in this small study (PR5I = 305: Control=153) was similar over the four doses of vaccines administered when compared to the Control vaccine. Thus, it is anticipated that adverse reaction rates following catch-up vaccination with VAXELIS in children 19 months through 4 years would not be meaningfully higher than those observed in younger children and infants following the analogous doses in the four-dose series.

9.1.1 Human Reproduction and Pregnancy Data
This product was not studied and is not indicated for use in women of reproductive age.

9.1.2 Use During Lactation
This product was not studied and is not indicated for use in lactating women.

9.1.3 Pediatric Use and PREA Considerations
In addressing the requirements of the Pediatric Research Equity Act (PREA), the applicant submitted a request for a partial waiver of the requirement to submit pediatric assessments for the age groups 0 to 5 weeks (i.e., before 6 weeks of age) and 5 to 16 years (5 years to prior to 17th birthday). This request was reviewed and granted as an initial (iPSP) Pediatric Study Plan.

9.1.4 Immunocompromised Patients
This product was not studied in a population of immunocompromised children.

9.1.5 Geriatric Use
Not applicable.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Consistent with the pivotal clinical studies, the proposed dosage regimen is administration of a single injection of 0.5 mL of VAXELIS by the intramuscular route at ages 2, 4, and 6 months of age. To complete the primary series of DTaP-containing vaccine another dose of either Pentacel or DAPTACEL will be required.

Of note, a child who receives the proposed schedule of VAXELIS and then receives Pentacel will receive 4 doses of IPV during the first two years of life. While this schedule is generally consistent with the ACIP recommendations for IPV immunization, including acceptable ages at vaccination and spacing between doses, the routinely recommended age for administration of the fourth dose of IPV is 4-6 years. Some State immunization requirements for school entry include receipt of the last dose of IPV after the fourth birthday. Thus, some children who receive three doses of VAXELIS according to the proposed schedule may receive an extra (fifth) dose of IPV at 4-6 years of age.

Additionally, an infant who has received a birth dose of a mono-valent hepatitis vaccine will receive three more doses of hepatitis B vaccine upon completing the infant series with VAXELIS, to give a total of four doses. The data provided do not indicate a safety concern for infants who receive four doses of Hepatitis B vaccine in the first year of life.

Children who receive three doses of VAXELIS at ages 2, 4, and 6 months of age will need to receive fourth and fifth doses of DTaP vaccine at 12-15 months of age and at 4-6 years of age to complete the 5-dose DTaP series, as recommended by the ACIP.

10. CONCLUSIONS

Overall, the immunogenicity data presented for the pivotal studies demonstrated that a 3-dose infant series of PR5I (VAXELIS) administered at 2, 4, and 6 months of age was comparable to licensed control vaccines for all pre-specified endpoints, except for the GMT of the pertussis FHA antigen at one-month Post-dose 3. No serious or new safety signals were identified.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See Table 86 below.

Table 86. STN 125563: Summary of Risk-Benefit Analysis

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Unmet Medical Need	• Currently several vaccines are licensed for the prevention of diphtheria, tetanus, pertussis and polio, *Haemophilus influenza* and Hepatitis B either as stand-alone or combination vaccines in this age group (6 weeks through 4 years of age). • These vaccines are generally well-tolerated and effective in preventing disease. • Depending upon the combination of vaccines administered, children may receive several immunizations/injections at 2, 4, and 6 months of age.	• VAXELIS [V419 (PR5I: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated, poliovirus, *Haemophilus influenza* b conjugate [meningococcal outer membrane protein complex], and hepatitis B [recombinant] vaccine)] is a hexavalent vaccine which will provide active immunization against 6 diseases with the convenience of one injection.
Clinical Benefit	• Two Phase 3 clinical trials (open-label and lot consistency studies) were conducted in the US and were submitted for assessment of safety and immunogenicity of PR5I when administered at 2, 4, and 6 months of age. • The pre-specified non-inferiority endpoints were met for most of the antigens contained in PR5I when compared to separate immunizations with the currently approved vaccines which are the standard of care; Pentacel and Recombivax Hib. • There was no interference with the immune responses to concomitant vaccinations with Prevnar 13 and RotaTeq, which represent the current standard of care. • Higher antibody responses to Hib were observed as early as the 3rd dose of PR5I when compared to licensed controls, this may be important in populations at high-risk of Hib disease when a multivalent combination vaccine is preferred	• Clinical disease endpoint studies are currently infeasible, given the epidemiology of these diseases. However, multiple previous studies of the component and combination vaccines containing the antigens in PR5I provide data establishing the correlation between immunogenicity and protection from disease. Therefore, the immunologic non-inferiority study submitted to the BLA is sufficient to provide substantial evidence of effectiveness.
Risk	• Common adverse events expected for PR5I post-vaccination included injection-site reactions (e.g., pain/tenderness, erythema, and swelling) and systemic adverse events such as crying, decreased appetite, irritability, pyrexia, somnolence and vomiting. These events mirror the adverse event profiles seen with the licensed component vaccines and other combination vaccines. • Fever was found to be higher in subjects who received PR5I, but most cases of fever were mild to moderate in nature and resolved without medical intervention. There were no reports of febrile convulsion or seizures Day 1-15 following any vaccination.	• All the evidence indicates that the risk of vaccination with PR5I is consistent with similar licensed products; however, the database was relatively small and may not have captured adverse events which happen with less frequency. • No new safety signals were identified during the course of the study.
Risk Management	• Most adverse reactions resolved without intervention or sequelae.	• Post-marketing surveillance will include routine pharmacovigilance monitoring, with updates to the package insert to manage any newly identified risks seen in the post-marketing period.

11.2 Risk-Benefit Summary and Assessment

VAXELIS contains the same components of products already licensed in the U.S. for active immunization against diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenza* b and polio. This vaccine represents a convenience vaccine which could reduce the number of injections at a study visit when compared to administration of separate licensed vaccines for the same indication. The observed adverse events were generally mild to moderate and resolved without medical intervention. Overall, the risk-benefit balance is favorable for use of this vaccine consistent with the indications and usage section of the package insert.

11.3 Discussion of Regulatory Options

Please see below section 11.4.

11.4 Recommendations on Regulatory Actions

The safety and immunogenicity data in the BLA support a recommendation for approval of VAXELIS (PR5I) in infants and children, 6 weeks through 4 years of age (prior to the fifth birthday for active immunization against invasive *H. influenzae* disease, diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis. The dosage regimen supported by clinical data is a single 0.5 mL dose of VAXELIS, administered by the intramuscular route, at 2, 4, and 6 months of age.

11.5 Labeling Review and Recommendations

The initial package insert submitted by the applicant was in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006. The package insert was revised to include the format required by FDA's Final Rule titled "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling", referred to as the "Pregnancy and Lactation Labeling Rule (PLLR)" effective 30 June 2015. The PLLR revises the PLR content and format requirements for subsections 8.1 through 8.3 of 62 section 8 USE IN SPECIFIC POPULATIONS of the FPI [21 CFR 201.57(c)(9)(i) through 63 (c)(9)(iii)]. The discussion in Section 9.2 of this review is elaborated in section 2 Dosage and Administration of the package insert regarding previous vaccination with DTaP, hepatitis B, poliovirus, and *Haemophilus influenza* b conjugate vaccines and use of VAXELIS. Specifically, these sections of the package insert define the subpopulation for which VAXELIS is indicated as infants and children 6 weeks through 4 years of age and addresses the vaccination requirements based on previous vaccination history. No other major labeling issues have been identified.

11.6 Recommendations on Post-marketing Actions

No PMCs or PMRs are currently in place for VAXELIS (PR5I). Routine pharmacovigilance is planned after licensure.