17 December 2015
EMA/CHMP/72003/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vaxelis

Common name: diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed)

Procedure No. EMEA/H/C/003982/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAHS	Aluminium Hydroxyphosphate Sulfate
AlPO4	aluminium phosphate
aP	acellular pertussis
BAP	Bulk alum Product
BSA	Bovine Serum Albumin
CHO	Chinese Hamster Ovary
CPP	Critical Process Parameters
CPVS	Concentrated Purified Viral Suspension
CQAs	Critical Quality Attributes
D	Diphtheria
DNA	Deoxyribonucleic Acid
DP	Drug Product
dPRP	derivatised Polyribosyl Ribitol Phosphate
DS	Drug substance
ELISA	Enzyme Linked Immunosorbent Assay
EU	European Union
FHA	Purified Filamentous Hemagglutinin
FIM-2 and FIM-3	Fimbriae 2 and 3 respectively
GMP	Good Manufacturing Practices
HBsAg	Hepatitis B surface Antigen
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPV	Inactivated Vero Trivalent Poliovaccine
IVRP	In Vitro Relative Potency
kDa	Kilo Dalton
L	Litre
LAL	Limulus Amoebocyte Lysate
Lf	Limit of flocculation
MAA	Marketing Authorisation Application
MCB	Master Cell Bank
MS	Mass Spectrometry
MSL	Master Seed Lot

MW	Molecular Weight
OMPC	Outer Membrane Protein Complex
OOS	Out Of Specification
PEG	Polyethylene Glycol
PFS	Pre-filled Syringe
Ph. Eur.	European Pharmacopeia
PR5I	Vaxelis vaccine
PRN	Pertactin
PRP	Polyribosyl Ribitol Phosphate
PRP-OMPC	*Haemophilus influenzae* type b polysaccharide conjugated to Outer membrane protein complex
PT	Pertussis Toxoid
PTx	Pertussis Toxin
QC	Quality Control
REC	Recommendation
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
T	Tetanus
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopeia
vIPV	Inactivated Vero Trivalent Poliomyelitis Vaccine bulk
WCB	Working Cell Bank
WFI	Water For Injection
WHO	World Health Organization
WSL	Working seed lot

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi Pasteur MSD SNC submitted on 17 December 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Vaxelis, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 March 2014.

The applicant applied for the following indication: Vaxelis (DTaP-HB-IPV-Hib) is indicated for primary and booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib), in children from the age of 6 weeks up to the fifth birthday. Vaxelis should be used in accordance with official recommendations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that 'diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed)' was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0034/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0034/2012 was completed.

The PDCO issued an opinion on compliance for PIP P/0034/2012.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 January 2014. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

A new application was filed in the following countries: United States.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniel Brasseur Co-Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 17 December 2014.
- The procedure started on 21 January 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 April 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 April 2015.
- During the meeting on 7 May 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 21 May 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 May 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 August 2015.
- GMP and GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 October 2015.
- During the meeting on 08 October 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 22 October 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 November 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 04 December 2015.
- During the meeting on 03 December 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 17 December 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Vaxelis.

2. Scientific discussion

2.1. Introduction

Vaxelis or PR5I is a hexavalent paediatric combination vaccine for primary and booster immunization of infants and toddlers above the age of 6 weeks. Vaxelis is referred to as PR5I throughout the report. It is designed to provide active immunization against diseases caused by *Corynebacterium diphtheria*, *Clostridium tetani*, *Bordetella pertussis*, poliovirus types 1, 2, and 3, *Haemophilus influenzae* type b (Hib), and hepatitis B virus. World-wide these diseases still causes significant morbidity and death, but in most developed countries, extensive immunization programs have made these diseases rare.

The licensure of PR5I in the EU would offer an additional hexavalent vaccine option to healthcare providers and would, therefore, increase assurance of availability of hexavalent vaccines.

2.1.1. Problem statement

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. Humans are the only natural host for C. diphtheriae. Transmission occurs through droplets and close physical contact.

In most developed countries, endemic diphtheria has disappeared or become extremely rare due to vaccination. Since implementation of universal vaccination in 1980, the incidence in the U.S. has declined to approximately 0.001 cases per 100,000 in the population. No cases of diphtheria were reported in the US in 2005.

At the peak of a diphtheria epidemic in the Russian Federation and the Newly Independent States (NIS) in 1995, 50,425 cases were reported in the NIS, compared with 24 cases in other countries in the European Region. The NIS epidemic was attributed to low vaccine coverage, among other factors stemming from the breakdown of the Soviet Union. It accounted for 88% of cases reported worldwide. Following mass immunization campaigns and additional control measures, diphtheria is largely under control in the World Health Organization Europe (EURO) region, with only 500 cases reported in 2005. Notification rates were < 0.01 cases per 100,000 population in most countries in 2011.

Diphtheria is rare in infants younger than 6 months of age due to the presence of maternal antibody. Diphtheria continues to cause substantial morbidity and mortality in developing countries with low vaccine coverage. Persons in all age groups are susceptible to diphtheria if not vaccinated.

Tetanus is an infectious bacterial disease caused by *Clostridium tetani*, a ubiquitous sporeforming anaerobic bacillus, which can produce a potent neurotoxin, tetanospasmin. The toxin blocks inhibitory neurotransmitters in the central nervous system and causes the muscular stiffness and spasms typical of generalized tetanus. Tetanus can never be eradicated as C. tetani spores are prevalent in the environment and may be carried in the intestinal tracts of humans and animals. Tetanus is not transmitted from person to person. Tetanus, with an incubation period varying between 2 days and 2 months, typically presents as trismus (lockjaw) and sudden, generalized tonic seizures.

Tetanus affects all age groups and case-fatality rates can be high even where modern intensive care is available. The overall tetanus case-fatality rate varies from 10% to 70%, depending on treatment, age and general health of the patient. Without hospitalization and intensive care, fatality is almost 100% among the oldest and the youngest patients. Since the 1940s, when the tetanus toxoid became a component of routine childhood vaccination in the U.S., reported tetanus cases have declined >95%, and since the disease became reportable nationally in 1947, deaths have declined >99%. No cases were reported in children less than five years of age from 2001 to 2008, excluding one non-fatal neonatal case. The overall tetanus notification rate for Europe in 2011 was 0.04 per 100,000, with almost two-thirds of the European cases reported in Italy alone. In 2009, there were no cases of neonatal tetanus in all of the EU and EEA/EFTA countries.

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 and is usually 7 to 10 days. Pertussis begins with mild upper respiratory tract symptoms (catarrhal stage), progresses 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.

Adolescents and adults can become susceptible to pertussis because of waning immunity approximately 5 to 10 years after booster vaccination. A case-control study following a 2010 pertussis outbreak in California showed that receipt of 5 doses of DTaP was initially effective but that the estimated vaccine efficacy decreased yearly, consistent with waning immunity. Routine adolescent and adult Tdap vaccination has been recommended by the Advisory Committee on Immunization Practices (ACIP). In 2009, the vaccine coverage in the U.S. was 56% among adolescents and less than 6% in adults. Furthermore, in 2012, the ACIP updated the recommendations for Tdap vaccination in pregnant women and now recommends Tdap vaccination during every pregnancy, with a goal to optimize strategies for preventing pertussis morbidity and mortality in infants.

In Europe, the reported incidence varies widely from 0.12 in Portugal to 95.44 per 100,000 in Estonia in 2010. The reported pertussis incidence among EU/EEA countries must be interpreted with caution due to country-to-country variations in factors influencing pertussis surveillance systems including vaccination policies, disease awareness and recognition, case definitions, laboratory confirmation methods, reporting procedures and surveillance systems performance.

Overall, pertussis incidence remains relatively high in infants younger than 1 year of age in Europe. Even with high immunization coverage against pertussis and a subsequent decrease in the disease incidence, a resurgence of pertussis for all ages combined has been reported in several countries including countries across Europe. Adolescents and adults have been demonstrated to be a reservoir for pertussis infection and serve as a source of spread to younger children, mainly infants. In a study conducted by Celentano et al. in 16 Western European countries covering the period 1998-2002, although infants less than 1 year of age were the most or among the most affected age groups in all countries due to the severity of disease in this age group, the 5 to 14 year-olds were overall the age groups with the highest incidence of pertussis in countries reporting the highest number of cases. The overall incidence in 25 countries of the EU/EEA increased in 2011 for the first time since 2008, with an overall notification rate of 5.57 cases per 100,000 compared to 4.49 per 100,000 in 2010.

In 2012, the UK faced an outbreak situation with the highest number of reported cases mainly in adolescents and adults 14 years of age and above (> 80% of cases) and in infants less than three months of age. The UK Department of Health introduced immunization of pregnant women to control the outbreak and to reduce the morbidity-mortality among young infants too young to be immunized. In a prospective cohort study, Public Health England estimated that vaccinating pregnant women with a Tdap-IPV vaccine in the 3rd trimester of pregnancy had a 92% effectiveness in protecting unvaccinated infants in the first 2 months of life against pertussis. The outbreak of pertussis subsided in 2013, with incidence diminishing from more than 1600 cases at the peak in October 2012 to less than 250 cases per month on average in October through December 2013.

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. Case fatality rates of 5 and 10% have been reported based on epidemic cases in the early 20th century. Childhood immunization programs with Oral polio vaccine (OPV) or with IPV have been very effective.

Since the Global Polio Eradication Initiative was launched in 1988, three WHO regions have been certified polio-free: the Americas in 1994, the Western Pacific in 2000 and the European region on 21 June 2002.

So far, the global fight against Polio is estimated to have saved 5 million persons from paralysis. In 2011, no cases of polio disease were reported in any of the 29 reporting EU and EEA/EFTA countries. Imported wild-type and vaccine-type polioviruses still remain a threat to unvaccinated European populations and, in fact, in 2010 an outbreak with imported WPV1 occurred in the eastern WHO European region (mainly Tajikistan) with nearly 500 confirmed cases. Major supplementary immunization activities were undertaken in all countries of the WHO European Region to stop transmission. Twelve months after WPV1 was imported into the region, no transmission was detected within the region, including the EU and EEA/EFTA countries.

The Commission which monitors the European region's polio-free status has recently expressed concerns about the risk of polio importation in polio-free counties. This was illustrated with the detection of cases of acute flaccid paralysis caused by poliovirus type 1 in Syria between October 2013 and March 2014, 14 years after the country was declared poliofree, and the subsequent spread of the virus to neighboring Iraq. As a result of the armed conflict in Syria, infant vaccination rates have diminished from 91% in 2010 to an estimated 68% in 2012. A strain of poliovirus type 1 recently documented to have spread from Pakistan to the Middle East was confirmed to have caused these cases in undervaccinated children in Syria and Iraq.

Haemophilus influenzae is a Gram-negative coccobacillus that enters the body through the nasopharynx. Encapsulated Haemophilus influenzae has 6 serological types (types a to f); however most invasive diseases are 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 most important 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%. Antibodies to Hib capsular polysaccharide are protective; a serum level of 0.15 µg/mL of antibody to the Hib capsular polysaccharide has been proposed to be protective. The short-term seroprotective anti-PRP level of 0.15 µg/mL is based on passive protection studies of subjects with hypogammaglobulinemia supported with gammaglobulin. The long-term seroprotective anti-PRP level of 1.0 µg/mL is derived from the results of active immunization following a single dose of the original nonconjugated native PRP vaccine, Hib polysaccharide vaccine.

Hib infections became nationally reportable in the U.S. in 1991. Before the availability of national reporting data, several areas conducted active surveillance for Hib disease. In the early 1980s, it was estimated that about 20,000 cases occurred annually in the US alone, primarily among children younger than 5 years of age (40 to 50 cases per 100,000 population). The introduction of effective Hib conjugate vaccines has decreased the rate of invasive Hib disease in the U.S. by over 99%. Data from the European Union Invasive Bacterial Infections Surveillance (EU-IBIS) observed that the incidence in infants < 1 year of age and children 1-4 years of age has decreased in the period from 1999 to 2006. Invasive Hib incidence remains highest in infants < 1 year of age at about 1.1 cases per 100,000 in 2006, and decreases with increasing age. In the Czech Republic, Hib incidence fell particularly in children < 5 years of age following the introduction of routine Hib vaccination into childhood immunization schedule in 2001. Similarly, the introduction of a booster dose of vaccine in the second year of life in the UK in 2003 was followed by a reduction in the number of cases in children < 5 years of age, after a rise had been observed between 1999 and 2002.

In 2011, 2,133 confirmed cases of invasive H. influenzae disease (all serotypes) were reported by 29 European countries. The overall notification rate was 0.38 per 100,000 population, a stable incidence

estimate since 2007. The most affected age groups were children under five years and elderly (≥ 65 years) with respectively a notification rate of 0.91 and 1.02 per 100,000 population.

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. Individuals with hepatitis B chronic infection are at increased risk of developing cirrhosis and hepatocellular carcinoma.

Among patients who successfully complete the 3-dose vaccination series, the clinical effectiveness is thought to be high. In the US, since 1990 and coinciding with the implementation of universal hepatitis B vaccination, the number of acute hepatitis B cases has declined 84%, from 8.5 cases per 100,000 in 1990 to 1.1 cases per 100,000 in 2009. During this time, the greatest decline in acute hepatitis B infection has been in children <15 years of age, the population targeted for routine vaccination. Incidence has declined 98% in children aged <15 years, from 1.2 per 100,000 in 1990 to 0.02 per 100,000 in 2007. In 2009, the lowest rates of acute hepatitis B infection were in adolescents and children age ≤ 19 years (0.06 cases per 100,000).

In Europe, following the introduction of universal childhood immunization against hepatitis B, the incidence of acute hepatitis B cases has declined over the past ten years from 6.7 per 100,000 population in 1995 to 0.78 per 100,000 in 2011. Revised estimates of the total burden of hepatitis B, based upon the implementation of a revised case definition for both acute and chronic infections in 29 European countries, have shown relatively stable rates of infection incidence of 3.09 and 3.43 cases per 100,000 in 2007 and 2011, respectively. Significant heterogeneity in the incidence of hepatitis B infection observed across European countries can be partially attributed to the variable uptake of reporting standards for hepatitis B as well as difference in laboratory and clinical practices.

2.1.2. About the product

PR5I is an hexavalent paediatric combination vaccine containing diphtheria toxoid (D), tetanus toxoid (T), 5-component acellular pertussis including pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 and 3 (FIM), inactivated poliomyelitis virus types 1,2 and 3 (IPV), Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) conjugated to meningococcal protein (PRP-OMPC) and Hepatitis B surface antigen (HBsAg).

PR5I is a fully liquid preservative free suspension for injection adjuvanted onto aluminium phosphate and amorphous aluminium hydroxyphosphate sulfate. It is presented in single dose (0.5 mL) vial or syringe.

PR5I is a combination vaccine containing components of vaccines currently licensed in the United States (US), the European Union (EU), and other countries. Except for the Hib PRP-OMPC antigen, all antigens are components of vaccines currently licensed in Europe, e.g. Pediacel and Repevax (D, T, aP, IPV), and HBVaxPro (HBsAg).

PR5I is indicated for:

primary and booster vaccination in infants and toddlers from the age of 6 weeks against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib).

PR5I should be administered intramuscularly. The primary vaccination schedule consists of two or three doses, with an interval of at least 1 month between doses, and may be commenced from 6 weeks of age, in accordance with the official recommendations.

After a 2-dose or a 3-dose primary series vaccination with PR5I, a booster dose should be given at least 6 months after the last priming dose, and in accordance with the official recommendations. As a minimum, a dose of Hib vaccine must be administered.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a suspension for injection. The Active Substance (hereby referred to as drug substance) consists of the following: Tetanus toxoid adsorbed, Diphtheria toxoid adsorbed, 5-component acellular pertussis antigens (PT, FHA, PRN, FIM-2 and FIM-3), trivalent Inactivated Poliomyelitis Virus (IPV), Hepatitis B surface Antigen (HBsAg) and *Haemophilus influenzae* type b polysaccharide conjugated to Outer membrane protein complex (PRP-OMPC). Other ingredients are: are amorphous aluminium hydroxyphosphate sulfate, aluminium phosphate, phosphate solution and water for injection (WFI). The applicant refers to Vaxelis as PR5I vaccine.

The product is available in a 0.5ml single dose pre-filled syringe as described in section 6.5 of the SmPC.

The components are the same components as in vaccines that are currently licensed or were previously licensed in Europe.

The active substance and finished product are referred to as drug substance and drug product in this report as per CTD.

2.2.2. Active Substance

The DS contains Tetanus Toxoid (Adsorbed), Diphtheria Toxoid (Adsorbed), 5-component acellular Pertussis (adsorbed), Inactivated Vero Trivalent Poliomyelitis Vaccine bulk (vIPV), Hepatitis B (rDNA, adsorbed) and Haemophilus type b conjugate (adsorbed).

a) Tetanus Toxoid Adsorbed

General information

Toxoid is prepared by formaldehyde inactivation of Tetanus Toxin, from the Boston II 60 strain of *Clostridium tetani*. Tetanus toxin has a molecular weight of approximately 150 kDa and is synthesised as a single polypeptide chain of 1315 amino acid residues. Upon cellular release, Tetanus Toxin is cleaved by proteases to form a light chain (toxic moiety) of approximately 52 kDa molecular weight, and a heavy (binding) chain of approximately 98 kDa. The two chains are linked by a single disulfide bond. The light chain is composed of the N-terminal 457 amino residues, and contains a zinc protease catalytic site. The heavy chain is composed of the remaining 858 residues. Satisfactory information on the structure and specific properties of the Tetanus Toxoid Adsorbed has been provided.

Manufacture, characterisation and process controls

The Tetanus Toxoid adsorbed Drug Substance is manufactured and tested at the Sanofi Pasteur Limited facility located at 1755 Steeles Avenue West, Toronto, Ontario, Canada M2R 3T4. This site is used for production of this component for EU authorised product. The manufacturing process too, is largely similar and differences have been detailed and justified.

Description of manufacturing process and process controls

Tetanus Toxin is manufactured through fermentation of *Clostridium tetani*. The harvested toxin is detoxified by formaldehyde and the resulting toxoid is purified through selective precipitation by ammonium sulfate. The Tetanus Toxoid Pre-adsorbed concentrate is stored until it is adsorbed to aluminium phosphate to produce the Tetanus Toxoid Adsorbed concentrate. There is no reprocessing during DS manufacture and no shipment of Tetanus Toxoid Adsorbed concentrate between manufacturing sites.

The hold-time for Tetanus Toxoid Pre-adsorbed concentrate is supported by stability data. The Tetanus Toxoid Adsorbed concentrate (DS) storage conditions are described. Container closure integrity testing has been demonstrated. The manufacturing process has been sufficiently described and is considered acceptable.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. This is the case for all components of Vaxelis, unless otherwise specified. Information on human or animal-derived materials used in the establishment of Tetanus cell substrate and during the manufacturing process is provided. This includes substances of bovine, avian, rabbit, porcine and human (human hair) origin.

Information on the species and tissue, country of origin (if known) and stage of use in the manufacturing process for each of the raw materials is indicated and appropriate certificates supplied if available. Stringent conditions such as physical and chemical treatments applied during the manufacture of specified raw materials are known for their capacity to inactivate viruses. This is the case for all components of Vaxelis, unless otherwise specified.

The Bacterial Seed lot system has been used historically for other EU authorised vaccines and guarantees sufficient stocks of the seed lots. Sufficient information is provided regarding testing of Master Seed Lot (MSL) and Working Seed Lot (WSL). Stability data have been provided. A similar approach has been used for other Vaxelis components.

The applicant has committed to submitting for approval (this would be by variation) any future working cell banks and working seed (for all Vaxelis components) that have not been derived and tested according to the protocols defined in the MAA file.

In-process controls for the intermediates of the drug substance include tests with specified acceptance criteria and appropriate controls for purity. Critical in-process controls and QC release tests are described for each step. Again, this is the approach taken for other Vaxelis components.

The steps considered critical (i.e. where critical in-process controls or Quality Control release tests are performed) during the manufacture of the Tetanus Toxoid Adsorbed concentrate are defined. Acceptable information has been provided on the control system, including documentation for the assignment of critical/non-critical steps for each of the DTaP components. The specification (QC release tests) applied for release of Tetanus Toxoid Pre-adsorbed concentrate has been presented (tests include appropriate tests for content, identity and purity). Appropriate release and stability data have been provided.

Process validation

The process validation comprises the following: Concurrent Validation Studies (to demonstrate consistency and show compliance to pre-defined acceptance criteria); Supportive Studies (to further evaluate any gaps or deficiencies identified in the concurrent studies) and Continuous Process Verification (used to maintain assurance that the process remains in a state of control during commercial manufacture). The same principles are applied to validation of DS manufacturing for other Vaxelis components.

Results show that the Tetanus drug substance manufacturing process has been validated adequately demonstrating that the purification process consistently produces drug substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

The company has provided the rationale for the current manufacturing process for Tetanus Toxoid Adsorbed concentrate. Significant change(s) made to the Tetanus Toxoid Adsorbed concentrate manufacturing process since the formulation of the four PR5I Vaccine Phase III clinical lots have been described.

Characterisation

The analyses were designed to allow for the evaluation of purity and identity of the antigen, including composition, structural integrity and Tetanus Toxoid adsorption analysis. For all lots investigated, it was demonstrated that purified Tetanus Toxoid was of the expected molecular weight and had the correct amino acid composition. Lot-to-lot consistency (including for adsorption) was observed and all lots had the expected conformation. Biological activity characterisation of Tetanus Toxoid was also performed. In summary, the characterisation is considered appropriate for this type of molecule.

Specification

The release specification for the Tetanus Toxoid Adsorbed concentrate drug substance includes appropriate tests for identity, purity and content (antigen and adjuvant). The applicant has validated the clearance of formaldehyde during the manufacturing process. Additionally, formaldehyde is also determined at the Drug Product level.

The purification process for Tetanus Toxoid Adsorbed concentrate and other Vaxelis components has been designed to eliminate or reduce potential process-related impurities and product-related impurities during manufacturing. Adequate procedures are in place to control and reduce the impurities to acceptable levels.

The consistent removal of those other impurities which are not routinely tested for, has been demonstrated. Several lots of Tetanus Toxoid were tested. This study also showed the effective reduction of product-related impurities (e.g. degradation products) and DNA/ media components. Since the stated impurities have been present in product used in clinical trials, their presence in the commercial DP is considered clinically qualified.

The analytical methods have been described. The limit of flocculation (Lf) Test is performed to determine the Tetanus Toxoid content (Lf/mL) in the Tetanus Toxoid Pre-adsorbed and Adsorbed concentrates. The Lf Test is an *in vitro* immunological flocculation test measuring the amount of Tetanus Toxoid that flocculates one unit of U.S. Standard Reference Tetanus Antitoxin.

Batch analysis data (several production scale lots) of the Tetanus Toxoid adsorbed concentrate were provided. Some of these batches were used in stability studies and the some batches were used in the formulation of the four PR5I Phase III clinical and production consistency lots. The results are within the specifications and confirm consistency of the manufacturing process. Adequate information on reference materials is provided.

Stability

Real time, real condition stability data on full-scale production scale lots of drug substance from the commercial manufacturing process stored in scaled down containers (representative of the containers for commercial use) indicate that the drug substance is sufficiently stable and justify the proposed shelf life in the proposed container.

b) Diphtheria Toxoid Adsorbed

General information

Diphtheria Toxoid Adsorbed is prepared by adsorption of diphtheria toxoid, which is itself formaldehyde-inactivated Diphtheria Toxin, a single polypeptide of an approximate molecular weight of 62 kDa. It is produced by *Corynebacterium diphtheriae*. The structure corresponds to the three major functions of Diphtheria Toxin (catalysis represented by fragment A and translocation and receptor binding domains, both represented by fragment B). Satisfactory information on the structure and specific properties of the Diphtheria Toxoid Adsorbed has been provided.

Manufacture, characterisation and process controls

The Diphtheria Toxoid Adsorbed (drug substance, DS) is manufactured and tested at the same site as the Tetanus DS, Sanofi Pasteur Limited facility located at 1755 Steeles Avenue West, Toronto, Ontario, Canada M2R 3T4. This site is used for production of the Diphtheria component for EU authorised product. The manufacturing process too, is largely similar to that of EU authorised vaccines and differences have been detailed and justified.

Description of manufacturing process and process controls

Diphtheria Toxoid Adsorbed is manufactured through the fermentation of *Corynebacterium diphtheria*, the toxin being harvested and then detoxified by formaldehyde. The resulting toxoid is further purified through selective precipitation using ammonium sulfate. The pre-adsorbed diphtheria toxoid is then stored prior to adsorption to aluminium phosphate yielding the Diphtheria Toxoid Adsorbed concentrate. The manufacturing process has been sufficiently described and is considered acceptable.

The storage conditions for intermediates and Diphtheria Toxoid Adsorbed concentrate are described. Container closure integrity testing has been demonstrated. There is no reprocessing during DS manufacture.

See the corresponding section for Tetanus for information on raw material specifications and general principles adopted on the use of human or animal-derived materials in Vaxelis DS manufacture (certification and manufacturing processes).

The manufacturing process uses substances of bovine, avian, porcine and human (human hair) origin. The Bacterial Seed lot system is satisfactorily described. The control (includes definition of critical vs non-critical steps and in-process controls) system is as described for Tetanus DS. The steps considered critical during the manufacture of the Diphtheria Toxoid Adsorbed concentrate are defined. Acceptable information has been provided on the control system. The specification applied for release of Diphtheria Toxoid Pre-adsorbed concentrate has been presented. Tests include appropriate tests for content, identity and purity. Appropriate release and stability data have been provided.

Process validation

The process validation approach for Diphtheria DS follows that described for Tetanus DS. Concurrent (using consecutive production lots) and supportive validation reports have been provided.

Results show that the drug substance manufacturing process has been validated adequately. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces drug substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

The company has provided the rationale for the current manufacturing process. Significant change(s) made to the Diphtheria Toxoid Adsorbed concentrate manufacturing process since the formulation of the four PR5I Vaccine Phase III clinical lots have been described.

Characterisation

The analyses were designed to allow for the evaluation of purity and identity of the antigen, including composition, structural integrity and Diphtheria Toxoid adsorption analysis. Biological activity characterisation of Diphtheria Toxoid has also been performed. Potency was measured by the Lf Test. In summary, the characterisation is considered appropriate for this type of molecule.

Specification

The release specification for the Diphtheria Toxoid Adsorbed concentrate drug substance includes appropriate tests for identity, purity and content (antigen and adjuvant). The applicant has validated the clearance of formaldehyde during the manufacturing process. Additionally, formaldehyde is also determined at the Drug Product level.

See the corresponding section of the Tetanus DS as regards the approach to impurity reduction. The consistent removal of impurities which are not routinely tested for has been demonstrated. Several lots of Diphtheria Toxoid were tested. This study also showed the effective reduction of product-related impurities (e.g. degradation products) and DNA/ media components. Since the stated impurities have been present in product used in clinical trials, their presence in the commercial DP is considered clinically qualified. Adequate information on reference materials is provided.

The analytical methods have been described. As for Tetanus, an appropriately validated in-house method is used for the limit of flocculation assay.

Batch analysis data (production scale lots) of the diphtheria toxoid adsorbed concentrate were provided. Some of these batches were used in stability studies to support the hold-time at the adsorbed stage and the remaining batches were used in the formulation of the four PR5I Phase III clinical and production consistency lots. The results are within the specifications and confirm consistency of the manufacturing process.

Stability

Real time, real condition stability data on full scale lots of drug substance from the commercial manufacturing process stored in scaled-down containers (representative of the containers for commercial use) indicate that the drug substance is sufficiently stable and justify the proposed shelf life in the proposed container.

c) 5-Component Acellular Pertussis Adsorbed

General information

5-Component Acellular Pertussis Adsorbed is comprised of the following five antigens isolated from *Bordetella pertussis* culture:

- Fimbriae (FIM) are extracellular filamentous proteins. Fimbria Type 2 and Fimbria Type 3 are homologous polypeptides of molecular weight (MW) 22.5 kDa and 22 kDa respectively.
- Pertactin (PRN) is a non-fimbrial membrane-associated protein displaying an apparent molecular weight (MW) of 69 kDa in SDS-PAGE.

- The Pertussis toxoid (PT) results from the detoxification of the Pertussis toxin (PTx), a major contributor to pathogenesis. The PTx contains 2 distinct domains (A & B) consisting of one (S1) and five (S2, S3, 2 x S4 and S5) subunits.
- The Filamentous Haemagglutinin (FHA) is a surface-associated protein. The mature FHA has a MW of about 220 kDa.

Manufacture, characterisation and process controls

The 5-Component Acellular Pertussis Adsorbed (DS) is manufactured and tested at the same site as the Tetanus DS, Sanofi Pasteur Limited facility located at 1755 Steeles Avenue West, Toronto, Ontario, Canada M2R 3T4. This site is used for production of the Acellular Pertussis DS component for EU authorised product.

Description of manufacturing process and process controls

The Component Pertussis antigens are produced from strain 10536, grown in fermenters under aerobic conditions. Each antigen is purified individually except for FIM (2 and 3) which are co-purified. PTx is detoxified using glutaraldehyde to produce PT, and any residual PTx present in the FHA fraction is detoxified with formaldehyde. PRN is purified and isolated by ammonium sulfate precipitation and is purified by sequential chromatography. FIM Types 2 and 3 are co-purified by precipitation with polyethylene glycol and chromatography. Component Pertussis pre-adsorbed concentrates are adsorbed onto aluminium phosphate and WFI is added to produce the Component Pertussis Adsorbed concentrates.

The hold time for FIM, PRN and FHA pre-adsorbed concentrates is supported by stability data. The storage conditions for the 5-Component Adsorbed concentrates are described. Container closure integrity testing has been demonstrated.

Reprocessing may occur during the production process of the 5-Component Acellular Pertussis drug substance and the conditions under which this occurs have been justified and are acceptable. The manufacturing process has been sufficiently described and is considered acceptable.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Information on human or animal-derived materials used in the establishment of cell substrate and during the manufacturing process has been provided and the approach taken is in line with that described for Tetanus DS. These include substances of bovine, avian, ovine, porcine and human (human hair) origin.

The Bacterial Seed lot system has been described. Supportive information provided is in line with that described for Tetanus. Critical steps have been identified in the DS manufacturing process. Information provided on the control system (critical/non-critical) is acceptable.

The intermediates produced during the manufacture of the 5-Component Acellular Pertussis Adsorbed concentrates and the specification (QC release tests) applied for release of the individual Pre-adsorbed concentrates for each of these components has been presented. The respective specifications include appropriate tests for purity, specific activity, and impurities.

Process validation

A number of validation studies are presented. The process validation was based on the results obtained from consecutive batches. In particular, there was a specific study to examine the ability of the formaldehyde treatment of FHA to inactivate any residual PTx after exposure. Appropriate scale studies have been conducted. Holding times of intermediates have been validated. The process has been effectively validated to demonstrate the effective detoxification of PTx. Consistency of adsorption has also been addressed.

The DS production process was designed to allow the purification of all five Pertussis antigens from a single fermentation using the same strain, optimised to obtain high yields. Any residual PTx is removed during purification. Characterisation studies on PRN and FIM have also confirmed the absence of PTx (see below). Residual PTx has been detected in FHA and therefore formaldehyde is routinely used in the manufacturing process to detoxify contaminating PTx. Additionally, the choice of glutaraldehyde for PTx detoxification, the chosen manufacturing steps to purify each component and the adjuvanting system used are all well-justified. The significant changes to the process since the Phase III clinical studies are clearly described and are acceptable.

Characterisation

Physicochemical characterisation of the 5-Component Acellular Pertussis antigens was conducted and showed DS composition and structural integrity. Biological activity characterisation included results of routine testing of manufactured lots using an identity test for PTx. This test was also used to confirm the absence of active PTx in the respective components. The characterisation of the antigens also included testing for active toxins other than PTx, to confirm their absence in the purified preparations. Percent adsorption of 5-Component Acellular Pertussis antigens to aluminium phosphate was also examined.

The lots of 5-Component Acellular Pertussis antigens examined were from production material and were, therefore, subjected to the routine release testing.

Specification

Residual pertussis toxin, i.e. the PTx toxicity test by the use of CHO cells is performed as a QC release test on the pre-adsorbed concentrates for all antigens. The release specification for each of the 5-Component Acellular Pertussis drug substance is described.

Regarding impurities, aside from those which are routinely tested for, the consistent removal of other impurities is reported. Glutaraldehyde is removed after PT detoxification. Adequate clearance of this, and absence of active PTx was shown on consecutive lots. Since the stated impurities have been present in product used in clinical trials, their presence in the commercial DP is considered clinically qualified.

In addition, other *B. pertussis* virulence-associated factors were not detected when several lots of each component were tested. Formaldehyde is adequately removed after its use to detoxify any residual PTx in the purified FHA. The level of residual formaldehyde was monitored for several consecutive production lots during the process validation study. During process development, the level of contamination of one antigen with the other 5-Component Acellular Pertussis antigens was routinely measured and it was found that levels of the other antigens in the purified antigen concentrate were not detectable.

The tests and specifications for the control of the acellular Pertussis drug substance are in compliance with the Ph. Eur. Monograph and/or internal specifications. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Acceptable batch data were provided for FIM, PRN, PT and FHA Adsorbed Concentrates respectively. These include lots used in stability studies and lots which were manufactured at production scale and were used in clinical trial lot formulation.

Stability

Two long term stability studies evaluated the stability of Adsorbed concentrate lots representative of the commercial scale and commercial process stored in scaled-down containers, representative of commercial scale containers. The stability results indicate that the drug substance (including all Adsorbed concentrates) is sufficiently stable and justifies the proposed shelf life in the proposed containers.

d) Inactivated Vero Trivalent Poliomyelitis Vaccine bulk (vIPV)

General information

The poliovirus is a non-enveloped Picornavirus. The virion contains a single strand of about 7.5 kb positive RNA. The poliovirus capsid has icosahedral symmetry and consists of 60 identical asymmetric protomers. Each protomer is composed of a single copy of each of the three non-identical capsid proteins VP1, VP2 and VP3. The smallest capsid protein, VP4, is located on the inner surface of the virion. The poliomyelitis virus comprises three serotypes (1, 2 and 3) which are antigenically distinct. According to Ph.Eur. and WHO, the trivalent poliovirus vaccine should contain 40, 8 and 32 D-antigen units for type 1, 2 and 3 serotypes respectively.

Manufacture, characterisation and process controls

The Inactivated Vero Trivalent Poliomyelitis Vaccine bulk (vIPV) Drug Substance is manufactured at Sanofi Pasteur, 1541 avenue Marcel Mérieux, 69280 Marcy l'Etoile, France. This site is used for production of the trivalent IPV DS component for EU authorised product. The manufacturing process too, is identical to that used for this DS component in EU approved vaccines.

Description of manufacturing process and process controls

The IPV trivalent drug substance comprises the three serotypes 1, 2 and 3 and each monovalent is manufactured separately on Vero cell substrate. Following expansion of the Vero cells in bioreactors using microcarriers, the cells are infected by the respective serotype. The virus harvests are clarified, concentrated and purified by chromatography and subsequently inactivated by formaldehyde. The viral inactivation takes place in two stages and is confirmed by control test results. To produce the Inactivated Vero Trivalent Poliomyelitis Vaccine bulk, quantities of monovalents of each serotype (type 1, 2 and 3) are blended in proportions calculated to obtain the required D-antigen content in the Drug Substance. There is no reprocessing during the manufacturing process. The storage conditions for the concentrated trivalent bulk DS are described.

The type of information provided for raw materials and materials of human/ animal origin is consistent with the approach taken for the Tetanus DS. Substances of bovine (irradiated calf sera, certificates of suitability provided), avian, ovine (cholesterol used to prepare media- harsh chemical process used in manufacture of the media) and porcine origin (irradiated trypsin) are used during manufacturing. Porcine trypsin is tested for pestiviruses, circoviruses and parvoviruses.

The Viral Seed lot system has been described. Justification of the tiered approach and storage of seed lots is as described for Tetanus. The Vero cell banking system consists of a tiered system. The Quality Control profile that is applied for the produced Vero Working Cell Banks meet the requirements of the Ph. Eur. and WHO. The applicant has sufficiently described passage history, the methods applied for the quality control testing and tests in place to ensure safety and consistent quality of the working cell banks.

Process validation

Satisfactory information has been provided on the control system (critical/non-critical). The specification (QC release tests) applied for release of the individual monovalent bulks has been presented. The respective specifications include appropriate tests for: purity, identity, and D-antigen content (potency measurement). Holding times for the storage of specified intermediates are supported by stability data. Batch and stability data were provided for several lots of each 'type' intermediate. Importantly, the validation exercise shows effective control and consistency of the inactivation step. The validation of the concentrated trivalent manufacturing process is supported by data from studies. The applicant provided a detailed description of the development of the manufacturing process. The significant changes to the process since the Phase III clinical studies are clearly described and are acceptable.

Characterisation

The identity and concentration of each serotype is tested through the process and each batch of DS characterised in terms of physico-chemical properties and D-antigen content. Several lots were used in the characterisation study. All the data presented confirm that each routine IPV bulk batch is well characterised in terms of physicochemical properties and D-antigen content.

Specification

The release specification for the vIPV bulk includes appropriate physicochemical tests, tests for purity, and D-antigen content. The assays have been properly validated and comply with the requirements given either in Ph. Eur. or WHO TRS910 Annex 2. An ELISA method is adopted to specifically determine the D-antigen titre of poliomyelitis virus suspensions for each serotype in relation to a standard of known titre.

In-process controls and quality control release tests are performed during the manufacturing process. Some impurity tests are actually used for quality control release. Additional tests including for cellular DNA content, and residual antibiotic content have been carried out on the validation batches to verify the consistent elimination of potential impurities. Since the stated impurities have been present in product used in clinical trials, their presence in the commercial DP is considered clinically qualified.

Batch analysis data (lots used in clinical trial lots and lots representative of the commercial process at full scale) of the vIPV were provided. The results are within specification and confirm consistency of the manufacturing process.

Stability

The stability results indicate that the drug substance is sufficiently stable and justifies the proposed shelf life in the chosen container.

e) Hepatitis B surface antigen (HBsAg)

General information

The HBsAg bulk drug substance is manufactured following the same fermentation (in yeast cells) and purification operations used to manufacture the currently licensed recombinant Hepatitis B vaccine HBVaxPro (EMEA/H/C/373). The protein component is an approximately 24 kDa membrane protein called the S protein. During expression within the yeast cell, approximately 100 S proteins spontaneously associate to form a 22 nm particle. The particle consists of both the S protein and yeast cell lipids. The S protein contains 14 cysteine residues which oxidise during the manufacturing process to form both inter and intramolecular disulfide crosslinks. The HBsAg particle is thus a disulfide-cross-linked, hydrophobic entity. The drug substance is provided as HBsAg adsorbed onto an aluminium adjuvant (amorphous aluminium hydroxyphosphate sulfate).

Manufacture, characterisation and process controls

The HBsAg drug substance (including the aluminium adjuvant) is manufactured and tested by Merck & Co. Inc., 770 Sumneytown Pike, P.O. Box 4, West Point, PA 19486-0004 USA. This is the same site as used for the same component in the EU authorised HBVaxPro.

Description of manufacturing process and process controls

The fermentation process of Hepatitis B Vaccine (Recombinant) uses the same fermentation and purification processes that are employed for the manufacture of the currently licensed and approved Hepatitis B Vaccine (rDNA) (HBVaxPro, EMEA/H/C/373). Working cell banks are used to initiate the

fermentation process. Following fermentation, harvest is concentrated and diafiltered. Purification of the HBsAg involves dialiftration, concentration and chromatography steps. The substance is treated to release impurities from the HBsAg. The product is finally sterile filtered (0.22 µm). The sterile-filtered product is treated with formaldehyde and the antigen then co-precipitated with adjuvant (the antigen thereby adsorbs to the adjuvant prior to final formulation to a concentration required for use in Vaxelis). Reprocessing conditions for specified steps are described. Storage conditions for any intermediates and DS are described. The manufacturing process has been sufficiently described and is considered acceptable.

Information on raw materials including of animal- human origin has been provided and the approach taken consistent with that described for Tetanus. This includes a substance of human hair origin. For routine manufacture, this substance is sourced from poultry feathers. Reagents from bovine milk have been changed to a soy source for routine manufacture.

The Viral Seed lot system consists of a standard two-tiered system of MCB and WCBs. Appropriate cell bank testing information is provided. There is no stability testing plan for the cell bank system. However, each new working cell bank is tested extensively. This is deemed sufficient to control stability of the cell bank system. The same approach was accepted for the component used in EU approved vaccines.

Satisfactory information has been provided on the control system in place to monitor and control the drug substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process/quality control tests. The approach taken for the control strategy is consistent with that for Tetanus DS. Critical process parameters are described for fermentation, purification and BAP formulation.

Process validation

A comprehensive process validation has been presented demonstrating a robust and controlled process. The applicant has provided information on the development of the HBsAg process from the originally approved process (as developed for the monovalent product) to the current process used to manufacture the phase III lots and commercial HBsAg drug substance for Vaxelis vaccine.

Characterisation

Characterisation of the HBsAg and the adjuvant-adsorbed HBsAg has been provided. Analyses were in agreement with the expected sequence and confirmed that the HBsAg-containing intermediates prepared by the final commercial process were comparable to those of the earlier processes.

The HBsAg particle is a complex macromolecular association of protein and host-derived lipids forming spherical, 22 nm particles. Complementary lipid techniques (chemical analyses, chromatography) were used to provide an overall lipid profile. Overall, all lots of HBsAg studied show very similar conformation of the HBsAg S protein, and similar size particles are formed in all of them.

Specification

Release specifications for Hepatitis B surface antigen recombinant BAP (DS) includes appropriate physicochemical tests (including formaldehyde content), tests for identity, potency and purity. The assays have been properly validated according to ICH (except for compendial tests) and comply with the requirements given either in Ph. Eur. or WHO TRS910 Annex 2. Release specifications for specified intermediates have also been provided. The reference materials used are considered appropriate.

Extensive characterisation studies support the high level of product purity. Levels of impurities including host cell protein and DNA were monitored during the purification process validation. Data demonstrate that the process consistently cleared these host cell impurities below the process validation limits. Results provided demonstrate that investigated process residuals (including residual formaldehyde) consistently

are below the process validation limits. Since the stated impurities have been present in product used in clinical trials, their presence in the commercial DP is considered clinically qualified.

The HBsAg master standard and reference standards are described. All standards are properly qualified.

Batch data are provided for several drug substance lots including batches used in Phase III trials and in stability studies. These lots are full-scale and representative of commercial product). The results are within the specifications and confirm consistency of the manufacturing process.

Stability

The stability results generated for all lots met acceptance criteria and support a storage period at the long term storage condition.

e) AAHS-PRP-OMPC

Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) is a highly purified capsular polysaccharide (polyribosylribitol phosphate or PRP) of *Haemophilus influenza* type b (Haemophilus b, Ross strain) that is covalently bound to an Outer Membrane Protein Complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B.

PRP-OMPC (PRP covalently bound to OMPC-outer membrane protein complex of *Neisseria meningitidis* serogroup B) is used in PR5I while PRP-T (PRP covalently bound to Tetanus Protein-Conjugate) is used in EU licensed PEDIACEL.

Manufacture, characterisation and process controls

Manufacture of drug substance is performed at Merck & Co. Inc., 770 Sumneytown Pike, P.O. Box 4, West Point, Pennsylvania 19486-0004 USA.

Description of manufacturing process and process controls

In the manufacture of the aluminium-adjuvanted PRP-OMPC drug substance, *Haemophilus influenzae* is fermented and the capsular polysaccharide, polyribosylribitol phosphate (PRP), is isolated. *Neisseria meningitidis* is also fermented and the OMPC (Outer Membrane Protein Complex) is isolated. The OMPC is covalently bound to PRP to form the final PRP-OMPC Conjugate Bulk. The PRP-OMPC Conjugate Bulk is mixed with Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS) to form the drug substance. The bulk drug substance is used in the formulation of PR5I bulk drug product.

Appropriate batch sizes have been defined for the drug substance process steps. It should be noted that PRP3 was used as the PRP source for Phase III Vaxelis clinical studies. The commercial process uses PRP4 (which was shown to be comparable to PRP3).

The storage conditions for the drug substance and intermediates are described.

Information on raw materials including of animal and human origin has been provided and the approach taken consistent with that described for Tetanus. Animal-derived materials used in manufacturing and WCBs include bovine (blood, milk derivatives), avian (feathers), porcine (blood) and ovine. Countries of origin have been reported where relevant. Many of these substances are produced using harsh manufacturing conditions which would be expected to inactivate bacteria and viruses.

The cell bank system for *H. influenzae* and *N. meningitidis* consist of Pre-master MCB, MCB and WCBs. Justification of the tiered approach and storage of seed lots is as described for Tetanus. Acceptable information has been provided on the control system in place to monitor and control the drug substance manufacturing process with regard to critical, as well as non-critical operational parameters and

in-process tests. Rationale and justification for specifications of in-process controls and release tests of PRP intermediates and OMPC intermediates have been provided.

Process validation

The applicant has provided a data package demonstrating the comparability of commercial PRP4 and PRP3 which is used in clinical trials. The PRP4 comparability was performed using the new *H. influenzae* master and working cell banks (MCB and WCB, respectively), *H. influenzae* fermentation lots, and PRP purification lots. Analysis was also extended to drug substance intermediates downstream of the PRP purification process. Process validation of the other steps of the manufacturing process has also been performed. The stability studies for adsorbed PRP-OMPC and PRP intermediate from the final commercial process (PRP4) are still ongoing. Results will be provided post-approval when these stability studies have been finished.

Characterisation

A wide array of different physicochemical/ biophysical /immunochemical have been utilised in the characterisation of PRP3 (including OMPC and AAHS PRP-OMPC).

Specification

The panel of release tests for the AAHS PRP-OMPC-conjugate includes appropriate physicochemical tests for content and purity. These are considered appropriate. Additional release tests are in place at the PRP-OMPC-conjugate and intermediate levels in order to comply with Ph.Eur. 1219, Haemophilus Type b conjugate vaccine.

The potential impurities and contaminants, the steps where they are removed during the manufacturing process and the residual quantities in the bulk intermediates have been detailed by the company for the adsorbed PRP-OMPC and all the intermediates. Clearance of host cell and process related impurities have been demonstrated and are well controlled. Since the stated impurities have been present in product used in clinical trials, their presence in the commercial DP is considered clinically qualified. Adequate information on reference materials has been provided. Presented batch analysis data from several clinical and stability lots, all conform to the pre-set acceptance criteria.

Stability

Data are presented for lots of AAHS PRP-OMPC-conjugate (representative of commercial scale, including lots used in clinical trials). Most stability data presented are from lots manufactured by the PRP3 process (although a lot using PRP4 is placed on stability). The presented stability data support a shelf life for AAHS PRP-OMPC-conjugate for DS. The proposed shelf-lives for the intermediates are acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Vaxelis (referred to as PR5I Vaccine) is a sterile, preservative-free, uniform, cloudy, white-to off-white suspension for intramuscular injection. PR5I Vaccine is presented as a 0.5-mL single-dose pre-filled syringe. PR5I is a hexavalent combination vaccine formulated with preservative-free bulk concentrates as described in the DS section. Excipients (Aluminium phosphate and aluminium hydroxyphosphate sulfate used as adjuvants, Sodium phosphate and Water for injections) in Vaxelis are in compliance with the specifications required by the relevant Ph.Eur. monographs, and USP or in-house methods where no Ph.Eur. monograph exist for the raw material. There are no novel excipients used in the finished product formulation.

The final formula selected for Vaxelis for commercial purpose is the same as the formulation shown to be safe and immunogenic in the Phase III pivotal clinical trials. Information on the composition, dimensions and component specification (in compliance with Ph.Eur./USP) of the different components of the container closure system are sufficiently described. The PR5I Filled Product is filled in a single-dose 1.5-mL syringe barrel (Type I borosilicate clear glass) containing a Luer-Lok adapter with a tip cap (non-latex rubber), and a grey butyl plunger stopper (non- latex rubber). The choice of the container-closure system is validated by stability data and container-closure integrity studies.

Manufacture of the product and process controls

The final bulk manufacture of Vaxelis is performed by Sanofi Pasteur Limited in Toronto, Canada, and filling of final lot is performed by Sanofi Pasteur Inc. at Swiftwater, USA. The manufacture of Vaxelis consists of the following three principal steps: Manufacture of the Final Bulk Product; Filling of the Final Bulk Product and Packaging of final drug product.

Critical steps of the final bulk product manufacturing process and the filled product process are defined. The critical process parameters (CPPs) are presented for both the bulk formulation and for the filling and critical quality attributes (CQAs) that are monitored during bulk formulation are defined.

A Process Validation Study for the PR5I Final Bulk Formulation Process was conducted to verify the consistency of the manufacturing operations associated with formulation and blending of drug substances. The filling and stoppering process were appropriately validated. Satisfactory summaries have been provided for the validation reports. There is no reprocessing. Leachable studies have been performed to qualify filter equipment used during manufacture.

The applicant has detailed changes during process development including optimising the formulation prior to Phase III studies. There are no new impurities introduced during DP manufacture (See respective DS sections for information on impurities). The container closure system is adequately described; compatibility was demonstrated by the stability studies and extractable studies (no compounds of concern identified). There is no change proposed to the formulation of commercial PR5I compared to that used in clinical trials.

Product specification

Tests performed on the final bulk and filled product include appropriate physicochemical tests including those to check physical appearance, measure formaldehyde content, other purity tests, measurement of the level of adsorption and potency of all DSs in line with Ph.Eur., where relevant.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch data analysis from both clinical and consistency lots have been presented. These include data from several lots filled in vials and used in clinical trials. Batch data from several lots of syringes are also presented. The applicant has committed to revise certain potency specification limits once data from a higher number of DP lots is available. Adequate information on reference materials is provided.

Stability of the product

Based upon the presented data, the proposed shelf-life of PR5I Vaccine DP of 48 months from the date of Final Bulk Product formulation at 2°C to 8°C (in a pre-filled syringe), including up to 6 months storage of the final bulk product at 2°C to 8°C (the combined hold time for the Final Bulk Product and Finished Product and consequently DP expiry, does not exceed 48 months) is acceptable.

The Applicant has provided an extensive stability package, including data from final bulks, several final lots in vials (including clinical lots) and several final lots in prefilled syringe (all commercial scale). Data from clinical batches stored in vials have been provided for up to 48 months. Data from lots of PFS are available in two different filling lines for up to 48 months. This study is ongoing for some of these lots . In accordance with EU GMP guidelines,[1] any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA. The panel of tests used for stability testing consists of most of the tests performed in the release program. All stability results conformed to the pre-set acceptance criteria and there are no apparent negative trends in the data presented. For time points where OOS results were observed, the Applicant has appropriately justified the results based on unsuitable and not robust assays in place at the time, which have been replaced. The data also support that the stability profile for prefilled syringes and vials is comparable. The Applicant has committed to continue the ongoing stability studies as per the protocol.

Adventitious agents

The adventitious agents' safety evaluation has been acceptably addressed for each DS and no substances of animal/ human origin are additionally used in the DP manufacturing process

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The chemical/pharmaceutical and biological part of the Vaxelis dossier is of acceptable standard. Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate appropriate consistency of product quality characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

All concerns and questions have been sufficiently clarified and/or adequately addressed by the applicant. There are no remaining outstanding issues. The quality part of the Vaxelis dossier is deemed approvable. A list with 3 recommendations was adopted by CHMP.

Data from ongoing stability studies for the adsorbed conjugated PRP-OMPC and PRP intermediate are requested at study completion. Although supporting data have been submitted, most stability data relate to the process PRP3. Comparability was shown between the PRP3 and PRP4. Nonetheless, given the (specified) differences between PRP3 and PRP4, data from the completed stability study are requested.

Finally, commitments have been made regarding the HBsAg IVRP specification and acellular pertussis potency. For both, limits have been established based upon the limited number of lots provided, which is acceptable since these limits are clinically justified. However, there is a need to re-evaluate these limits on the basis of manufacturing experience to provide better assurance of product consistency.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The applicant indicated in section 1.4 of the application form that the active substances contained in the medicinal product Vaxelis are to be considered as known active substances. The antigens present in the hexavalent vaccine Vaxelis indeed contain antigens that have been used previously in other licensed vaccines.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Pharmacology

No pharmacology studies have been performed in animals with PR5I. In view of the extensive body of data that is already available documenting the ability of each of the antigen components in PR5I to generate an immune response in humans and on the acceptable immunogenicity of PR5I observed in Phase IIb studies and the fact that no cardiotoxic, respiratory or neurotoxic specific risks were identified, this is considered acceptable.

2.3.2. Pharmacokinetics

In accordance with the EMA "Note for Guidance on Preclinical Pharmacological Toxicological Testing of Vaccines" (CPMP/SWP/465/95) and the WHO guideline on nonclinical evaluation of vaccines, pharmacokinetic studies that assess serum or tissue concentrations of vaccine components were not performed for this vaccine.

2.3.3. Toxicology

Single dose toxicity

The nonclinical safety of PR5I(6,15), containing 6µg PRP-OMPC and 15µg HBsAg per vaccine dose, was evaluated in a single dose toxicity study in rats, which focused on local tolerance and included specific systemic toxicity endpoints. This formulation was slightly different from the optimal formulation, PR5I (3 µg PRP-OMPC per vaccine dose and 10 µg HBsAg per vaccine dose), that was selected for further study in Phase IIb (V419-004/PR504) and Phase III based on favourable safety and tolerability data as well as acceptable immunogenicity data that were obtained from the Phase I/IIa clinical studies.

In the single dose rat study, the PR5I(6,15) vaccine was administered on a single occasion via the IM route and included 1- and 14-day observation periods. The dose administered to each animal matched (for D, T, aP and IPV components) or exceeded (for PRP-OMPC and HepB components) the human dose and the human dose-volume (0.5 mL) was used.

No premature deaths, adverse clinical signs or effects on food consumption were reported in the study. There was a minor decrease in female body weight during week 1. However this was considered not toxicologically significant and was reversed by week 2.

Clinical pathology changes consistent with an immune response were observed on Day 2 and consisted of a transient elevation in mean absolute neutrophil counts associated with a lower mean relative lymphocyte count in both genders, when compared to controls. These changes were reversible and were considered not to be toxicologically significant.

Histopathologically, inflammation was noted at the injection sites in the form of a granuloma and was not reversible after the 14-day observation period, consistent with the administration of an aluminum-adjuvanted vaccine; therefore changes at the injection sites were considered of low toxicological significance.

In conclusion, the nonclinical rat toxicity study conducted with PR5I(6,15) showed an acceptable safety profile after a single intramuscular injection. The findings noted were as expected and are typical of vaccines containing multiple antigens and an aluminum-based adjuvant.

Repeat dose toxicity

Repeat dose toxicity studies have not been conducted. The CHMP and WHO guidelines state that the need to evaluate the safety of new antigen combinations in animal models should be considered case-by-case, and that such an evaluation may be necessary if there is concern that combining antigens and/or adjuvants may lead to problems of toxicity. Based on the results from the single dose toxicity study and available clinical data, it is agreed that there are no indications to do further toxicity testing in animals. The lack of repeat-dose toxicity studies is therefore considered acceptable.

Genotoxicity and Carcinogenicity

No genotoxicity or carcinogenicity studies were performed as PR5I was considered not to have any genotoxicity potential or carcinogenic effect. Carcinogenicity studies are usually not required for vaccine antigens. In addition, there were no new raw materials, preservatives, adjuvants, or process residuals used or identified in PR5I compared to those in currently licensed monovalent and/or combination vaccines with the same antigens manufactured by either Sanofi Pasteur or Merck. It was noted that these substances do not have genotoxic potential. Therefore, no genotoxicity tests were considered necessary.

Reproduction Toxicity

No reproductive or developmental toxicity studies were conducted for PR5I as the target population is limited to infants and toddlers from 6 weeks of age and it is not expected to be given to women of child bearing potential.

2.3.4. Ecotoxicity / environmental risk assessment

The combined antigens and adjuvants are already used in existing marketed products and no significant increase in environmental exposure is anticipated. Considering the above, the combined antigens and adjuvants are not expected to pose a risk to the environment. In addition, the lack of ERA studies was justified and found acceptable, in line with the CHMP guideline on the environmental risk assessment of medicinal products for human use. Vaccines are usually exempted due to the nature of their constituents.

2.3.5. Discussion on non-clinical aspects

Although the collective information on PR5I indicated that administering the combined antigens and adjuvants in PR5I would not pose a safety risk in humans, a single dose toxicity study was conducted in which PR5I(6,15) was administered to rats to confirm there were no safety concerns. The study was mainly focused on local tolerance, although it included specific systemic toxicity endpoints (Study No. 407/121). This study supported all stages of development from Phase I onwards and has been conducted in a country that is a member of the OECD Mutual Acceptance of Data scheme. For this study, the rat was chosen as it is a well-known toxicology species and has been shown to develop an immune response with similar combination vaccines and/or antigens. The design of the study supported the number and frequency of administrations in clinical Phase I (single dose) using PR5I (6,15). A dose matching (for D, T, aP and IPV components) or exceeding (for PRP-OMPC and HepB components) the full human dose and dose-volume was administered intramuscularly (IM), which is the route of administration in humans. The data from the clinical Phase I trial showed an acceptable tolerability profile consistent with the toxicology data.

No genotoxicity or carcinogenicity studies were performed as PR5I was considered not to have any genotoxicity potential or carcinogenic effect.

No reproductive or developmental toxicity studies were conducted for PR5I as the target population is limited to infants and toddlers from 6 weeks of age and it is not expected to be given to women of child bearing potential.

All raw materials, process residuals, preservatives, excipients, and adjuvants present in PR5I are similar to those found in other vaccines licensed by Sanofi Pasteur or Merck and have been demonstrated to be well tolerated in humans. As such, a specific toxicological assessment to evaluate the safety in humans is not deemed necessary.

The nonclinical safety strategy was in accordance with the EC Directive 2010/63/EU on the principle of the 3Rs (replacement, refinement and reduction of use of animals in research) and the World Health Organization (WHO) and European Medicines Agency (EMA) nonclinical guidelines for vaccines in which it is acknowledged that in the case of combined vaccines with known antigens, a full evaluation of toxicity is not required unless there is a cause for concern.

2.3.6. Conclusion on the non-clinical aspects

The nonclinical safety strategy took into account the extensive clinical and nonclinical data generated with vaccines containing one or more of the PR5I antigens which have shown no major safety issues. Although the collective information on PR5I indicated that administering the combined antigens and adjuvants in PR5I would not pose a safety risk in humans, a toxicity study was conducted in which PR5I(6,15) was administered to rats to confirm there were no safety concerns. The nonclinical safety strategy was in accordance with the EC Directive 2010/63/EU on the principle of the 3Rs (replacement, refinement and reduction of use of animals in research) and the World Health Organization (WHO) and European Medicines Agency (EMA) nonclinical guidelines for vaccines in which it is acknowledged that in the case of combined vaccines with known antigens, a full evaluation of toxicity is not required unless there is a cause for concern.
The nonclinical safety strategy as performed by the Applicant is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

PR5I is a new hexavalent paediatric combination vaccine co-developed by Sanofi Pasteur and MSD for primary and booster immunization of infants and toddlers above 6 weeks of age. It is a hybrid vaccine of 5 pertussis antigen component DTaP, Vero IPV, Hepatitis B and PRP-OMPC.

PR5I is a combination vaccine containing components of vaccines currently licensed in the US, the EU, and other countries. It contains the same DTaP as PENTACEL (US) and PEDIACEL (EU) and therefore 5 acellular pertussis components (PT, FHA, pertactin, fimbriae types 2 and 3) in combination with IPV (from Vero cells), polyribosylribitol phosphate (PRP, a Hib antigen) conjugated to outer membrane protein complex of Neisseria meningitidis to form PRP-OMPC, and recombinant hepatitis B surface antigen (HBsAg). All these antigens have been extensively investigated in clinical trials as part of various licensed vaccines produced by Sanofi Pasteur and MSD:

Table 3. Composition of PR5I vaccine as a combination of licensed vaccines.

Antigen(s)			Amounts	Licensed vaccine containing the same antigen(s)
P		PRP-OMPC Polyribosylribitol phosphate polysaccharide coupled to the outer membrane protein complex of *Neisseria meningitidis*	3 µg	PedvaxHIB (US)
R		HBsAg Recombinant hepatitis B surface antigen	10 µg	HBVAXPRO / RECOMBIVAX HB (US)
5		5 component acellular pertussis • PT: Pertussis Toxoid • FHA: Filamentous Haemagglutinin • PRN: Pertactin • FIM: Fimbriae Types 2 and 3 Diphtheria Toxoid Tetanus Toxoid	20 µg 20 µg 3 µg 5 µg 15 Lf (≥20 IU) 5 Lf (≥40 IU)	PENTACEL (US) PEDIACEL COVAXIS REPEVAX
I		IPV Inactivated Poliovirus • Type 1 • Type 2 • Type 3 * Expressed as D-antigen content as measured by the sigmoid method	40-DU* 8-DU* 32-DU*	IMOVAX POLIO PENTAVAC PEDIACEL TETRAVAC REPEVAX HEXYON/HEXACIMA
		Aluminium (0.319 mg) used as adjuvant		

The clinical development program for PR5I consists of 10 clinical studies, tabulated below. There are no clinical efficacy studies. All studies evaluating efficacy use established immunogenicity correlates or surrogates of protection. Three early phase studies were conducted using 4 non-final vaccine formulations. One Phase IIb and six Phase III clinical studies were conducted using the final vaccine formulation containing the lowest doses of PRP-OMPC and HBsAg (3 µg and 10 µg, respectively) and a modified adjuvant composition of the HBsAg component. Two studies are considered pivotal: 007 and 008. Four studies are considered supportive: 005 and 006 (which are pivotal studies in the US), PRI01C (which investigates the concomitant administration of a meningococcal serotype C vaccine, pneumococcal conjugate vaccine PCV13 and a MMR vaccine), and PRI02C (which investigates a mixed hexa-penta-hexa schedule).

The approach for PR5I approval in Europe with respect to efficacy has been to demonstrate non-inferiority of PR5I when compared to Infanrix hexa or to separate administration of the US licensed individual component vaccines.

Overview of immunogenicity studies and dosing schedules

Phase 1

Study 001 (Canada):	PR5I (6,15) and AR5I (12,10)

Phase 2

Study 002 (Canada):	PR5I (3,10) PR5I (6,10) PR5I (6,15) and AR5I (12,10)
Study 003 (Canada):	PR5I (3,10), PR5I (6,10) and AR5I (12,10)
Study 004 (Canada):	2,4,6+15 Month [3+1], concomitant PCV7

Phase 3

US pivotal

Study 005 (US):	2,4,6+15 Month [3+1], concomitant RV5 and PCV13
Study 006 (US):	2,4,6+15 Month [3+1], concomitant RV5 and PCV13

EU pivotal

Study 007 (BE, FI, DE):	2,3,4+12 Month [3+1], concomitant RV5, PCV13, MMRV
Study 008 (FI, IT, SE):	2,4+12 Month [2+1], concomitant RV2 or RV5, PCV13

EU supportive

Study PRI01C (UK):	2,3,4+12 Month [3+1], concomitant MenC, PCV13, MMR
Study PRI02C (ES):	2,4,6 Month mixed hexa-penta-hexa schedule, concomitant MenC, PCV13, RV5

US studies vs. EU studies

Because of the diversity of vaccination schedules across the EU, it was not feasible to test each schedule individually. Therefore, two Phase III clinical studies (Protocols 007 and 008) were designed to meet immunization requirements of the EU, including varied vaccination schedules and concomitant administration with pneumococcal conjugate vaccine (Prevenar 13), rotavirus vaccines (RotaTeq and Rotarix), and Quadrivalent MMRV vaccine (ProQuad). The schedules chosen for the Phase III program were designed to provide information on the condensed infant schedule (2, 3, 4 and 12 months in Protocol 007) and the most immunologically rigorous example of a 3-dose schedule (2, 4, and 11 to 12 months in Protocol 008). Additionally, studies PRI01C and PRI02C were conducted with PR5I in the UK and in Spain, respectively, to evaluate PR5I co-administered with MCC vaccines using country-specific immunization schedules. Therefore, the immunogenicity results for Protocol 007, Protocol 008, PRI01C and PRI02C are provided individually.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Protocol	Study design/sites/date	Study vaccine/arm/No. of subjects	Population and age	Main Endpoints	Duration and follow-up (FU)
EARLY VACCINE FORMULATIONS					
001 Phase I Safety and tolerability Immunogenicity of a single dose of 2 different formulations	Partially double-blind, controlled 1 center in Canada Nov. 2000 – March 2001	Vaccinated: 90 AR5I (12, 10): 30 PR5I (6, 15): 30 Control: Pentacel (DTaP/IPV + Hib): 30 1 booster dose at 15-18 months	15 – 18 months old infants Primary vaccination with DTaP and OPV/IPV and Hib but HepB and Pw vaccine naïve	Primary endpoint *Safety and tolerability* Secondary endpoint *Immunogenicity* - % of subjects with antibody responses ≥ threshold - GMT for each vaccine antigen	6 weeks
002 Phase IIa Immunogenicity Safety and tolerability of 3+1 doses of 4 different formulations	Double-blind 4 centers in Canada May 2001 – March 2003	Vaccinated: 708 AR5I (12, 10): 178 PR5I (3, 10): 176 PR5I (6, 10): 178 PR5I (6, 15): 176 3+1 doses at 2,3,4 + (12-14) months	7 – 12 weeks old infants HepB vaccine naïve	Primary endpoint *Immunogenicity* - % of subjects with antibody responses ≥ threshold Secondary endpoint *Safety and tolerability* *Immunogenicity* - GMT for each vaccine antigen	11 to 13.5 months
003 Phase IIa Immunogenicity Safety and tolerability of 3+1 doses of 3 different formulations	Partially double-blind, comparator-controlled (open label) 7 centers in Canada May 2001 – Jan 2003	Vaccinated: 756 AR5I (12, 10): 192 PR5I (3, 10): 188 PR5I (6, 10): 189 Control: Pentacel/Recombivax HB: 187 3+1 doses at 2,4,6 + (12-14) months	7 – 14 weeks old infants HepB vaccine naïve	Primary endpoint *Immunogenicity* - % of subjects with antibody responses ≥ threshold Secondary endpoint *Safety and tolerability* *Immunogenicity* - GMT for each vaccine antigen	
FINAL VACCINE FORMULATION					
004 Phase IIb Immunogenicity Safety and tolerability of 3+1 doses	Open-label, comparator-controlled, co-administration PCV7 8 centers in Canada Aug 2006 – April 2008	Vaccinated: 460 **Group A: PR5I + PCV7: 157** **Group B: PR5I + PCV7 staggered: 150** Group C: Pentacel/EngerixB + PCV7: 153 3+1 doses at 2,4,6 + 15 months	7 – 14 weeks old infants vaccine naïve	Primary endpoint *Immunogenicity* - % of subjects with antibody responses ≥ threshold Secondary endpoint *Safety and tolerability* *Immunogenicity* - GMT for each vaccine antigen of PR5I and PCV	14 months

005 Phase III Immunogenicity Safety and tolerability of 3+1 doses	Open-label, comparator-controlled, co-administration rota RV5 and PCV13 39 centers in US April 2011 – May 2013	Vaccinated: 1465 **PR5I Group: 981** PR5I + PCV13 + rota RV5 + booster with Daptacel+PedvaxHIB Control group: 484 Pentacel/RecombivaxHB + PCV13 + rota RV5 + booster with Daptacel+ActHIB 3+1 doses at 2,4,6 + 15 months	46 - 89 days old infants HepB vaccine at birth	Primary endpoints *Immunogenicity* - non-inferior response rate to all PR5I antigens post primary series and to pertussis antigens post booster - non-inferior pertussis antibody GMT responses post primary series - % of subjects with anti-IPV responses ≥ threshold Secondary endpoints *Safety and tolerability* *Immunogenicity* - Non-Inferior Anti-PRP Responses post primary series	14 months
006 Phase III Immunogenicity Safety and tolerability of 3+1 doses of three different lots	Partially double-blind, comparator-controlled, co-administration rota RV5 and PCV13, lot-to-lot consistency 73 centers in US May 2011 – July 2013	Vaccinated: 2800 **PR5I Group: 2399** PR5I + PCV13 + RV5 + booster with Pentacel Lot A: 800 Lot B: 792 Lot C: 807 Control group: 401 Pentacel/RecombivaxHB + PCV13 + RV5+ booster with Pentacel 3+1 doses at 2,4,6+ 15 months	46 - 89 days old infants HepB vaccine at birth	Primary endpoints Immunogenicity - lot consistency: equivalent GMTs for all PR5I antigens of three different lots post primary series Secondary endpoints *Immunogenicity* - Lot consistency: equivalent response rates for all PR5I antigens post primary series - Non-inferiority of response rates for pertussis components post booster - Non-inferiority of GMTs for PR5I pertussis components post booster - Non-inferiority of response rates for all PR5I Antigens post primary series - Non-inferiority of GMTs for pertussis components post primary series - Non-inferiority of GMTs for all Prevnar 13 antigens post primary series	14 months
007 Phase III Immunogenicity Safety and tolerability of 3+1 doses	Double-blind, comparator-controlled, co-administration RV5, PCV13 and MMRV 40 centers in Europe (BE, FI, DE) May 2011 – March 2013	Vaccinated: 1250 **PR5I Group: 611** PR5I + PCV13 + RV5 + booster with PR5I + MMRV Control group: 606 Infanrix hexa + PCV13 + RV5+ booster with Infanrix hexa + MMRV 3+1 doses at 2,3,4+ 12 months	46 - 78 days old infants Vaccine naïve	Primary endpoint *Immunogenicity* - % of subjects with antibody responses ≥ threshold for all PR5I antigens **except pertussis and HepB** post primary series and for all PR5I antigens post booster - non-inferiority regarding response rates for all antigens **except pertussis and HepB** post primary series, and for all pertussis antigens and HepB post booster Secondary endpoints *Immunogenicity* - Non-Inferior Anti-MMRV Responses at 1 Month Post toddler dose Safety and tolerability	14 months

008 Phase III Immunogenicity Safety and tolerability of 2+1 doses	Double-blind, comparator-controlled, co-administration RV5 or RV2 and PCV13 23 centers in Europe (IT, FI, SE) Nov 2011 – Oct 2013	Vaccinated: 1312 **PR5I Group: 653** PR5I + PCV13 + RV5 or RV2 + booster with PR5I Control group: 659 Infanrix hexa + PCV13 + RV5 or RV2 booster with Infanrix hexa 2+1 doses at 2,4+ 12 months	46 - 89 days old infants Vaccine naïve	Primary endpoint *Immunogenicity* - % of subjects with antibody responses ≥ threshold Secondary endpoints *Immunogenicity* - non-inferior PR5I/Infanrix hexa Antibody Responses 1 Month Postdose 3 Safety and tolerability	14 months
011 (PRI01C) Phase III Immunogenicity Safety and tolerability of 3 doses PR5I and 2 concomitant doses of two different MenC vaccines	Open-label, co-administration MenC and MMR and PCV13 11 centers in Europe (UK) March 2012 – Sept 2013	Vaccinated: 284 **PR5I Group: 284** 3 doses PR5I at 2,3,4 months 2 doses MCC-TT or MCC-CRM at 2,3,4 months	47 - 76 days old infants Vaccine naïve	Primary endpoints *Immunogenicity* - % of subjects with anti-MCC responses ≥ threshold 1 Month Postdose 2 Secondary endpoints *Immunogenicity* - % of subjects with anti-Hib responses ≥ threshold 1 Month Postdose 3 *Safety and tolerability*	14 months
011 (PRI02C) Phase III Immunogenicity Safety and tolerability of mixed hexa-penta-hexa schedule	Open-label, mixed schedule, single arm, co-administration MenC and RV5 and PCV13 12 centers in Europe (ES) April 2013 – Dec 2014	Vaccinated: ca. 385 Mixed schedule PR5I/Pediacel/PR5I: ca. 385 2 doses PR5I at 2,6 months 1 dose Pediacel at 4 months	46 - 76 days old infants HepB vaccine at birth	Primary endpoints *Immunogenicity* - % of subjects with anti-hepB and anti-pPRP responses ≥ threshold 1 Month Postdose 3 Secondary endpoints *Immunogenicity* - % of subjects with all other antibody responses ≥ threshold 1 Month Postdose 3 *Safety and tolerability*	14 months

2.4.2. Pharmacokinetics and pharmacodynamics

No pharmacokinetics or pharmacodynamic studies has been performed, which is in accordance with current guidance for vaccines with no new biological or chemical entities.

2.4.3. Conclusions on clinical pharmacology

N/A

2.5. Clinical efficacy

2.5.1. Dose response studies

With respect to safety, Protocols 001, 002, and 003 showed that all formulations tested [AR5I (12,10), PR5I (3,10), PR5I (6,10) and PR5I (6,15)] had an acceptable tolerability profile. Of the PRP-OMPC-containing formulations [PR5I (3,10), PR5I (6,10) and PR5I (6,15)], the formulation with the lower amount of PRP and HBsAg antigen [PR5I (3,10)] had the lowest rate of fever and systemic adverse experiences. Therefore, PR5I (3,10) was selected for further development based on a slightly more favourable safety and tolerability profile, compared to the other PR5I formulations studied.

With respect to immunogenicity, Protocols 002 and 003 demonstrated that the hexavalent vaccine formulation containing PRP-T (i.e. AR5I (12,10) did not meet the pre-specified acceptability criteria for the expected response rates for PRP; therefore, this formulation was not pursued for further clinical development. Each of the 3 PR5I formulations [PR5I (3, 10), (PR5I 6, 10), and PR5I (6, 15)] studied in Protocols 002 and 003 met the pre-specified acceptability criteria and were considered as candidates for further development.

With respect to safety, the Phase I/IIa program showed that all formulations tested had an acceptable tolerability profile; however, the PR5I (3,10) group was associated with the lowest rate of fever and systemic adverse events. This formulation was selected for evaluation in the Phase IIb study (Study 004) based on a slightly more favourable safety and tolerability profile, compared to the other PR5I formulations studied.

Study 001

- Sample size

With 30 subjects enrolled and evaluable for safety per group, if the true incidence rate of serious clinical adverse experiences was 1 in every 44 vaccine recipients (2.3%), there was a 50% chance of observing at least one serious adverse experience in each group. The chance of observing a serious adverse experience was 80%, if the true incidence rate was 1 in every 19 vaccine recipients (5.2%).

- Statistical methods

Prebooster and Postbooster antibody response rates were summarized, with 2-sided 95% CIs calculated by the exact method of Clopper-Pearson. Prebooster and Postbooster GMTs for each antigen were summarized, with 2-sided 95% CIs based on the t distribution, using log transformed titres. There was no imputation of missing data.

Study 002

- Sample size

The power calculation for the primary hypothesis was based on the exact binomial test using the multiplicity-adjusted error rate of =0.00625 (one-sided) to account for the 4 formulations tested in the hypothesis. It assumes that for each antigen, the true response rate is equal to the expected response rate and that the lower bound limit is as specified. With 177 subjects enrolled per group and assuming 85% evaluability, at least 150 subjects per group were expected to contribute to the primary analysis.

- Statistical methods

The primary hypothesis of the study was that at least 1 of the formulations of HR5I administered as a primary series starting at 2 months of age will be acceptable with respect to Postdose 3 antibody responses to all antigens. If the lower bound of the 95% confidence interval for the antibody response rate was above the specified lower bound limit (PRP, the 4 Pertussis : 70%, HBs, diphtheria: 80%, Tetanus and the 3 Polio: 85%), then that formulation was considered to have acceptable antibody response for that antigen. To address the primary hypothesis, for antibody response to each antigen, an exact one sided test for a 1 sample binomial proportion was performed at the multiplicity-adjusted 2.5% significance level for each of the 4 formulations.

If P0 is the pre-specified lower limit of antibody response, for each formulation f, such methodology tested a null hypothesis of an antibody response rate being P0 or less (H0: $Pf \leq P0$) against the alternative hypothesis that the antibody response rate is greater than P0 (HA: $Pf > P0$), where Pf is the true antibody response from formulation f. The null hypothesis was rejected if the p-value of this test was α or less. The $(1-2\alpha)\times 100\%$ confidence interval on the antibody response rate from formulation f was calculated by the exact method of Clopper-Pearson.

For secondary endpoints, confidence intervals on antibody response rates were provided by the Clopper-Pearson exact method and confidence intervals on GMTs were provided based on the t-distribution. Individual titre values were log transformed prior to analysis; means and confidence intervals were back transformed to the original scale.

Study 003

- Sample size

The power calculation for the primary hypothesis was based on the exact binomial test using the multiplicity-adjusted error rate of =0.0083 (one-sided) to account for the 3 formulations tested in the hypothesis. It assumes that for each antigen, the true response rate is equal to the expected response rate and that the lower bound limit is as specified. With 177 subjects enrolled per group and assuming 85% evaluability, at least 150 subjects per group should contribute to the primary analysis.

- Statistical methods

The primary hypothesis of the study was that at least 1 of the 3 formulations of HR5I administered as a primary series starting at 2 months of age will be acceptable (similar to targeted rates) with respect to Postdose 3 antibody responses to all antigens. If the lower bound of the 95% confidence interval for the antibody response rate was above the specified lower bound limit: PRP, the 4 Pertussis : 70%, HBs, diphtheria: 80%, Tetanus and the 3 Polio: 85%) ,then that formulation was considered to have acceptable

antibody response for that antigen. The same technique was used for the secondary hypothesis of the study. The secondary hypothesis was that at least 1 of the 3 formulations of HR5I administered as a primary series starting at 2 months of age will be acceptable (acceptability criteria are based on the lower bound limit of the CIs) with respect to Postdose 2 antibody responses to all antigens.

The statistical methods applied for studies P001, P002 and P003 are considered appropriate.

Study 004

A Phase IIb study (Protocol 004) was conducted to confirm the immunogenicity and safety profile of PR5I with the final formulation of PR5I, and the study results supported the initiation of the Phase III clinical development program. The study was also designed to obtain descriptive concomitant use data with pneumococcal conjugate vaccine (Prevenar 7-valent). Overall, the results show that the hepatitis B component as used in final formulation of PR5I (with the adjuvant composition change) elicited acceptable anti hepatitis B immune responses. Furthermore, the results support that the co-administration of Prevenar with PR5I met the pre-specified immunogenicity criteria. The safety profile of PR5I with concomitant Prevenar administration was also acceptable.

2.5.2. Main studies

Study 007

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 paediatric vaccines (ProQuad, RotaTeq, and Prevenar 13). This was a double-blind, randomized, active comparator controlled Phase III study conducted in healthy infants (46 to 74 days of age at enrolment) at 40 study centres across Finland, Germany, and Belgium.

Protocols 007 and 008 were designed to meet immunization requirements of the EU, including varied vaccination schedules and concomitant administration with pneumococcal conjugate vaccine (Prevenar 13), rotavirus vaccines (RotaTeq and Rotarix), and quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine (ProQuad). The schedules chosen for the Phase III program were designed to provide information on the condensed infant schedule (2, 3, 4 and 12 months in Protocol 007) and the most immunologically rigorous example of a 3-dose schedule (2, 4, and 11 to 12 months in Protocol 008).

Eligible subjects were randomized in a 1:1 ratio to receive either PR5I or INFANRIX hexa at 2, 3, 4, and 12 months of age. Subjects in both groups received the same concomitant vaccines (i.e. Prevenar 13 and RotaTeq at 2, 3, and 4 months of age; and ProQuad at 12 and 13 months of age) as part of the study.

This study was designed to (see also table 4):

(1) to test the acceptability of immune responses to PR5I,

(2) to compare the immunogenicity of PR5I to INFANRIX hexa,

(3) to evaluate the immunogenicity of concomitantly administered ProQuad,

(4) to ensure that PR5I can be administered with other pediatric vaccines given at the same age,

(5) to describe the safety and tolerability profile of PR5I.

Table 4. Study design of Protocol 007

Group	Infant Series[†]				Toddler Dose	Follow-up Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Age: 2 months	Age: 3 months	Age: 4 months	Age: 5 months	Age: 12 months	Age: 13 months
1	*Blood Draw* **PR5I** Prevenar 13™ RotaTeq™	**PR5I** Prevenar 13™ RotaTeq™	**PR5I** Prevenar 13™ RotaTeq™	*Blood Draw*	*Blood Draw* **PR5I** **ProQuad™**	*Blood Draw* Prevenar 13™[‡] ProQuad™
2	*Blood Draw* **INFANRIX ™ hexa** Prevenar 13™ RotaTeq™	**INFANRIX ™ hexa** Prevenar 13™ RotaTeq™	**INFANRIX ™ hexa** Prevenar 13™ RotaTeq™	*Blood Draw*	*Blood Draw* **INFANRIX™ hexa** **ProQuad™**	*Blood Draw* Prevenar 13™[‡] ProQuad™

[†] Blood specimens (~3 mL at Visit 1 and ~5 mL at Visits 4, 5, and 6) were collected for all subjects as follows: (1) within 5 days prior to administration of Dose 1 (Visit 1); (2) Postdose 3 (28 to 37 days) (Visit 4); (3) within 5 days prior to administration of Toddler dose (Visit 5); and (4) after Toddler Dose (28 to 37 days) (Visit 6). The method of blood draw was venipuncture (by vein).
[‡] Fourth dose of Prevenar 13™ and second dose of ProQuad™ were given at 13 mos, during the last study visit.
Note: The bold text indicates vaccines administered and analyzed by hypothesis-driven testing as part of the study. Injectable concomitant vaccines were administered to the leg opposite that receiving PR5I/INFANRIX™ hexa.
A telephone contact (Visit 7) was conducted between 28 and 35 days after the final doses of Prevenar 13™ and ProQuad™ were administered (Visit 6).

Methods

Study Participants

Inclusion Criteria

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

1. Subject is a healthy infant and is ≥ 46 days and ≤ 74 days of age on the day of vaccination.
2. Subject's parent(s)/legal representative understand the study procedures, alternate vaccinations available, and risks involved with the study, and voluntarily agree to participate by giving written informed consent.
3. Subject's parent(s)/legal representative are able to read, understand, and complete study questionnaires (i.e., the Vaccination Report Card [VRC]).
4. Subject is able to attend all scheduled visits and to comply with the study procedures.
5. Subject's parent(s)/legal representative has access to a telephone.

Exclusion Criteria

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

1. Subject is currently participating or has participated in a study with an investigational compound or device within 4 weeks of expected first dose of PR5I/ vaccine Control(s).
2. Subject's parent(s)/legal representative plans to enrol 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 entry, 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 (> 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 the 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 a 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 a dose of monovalent hepatitis B vaccine or hepatitis B based combination vaccine prior to study entry.
11. Subject has received previous vaccination with any DTaP- or diphtheria, tetanus, and whole cell pertussis (DTwP)-based combination vaccines, Hib conjugate, poliovirus, pneumococcal conjugate or pneumococcal polysaccharide, rotavirus, measles, mumps, rubella, or varicella vaccines, or combination thereof.
12. *Subject has had a febrile illness within 24 hours prior to enrolment or a rectal temperature $\geq$ 38^{o}C 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 enrolment, except for inactivated influenza vaccine, which is permitted 14 days or more prior to enrolment.
14. Subject has coagulation disorder contraindicating intramuscular (IM) vaccination.
15. Subject has clinically significant findings on review of systems (by medical history) determined by Investigator or sub-Investigator to be sufficient for exclusion.

16. Subject had developmental delay or neurological disorder (by medical history at study entry).
17. Subject or his/her mother has a medical history of HBsAg seropositivity.
18. Subject has history of measles, mumps rubella, varicella, Hib, hepatitis B, diphtheria, tetanus, pertussis, rotavirus, invasive pneumococcal, or poliomyelitis infection.
19. Subject's parent(s)/legal representative 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, Prevenar 13 and ProQuad) as specified in the Summary of Product Characteristics (SmPC).

Once enrolled, the total study duration for each subject (from first to last contact) was approximately 12 months.

Inclusion and exclusion criteria were considered acceptable by the CHMP.

Treatments

Subjects were randomized in a 1:1 ratio to receive either PR5I or INFANRIX hexa. Subjects in the PR5I group received a 0.5 mL dose of PR5I along with Prevenar 13 and RotaTeq at 2, 3, and 4 months, followed by PR5I and ProQuad at 12 months, and Prevenar 13 and ProQuad at 13 months. Subjects in the INFANRIX hexa group received a 0.5 mL dose of INFANRIX hexa along with Prevenar 13, and RotaTeq at 2, 3, and 4 months, followed by INFANRIX hexa and ProQuad at 12 months, and Prevenar 13 and ProQuad at 13 months.

PR5I, INFANRIX hexa, and Prevenar 13 were administered intramuscularly. RotaTeq was administered orally. ProQuad was administered subcutaneously. The preferable injection site of any vaccine for infants is the upper anterolateral thigh. PR5I or INFANRIX hexa were administered in separate limbs from the concomitant vaccines. Prevenar 13 was administered at the lower thigh at 13 months when administered concomitantly with ProQuad.

The schedule of vaccination for each study group is provided in table 5.

Table 5. Vaccine Administration by Vaccination Group

Group	Vaccine Administered	Dose	Route of Administration	Visit 1 2 months	Visit 2 3 months	Visit 3 4 months	Visit 5 12 months	Visit 6 13 months
PR5I	PR5I[1]	0.5 mL	IM	X	X	X	X	
	Prevenar 13™[2]	0.5 mL	IM	X	X	X		X[§]
	RotaTeq™[3]	2.0 mL	Oral	X	X	X		
	ProQuad™[4]	0.5 mL	SC				X	X[§]
INFANRIX hexa™	INFANRIX hexa™[5]	0.5 mL	IM	X	X	X	X	
	Prevenar 13™[2]	0.5 mL	IM	X	X	X		X[§]
	RotaTeq™[3]	2.0 mL	Oral	X	X	X		
	ProQuad™[4]	0.5 mL	SC				X	X[§]

[1] PR5I = V419 = DTaP-IPV-Hib-HepB.
[2] Prevenar 13™ = Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein).
[3] RotaTeq™ = Rotavirus Vaccine, Live, Oral, Pentavalent.
[4] ProQuad™ = Measles, Mumps, Rubella and Varicella Virus Vaccine Live.
[5] INFANRIX™ hexa = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (recombinant deoxyribonucleic acid), poliomyelitis (inactivated), and Haemophilus type b conjugate.
[§] Fourth dose of Prevenar 13™ and second dose of ProQuad™ were given at 13 months, during the last study visit.
DTaP = diphtheria, tetanus, and acellular pertussis, HepB = hepatitis B, Hib = *haemophilus influenzae* type b, IM = Intramuscular, IPV = Inactivated poliovirus, SC = Subcutaneous.

Objectives

Primary Objectives

1. To evaluate the immunogenicity of PR5I when given at 2, 3, 4, and 12 months.
2. To compare the immunogenicity elicited by PR5I to that of INFANRIX hexa when given at 2, 3, 4, and 12 months.

Secondary Objectives

1. To evaluate the immunogenicity of ProQuad when administered concomitantly with the Toddler dose of PR5I.
2. To describe the safety profile associated with the administration of each dose of PR5I or INFANRIX hexa when given concomitantly with Prevenar 13, RotaTeq, and ProQuad.
3. To describe the fever profile from Day 1 through Day 5 after the administration of each dose and after all doses of PR5I or INFANRIX hexa when given concomitantly with Prevenar 13, RotaTeq, and ProQuad.
4. 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 dose of PR5I or INFANRIX hexa when co-administered with Prevenar 13, RotaTeq, and ProQuad.
5. To summarize the incidence of serious adverse events reported during Day 1 through Day 15 following each hexavalent vaccination. Additionally, any serious adverse event brought to the attention of an Investigator at any time outside of the 15 day (Day 1 through Day 15) follow-up period was summarized if the event was either a death, which resulted in the subject discontinuing the study, or a serious adverse event that was considered by an Investigator to be vaccine related.

Tertiary Objectives (Immunogenicity Objectives)

1. To describe the response rates and geometric mean titres (GMTs)/geometric mean concentrations (GMCs) for all antigens in PR5I and INFANRIX hexa at one month after Dose 3 and one month after Toddler dose with 95% CI.
2. To describe the percentage of subjects with titress ≥ 1.0 international units per millilitre (IU/mL) for diphtheria and tetanus after Toddler dose with 95% CI.

Outcomes/endpoints

The immunogenicity of PR5I was evaluated in four Phase III, randomized, active-comparator controlled clinical trials (Protocols 007 and 008 in the EU and Protocols 005 and 006 in the US) and one Phase III, randomized clinical trial (PRI01C in the UK) in support of product licensure. The non-inferiority margins used in the evaluations were based on clinical meaningfulness of the difference, the expected response rate for each antigen, and the observed variability in antibody titre measurement for each antigen. In line with guidance, the margin for response rate is 5 percentage points for antigens with an expected response rate >95% and 10 percentage points for antigens with an expected response rate ≤ 95%. The acceptability criteria are based on accepted thresholds and have been approved by regulatory agencies.

The primary endpoints for the primary hypothesis of acceptability of PR5I were antibody responses to PRP, diphtheria, tetanus, IPV1, IPV2 and IPV3 one month after the third dose of PR5I and antibody responses to all antigens contained in PR5I one month after the Toddler dose of PR5I.

The statistical criteria require that, for all of the PR5I antigens, the lower limit of the 2-sided 95% confidence interval (CI) for the response rate (%) is greater than the predetermined lower limit (P0) as defined in table 6.

Table 6. Postdose 3 and After Toddler Dose Endpoint (12 months) Acceptability Criteria for All Antigens Contained in PR5I

	Primary Endpoint (Postdose 3) EU Criteria	Primary Endpoint (After Toddler Dose) EU Criteria	Assumed True Response Rates (P)	Lower Limit for Acceptability (P0)
PRP	% with titer ≥ 0.15 µg/mL	% with titer ≥ 1.0 µg/mL	90% for Postdose 3 85% for Toddler Dose‡	80% for Postdose 3 75% for Toddler Dose‡
HBsAg	N/A	% with titer ≥ 10 mIU/mL	95% for Toddler Dose	90% for Toddler Dose
Diphtheria	% with titer ≥ 0.01 IU/mL	% with titer ≥ 0.1 IU/mL	90% for Postdose 3 and Toddler Dose	80% for Postdose 3 and Toddler Dose
Tetanus	% with titer ≥ 0.01 IU/mL	% with titer ≥ 0.1 IU/mL	97% Postdose 3 and Toddler Dose	90% for Postdose 3 and Toddler Dose
Pertussis – PT	N/A	% seroresponse †	85% for Toddler Dose	75% for Toddler Dose
Pertussis – FHA	N/A	% seroresponse †	85% for Toddler Dose	75% for Toddler Dose
Pertussis – FIM	N/A	% seroresponse †	85% for Toddler Dose	75% for Toddler Dose
Pertussis – PRN	N/A	% seroresponse†	85% for Toddler Dose	75% for Toddler Dose
IPV1	% with NAb ≥ 1:8 dilution	% with NAb ≥ 1:8 dilution	97% for Postdose 3 and Toddler Dose	90% for Postdose 3 and Toddler Dose
IPV2	% with NAb ≥ 1:8 dilution	% with NAb ≥ 1:8 dilution	97% for Postdose 3 and Toddler Dose	90% for Postdose 3 and Toddler Dose
IPV3	% with NAb ≥ 1:8 dilution	% with NAb ≥ 1:8 dilution	97% for Postdose 3 and Toddler Dose	90% for Postdose 3 and Toddler Dose

† Pertussis seroresponse Post Toddler dose was defined as follows: (1) If prevaccination antibody concentration was < 4 x LLOQ, then the postvaccination antibody concentration was ≥ 4 x LLOQ, (2) If prevaccination antibody concentration was ≥ 4 x LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels.
‡ The After Toddler Dose criteria for the anti-PRP response in the EU was the % with titer ≥ 1.0 µg/mL, which was different from the Postdose 3 criteria, which was the % with titer ≥ 0.15 µg/mL.
EU = European Union, FHA = Filamentous hemagglutinin, FIM = Fimbriae types 2 and 3, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, LLOQ = Lower limit of quantitation, N/A = Not applicable, NAb = Neutralizing antibodies, PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid.

The primary endpoints for the primary hypothesis of non-inferiority of PR5I were antibody responses rates to antigens that are common to both PR5I and INFANRIX hexa and included PRP, diphtheria, tetanus, IPV1, IPV2 and IPV3 one month after the third dose of PR5I and pertussis and HBsAg one month after the Toddler dose of PR5I.

Conditional upon acceptance of primary hypothesis #1, when compared with subjects who receive INFANRIX hexa at 2, 3, 4, and 12 months, the subjects who receive PR5I at 2, 3, 4, and 12 months have:

(a) Non-inferior response rates against PRP, diphtheria, tetanus, IPV1, IPV2, and IPV3 at one month after the third dose of PR5I, assessed by seroprotection rates.

(b) Non-inferior response rates against pertussis antigens (PT, FHA and PRN) at one month after the Toddler dose of PR5I, assessed by seroresponse rates.

(c) Non-inferior response rates against HBsAg at one month after the Toddler dose of PR5I, assessed by the seroprotection rate.

The statistical criteria for non-inferior response rate require that the lower limit of the 2-sided 95% CI for the difference in rates (PR5I group minus INFANRIX hexa group) is greater than the prespecified non-inferiority margin (-δ) as defined in Table 7.

Table 7. Endpoints and Prespecified Non-inferiority Margin for Each Antigen Being Tested

Time Point	Antigen	Primary Endpoint EU Criteria	Assumed True Response Rates (P)	Non-inferiority Margin (δ)
Postdose 3	PRP	% with titer ≥ 0.15 µg/mL	90%	10%
After Toddler Dose	HBsAg	% with titer ≥ 10 mIU/mL	95%	10%
Postdose 3	Diphtheria	% with titer ≥ 0.01 IU/mL	90%	10%
Postdose 3	Tetanus	% with titer ≥ 0.01 IU/mL	97%	5%
After Toddler Dose	Pertussis–PT	% seroresponse[†]	85%	10%
After Toddler Dose	Pertussis–FHA	% seroresponse[†]	85%	10%
After Toddler Dose	Pertussis–PRN	% seroresponse[†]	85%	10%
Postdose 3	IPV1	% with NAb ≥ 1:8 dilution	97%	5%
Postdose 3	IPV2	% with NAb ≥ 1:8 dilution	97%	5%
Postdose 3	IPV3	% with NAb ≥ 1:8 dilution	97%	5%

[†] Pertussis seroresponse Postdose 3 was defined as follows: (1) If prevaccination antibody concentration was < LLOQ, then the postvaccination antibody concentration was ≥ LLOQ, (2) If prevaccination antibody concentration was ≥ LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. Pertussis seroresponse Post Toddler dose was defined as follows: (1) If prevaccination antibody concentration was < 4 x LLOQ, then the postvaccination antibody concentration was ≥ 4 x LLOQ, (2) If prevaccination antibody concentration was ≥ 4 x LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels.

EU = European Union, FHA = Filamentous hemagglutinin, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, LLOQ = Lower limit of quantitation, NAb = Neutralizing antibodies, PRN = Pertactin, PRP = Polyribosylribitol phosphate; PT = Pertussis toxoid.

The secondary endpoints for the non-inferiority and acceptability of ProQuad concomitantly administered with the Toddler dose of PR5I were antibody response rates at one month after the concomitant administration of ProQuad and the Toddler dose of PR5I (Table 8).

The statistical criteria required that:

a. For each antigen contained in ProQuad, the lower limit of the 2-sided 95% CI is greater than the prespecified limit (90% for measles, mumps, and rubella, and 76% for varicella).

b. For each antigen contained in ProQuad, the lower limit of the 2-sided 95% CI for the difference in rates (PR5I with ProQuad group vs. INFANRIX hexa with ProQuad group) is greater than the prespecified margins (-0.05 for measles, mumps, and rubella, and -0.10 for varicella).

Table 8. Definition of Endpoints and Non-inferiority Criteria for Concomitant Use Vaccines

Concomitant Use Vaccine	Antigens	Endpoint	Assumed True Response Rates (P)	Non-inferior Margin (δ)	Lower Limit for Acceptability (P0)
ProQuad™	Measles	% with titer ≥ 255 mIU/mL	96%	5%	90%
	Mumps	% with titer ≥ 10 Ab Units/mL	96%	5%	90%
	Rubella	% with titer ≥ 10 IU/mL	96%	5%	90%
	Varicella	% with titer ≥ 5 gpELISA Units/mL	90%	10%	76%
gpELISA = glycoprotein enzyme-linked immunosorbent assay.					

For pertussis, the predetermined lower limit was established by surveying results from previous phase II studies, other studies with monovalent PR5I components tested in different laboratories and study 004. These data were used to adjust the acceptability criteria used in phase III trials. Margins and non-inferiority criteria were discussed with US and EU Regulatory authorities and were accepted. The non-inferiority margins used for pertussis are also commonly used for licensure of different vaccines. The CHMP found this justification acceptable.

It was noted that the evaluation of the pertussis antigens after 3 doses and the evaluation of the Hib, diphtheria, tetanus and polio components post-booster/toddler were explored as tertiary endpoints.

Diseases targeted by PR5I

For all antigens but pertussis, defined correlates of protection have been established and are accepted as indicators of protection against the disease:

- For diphtheria and tetanus, Ab levels ≥ 0.01 IU/mL and ≥ 0.1 IU/mL are associated with the minimum and the optimal recognized seroprotective levels, respectively, following primary series vaccination. For the booster, an Ab level ≥ 1.0 IU/mL is associated with Ab long-term persistence;
- For each poliomyelitis type, neutralizing Ab titres ≥ 8 (1/dil) are considered protective against their respective 3 poliovirus strains;
- For hepatitis B, Ab level of 10 mIU/mL is accepted as the minimal level correlating with short- and long-term protection;
- For Haemophilus influenzae type b, antibody levels ≥ 0.15 µg/mL and ≥ 1.0 µg/mL are associated with short- and long-term protection, respectively.

There are no established correlates of protection for pertussis.

Sample size

Target enrolment was 620 subjects would be enrolled in each vaccination group, with the evaluability was assumed to be 85% at Postdose 3 and 80% after the Toddler dose. The assumed true response rates and standard deviation (SD) were based on previous studies in the program development as well as the studies using component vaccines. With the sample size of this study, the power was 98.8% for the primary hypothesis of acceptability and 94.5% for the primary hypothesis of non-inferiority. The overall Type I error rate was α=0.025 one-sided. The power calculation was based on the normal approximation of a binary response for the acceptability hypothesis, and a method by Farrington and Manning for the non-inferiority

hypothesis. The pre-defined non-inferiority margins applied were 10% for PRP, HBs, diphtheria, Pertussis and 5% for the 3 polio, and tetanus.

The methods applied for sample size calculation are acceptable.

Randomisation

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 number using the Interactive response technology (IRT) system. The IRT system assigned the subject an allocation number according to the allocation schedule and then subsequently assigned a unique Component Identification number for the vial of clinical material to be administered at that visit. The study personnel accessed the IRT at each subsequent visit when administration of vaccine occurred for assignment of a unique vial identification number for the clinical material to be administered to the subject. Each allocation number was used only once. Allocation numbers were not reassigned for any reason. Randomization deviations (e.g., a subject being assigned 2 allocation numbers by mistake through IRT) required written documentation. A single subject could not be assigned more than one allocation number.

The described randomization procedure is considered appropriate.

Blinding (masking)

This was a double-blind (operating under in-house and third party blinding procedures) study. The parent(s)/legal representative of the subject, the Investigator (with the exception of the unblinded study personnel responsible for preparation of study vaccines), laboratory testing personnel, and SPONSOR/SPONSOR Representative personnel were blinded to the vaccination group assigned until the subjects had completed the study, the data were screened for completeness and accuracy, and the database was locked and unblinded.

Because INFANRIX hexa was provided as 2 components (i.e., lyophilized Hib and liquid DTaP, IPV, and hepatitis B) to be reconstituted; an unblinded individual at each study site who was otherwise not involved in the conduct of the study was required to prepare study vaccines to maintain the study blind. This member of the study site staff was unblinded for the purpose of receiving, maintaining, accounting and preparing the study vaccines. No blinded study person(s) who had contact with the subjects had access to the study vaccines at any time. Site staff performing the safety assessments (including injection-site adverse events) and immunogenicity assessments, were blinded to the identity of study vaccines.

Statistical methods

The analysis sets and the statistical methods for the primary and secondary immunogenicity analyses are presented in the following table:

Table 9. Summary of key immunogenicity analysis performed

Analysis/Endpoint		Type of Analysis	Method	Population	
				Main Analysis	Supportive Analysis
Primary Immunogenicity Analysis					
Acceptability regarding response rates for PRP, diphtheria, tetanus, IPV Types 1, 2, and 3 at Postdose 3, and for all PR5I antigens at Toddler Dose		95% CI for single group proportion	Exact binomial	PP-RW, PP-OW	FAS
Non-inferiority regarding response rates for PRP, diphtheria, tetanus, IPV Types 1, 2, and 3 at Postdose 3, and for HBsAg and pertussis PT, FHA, PRN at Toddler Dose		p-value and 95% CI for response rate difference	Miettinen and Nurminen method	PP-RW PP-OW	FAS
Secondary Immunogenicity Analysis					
Concomitant use with ProQuad™	Acceptability regarding response rates at Toddler Dose	95% CI for single group proportion	Exact binomial	PP-RW, PP-OW	FAS
	Non-inferiority regarding response rates at Toddler Dose	p-value and 95% CI for response rate difference	Miettinen and Nurminen method	PP-RW, PP-OW	FAS

CI = Confidence interval, FAS = Full analysis set, FHA = Filamentous hemagglutinin, HBsAg = Hepatitis B surface antigen, IPV = Inactivated polio vaccine, PP-OW = Per-protocol-Original Windows (defined as a blood draw sample window of Days 28 to 44 following Dose 3 or the toddler dose), PP-RW = Per-protocol-Revised Windows (defined as 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.

The primary hypothesis was the acceptability of the vaccine-induced antibody response rates as listed in the following table:

Table 10. Postdose 3 and after Toddler dose endpoint (12 months) acceptability criteria for all antigens contained in PR5I

	Primary Endpoint (Postdose 3) EU Criteria	Primary Endpoint (After Toddler Dose) EU Criteria	Assumed True Response Rates (P)	Lower Limit for Acceptability (P0)
PRP	% with titer ≥ 0.15 µg/mL	% with titer ≥ 1.0 µg/mL	90% for Postdose 3 85% for Toddler Dose‡	80% for Postdose 3 75% for Toddler Dose‡
HBsAg	N/A	% with titer ≥ 10 mIU/mL	95% for Toddler Dose	90% for Toddler Dose
Diphtheria	% with titer ≥ 0.01 IU/mL	% with titer ≥ 0.1 IU/mL	90% for Postdose 3 and Toddler Dose	80% for Postdose 3 and Toddler Dose
Tetanus	% with titer ≥ 0.01 IU/mL	% with titer ≥ 0.1 IU/mL	97% Postdose 3 and Toddler Dose	90% for Postdose 3 and Toddler Dose
Pertussis – PT	N/A	% seroresponse†	85% for Toddler Dose	75% for Toddler Dose
Pertussis – FHA	N/A	% seroresponse†	85% for Toddler Dose	75% for Toddler Dose
Pertussis – FIM	N/A	% seroresponse†	85% for Toddler Dose	75% for Toddler Dose
Pertussis – PRN	N/A	% seroresponse†	85% for Toddler Dose	75% for Toddler Dose
IPV1	% with NAb ≥ 1:8 dilution	% with NAb ≥ 1:8 dilution	97% for Postdose 3 and Toddler Dose	90% for Postdose 3 and Toddler Dose
IPV2	% with NAb ≥ 1:8 dilution	% with NAb ≥ 1:8 dilution	97% for Postdose 3 and Toddler Dose	90% for Postdose 3 and Toddler Dose
IPV3	% with NAb ≥ 1:8 dilution	% with NAb ≥ 1:8 dilution	97% for Postdose 3 and Toddler Dose	90% for Postdose 3 and Toddler Dose

† Pertussis seroresponse Post Toddler dose was defined as follows: (1) If prevaccination antibody concentration was < 4 x LLOQ, then the postvaccination antibody concentration was ≥ 4 x LLOQ, (2) If prevaccination antibody concentration was ≥ 4 x LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels.
‡ The After Toddler Dose criteria for the anti-PRP response in the EU was the % with titer ≥ 1.0 µg/mL, which was different from the Postdose 3 criteria, which was the % with titer ≥ 0.15 µg/mL.
EU = European Union, FHA = Filamentous hemagglutinin, FIM = Fimbriae types 2 and 3, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, LLOQ = Lower limit of quantitation, N/A = Not applicable, NAb = Neutralizing antibodies, PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid.

For antibody response to each component, 95% CI for the single group proportion was calculated based on the exact binomial method proposed by Clopper-Pearson. The success criterion required the lower limit of the 2-sided 95% CI for each of the PR5I antigens to be greater than the corresponding pre-specified limit as given in the last column of the table. In addition to the primary analysis, supportive analyses were also performed using the FAS population. For each PR5I antigen, the antibody response rate and its 95% CI were calculated using the same exact binomial method as for the primary acceptability analysis.

The non-inferiority of the vaccine-induced response rate was tested individually for each component involved. For each tested antigen, the hypotheses tested were as follows:

Null hypothesis H_0: $P_1 - P_2 \leq -\delta$ versus

Alternative hypothesis H_1: $P_1 - P_2 > -\delta$

The δ non-inferiority limit is set at 10% for PRP, HbsAg, Diphtheria, Pertussis-PT, Pertussis-FHA, Pertussis-PRN, and at 5% for tetanus and the 3 poliovirus. For each antigen, non-inferiority was

demonstrated if the lower limit of the 2-sided 95% CI was greater than - δ. The non-inferiority of PR5I was reached if the null hypotheses for each valence tested were rejected. The p-value and 95% CI were calculated based on an asymptotic method proposed by Miettinen and Nurminen stratified by country.

Table 11. Endpoints and prespecified non-inferiority margin for each antigen being tested.

Time Point	Antigen	Primary Endpoint EU Criteria	Assumed True Response Rates (P)	Non-inferiority Margin (δ)
Postdose 3	PRP	% with titer ≥ 0.15 µg/mL	90%	10%
After Toddler Dose	HBsAg	% with titer ≥ 10 mIU/mL	95%	10%
Postdose 3	Diphtheria	% with titer ≥ 0.01 IU/mL	90%	10%
Postdose 3	Tetanus	% with titer ≥ 0.01 IU/mL	97%	5%
After Toddler Dose	Pertussis–PT	% seroresponse[†]	85%	10%
After Toddler Dose	Pertussis–FHA	% seroresponse[†]	85%	10%
After Toddler Dose	Pertussis–PRN	% seroresponse[†]	85%	10%
Postdose 3	IPV1	% with NAb ≥ 1:8 dilution	97%	5%
Postdose 3	IPV2	% with NAb ≥ 1:8 dilution	97%	5%
Postdose 3	IPV3	% with NAb ≥ 1:8 dilution	97%	5%

[†] Pertussis seroresponse Postdose 3 was defined as follows: (1) If prevaccination antibody concentration was < LLOQ, then the postvaccination antibody concentration was ≥ LLOQ, (2) If prevaccination antibody concentration was ≥ LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. Pertussis seroresponse Post Toddler dose was defined as follows: (1) If prevaccination antibody concentration was < 4 x LLOQ, then the postvaccination antibody concentration was ≥ 4 x LLOQ, (2) If prevaccination antibody concentration was ≥ 4 x LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels.

EU = European Union, FHA = Filamentous hemagglutinin, HBsAg = Hepatitis B surface antigen, IPV = Inactivated poliovirus, LLOQ = Lower limit of quantitation, NAb = Neutralizing antibodies, PRN = Pertactin, PRP = Polyribosylribitol phosphate; PT = Pertussis toxoid.

The analysis method for testing secondary hypothesis of concomitant use of ProQuad was the same method by Clopper and Pearson and the analysis method for the evaluation of Non-inferiority of ProQuad antigens based on response rates was the same method by Miettinen and Nurminen.

Overall, the statistical methods applied were considered appropriate.

Handling of dropouts or missing data

For subjects whose antibody titre values were below the LLOQ, their antibody titre values, reported as < LLOQ by the testing laboratory, were replaced by 0.5xLLOQ for calculating GMT. Values that were greater than the ULOQ were converted to the ULOQ. Missing and incomplete data were not replaced. Subjects with missing or incomplete data of a particular endpoint were not included in the primary analyses of the endpoint.

No search for outliers was done. Immunogenicity data were considered validated.

Amendments

There were 5 protocol amendments following finalization of the original protocol and the amendments were initiated and finalized prior to the database lock and unblinding. The original protocol was not submitted to the countries' Ethical Committees as the protocol was amended and first amendment finalized prior to the initiation of the study.

The introduced changes have no impact on study population and unlikely to jeopardize the integrity of the study.

Study populations for Immunogenicity Analysis

Two Per-Protocol populations (PP), PP-Revised Windows (PP-RW) and PP-Original Windows (PP-OW), were used in the 4 Phase III studies (Protocols 005, 006, 007 and 008). The two PP populations were the same except for the allowed day ranges for vaccinations (Protocols 005 and 006) and blood sample draws (Protocols 005, 006, 007 and 008). The day ranges for vaccination in the EU studies were not changed due to the compressed vaccination schedules (compressed 3-dose infant series in Protocol 007 and 2-dose infant series in Protocol 008). PP-RW is defined as the per-protocol population using a blood draw sample window of Days 28 to 51 following Dose 3 or the toddler dose. PP-OW is defined as the per-protocol population using a blood draw sample window of Days 28 to 44 following Dose 3 or the toddler dose (see Table 12).

These revised visit windows for the PP-RW population allow for more subjects to be included in the statistical analyses for these studies and are consistent with the windows used to define PP population in the Phase IIa studies (Protocols 002 and 003). Prior to this change, the data from Protocol 003, as a model dataset for PR5I, were analysed using both PP-OW and PP-RW vaccination and blood draw windows. Importantly, GMT for all antigen responses were similar and the main immunogenicity conclusions from these early phase studies remained the same regardless of the visit window used to define the PP population.

The statistical analyses for the Phase III studies (Protocols 005, 006, 007 and 008) were conducted using both PP populations. As pre-specified in the individual study protocols, the success of the hypothesis test was based on the results from the PP-RW population. This change was provided to CBER as part of an amendment to the statistical analysis plans for the US studies which was implemented prior to unblinding/the database lock for Protocols 005 and 006. The amended protocols for Protocols 007 and 008 were also submitted to the respective EU health authorities in 2013.

Key immunogenicity summaries and analyses were also provided for all endpoints associated with hypotheses using the Full Analysis Set (FAS) population. The FAS population included all randomized subjects with available serology data for each serology time point. Subjects were included in the vaccination group to which they were randomized for data analysis.

Table 12. Definitions of PP Populations based on vaccination and serology visit windows

Vaccination	Population (Protocols 005 and 006)	
	PP-RW	PP-OW
Dose 1	46 to 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.	
Serology Sample	Population (Protocols 005, 006, 007)	
	PP-RW	PP-OW
Prior to Dose 1	within 5 days of vaccination	
Postdose 3	28 to 51 days	28 to 44 days
Prior to Toddler Dose	within 5 days of vaccination	
Post Toddler Dose	28 to 51 days	28 to 44 days
	Population (Protocol 008)	
	PP-RW	PP-OW
Prior to Dose 1	within 5 days of vaccination	
Postdose 2	28 to 51 days	28 to 44 days
Prior to Toddler Dose	within 5 days of vaccination	
Toddler Dose	28 to 51 days	28 to 44 days
PP-RW= Per-protocol Revised Window population; PP-OW = Per-protocol Original Window population.		

Non-inferiority margins

The non-inferiority margins used in the evaluations were based on clinical meaningfulness of the difference, the expected response rate for each antigen, and the observed variability in antibody titre measurement for each antigen. In line with guidance, the margin for response rate is 5 percentage points for antigens with an expected response rate >95% and 10 percentage points for antigens with an expected response rate ≤ 95%.

As mentioned above, acceptability criteria are based on accepted thresholds and have been approved by regulatory agencies. This approach was endorsed by the CHMP.

Results

Subject disposition

Overall, 40 investigative sites were evaluated and considered eligible to screen a total of 1271 subjects for study participation. A total of 1250 healthy infants were randomized in a 1:1 ratio to receive either PR5I or INFANRIX hexa. Following an audit at Site 0048 in Germany, it was identified that safety data from this study site were noted to be outside of the range of results for the study as a whole (e.g. all temperatures were in the afebrile range and the rate of unsolicited systemic adverse events was 0 as compared with >70% of subjects from the other study sites who reported fever, and >70% of subjects from the other study sites who reported unsolicited systemic adverse events), as well as noting major findings in study conduct and monitoring. Therefore, all data from this site (33 subjects) were excluded from main safety and immunogenicity analyses. This decision was made prior to database lock and was communicated to the regulatory authorities

Of the 1271 subjects screened, 1250 subjects were randomized. Excluding the 33 subjects from Site 0048, 1217 randomized subjects were used for all subsequent analyses in this clinical study report. A total of 1215

subjects received study vaccinations. The disposition of subjects is provided by vaccination group for all randomized subjects in Table 13. The subjects randomized to the PR5I group (611 subjects) received PR5I, Prevenar 13, and RotaTeq at 2, 3, and 4 months followed by PR5I and ProQuad at 12 months, and Prevenar 13 and ProQuad at 13 months. The subjects randomized to the INFANRIX hexa group (606 subjects) received INFANRIX hexa, Prevenar 13, and RotaTeq at 2, 3, and 4 months, followed by INFANRIX hexa and ProQuad at 12 months, and Prevenar 13 and ProQuad at 13 months.

Table 13. Subject Disposition (All Subjects)

	PR5I		INFANRIX™ hexa		Total	
	n	(%)	n	(%)	n	(%)
All subjects screened					1271	
Screened subjects excluding Site 0048					1238	
All subjects randomized	628		622		1250	
Randomized subjects excluding Site 0048	611		606		1217	
Not vaccinated	1	(0.2)	1	(0.2)	2	(0.2)
Received all 3 doses of the Infant Series (PR5I / INFANRIX™ hexa)[1]	598	(97.9)	590	(97.4)	1188	(97.6)
Received all 3 doses of the Infant Series (PR5I / INFANRIX™ hexa) and all doses of concomitant study vaccines [2]	598	(97.9)	589	(97.2)	1187	(97.5)
Did not complete the Infant Series (PR5I / INFANRIX™ hexa)	12	(2.0)	15	(2.5)	27	(2.2)
Reason for Withdrawal: [3]						
Adverse Event	0	(0.0)	5	(0.8)	5	(0.4)
Lost to Follow-up	0	(0.0)	2	(0.3)	2	(0.2)
Protocol Violation	1	(0.2)	0	(0.0)	1	(0.1)
Withdrawal by Subject	11	(1.8)	8	(1.3)	19	(1.6)
Discontinued between the Infant Series and Toddler Dose	8	(1.3)	9	(1.5)	17	(1.4)
Reason for Withdrawal: [3]						
Lost to Follow-up	2	(0.3)	0	(0.0)	2	(0.2)
Physician Decision	0	(0.0)	1	(0.2)	1	(0.1)
Protocol Violation	0	(0.0)	1	(0.2)	1	(0.1)
Withdrawal by Subject	6	(1.0)	7	(1.2)	13	(1.1)
Received Toddler Dose vaccinations [4]	590	(96.6)	582	(96.0)	1172	(96.3)
Completed Toddler Dose [5]	539	(88.2)	548	(90.4)	1087	(89.3)
Discontinued after Toddler Dose	0	(0.0)	3	(0.5)	3	(0.2)
Reason for Withdrawal: [3]						
Adverse Event	0	(0.0)	2	(0.3)	2	(0.2)
Withdrawal by Subject	0	(0.0)	1	(0.2)	1	(0.1)

Note: Row 1 and row 3 were based on all subjects in the study. All other rows were based on the subjects excluding Site 0048.
[1] Received all 3 infant dose vaccinations of PR5I / INFANRIX™ hexa.
[2] Received all 3 infant full dose vaccinations of PR5I / INFANRIX™ hexa and all full doses of concomitant associated study vaccines.
One subject did not receive a full dose of INFANRIX™ hexa and was not included in this summary.
[3] Percentages were based on the number of randomized subjects excluding Site 0048 who received at least 1 dose of PR5I or INFANRIX™ hexa.
[4] Received Toddler Dose of PR5I / INFANRIX™ hexa (including 1 subject who received INFANRIX™ hexa at non-study visits).
[5] Received Toddler Dose of PR5I / INFANRIX™ hexa and ProQuad™ (including subjects who received vaccines at non-study visits).
Percentages were based on the number of randomized subjects excluding Site 0048.
Subjects received PR5I / INFANRIX™ hexa at 2, 3, 4 and 12 mos; RotaTeq™ at 2, 3 and 4 mos; Prevenar 13™ at 2, 3, 4 and 13 mos; ProQuad™ at 12 and 13 mos.
One primary reason for discontinuation per subject was reported.
mos = Months, n = Number of subjects in analysis.

The most frequent reason for discontinuing from the infants series or between the infant series and the Toddler dose was Withdrawal by subject. The reasons for discontinuing the Toddler dose were Adverse event

and Withdrawal by subject. Adverse events were reported as reason for withdrawal only in the active comparator group (Infanrix hexa).

Recruitment

The study was conducted between 26 May 2011 and 13 March 2013 in the EU (Belgium, Finland, Germany).

Conduct of the study

Studies were conducted in accordance with Good Clinical Practice as described in ICH Harmonized Tripartite Efficacy Guideline E6, including compliance with Ethics Committee/Institutional Review Board and informed consent regulations/guidances/guidelines.

Baseline data

The baseline subject's demographics and other characteristics were well balanced between two study groups (Table 14). Among all randomized subjects, 52.3% were male and 47.7% were female. The mean age of subjects was 61.5 days (range: 46 days to 78 days). The mean weight of subjects was 5.4 kg (range: 3.1 kg to 8.0 kg).

Table 14. Subjects characteristics

	PR5I		INFANRIX™ hexa		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	611		606		1217	
Gender						
Male	320	(52.4)	316	(52.1)	636	(52.3)
Female	291	(47.6)	290	(47.9)	581	(47.7)
Age (days) [1]						
Mean	61.4		61.5		61.5	
SD	6.9		6.9		6.9	
Median	62.0		62.0		62.0	
Range	46 to 78		46 to 78		46 to 78	
Weight (kg)						
Mean	5.4		5.4		5.4	
SD	0.7		0.7		0.7	
Median	5.4		5.4		5.4	
Range	3.2 to 8.0		3.1 to 7.7		3.1 to 8.0	
Unknown [2]	1	(0.2)	0	(0.0)	1	(0.1)

[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.
Subjects received PR5I / INFANRIX™ hexa at 2, 3, 4 and 12 mos; RotaTeq™ at 2, 3 and 4 mos; Prevenar 13™ at 2, 3, 4 and 13 mos; ProQuad™ at 12 and 13 mos.
Percentages were based on the number of randomized subjects.
mos = Months, SD = Standard deviation.

The demographics and other baseline characteristics are comparable between treatment groups.

Outcomes and estimation

1. Primary Immunogenicity Analyses

a. Acceptability Analysis of PR5I Antigen Responses One Month Postdose 3

Acceptability analysis of PR5I antigen responses one month Postdose 3 based on the PP-RW population is provided in Table 15. The lower limit of the 2-sided 95% CI for the response rate (%) was greater than the predetermined lower limit for all prespecified endpoints, indicating that the PR5I group met the response rate acceptability criteria. The results of the statistical analyses in the PP-OW population are consistent with those seen in the PP-RW population.

Table 15. Analysis of Acceptability of PR5I Antigen Responses in the PR5I Group One Month Postdose 3 (PP-RW Population) (Protocol 007)

Antigen	Endpoint	N	n	Point Estimate (95% CI) [1]	Lower Bound Limit	One-Sided P-Value[1]	Conclusion: Acceptability Criterion Met/ Not Met
PRP	% with titre ≥ 0.15 µg/mL	598	550	98.36 (96.92, 99.25)	80%	<0.001	Met
Diphtheria	% with titre ≥ 0.01 IU/mL	598	542	99.82 (98.98, 100.00)	80%	<0.001	Met
Tetanus	% with titre ≥ 0.01 IU/mL	598	538	100.00 (99.32, 100.00)	90%	<0.001	Met
IPV1	% with NAb ≥ 1:8 dilution	598	547	100.00 (99.33, 100.00)	90%	<0.001	Met
IPV2	% with NAb ≥ 1:8 dilution	598	547	99.82 (98.99, 100.00)	90%	<0.001	Met
IPV3	% with NAb ≥ 1:8 dilution	598	545	100.00 (99.33, 100.00)	90%	<0.001	Met

[1] 95% CI and p-value were calculated based on an exact binomial method by Clopper and Pearson.
Subjects received PR5I at 2, 3, 4 and 12 mos; RotaTeq™ at 2, 3 and 4 mos; Prevenar 13™ at 2, 3, 4 and 13 mos; ProQuad™ at 12 and 13 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 a blood draw sample window of Days 28 to 51 following Dose 3 or the Toddler dose), PRP = Polyribosylribitol phosphate.

b. Acceptability Analysis of PR5I Antigen Responses One Month After the Toddler Dose

Acceptability analysis of PR5I antigen responses one month after the Toddler dose based on the PP-RW population is provided in Table 16. The lower limit of the 2-sided 95% CI for the response rate (%) was greater than the predetermined lower limit for all pre-specified endpoints, indicating that the PR5I group met the response rate acceptability criteria. The results of the statistical analyses in the PP-OW population are consistent with those seen in the PP-RW population.

Table 16. Analysis of Acceptability of PR5I Antigen Responses in the PR5I Group One Month After the Toddler Dose (PP-RW Population) (Protocol 007)

Antigen	Endpoint	N	n	Point Estimate (95% CI) [2]	Lower Bound Limit	One-Sided P-Value[2]	Conclusion: Acceptability Criterion Met/ Not Met
PRP	% with titre ≥ 1.0 µg/mL	590	439	94.99 (92.51, 96.83)	75%	<0.001	Met
HBsAg	% with titre ≥ 10 mIU/mL	590	551	99.64 (98.70, 99.96)	90%	<0.001	Met
Diphtheria	% with titre ≥ 0.1 IU/mL	590	531	99.81 (98.96, 100.00)	80%	<0.001	Met
Tetanus	% with titre ≥ 0.1 IU/mL	590	528	100.00 (99.30, 100.00)	90%	<0.001	Met
PT	% seroresponse [1]	590	543	99.82 (98.98, 100.00)	75%	<0.001	Met
FHA	% seroresponse [1]	590	542	97.23 (95.48, 98.44)	75%	<0.001	Met
FIM	% seroresponse [1]	590	508	99.61 (98.59, 99.95)	75%	<0.001	Met
PRN	% seroresponse [1]	590	543	98.90 (97.61, 99.59)	75%	<0.001	Met
IPV1	% with NAb ≥ 1:8 dilution	590	538	99.81 (98.97, 100.00)	90%	<0.001	Met
IPV2	% with NAb ≥ 1:8 dilution	590	538	100.00 (99.32, 100.00)	90%	<0.001	Met
IPV3	% with NAb ≥ 1:8 dilution	590	541	100.00 (99.32, 100.00)	90%	<0.001	Met

[1] The Post Toddler pertussis seroresponse was defined as follows: (1) If prevaccination antibody concentration was < 4X LLOQ, then the postvaccination antibody concentration was ≥ 4X LLOQ, (2) If prevaccination antibody concentration was ≥ 4X LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. The prevaccination level was defined as the antibody titre at pre-Dose 1.
[2] 95% CI and p-value were calculated based on an exact binomial method by Clopper and Pearson.
Subjects received PR5I at 2, 3, 4 and 12 mos; RotaTeq™ at 2, 3 and 4 mos; Prevenar 13™ at 2, 3, 4 and 13 mos; ProQuad™ at 12 and 13 mos.
CI = Confidence interval, FHA = Filamentous haemagglutinin, FIM = Fimbriae types 2 and 3, 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, PP-RW = Per-protocol-Revised Windows (defined as 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.

c. Non-Inferiority Analysis of PR5I Antigen Responses One Month Postdose 3

Non-inferiority analysis of PR5I antigen responses one month Postdose 3 based on the PP-RW population is provided in Table 17. The lower limit of the 2-sided 95% CI for the group difference (PR5I group minus INFANRIX hexa group) was above the pre-specified non-inferiority margin for all pre-specified endpoints, indicating that PR5I group was non-inferior to the INFANRIX hexa group.

The results of the statistical analyses in the PP-OW population are consistent with those seen in the PP-RW population. Furthermore, the group difference regarding anti-PRP ≥ 0.15 μg/mL one month Postdose 3 was 11.37% (95% CI: 8.44% to 14.68%; p < 0.001) with its entire 95% CI above 0, suggesting a superior anti-PRP response elicited by PR5I Postdose 3.

Table 17. Analysis of Non-Inferiority Regarding PR5I Antigen Responses One Month Postdose 3 (PP-RW Population) (Protocol 007)

Antigen	Endpoint	PR5I (N=598)		INFANRIX™ hexa (N=590)		Estimated Difference [1] (95% CI)	NI Margin	One-Sided P-Value [1]	Conclusion: Non-inferiority Criterion Met/Not Met
		n	Estimated Response [1]	n	Estimated Response [1]				
PRP	% with titre ≥ 0.15 µg/mL	550	98.36	521	86.99	11.37 (8.44, 14.68)	-10%	<0.001	Met
Diphtheria	% with titre ≥ 0.01 IU/mL	542	99.81	517	99.81	-0.00 (-0.95, 0.96)	-10%	<0.001	Met
Tetanus	% with titre ≥ 0.01 IU/mL	538	100.00	519	100.00	0.00 (-0.71, 0.74)	-5%	<0.001	Met
IPV1	% with NAb ≥ 1:8 dilution	547	100.00	528	99.81	0.19 (-0.51, 1.07)	-5%	<0.001	Met
IPV2	% with NAb ≥ 1:8 dilution	547	99.82	530	99.62	0.19 (-0.69, 1.21)	-5%	<0.001	Met
IPV3	% with NAb ≥ 1:8 dilution	545	100.00	525	100.00	0.00 (-0.70, 0.73)	-5%	<0.001	Met

[1] The estimates for the response rate, rate difference (PR5I group minus INFANRIX™ hexa group), 95% CI and p-value were based on the method by Miettinen and Nurminen stratified by country.
Subjects received PR5I / INFANRIX™ hexa at 2, 3, 4 and 12 mos; RotaTeq™ at 2, 3 and 4 mos; Prevenar 13™ at 2, 3, 4 and 13 mos; ProQuad™ at 12 and 13 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, NI = Non-inferiority, PP-RW = Per-protocol-Revised Windows (defined as a blood draw sample window of Days 28 to 51 following Dose 3 or the Toddler dose), PRP = Polyribosylribitol phosphate.

d. Non-Inferiority Analysis of PR5I Antigen Responses One Month After the Toddler Dose

Non-inferiority analysis of PR5I antigen responses one month after the Toddler dose based on the PP-RW population is provided in Table 18. The lower limit of the 2-sided 95% CI for the group difference (PR5I group minus INFANRIX hexa group) was above the pre-specified non-inferiority margin for all pre-specified endpoints, indicating that PR5I group was non-inferior to the INFANRIX hexa group. The FIM component is not contained in INFANRIX hexa and as a result no non-inferiority comparison was made for this pertussis antigen. The results of the statistical analyses in the PP-OW population are consistent with those seen in the PP-RW population.

Table 18. Analysis of Non-Inferiority Regarding PR5I Antigen Responses One Month After the Toddler Dose (PP-RW Population) (Protocol 007)

		PR5I (N=590)		INFANRIX™ hexa (N=581)					
Antigen	Endpoint	n	Estimated Response [2]	n	Estimated Response [2]	Estimated Difference [2] (95% CI)	NI Margin	One-Sided P-Value [2]	Conclusion: Non-inferiority Criterion Met/Not Met
HBsAg	% with titre ≥ 10 mIU/mL	551	99.64	531	99.06	0.58 (-0.49, 1.85)	-10%	<0.001	Met
PT	% seroresponse [1]	543	99.82	523	98.49	1.33 (0.32, 2.86)	-10%	<0.001	Met
FHA	% seroresponse [1]	542	97.22	524	99.81	-2.59 (-4.39, -1.29)	-10%	<0.001	Met
PRN	% seroresponse [1]	543	98.89	523	98.86	0.03 (-1.40, 1.52)	-10%	<0.001	Met

[1] The Post Toddler pertussis seroresponse was defined as follows: (1) If prevaccination antibody concentration was < 4X LLOQ, then the postvaccination antibody concentration was ≥ 4X LLOQ, (2) If prevaccination antibody concentration was ≥ 4X LLOQ, then the postvaccination antibody concentration was ≥ preimmunization levels.
[2] The estimates for the response rate, rate difference (PR5I group minus INFANRIX™ hexa group), 95% CI, and p-value were based on the method by Miettinen and Nurminen stratified by country.
Subjects received PR5I / INFANRIX™ hexa at 2, 3, 4 and 12 mos; RotaTeq™ at 2, 3 and 4 mos; Prevenar 13™ at 2, 3, 4 and 13 mos ; ProQuad™ at 12 and 13 mos.
CI = Confidence interval, FHA = Filamentous haemagglutinin, HBsAg = Hepatitis B surface antigen, 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 a blood draw sample window of Days 28 to 51 following Dose 3 or the Toddler dose), PRN = Pertactin, PT = Pertussis toxoid.

Primary analysis for antigen response specific to pertussis were limited to the toddler dose. All the acceptability and non-inferiority criteria for the primary endpoints were met at one month post-dose 3 and one month post toddler dose. Seroresponse rate differences between PR5I and INFANRIX hexa for FHA antigen were seen (respectively 97.22% and 99.81%). After post-dose 3 differences in the seroresponse rates occur particularly for PRN and FHA. Indeed, seroresponse rates for PR5I PRN and FHA (86.74% and 89.02% respectively) antigens were lower than the seroresponse rates for the same antigen after INFANRIX hexa (92.32% and 96.65% respectively) (see table 22).

2. Secondary Immunogenicity Analyses

The endpoints for the acceptability and non-inferiority of ProQuad concomitantly administered with the Toddler dose of PR5I were antibody response rates at one month after the concomitant administration of ProQuad and the Toddler dose of PR5I.

a. Acceptability Analysis Regarding Concomitant Use of PR5I and ProQuad at One Month After the Toddler Dose of PR5I

Secondary acceptability analysis regarding the concomitant use of PR5I and ProQuad one month after the Toddler dose of PR5I based on the PP-RW population is provided in Table 19. The lower limit of the 2-sided 95% CI for the response rate (%) was greater than the predetermined lower limit regarding all pre-specified endpoints, indicating that the PR5I group met the response rate acceptability criteria. Similar results were obtained for the PP-OW and FAS populations.

Table 19. Analysis of Acceptability Regarding Concomitant Use of PR5I and ProQuad at One Month After the Toddler Dose (PP-RW Population)

Antigen	Endpoint	N	n	Point Estimate (95% CI) [1]	Lower Bound Limit	One-Sided P-Value [1]	Conclusion: Acceptability Criterion Met/Not Met
Measles	% with titer ≥ 255 mIU/mL	590	467	96.15 (93.98, 97.70)	90%	<0.001	Met
Mumps	% with titer ≥ 10 Ab Units/mL	590	467	94.86 (92.45, 96.68)	90%	<0.001	Met
Rubella	% with titer ≥ 10 IU/mL	590	467	98.29 (96.65, 99.26)	90%	<0.001	Met
Varicella	% with titer ≥ 5 gpELISA Units/mL	590	467	97.64 (95.82, 98.82)	76%	<0.001	Met

[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.
Subjects received PR5I at 2, 3, 4 and 12 mos; RotaTeq™ at 2, 3 and 4 mos; Prevenar 13™ at 2, 3, 4 and 13 mos; ProQuad™ at 12 and 13 mos.
CI = Confidence interval, mos = Months, N = Number of vaccinated subjects, n = Number of subjects included in the analysis, PP RW = Per-protocol-Revised Windows (defined as a blood draw sample window of Days 28 to 51 following Dose 3 or the toddler dose).

b. Non-Inferiority Analysis Regarding Concomitant Use of PR5I and ProQuad at One Month After the Toddler Dose of PR5I

Non-inferiority analysis regarding the concomitant use of PR5I and ProQuad one month after the Toddler dose of PR5I based on the PP-RW population is provided in Table 20. The lower limit of the 2-sided 95% CI for the group difference in rates (PR5I with ProQuad group vs. INFANRIX hexa with ProQuad group) was above the pre-specified non-inferiority margin regarding all pre-specified endpoints, indicating that the PR5I group was non-inferior to the INFANRIX hexa group. Similar results were obtained for the PP-OW and FAS populations.

Table 20. Analysis of Non-Inferiority Regarding Concomitant Use of PR5I and ProQuad at One Month After the Toddler Dose (PP-RW Population)

Antigen	Endpoint	PR5I (N=590)		INFANRIX™ hexa (N=581)		Estimated Difference [1] (95% CI)	NI Margin	One-Sided P-Value [1]	Conclusion: Non-inferiority Criterion Met/Not Met
		n	Estimated Response [1]	n	Estimated Response [1]				
Measles	% with titer ≥ 255 mIU/mL	467	96.15	474	96.41	-0.26 (-2.82, 2.25)	-5%	<0.001	Met
Mumps	% with titer ≥ 10 Ab Units/mL	467	94.86	474	91.78	3.07 (-0.12, 6.40)	-5%	<0.001	Met
Rubella	% with titer ≥ 10 IU/mL	467	98.28	474	97.89	0.39 (-1.50, 2.34)	-5%	<0.001	Met
Varicella	% with titer ≥ 5 gpELISA Units/mL	467	97.64	471	97.66	-0.02 (-2.11, 2.06)	-10%	<0.001	Met

[1] The estimates for the response rate, rate difference (PR5I group minus INFANRIX™ hexa group), 95% CI, and p-value were based on the method by Miettinen and Nurminen stratified by country.
Subjects received PR5I / INFANRIX™ hexa at 2, 3, 4 and 12 mos; RotaTeq™ at 2, 3 and 4 mos; Prevenar 13™ at 2, 3, 4 and 13 mos; ProQuad™ at 12 and 13 mos.
CI = Confidence interval, N = Number of vaccinated subjects, mos = Motnths, n = Number of subjects included in the analysis, NI = Non-inferiority, PP-RW = Per-protocol-Revised Windows (defined as a blood draw sample window of Days 28 to 51 following Dose 3 or the toddler dose).

All the acceptability and non-inferiority criteria for the secondary endpoints were met at one month post toddler dose.

3. Tertiary Immunogenicity Analyses

The GMTs and seroprotection/response rates for all antigens in PR5I and INFANRIX hexa based on the PP-RW population at one month Postdose 3 and after the Toddler dose are summarized below.

a. PRP

The anti-PRP GMT was significantly higher in subjects who received PR5I as compared to subjects who received INFANRIX hexa at one month Postdose 3 (3.90 vs 0.65) and at Month 12 before the Toddler dose (1.19 vs 0.24). One month after the Toddler dose, the anti-PRP GMT was lower in subjects who received PR5I as compared to subjects who received INFANRIX hexa: 6.79 (95% CI: 6.11 to 7.54) in the PR5I group vs. 21.39 (95% CI: 18.77 to 24.37) in the INFANRIX hexa group.

Table 21. Summary of Anti-PRP Response by Time and Vaccination Group (PP-RW Population)

Time Point	Endpoint	Vaccination Group			
		PR5I		INFANRIX™ hexa	
		n	Observed Response (95% CI) [1]	n	Observed Response (95% CI) [1]
One Month Postdose 3	% with titer ≥ 1.0 µg/mL (s/n)	550	83.27 (458/550) (79.89, 86.30)	521	36.66 (191/521) (32.51, 40.96)
	% with titer ≥ 0.15 µg/mL (s/n)	550	98.36 (541/550) (96.92, 99.25)	521	86.95 (453/521) (83.75, 89.72)
	GMT	550	3.90 (3.46, 4.41)	521	0.65 (0.58, 0.73)
Pre-Toddler Dose	% with titer ≥ 1.0 µg/mL (s/n)	542	57.75 (313/542) (53.47, 61.95)	511	11.74 (60/511) (9.08, 14.85)
	% with titer ≥ 0.15 µg/mL (s/n)	542	94.65 (513/542) (92.41, 96.39)	511	64.19 (328/511) (59.86, 68.35)
	GMT	542	1.19 (1.07, 1.32)	511	0.24 (0.22, 0.26)
One Month After the Toddler Dose	% with titer ≥ 1.0 µg/mL (s/n)	439	94.99 (417/439) (92.51, 96.83)	432	97.69 (422/432) (95.78, 98.88)
	% with titer ≥ 0.15 µg/mL (s/n)	439	99.54 (437/439) (98.36, 99.94)	432	99.31 (429/432) (97.98, 99.86)
	GMT	439	6.79 (6.11, 7.54)	432	21.39 (18.77, 24.37)

[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.
Subjects received PR5I / INFANRIX™ hexa at 2, 3, 4 and 12 mos; RotaTeq™ at 2, 3 and 4 mos; Prevenar 13™ at 2, 3, 4 and 13 mos; ProQuad™ at 12 and 13 mos.
CI = Confidence interval, GMT = Geometric mean titer, mos = Months, n = Number of subjects included in the analysis, PP-RW = Per-protocol-Revised Windows (defined as a blood draw sample window of Days 28 to 51 following Dose 3 or the toddler dose), PRP = Polyribosylribitol phosphate, s = Number of responders.

b. HBsAg

The percentage of subjects with anti-HBsAg (≥ 10 mIU/mL) at one month Postdose 3 was 97.84% (95% CI: 96.17, 98.92) in the PR5I group and 96.07% (95% CI: 93.92, 97.62) in the INFANRIX hexa group at one month Postdose 3 in the PP-RW population. One month Postdose 3, the anti-HBs response rates were high (>96%) in both vaccination groups, even in the absence of a birth dose of hepatitis B.

The percentage of subjects who achieved an anti-HBsAg response (≥ 10 mIU/mL) at one month after the Toddler dose in the PP-RW population was 99.64% (95% CI: 98.70, 99.96) in subjects who received PR5I compared with 99.06% (95% CI: 97.82, 99.69) in subjects who received INFANRIX hexa. One month post-Toddler, the anti-HBs response rates were high (>99%) in both vaccination groups with similar GMT.

c. Tetanus

The GMT for anti-tetanus one month Postdose 3 and one month after the Toddler dose was higher in subject who received PR5I as compared to subjects who received INFANRIX hexa.

d. Pertussis

Table 22 presents the summary of immune responses to pertussis antigens at pre-vaccination with Dose 1 and at one month after the Dose 3 and Toddler dose in Protocol 007. In this table, the Protocol 007 data was analyzed using the Protocol 008 pertussis seroresponse definition: (1) if prevaccination antibody

concentration was < LLOQ, then the postvaccination antibody concentration was ≥ LLOQ, (2) if prevaccination antibody concentration was ≥ LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. The prevaccination level was defined as the antibody titre at pre-Dose 1.

Table 22. Summary of Anti-Pertussis Response by Time and Vaccination Group (PP-RW Population)

Time Point	Endpoint	Vaccination Group			
		PR5I		INFANRIX™ hexa	
		n	Observed Response (95% CI) [1]	n	Observed Response (95% CI) [1]
Antigen: PT					
Pre-Vaccination 1	GMT	602	3.41 (3.18, 3.66)	596	3.63 (3.38, 3.90)
One Month Postdose 3	% seroresponse (s/n) [2]	529	99.43 (526/529) (98.35, 99.88)	508	98.62 (501/508) (97.18, 99.44)
	GMT	534	129.58 (123.92, 135.50)	514	83.66 (79.54, 87.99)
Pre-Toddler Dose	GMT	565	12.91 (12.19, 13.68)	537	13.49 (12.73, 14.29)
One Month After the Toddler Dose	% seroresponse (s/n) [3]	543	99.82 (542/543) (98.98, 100.00)	523	98.47 (515/523) (97.01, 99.34)
	GMT	548	196.81 (186.52, 207.67)	529	90.69 (85.82, 95.84)
Antigen: FHA					
Pre-Vaccination 1	GMT	602	6.58 (6.00, 7.22)	597	6.98 (6.39, 7.64)
One Month Postdose 3	% seroresponse (s/n) [2]	528	89.02 (470/528) (86.03, 91.55)	508	96.65 (491/508) (94.70, 98.04)
	GMT	533	49.51 (46.90, 52.27)	513	96.80 (91.70, 102.18)
Pre-Toddler Dose	GMT	565	8.63 (7.99, 9.31)	537	22.85 (21.45, 24.34)
One Month After the Toddler Dose	% seroresponse (s/n) [3]	542	97.23 (527/542) (95.48, 98.44)	524	99.81 (523/524) (98.94, 100.00)
	GMT	547	121.59 (115.68, 127.80)	529	196.53 (186.88, 206.67)

Time Point	Endpoint	Vaccination Group			
		PR5I		INFANRIX™ hexa	
		n	Observed Response (95% CI) [1]	n	Observed Response (95% CI) [1]
Antigen: PRN					
Pre-Vaccination 1	GMT	601	4.91 (4.47, 5.40)	596	5.37 (4.89, 5.90)
One Month Postdose 3	% seroresponse (s/n) [2]	528	86.74 (458/528) (83.55, 89.52)	508	92.32 (469/508) (89.65, 94.48)
	GMT	534	46.76 (42.72, 51.17)	514	77.79 (72.63, 83.32)
Pre-Toddler Dose	GMT	565	11.47 (10.60, 12.41)	537	12.09 (11.13, 13.13)
One Month After the Toddler Dose	% seroresponse (s/n) [3]	543	98.90 (537/543) (97.61, 99.59)	523	98.85 (517/523) (97.52, 99.58)
	GMT	548	166.67 (155.40, 178.75)	529	182.08 (168.93, 196.24)
Antigen: FIM					
Pre-Vaccination 1	GMT	565	7.71 (6.86, 8.66)	579	8.05 (7.20, 9.00)
One Month Postdose 3	% seroresponse (s/n) [2]	498	97.19 (484/498) (95.33, 98.45)	487	1.64 (8/487) (0.71, 3.21)
	GMT	534	353.61 (327.75, 381.51)	509	2.94 (2.75, 3.14)
Pre-Toddler Dose	GMT	565	45.97 (42.43, 49.81)	537	2.17 (2.09, 2.25)
One Month After the Toddler Dose	% seroresponse (s/n) [3]	508	99.61 (506/508) (98.59, 99.95)	507	4.73 (24/507) (3.06, 6.96)
	GMT	548	803.76 (745.50, 866.57)	529	2.60 (2.43, 2.79)

[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.
[2] The pertussis seroresponse Postdose 3 was defined as follows: (1) If prevaccination antibody concentration was < LLOQ, then the postvaccination antibody concentration was ≥ LLOQ, (2) If prevaccination antibody concentration was ≥ LLOQ, then the postvaccination antibody concentration was ≥ preimmunization levels.
[3] The pertussis seroresponse Post-toddler dose was defined as follows: (1) If prevaccination antibody concentration was < 4X LLOQ, then the postvaccination antibody concentration was ≥ 4X LLOQ, (2) If prevaccination antibody concentration was ≥ 4X LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. The prevaccination level was defined as the antibody titer at pre-Dose 1.
Subjects received PR5I / INFANRIX™ hexa at 2, 3, 4 and 12 mos; RotaTeq™ at 2, 3 and 4 mos; Prevenar 13™ at 2, 3, 4 and 13 mos; ProQuad™ at 12 and 13 mos.
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 subjects included in the analysis, PP-RW = Per-protocol-Revised Windows (defined as a blood draw sample window of Days 28 to 51 following Dose 3 or the toddler dose), PRN = Pertactin, PT = Pertussis toxoid, s = Number of responders.

Discussion on study 007

Some notable differences were observed between the 2 vaccination groups for anti-PRP, PT, FHA and PRN GMTs at one month Postdose 3 and at one month Post Toddler dose. An overview of the pre-specified and post-hoc non-inferiority analyses of all antigens is presented in Figures 1 and 2 below.

Compared to INFANRIX hexa, PR5I achieved a higher anti-PRP GMT after the primary doses compared to INFANRIX hexa, at one month Postdose 3 and persisting at Month 12 before the Toddler dose. Since the Hib-antigen in PR5I is conjugated to the strongly immunogenic OMPC protein, this result confirms the

expectation. However, the superiority in terms of GMT after the primary series was not sustained after the booster dose, which is somehow unexpected. Subjects who received PR5I had a significantly lower GMT one month after the toddler dose compared to those receiving INFANRIX hexa (6.79 (95% CI: 6.11 to 7.54) vs. 21.39 (95% CI: 18.77 to 24.37) respectively). Although all primary endpoints defined by the Applicant for PRP were met, this lower boosting response may indicate a risk of more rapid waning after the toddler dose of PR5I compared to INFANRIX hexa.

PR5I induced an early and sustained Hib response in the first year of life. Furthermore, the percentage of vaccinees achieving the >0.15 and >1.0 µg/ml titres in the PR5I and control groups after the toddler dose is similar. Considering that about 95% of PR5I vaccinees achieved a titre of > 1.0 µg/ml indicative of long-term protection after the toddler dose, and considering the high vaccination coverage in Europe, the lower post-toddler dose GMT are unlikely to negatively affect Hib disease burden in Europe.

Pertussis

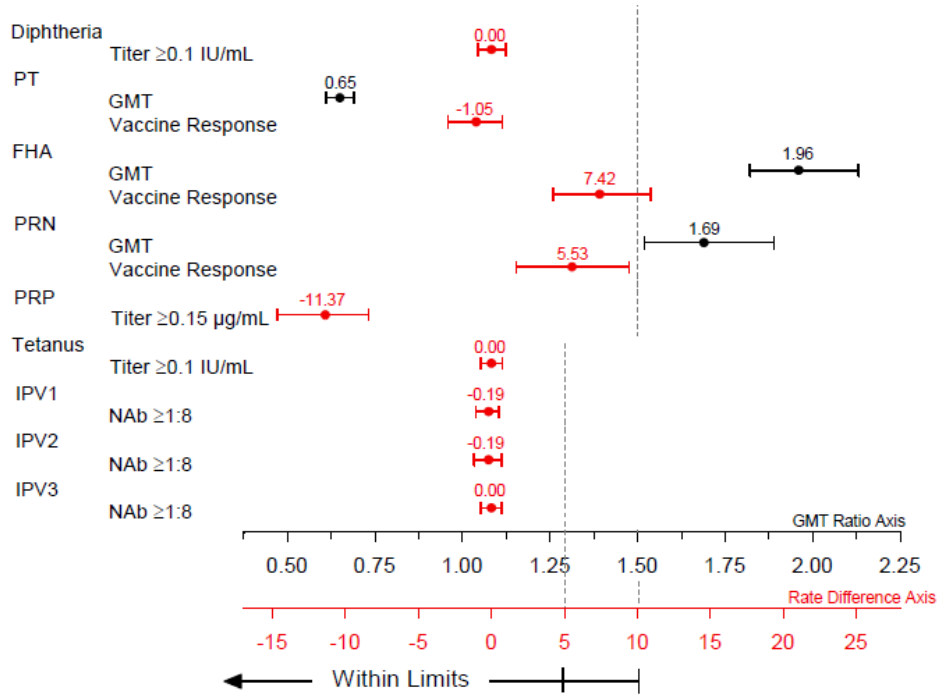
The GMT for anti-PT one month Postdose 3 and one month after the Toddler dose was higher in subjects who received PR5I as compared to subjects who received INFANRIX hexa.

The GMTs for anti-FHA and anti-PRN one month Postdose 3 and one month after the Toddler dose were lower in subjects who received PR5I as compared to subjects who received INFANRIX hexa. Likewise, the percentage of subjects with seroresponse after 3 doses was significantly lower for FHA and PRN antigens in subjects who received PR5I (89.02% and 86.74% respectively) as compared to subjects who received INFANRIX hexa (96.65% and 92.32% respectively, Table 22). The pre-toddler GMT for FHA was also significantly lower in subjects who received PR5I as compared to subjects who received INFANRIX hexa, returning to level close to the pre-vaccination GMT (8.63 vs. 6.58), suggesting a more rapid waning after 3 doses of PR5I compared to INFANRIX hexa. The clinical significance of these GMT results differences is unknown.

The higher anti-FIM GMT for the PR5I group was expected, since the FIM component is not contained in INFANRIX hexa.

In order to investigate the lower boosting response and the potential higher risk of waning of Hib immunity after the toddler dose, and the lower pertussis FHA and PRN response after the 3 doses, and a more rapid waning after 3 doses according to GMT, in subjects vaccinated with PR5I compared to subjects vaccinated with INFANRIX hexa, additional analyses were requested (see also section on additional analysis).

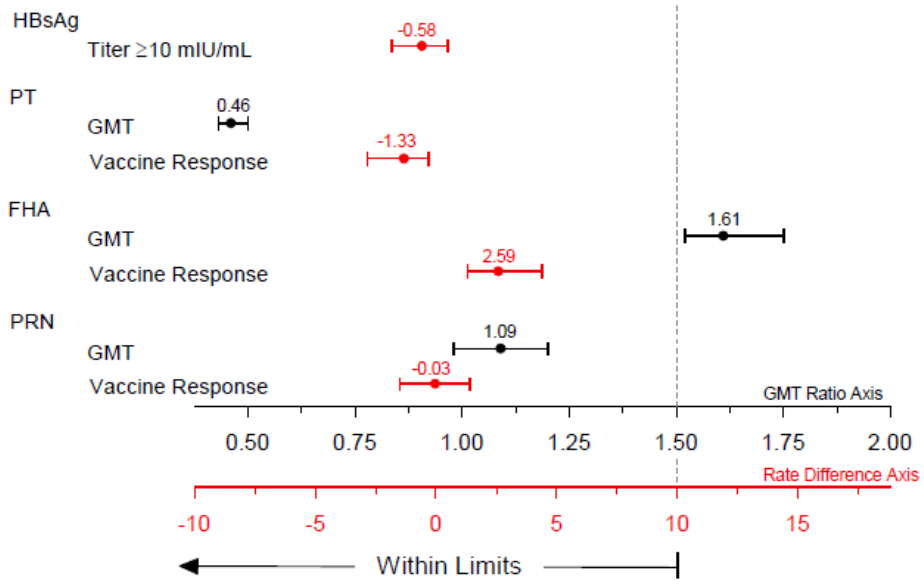
Figure 1. Study 007 PR5I vs Control – non-inferiority analysis (post-dose 3)



GMT ratio = $GMT_{control}/GMT_{PR5I}$, Rate Difference = $P_{control}-P_{PR5I}$

GMT comparisons were post-hoc and not part of the study objectives.
The right dash line shows a margin of 1.5 for GMT ratio or a margin of 10% for rate difference. The left dash line shows a margin of 5% for rate difference for the corresponding endpoints at the bottom.
Note 1: Pertussis vaccine response was defined as follows: (1) If pre-vaccination antibody concentration was < LLOQ, then the post-vaccination antibody concentration was ≥ LLOQ, (2) If pre-vaccination antibody concentration was ≥ LLOQ, then the post-vaccination antibody concentration was ≥ pre- vaccination levels.
Note 2: FIM comparisons were not able to be shown on the same scale, due to the markedly higher FIM responses for PR5I (FIM not contained in Control).

Figure 2. Study 007 PR5I vs control – non-inferiority analysis (post-toddler dose)



GMT ratio = GMTcontrol/GMTPR5I, Rate Difference = Pcontrol-PPR5I

GMT comparisons were post-hoc and not part of the study objectives.
Note 1: 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.
Note 2: FIM comparisons were not able to be shown on the same scale, due to the markedly higher FIM responses for PR5I (FIM not contained in Control).

Conclusions from study 007

The primary and secondary immunogenicity findings demonstrate the acceptability criteria defined by the Applicant for PR5I immunogenicity, and non-inferiority to INFANRIX hexa, supporting the administration of PR5I given to healthy infants at 2, 3, 4, 12 months of age.

The immunogenicity data also support the administration of PR5I with licensed paediatric vaccines (i.e. RotaTeq, Prevenar 13, and ProQuad).

In healthy infants who received PR5I concomitantly with Prevenar 13 and RotaTeq at 2, 3, and 4 months followed by PR5I and ProQuad at 12 months, and Prevenar 13 and ProQuad at 13 months, the following conclusions could be drawn

- PR5I elicited acceptable response rates to all antigens contained in PR5I, according to criteria defined by the applicant.
- PR5I was non-inferior to INFANRIX hexa regarding the response rates to antigens contained in both PR5I and INFANRIX hexa, according to predefined endpoints.
- The concomitant use of ProQuad with PR5I was acceptable, and was non-inferior to ProQuad given concomitantly with INFANRIX hexa.

- Although not included in the primary endpoints, there are two concerns that emerge from the non-inferiority analyses in subjects vaccinated with PR5I compared to Infanrix hexa:
    - Hib: the boosting effect on GMT anti-PRP was lower in PR5I vaccinees one month after the toddler dose compared to those receiving INFANRIX hexa (6.79 (95% CI: 6.11 to 7.54) vs. 21.39 (95% CI: 18.77 to 24.37) respectively (tertiary endpoints).
    - Pertussis: the seroresponse to the 3 primary doses was lower for antigens FHA and PRN in PR5I vaccinees compared to those receiving INFANRIX hexa. In PR5I vaccinees, the pre-toddler GMT for FHA returned to a level close to the pre-vaccination GMT, suggesting a rapid waning after 3 doses of PR5I.

Overall, the results presented in this clinical summary for Protocol 007 demonstrate that the observed responses to the antigens contained in PR5I were generally similar to INFANRIX hexa, with two exceptions: Hib/PRP after the toddler dose and FHA and PRN after the 3 primary doses. These endpoints were not included in the primary endpoints for non-inferiority but may have public health consequences due to more rapid waning of immunity after vaccination. Therefore further analyses were requested (see section on Additional analyses).

Study 008

Study 008 compared the immunology and tolerability of a 2+1 dose schedule of PR5I and Infanrix hexa given to vaccine naïve infants at 2, 4, and 11 to 12 months.

This study was designed (1) to test the acceptability of immune responses to PR5I, (2) to compare the immunogenicity of PR5I to Infanrix hexa, (3) to evaluate the immunogenicity of concomitantly administered Rotarix, (4) to ensure that PR5I can be administered with other paediatric vaccines routinely given at the same age, and (5) to describe the safety and tolerability profile of PR5I.

Methods

Study Participants

Inclusion Criteria

All infants enrolled in all five protocols were in good health and had no previous vaccination with any acellular pertussis- (DTaP) or whole cell pertussis- (DTwP) based combination vaccine, Haemophilus influenzae type b conjugate, poliovirus, pneumococcal conjugate or pneumococcal polysaccharide, or rotavirus vaccine.

Exclusion criteria

Infants were excluded from participation in these studies if they met any of the following criteria:

1. participation/planned participation in a study with an investigational compound or device or in another clinical study during the study period,
2. history of Haemophilus influenzae type b, hepatitis B, diphtheria, tetanus, pertussis, poliomyelitis, rotavirus or pneumococcal infection,
3. history of congenital immunodeficiency or acquired immunodeficiency,
4. receipt of immunosuppressive agents as specified in the study protocols,

5. receipt of systemic immunomodulatory steroids (> the equivalent of 2 mg/kg total daily dose of prednisone) since birth or any dose of systemic modulatory steroids with 7 days of study entry,
6. history of leukemia, lymphoma, malignant melanoma, or myeloproliferative disorder,
7. known or suspected hypersensitivity to any of the vaccine components or a history of a life-threatening reaction to a vaccine containing the same substances as the study vaccines or the concomitant vaccines,
8. chronic illness that could interfere with study conduct or completion,
9. receipt of any immune globulin, blood, or blood-derived product since birth,
10. history of coagulation disorder that contraindicates intramuscular injection,
11. history of developmental delay or neurological disorder at time of enrollment by review of medical history,
12. history or mother's medical history of HBsAg seropositivity.

The majority of subjects were enrolled in Finland (ca. 70% of subjects in Subset 2). Italy and Sweden enrolled 20% and 10% of subjects, respectively, in Subset 1.

Treatments

Due to a change in Rotarix availability in some EU countries, the initial study protocol was amended to allow for two subsets of subjects to receive either Rotarix (IT, SE) or RotaTeq (FI).

The protocol was further amended because in the Finnish paediatric vaccination schedule, RotaTeq is recommended to be given as early as 6 weeks of age. To allow for flexibility, study entry within the full prespecified age range (46 to 89 days) was acceptable even if a subject had received RotaTeq prior to Visit 1 outside the study, e.g. through the Finnish national vaccine program.

A total of 1315 healthy infants were randomized in a 1:1 ratio to receive either PR5I or Infanrix hexa. Within each vaccination group subjects were assigned to one of 2 subsets based on the rotavirus vaccine supplied to the study site.

- Subset 1 (IT, SE) received 2 doses of RV2 (Rotarix), n=231 (30% of the study population)
- Subset 2 (FI) received 3 doses of RV5 (RotaTeq). n=934 (70% of the study population). The first dose could have been given concomitantly at Visit 1 or outside the study prior to Visit 1 (beginning at 6 weeks of age).

Group	Subset	Vaccine Administered	Dose	Route of Administration	Age ~2M (Visit 1)	Age ~4M (Visit 2)	Age ~5m (Visit 3)	Age ~11 to 12M (Visit 4)
1 (n=650)	1 and 2	PR5I†	0.5mL	IM	X	X		X
	1 and 2	Prevenar 13™‡	0.5mL	IM	X	X		X
	1	Rotarix™§	1.5mL	Oral	X	X		
	2	RotaTeq™‖	2.0mL	Oral	X#	X	X	
2 (n=650)	1 and 2	INFANRIX™ hexa¶	0.5mL	IM	X	X		X
	1 and 2	Prevenar 13™‡	0.5mL	IM	X	X		X
	1	Rotarix™§	1.5mL	Oral	X	X		
	2	RotaTeq™‖	2.0mL	Oral	X#	X	X	

† PR5I = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Outer Membrane Protein Complex], and Hepatitis B [Recombinant] Vaccine.
‡ Prevenar 13™ = Pneumococcal polysaccharide conjugate vaccine 13-valent, adsorbed.
§ Rotarix™ = Rotavirus Vaccine, Live, Oral. Administered only to subjects in Subset 1.
‖ RotaTeq™ = Rotavirus Vaccine, Live, Oral, Pentavalent. Administered only to subjects in Subset 2. The 3rd dose of RotaTeq™ is to be given to subjects at least 4 weeks after the 2nd dose and no later than 26 weeks of age.
¶ INFANRIX™ hexa = Combined Diphtheria-Tetanus-acellular Pertussis [DTPa], Hepatitis B, Poliovirus and Haemophilus influenzae type b vaccine.
# The first dose of RotaTeq™ may be given either outside of the study prior to Visit 1 (beginning at 6 weeks of age), or concomitantly at Visit 1.

M = Months; IM = Intramuscular.

Objectives

Primary Objective

1. To evaluate the immunogenicity of PR5I when given at 2, 4, and 11 to 12 months of age.

Secondary Objectives

1. To compare the post-infant series anti-polyribosylribitol phosphate (PRP) response elicited by PR5I to that of Infanrix hexa.
2. To compare the immunogenicity elicited by PR5I to that of Infanrix hexa when given at 2, 4, and 11 to 12 months.
3. To evaluate the immunogenicity of Rotarix when administered concomitantly with PR5I.
4. To describe the safety profile associated with the administration of each dose of PR5I or Infanrix hexa when given concomitantly with Prevenar 13 and Rotarix or RotaTeq.
5. To describe fever occurring within 5 days after the administration of each dose and after all doses of PR5I or Infanrix hexa when given concomitantly with Prevenar 13 and Rotarix or RotaTeq.
6. 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 loss, and irritability) within 5 days after each dose and after all doses of PR5I or Infanrix hexa when co-administered with other recommended vaccines.
7. To summarize the incidence of serious adverse events.

Tertiary Objectives

1. To compare the anti-PRP response elicited by PR5I to that of Infanrix hexa before the Toddler dose.

2. To describe the response rates and geometric mean titres (GMTs)/geometric mean concentrations (GMCs) for all antigens in PR5I and Infanrix hexa at one month after Dose 2 and one month after Toddler dose with 95% confidence interval (CI).
3. To describe the percentage of subjects with titres ≥ 1.0 IU/mL for diphtheria and tetanus after Toddler dose with 95% CI.

The study design did not include a formal comparison of the seroresponses of PR5I and Infanrix hexa after the primary series (except for PRP in secondary endpoints). The Applicant was requested to provide a post-hoc analysis of non-inferiority Regarding PR5I Antigen Response one month Postdose 2 using the same NI margin as for the non-inferiority analysis one month post-Toddler dose (see section on Additional analyses).

Outcomes / endpoints

The primary endpoints for the acceptability hypothesis were PR5I-induced antibody responses to all antigens contained in PR5I one Month after the booster (Toddler) dose, i.e. at an infant age of about 12-13 Months. The statistical criteria require that, for each of the PR5I antigens, the lower limit of the 2-sided 95% CI is greater than the predetermined lower limit (P0) as defined in Table 23.

Table 23. Primary endpoint acceptability criteria for all PR5I antigens one Month post-dose 3 (Toddler/booster dose).

Antigen	Endpoint (Toddler Dose) EU Criteria	Assumed True Response Rates (P)	Lower limit for Acceptability (P0)
PRP	% with titer ≥ 1.0 µg/mL	85%	75%
HBsAg	% with titer ≥ 10 mIU/mL	95%	90%
Diphtheria	% with titer ≥ 0.1 IU/mL	90%	80%
Tetanus	% with titer ≥ 0.1 IU/mL	97%	90%
Pertussis – PT	% seroresponse[†]	85%	75%
Pertussis – FHA	% seroresponse[†]	85%	75%
Pertussis – FIM	% seroresponse[†]	85%	75%
Pertussis – PRN	% seroresponse[†]	85%	75%
IPV1	% with NAb ≥ 1:8 dilution	97%	90%
IPV2	% with NAb ≥ 1:8 dilution	97%	90%
IPV3	% with NAb ≥ 1:8 dilution	97%	90%

[†] Pertussis seroresponse was defined as follows: (1) if prevaccination antibody concentration was < LLOQ, then the postvaccination antibody concentration was ≥ LLOQ, (2) if prevaccination antibody concentration was ≥ LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. The prevaccination level was defined as the antibody titer at pre-Dose 1.
FHA = Filamentous hemagglutinin; FIM = Fimbriae types 2 and 3; HBsAg = Hepatitis B surface antigen; IPV = Inactivated poliovirus vaccine; LLOQ = Lower limit of quantification; NAb = Neutralizing antibodies; PRN = Pertactin; PRP = Polyribosylribitol phosphate; PT = Pertussis toxoid.

The secondary endpoints for the non-inferiority hypothesis were PR5I-induced antibody responses against antigens that were contained in both PR5I and Infanrix hexa one month after the Toddler dose, i.e. at an infant age of about 12-13 months, for PRP, HBsAg, diphtheria, tetanus, pertussis PT, pertussis FHA, pertussis-PRN, IPV1, IPV2, and IPV3. The NI margins are defined in Table 24.

Table 24. Secondary endpoint non-inferiority criteria for all PR5I antigens one Month post-dose 3 (Toddler/booster dose)

Antigen	Primary Endpoint EU Criteria	Assumed True Response Rates (P)	Non-inferiority Margin (δ)
PRP	% with titer ≥ 1.0 µg/mL	85%	10%
HBsAg	% with titer ≥ 10 mIU/mL	95%	10%
Diphtheria	% with titer ≥ 0.1 IU/mL	90%	10%
Tetanus	% with titer ≥ 0.1 IU/mL	97%	5%
Pertussis – PT	% seroresponse†	85%	10%
Pertussis – FHA	% seroresponse†	85%	10%
Pertussis – PRN	% seroresponse†	85%	10%
IPV1	% with NAb ≥ 1:8 dilution	97%	5%
IPV2	% with NAb ≥ 1:8 dilution	97%	5%
IPV3	% with NAb ≥ 1:8 dilution	97%	5%

† Pertussis seroresponse was defined as follows: (1) if prevaccination antibody concentration was < LLOQ, then the postvaccination antibody concentration was ≥ LLOQ, (2) if prevaccination antibody concentration was ≥ LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. The prevaccination level was defined as the antibody titer at pre-Dose 1.
Note: Pertussis FIM is not a component of INFANRIX™ hexa, and therefore was not an endpoint for the non-inferiority hypothesis.
FHA = Filamentous hemagglutinin; HBsAg = Hepatitis B surface antigen; IPV = Inactivated poliovirus vaccine; LLOQ = Lower limit of quantification; NAb = Neutralizing antibodies; PRN = Pertactin; PRP = Polyribosylribitol phosphate; PT = Pertussis toxoid.

The other secondary immunogenicity endpoints were:

1. For the testing of non-inferiority and superiority of PRP (Hib) responses: the proportion of subjects with anti-PRP level ≥ 1.0 µg/mL at one month Post-dose 2 (primary series), i.e. infant age of about 5 months.
2. For the testing of non-inferiority of anti-rotavirus IgA: the GMT at one month Post-dose 2 (primary series) in subjects receiving Rotarix.

The tertiary immunogenicity endpoint was:

1. testing of superiority regarding PRP (Hib) response before the booster/Toddler dose was the proportion of subjects with anti-PRP level ≥ 0.15 µg/mL.

Diseases targeted by PR5I

For all antigens but pertussis, defined correlates of protection have been established and are accepted as indicators of protection against the disease (see study 007).

Sample size

Target enrolment was 650 subjects into each vaccination group, with the evaluability was assumed to be 85% at Postdose 2 and 80% after the Toddler dose. With the sample size of this study, the power was 99% for the primary acceptability of all PR5I antigens after the Toddler dose. The power calculation was based on the normal approximation of a binary response, and a method by Farrington and Manning for the non-inferiority hypothesis. The overall alpha-level was one-sided α = 0.025.

Sample size calculation is acceptable.

Randomisation

The randomized allocation schedule was generated by an external vendor, and implemented by the vendor of the study interactive voice response system (IVRS). Further information was provided by the Applicant upon request and was found acceptable.

Blinding (masking)

This was a double-blind study operating under in-house and third party blinding procedures in which the parent(s)/legal representative of the subject, the Investigator, laboratory testing personnel, and sponsor personnel were blinded, except for:

- unblinded study personnel responsible for preparation of study vaccines because INFANRIX hexa is provided as 2 components (i.e., lyophilized Hib and liquid DTPa, IPV, and HepB). This member of the study site staff was unblinded for the purpose of receiving, maintaining, accounting and preparing the study vaccines. No blinded study person(s) who had contact with the subjects was to have access to the study vaccines at any time.
- an unblinded sponsor representative.

Site staff performing the safety assessments (including injection-site adverse events) and immunogenicity assessments, were blinded to the identity of study vaccines.

No subjects were prematurely unblinded in this study.

Statistical methods

In general data were described by means of statistical characteristics (categorical variables: absolute and relative frequencies; numerical variables: mean, standard deviation, minimum and maximum) stratified for treatment group. Two per-protocol (PP) populations, i.e. PP-Revised Windows (PP-RW) and PP-Original Windows (PP-OW), were used in this study (see further below for populations' definition).

To address vaccine-induced antibody responses to all antigens contained in PR5I after the Toddler dose, 95% CIs for the single group proportion were calculated based on the exact binomial method proposed by Clopper-Pearson to each component. The statistical criteria for acceptability required that the lower limit of the 2-sided 95% CI of the response rate for each of the antigens was greater than the pre-specified lower limit. The primary acceptability analysis was based on the PP population. Supportive analyses were also performed using the FAS population. For each PR5I antigen, the antibody response rate and its 95% CI were calculated using the same exact binomial method as for the primary acceptability analysis.

The non-inferiority of response rate of each PR5I component was established by establishing that the lower limit of the 2-sided 95% CI for response rate difference between the 2 groups (PR5I group minus INFANRIX hexa group) for each of the PR5I antigens was greater than $-\delta$, with δ is the prespecified limit for each component and $\delta = 0$ for the superiority hypothesis testing. The p-value and 95% CI were calculated based on an asymptotic method proposed by Miettinen and Nurminen stratified by country.

The GMT for IgA at Postdose 2 in the subset of subjects who received Rotarix (The endpoint for evaluating the concomitant use with Rotarix) and associated 95% CI was calculated from an ANCOVA model with log-transformed postvaccination titre as the response variable, and the log-transformed prevaccination titres, vaccination group and country as fixed effect variables. Success criteria required that the lower bound limit of the 95% CI of the GMT ratio was > 0.5 (corresponding to a no more than a 2.0-fold decrease in the

GMT of the PR5I group compared with the Control group) based on the analysis of covariance with multiple imputation for missing baseline titres (MI ANCOVA) in the PP-RW population. Additionally a cLDA method proposed by Liang and Zeger on the log-transformed baseline and postvaccination titre values was used for supportive analyses.

Furthermore, 2 additional sensitivity analyses were performed: (1) analysis of GMT endpoints with no baseline adjustment, and (2) analysis of GMT endpoints with baseline adjustment, based on data from subjects with both baseline and postvaccination titres.

Overall, the statistical methods applied are considered appropriate.

Handling of dropouts or missing data

For the primary analyses regarding GMT using ANCOVA, the missing baseline titres were multiply imputed using the Proc MI procedure by SAS Institute Inc. A total of 20 imputations were carried out by the procedure using a regression method based on all subjects in the relevant analysis population (i.e., PP-OW, PP-RW or FAS). The response variable for the imputation model was the log-transformed prevaccination titres, and the covariates were age in days, gender, weight, country, and log transformed postvaccination antibody titres. The multiple imputation was carried out by vaccination group. After the imputation step was completed, the ANCOVA was performed to estimate the between-group difference and its associated variance based on each of the 20 datasets from the imputation step. The final estimated difference and the CI was calculated using the SAS Proc MIANALYZE procedure, which combines the results and generates valid statistical inferences according to the algorithm by Rubin and Schenker.

The CHMP considered that the multiple imputation method was selected because the missing baseline values were mostly caused by limitations in serum volume in 2-month-old infants. Therefore, the missing baseline values are unlikely to be biased and the Missing at Random assumption seems reasonable after including the baseline characteristic variables in the imputation model. The sensitivity analyses on GMT endpoints will allow assessing the potential impact of this assumption.

Amendments

Five protocol amendments were initiated and finalized prior to the database lock and unblinding.

Protocol Amendment 1: The primary reason for this amendment was in response to the change in Rotarix availability in some EU countries. This amendment allowed for subsets of subjects to receive one of 2 available rotavirus vaccines, either Rotarix or RotaTeq.

Protocol Amendment 2: The primary reason for this amendment was that RotaTeq, a vaccine administered concomitantly with PR5I that was not evaluated for immunogenicity, was originally planned to be sourced locally by study sites, but local sourcing was not operationally feasible.

Protocol Amendment 3: the primary reason for this amendment was because in the Finnish pediatric vaccination schedule, RotaTeq is recommended to be given as early as 6 weeks of age.

Protocol Amendment 4 and 5: the primary reasons for this amendment were:

- Added a new primary statistical analysis method for all GMT analyses (i.e., MI ANCOVA) to account for missing baseline titres due to limited serum volumes obtained from 2-month old infant subjects at study entry (Finland, Italy, Sweden)

- 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 (Finland, Italy, Sweden) .
- 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 postvaccination titres to support the ANCOVA MI primary analysis for GMT endpoints (Finland, Italy, Sweden).
- 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) (Italy, Sweden).

The CHMP concluded that the changes introduced did no impact on the integrity of the study.

Study population for Immunogenicity Analysis

Two PP populations, PP-Revised Windows (PP-RW) and PP-Original Windows (PP-OW), were used in the 4 Phase III studies (Protocols 005, 006, 007 and 008). The two PP populations were the same except for the allowed day ranges for vaccinations (Protocols 005 and 006) and blood sample draws (Protocols 005, 006, 007 and 008). The day ranges for vaccination in the EU studies were not changed due to the compressed vaccination schedules (compressed 3-dose infant series in Protocol 007 and 2-dose infant series in Protocol 008). In study 008 PP-RW is defined as the per-protocol population using a blood draw sample window of Days 28 to 51 following Dose 2 or the toddler dose. PP-OW is defined as the per-protocol population using a blood draw sample window of Days 28 to 44 following Dose 2 or the toddler dose. See study 007 for further details on the populations.

The statistical analyses for the Phase III studies (Protocols 005, 006, 007 and 008) were conducted using both PP populations but the study protocol(s) pre-specified that the success of the hypothesis test was based on the results from the PP-RW population. The results for the PP-RW population are reflected in this document; the results in the PP-OW population were provided in the dossier and assessed. Key immunogenicity summaries and analyses were also provided for all endpoints associated with hypotheses using the Full Analysis Set (FAS) population (included all randomized subjects with available serology data for each serology time point).

Due to limited serum volume and the high number of antigens to be tested, samples were prioritized in accordance with the priority of study hypotheses and based on expected antigen assay variability (primary hypotheses and more variable antigens were prioritized higher). Any remaining serum could have been used for additional immune response testing, limited to the antigens contained within the vaccines administered in the study, including PR5I/Infanrix hexa and concomitant vaccines.

Table 25. Number (%) of Subjects Excluded from the PP-RW Population at One Month Postdose 2 for PR5I Endpoints (All Randomized Subjects)

Vaccination Group = PR5I (N=656)											
	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	609 (92.8)	319 (48.6)	584 (89.0)	578 (88.1)	598 (91.2)	597 (91.0)	606 (92.4)	600 (91.5)	601 (91.6)	600 (91.5)	595 (90.7)
Number of subjects excluded	47 (7.2)	337 (51.4)	72 (11.0)	78 (11.9)	58 (8.8)	59 (9.0)	50 (7.6)	56 (8.5)	55 (8.4)	56 (8.5)	61 (9.3)
Reason for exclusion											
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	8 (1.2)	8 (1.2)	8 (1.2)	8 (1.2)	8 (1.2)	8 (1.2)	8 (1.2)	8 (1.2)	8 (1.2)	8 (1.2)	8 (1.2)
Received incomplete or incorrect concomitant vaccine regimen	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 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	25 (3.8)	25 (3.8)	25 (3.8)	25 (3.8)	25 (3.8)	25 (3.8)	25 (3.8)	25 (3.8)	25 (3.8)	25 (3.8)	25 (3.8)
Vaccination out of day range	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 collected out of day range	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)
Result not available/Insufficient serum	8 (1.2)	298 (45.4)	33 (5.0)	39 (5.9)	19 (2.9)	20 (3.0)	11 (1.7)	17 (2.6)	16 (2.4)	17 (2.6)	22 (3.4)

Non-inferiority margins and acceptability criteria

The non-inferiority margins used in the evaluations were based on clinical meaningfulness of the difference, the expected response rate for each antigen, and the observed variability in antibody titre measurement for each antigen. The margin for response rate is 5 percentage points for antigens with an expected response rate >95% and 10 percentage points for antigens with an expected response rate ≤ 95%.

Table 26. Secondary endpoint non-inferiority criteria for all PR5I antigens one Month post-dose 3 (Toddler/booster dose)

Antigen	Primary Endpoint EU Criteria	Assumed True Response Rates (P)	Non-inferiority Margin (δ)
PRP	% with titer ≥ 1.0 µg/mL	85%	10%
HBsAg	% with titer ≥ 10 mIU/mL	95%	10%
Diphtheria	% with titer ≥ 0.1 IU/mL	90%	10%
Tetanus	% with titer ≥ 0.1 IU/mL	97%	5%
Pertussis – PT	% seroresponse[†]	85%	10%
Pertussis – FHA	% seroresponse[†]	85%	10%
Pertussis – PRN	% seroresponse[†]	85%	10%
IPV1	% with NAb ≥ 1:8 dilution	97%	5%
IPV2	% with NAb ≥ 1:8 dilution	97%	5%
IPV3	% with NAb ≥ 1:8 dilution	97%	5%

[†] Pertussis seroresponse was defined as follows: (1) if prevaccination antibody concentration was < LLOQ, then the postvaccination antibody concentration was ≥ LLOQ, (2) if prevaccination antibody concentration was ≥ LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. The prevaccination level was defined as the antibody titer at pre-Dose 1.

Note: Pertussis FIM is not a component of INFANRIX™ hexa, and therefore was not an endpoint for the non-inferiority hypothesis.

FHA = Filamentous hemagglutinin; HBsAg = Hepatitis B surface antigen; IPV = Inactivated poliovirus vaccine; LLOQ = Lower limit of quantification; NAb = Neutralizing antibodies; PRN = Pertactin; PRP = Polyribosylribitol phosphate; PT = Pertussis toxoid.

Table 27. Primary endpoint acceptability criteria for all PR5I antigens one Month post-dose 3 (Toddler/booster dose)

Antigen	Endpoint (Toddler Dose) EU Criteria	Assumed True Response Rates (P)	Lower limit for Acceptability (P0)
PRP	% with titer ≥ 1.0 µg/mL	85%	75%
HBsAg	% with titer ≥ 10 mIU/mL	95%	90%
Diphtheria	% with titer ≥ 0.1 IU/mL	90%	80%
Tetanus	% with titer ≥ 0.1 IU/mL	97%	90%
Pertussis – PT	% seroresponse†	85%	75%
Pertussis – FHA	% seroresponse†	85%	75%
Pertussis – FIM	% seroresponse†	85%	75%
Pertussis – PRN	% seroresponse†	85%	75%
IPV1	% with NAb ≥ 1:8 dilution	97%	90%
IPV2	% with NAb ≥ 1:8 dilution	97%	90%
IPV3	% with NAb ≥ 1:8 dilution	97%	90%

† Pertussis seroresponse was defined as follows: (1) if prevaccination antibody concentration was < LLOQ, then the postvaccination antibody concentration was ≥ LLOQ, (2) if prevaccination antibody concentration was ≥ LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. The prevaccination level was defined as the antibody titer at pre-Dose 1.
FHA = Filamentous hemagglutinin; FIM = Fimbriae types 2 and 3; HBsAg = Hepatitis B surface antigen; IPV = Inactivated poliovirus vaccine; LLOQ = Lower limit of quantification; NAb = Neutralizing antibodies; PRN = Pertactin; PRP = Polyribosylribitol phosphate; PT = Pertussis toxoid.

The CHMP noted the following:

1. The PP-RW population includes infants that are up to several days older than in the PP-OW population. Although the maturity of the immune system is likely to affect the antibody levels, the results in the PP-RW, the PP-OW and the FAS population are comparable in study 007.
2. The acceptability criteria for the Hib and pertussis response rates are as low as 75%, whereas they are 80 to 90% for all other antigens (D, T, IPV, HepB). However, these two diseases are the real public health concern in the current time and pertussis shows a recrudescence in Europe.
3. The NI margins are set at 5 or 10% depending on the expected response rate. Acceptability criteria and non-inferiority margins are based on accepted thresholds and have been approved by regulatory agencies. This was assessed and found acceptable by the CHMP (see study 007 for further details).

Primary analysis

Table 28. Summary of key immunogenicity analysis performed

Analysis/Endpoint	Type of Analysis	Method	Population	
			Main Analysis‡	Supportive Analysis
Primary Immunogenicity Analysis				
Acceptability/response rates against all PR5I antigens after Toddler dose	95% CI for single group proportion	Exact binomial	PP-RW, PP-OW	FAS
Secondary Immunogenicity Analyses				
Non-inferiority and superiority of PRP (% ≥ 1.0 µg/ml) at Postdose 2	p-value and 95% CI for response rate difference	Miettinen and Nurminen method	PP-RW, PP-OW	FAS
Non-inferiority regarding antigens common in PR5I and INFANRIX™ hexa after Toddler dose				
Non-inferiority of Rotarix™ at Postdose 2	p-value and 95% CI for GMT Ratio	MI ANCOVA†	PP-RW, PP-OW	FAS
		cLDA model†	N/A	PP-RW
Tertiary Immunogenicity Analysis				
Superiority of PRP response (% ≥ 0.15 µg/ml) before Toddler dose	p-value and 95% CI for response rate difference	Miettinen and Nurminen method	PP-RW, PP-OW	FAS

† MI ANCOVA was the primary analysis method used; cLDA was a supportive analysis method.
‡ The success of the hypothesis test will be based on the results from the PP-RW population.
CI = Confidence interval, cLDA = Constrained longitudinal data analysis, FAS = Full analysis set, GMT = Geometric mean titer, MI ANCOVA = Analysis of covariance with multiple imputation for missing baseline titers, N/A = Not applicable, PP-OW = Per-protocol-Original Windows (blood draw window of Days 28 to 44 following Dose 2 or the toddler dose), PP-RW = Per-Protocol-Revised Window (blood draw window of Days 28 to 51 following Dose 2 or the toddler dose), PRP = Polyribosylribitol phosphate.

The proposed analyses were deemed acceptable. Since in this study only one primary hypothesis was tested there was no need to control for multiplicity.

Results

Subject disposition

A total of 1325 subjects were screened and 1315 subjects randomized. Overall, 1300 subjects (98.9%) received both doses of the infant series 649 (98.9%) in the PR5I group and 651 (98.8%) in the INFANRIX hexa group. 4 subjects in the PR5I group and 8 subjects in the INFANRIX hexa group did not complete the infant series. 10 subjects in the PR5I group and 9 in the INFANRIX hexa discontinued between the infant series and the toddler dose. Subsequently, 1281 subjects (97.4%) received the Toddler dose vaccinations; 639 subjects (97.4%) in the PR5I group and 642 subjects (97.4%) in the INFANRIX hexa group. Eleven subjects (0.8%) discontinued after the Toddler dose; 3 subjects (0.5%) in the PR5I group and 8 subjects (1.2%) in the INFANRIX hexa group. All drop outs where accounted for.

Table 29. Subject disposition (all subjects)

	PR5I		INFANRIX™ hexa		Total	
	n	(%)	n	(%)	n	(%)
Screened					1325	
Randomized subjects	656		659		1315	
Not vaccinated	3	(0.5)	0	(0.0)	3	(0.2)
Received all 2 doses of the Infant Series (PR5I / INFANRIX™ hexa) [1]	649	(98.9)	651	(98.8)	1300	(98.9)
Received all 2 doses of the Infant Series (PR5I / INFANRIX™ hexa and all doses of concomitant study vaccines) [2]	644	(98.2)	649	(98.5)	1293	(98.3)
Did not complete the Infant Series (PR5I / INFANRIX™ hexa)	4	(0.6)	8	(1.2)	12	(0.9)
Reason for Withdrawal: [3]						
Adverse Event	1	(0.2)	1	(0.2)	2	(0.2)
Physician Decision	0	(0.0)	1	(0.2)	1	(0.1)
Protocol Violation	2	(0.3)	0	(0.0)	2	(0.2)
Withdrawal by Subject	1	(0.2)	6	(0.9)	7	(0.5)
Discontinued between the Infant Series and Toddler Dose	10	(1.5)	9	(1.4)	19	(1.4)
Reason for Withdrawal: [3]						
Lost to Follow-up	0	(0.0)	2	(0.3)	2	(0.2)
Physician Decision	1	(0.2)	0	(0.0)	1	(0.1)
Protocol Violation	0	(0.0)	1	(0.2)	1	(0.1)
Withdrawal by Subject	9	(1.4)	6	(0.9)	15	(1.1)
Received the Toddler Dose [4]	639	(97.4)	642	(97.4)	1281	(97.4)
Completed Toddler Dose [5]	639	(97.4)	642	(97.4)	1281	(97.4)
Discontinued after Toddler Dose	3	(0.5)	8	(1.2)	11	(0.8)
Reason for Withdrawal: [3]						
Lost to Follow-up	1	(0.2)	6	(0.9)	7	(0.5)
Withdrawal by Subject	2	(0.3)	2	(0.3)	4	(0.3)

Conduct of the study

There were 5 protocol amendments following finalization of the original protocol. These included amendments related to changes in availability of Rotarix in some EU-countries, as well as addition of new statistical analysis methods for GMT analysis. All amendments were initiated and finalized prior to the database lock and unblinding.

Baseline data

The demographic profile of the PR5I and INFANRIX hexa groups where comparable. Among all randomized subjects, 51.6% were male and 48.4% were female. The mean age of subjects was 68.1 days (range 46-89 days). The mean weight was 5.5 kg (range 3.1-8.1 kg).

Outcomes and estimation

Primary immunological analysis (Acceptability of PR5I antigen responses one month after the toddler dose)

The table below shows acceptability analysis regarding PR5I antigen responses one month after the toddler dose based on the PP-RW. For all the pre-specified endpoints the lower limit of the 2 sided 95% CI for the response rate (%) was greater than the predetermined lower limit indicating that the PR5I group met the response rate acceptability criteria.

PP-RW results did not differ significantly from those obtained using PP-OW. Similar findings were observed for the PP-OW and the FAS populations.

Table 30. Acceptability of PR5I antigen responses one month after the toddler dose (PP-RW population)

Antigen	Endpoint	N	n	Point Estimate (95% CI) [2]	Lower Bound Limit	One-Sided P-Value[2]	Conclusion: Acceptability Criterion Met/Not Met
PRP	% with titre ≥ 1.0 µg/mL	638	454	89.87 (86.72, 92.49)	75%	<0.001	Met
HBsAg	% with titre ≥ 10 mIU/mL	638	377	98.14 (96.21, 99.25)	90%	<0.001	Met
Diphtheria	% with titre ≥ 0.1 IU/mL	638	590	99.83 (99.06, 100.00)	80%	<0.001	Met
Tetanus	% with titre ≥ 0.1 IU/mL	638	589	99.12 (97.95, 99.71)	90%	<0.001	Met
PT	% seroresponse [1]	638	566	99.82 (98.98, 100.00)	75%	<0.001	Met
FHA	% seroresponse [1]	638	582	97.23 (95.48, 98.44)	75%	<0.001	Met
FIM	% seroresponse [1]	638	581	98.28 (96.86, 99.17)	75%	<0.001	Met
PRN	% seroresponse [1]	638	582	96.91 (95.16, 98.16)	75%	<0.001	Met
IPV1	% with NAb ≥ 8 dilution	638	591	99.32 (98.28, 99.82)	90%	<0.001	Met
IPV2	% with NAb ≥ 8 dilution	638	591	99.83 (99.06, 100.00)	90%	<0.001	Met
IPV3	% with NAb ≥ 8 dilution	638	590	99.49 (98.52, 99.90)	90%	<0.001	Met

[1] The pertussis seroresponse was defined as follows: (1) If prevaccination antibody concentration was < 4X LLOQ, then the postvaccination antibody concentration was ≥ 4X LLOQ, (2) If prevaccination antibody concentration was ≥ 4X LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. The prevaccination level was defined as the antibody titre at pre-Dose 1. [2] 95% CI and p-value were calculated based on an exact binomial method by Clopper and Pearson. Subjects received PR5I at 2, 3, 4 and 12 months; RotaTeq at 2, 3 and 4 months; Prevenar 13 at 2, 3, 4 and 13 months; ProQuad at 12 and 13 months. LLOQ = Lower limit of quantification, N = Number of vaccinated subjects, n = Number of subjects included in the analysis, Nab = Neutralizing antibodies.

Secondary Immunogenicity Analyses

(a) Non-inferiority/superiority analysis of PRP antigen responses at one month post dose 2

The proportion of subjects with anti-PRP ≥ 1.0 µg/mL one month Postdose 2 was 72.86% for the PR5I group versus 26.66 for the INFANRIX hexa group. The difference (PR5I group minus INFANRIX hexa group) in the proportion of subjects with anti-PRP ≥ 1.0 µg/mL one month Postdose 2 was 46.20% (95% CI: 41.05% to 51.06%; p-value <0.001); the lower limit of the 2-sided 95% CI for the difference in response rates (PR5I group minus INFANRIX hexa group) was > 0, thus > -10%, indicating that both non-inferiority and superiority criteria were met. See tables below.

Table 31. Analysis of superiority regarding PRP antigen response one month postdose 2 (PP-RW Population)

Antigen	Endpoint	PR5I (N=649)		INFANRIX hexa (N=651)		Estimated Difference [1] (95% CI)	Superiority Margin	One-Sided P-Value [1]	Conclusion: Superiority Criterion Met/Not Met
		n	Estimated Response [1]	n	Estimated Response [1]				
PRP	% with titre ≥ 1.0 µg/mL	609	72.86	592	26.66	46.20 (41.05, 51.06)	0.00%	<0.001	Met

(b) Non-inferiority analysis regarding PR5I antigen responses one month after toddler dose

Table 32. Analysis of non-inferiority regarding PR5I antigen responses one month after toddler dose (PP-RW Population)

Antigen	Endpoint	PR5I (N=638)		INFANRIX hexa (N=642)		Estimated Difference [2] (95% CI)	NI Margin	One-Sided P-Value [2]	Conclusion: Non- inferiority Criterion Met/Not Met
		n	Estimated Response [2]	n	Estimated Response [2]				
PRP	% with titre ≥ 1.0 µg/mL	454	89.80	478	91.06	-1.27 (-5.13, 2.52)	-10%	<0.001	Met
HBsAg	% with titre ≥ 10 mIU/mL	377	98.14	391	98.73	-0.59 (-2.66, 1.35)	-10%	<0.001	Met
Diphtheria	% with titre ≥ 0.1 IU/mL	590	98.62	578	99.83	-1.21 (-2.54, -0.22)	-10%	<0.001	Met
Tetanus	% with titre ≥ 0.1 IU/mL	589	99.83	577	100.00	-0.17 (-0.95, 0.50)	-5%	<0.001	Met
PT	% seroresponse [1]	566	99.11	561	99.64	-0.54 (-1.75, 0.49)	-10%	<0.001	Met
FHA	% seroresponse [1]	582	97.40	571	99.13	-1.73 (-3.47, -0.26)	-10%	<0.001	Met
PRN	% seroresponse [1]	582	96.86	572	98.28	-1.42 (-3.42, 0.39)	-10%	<0.001	Met
IPV1	% with NAb ≥ 1:8 dilution	591	99.32	580	99.83	-0.51 (-1.59, 0.34)	-5%	<0.001	Met
IPV2	% with NAb ≥ 1:8 dilution	591	99.83	579	100.00	-0.17 (-0.96, 0.49)	-5%	<0.001	Met
IPV3	% with NAb ≥ 1:8 dilution	590	99.49	579	99.65	-0.16 (-1.20, 0.82)	-5%	<0.001	Met

1] The pertussis seroresponse was defined as follows: (1) If pre-vaccination antibody concentration was < LLOQ, then the post-vaccination antibody concentration was ≥ LLOQ, (2) If pre-vaccination antibody concentration was ≥ LLOQ, then the post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titre at pre-Dose 1.

[2] The estimates for the response rate, rate difference (PR5I group minus INFANRIX hexa group), 95% CI and p-value were based on the method by Miettinen and Nurminen stratified by country. Subset 1 consisted of subjects receiving Rotarix (Italy and Sweden); Subset 2 consisted of subjects receiving RotaTeq (Finland). Subjects received PR5I / INFANRIX hexa + Prevenar 13 at 2, 4 and 11 to 12 mos; Rotarix at 2 and 4 mos (Subjects in Subset 1); RotaTeq at 2, 4 and 5 mos (Subjects in Subset 2). The first dose of RotaTeq given at 2 mos can be received prior to enrollment to the study according to the protocol. CI = Confidence interval, FHA = Filamentous haemagglutinin, 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 a blood draw sample window of Days 28 to 51 following Dose 2 or the toddler dose), PRN = Pertactin, PRP = Polyribosylribitol phosphate, PT = Pertussis toxoid.

The lower limit of the 2 sided 95% CI for the difference in response rates (PR5I group minus INFANRIX hexa group) was greater than the prespecified non-inferiority margin regarding all prespecified endpoints, indicating that the PR5I group was non inferior to the INFANRIX hexa group.

Results presented above for the PP-RW have been confirmed in the PP-OW as well as the FAS.

(c) Summaries of antigen responses by time and vaccination group

Table 33. Summary of anti-pertussis response by time and vaccination group (PP-RW Population)

Time Point	Endpoint	Vaccination Group			
		PR5I		INFANRIX™ hexa	
		n	Observed Response (95% CI) [1]	n	Observed Response (95% CI) [1]
Antigen: PT					
Pre-Vaccination 1	GMT	624	3.89 (3.62, 4.19)	637	3.61 (3.37, 3.86)
One Month Postdose 2	% seroresponse (s/n) [2]	574	98.08 (563/574) (96.60, 99.04)	571	98.95 (565/571) (97.73, 99.61)
	GMT	598	113.10 (107.11, 119.42)	586	92.44 (88.14, 96.96)
Pre-Toddler Dose	% seroresponse (s/n) [2]	597	79.40 (474/597) (75.93, 82.57)	597	89.61 (535/597) (86.88, 91.94)
	GMT	624	11.21 (10.59, 11.86)	615	15.38 (14.58, 16.22)
One Month After the Toddler Dose	% seroresponse (s/n) [2]	566	99.12 (561/566) (97.95, 99.71)	561	99.64 (559/561) (98.72, 99.96)
	GMT	592	157.39 (149.64, 165.55)	580	109.96 (104.96, 115.19)
Antigen: FHA					
Pre-Vaccination 1	GMT	641	6.41 (5.89, 6.98)	648	6.19 (5.71, 6.72)
One Month Postdose 2	% seroresponse (s/n) [2]	590	88.98 (525/590) (86.17, 91.39)	578	96.54 (558/578) (94.71, 97.87)
	GMT	597	44.52 (42.16, 47.01)	583	86.55 (82.06, 91.29)
Pre-Toddler Dose	% seroresponse (s/n) [2]	614	58.79 (361/614) (54.79, 62.72)	607	82.37 (500/607) (79.10, 85.32)
	GMT	624	8.09 (7.56, 8.66)	615	22.70 (21.41, 24.07)
One Month After the Toddler Dose	% seroresponse (s/n) [2]	582	97.42 (567/582) (95.78, 98.55)	571	99.12 (566/571) (97.97, 99.72)
	GMT	592	120.79 (114.87, 127.01)	580	204.21 (194.99, 213.86)

Time Point	Endpoint	Vaccination Group			
		PR5I		INFANRIX™ hexa	
		n	Observed Response (95% CI) [1]	n	Observed Response (95% CI) [1]
Antigen: PRN					
Pre-Vaccination 1	GMT	641	4.57 (4.18, 4.99)	649	4.61 (4.24, 5.00)
One Month Postdose 2	% seroresponse (s/n) [2]	593	80.27 (476/593) (76.83, 83.40)	582	91.58 (533/582) (89.02, 93.71)
	GMT	600	37.84 (34.07, 42.03)	586	78.27 (71.53, 85.65)
Pre-Toddler Dose	% seroresponse (s/n) [2]	614	53.91 (331/614) (49.87, 57.91)	608	67.43 (410/608) (63.55, 71.15)
	GMT	624	6.53 (6.02, 7.09)	615	11.04 (10.15, 12.02)
One Month After the Toddler Dose	% seroresponse (s/n) [2]	582	96.91 (564/582) (95.16, 98.16)	572	98.25 (562/572) (96.81, 99.16)
	GMT	592	104.25 (96.59, 112.52)	580	153.50 (143.30, 164.44)
Antigen: FIM					
Pre-Vaccination 1	GMT	639	6.35 (5.73, 7.03)	644	5.57 (5.05, 6.13)
One Month Postdose 2	% seroresponse (s/n) [2]	597	93.30 (557/597) (90.99, 95.17)	577	4.33 (25/577) (2.82, 6.33)
	GMT	606	231.69 (214.28, 250.52)	587	3.45 (3.16, 3.77)
Pre-Toddler Dose	% seroresponse (s/n) [2]	612	78.10 (478/612) (74.61, 81.32)	603	2.49 (15/603) (1.40, 4.07)
	GMT	624	29.10 (26.73, 31.67)	615	2.18 (2.10, 2.25)
One Month After the Toddler Dose	% seroresponse (s/n) [2]	581	98.28 (571/581) (96.86, 99.17)	567	5.64 (32/567) (3.89, 7.87)
	GMT	592	553.60 (513.23, 597.15)	580	2.32 (2.20, 2.44)

[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.
[2] The pertussis seroresponse was defined as follows: (1) If pre-vaccination antibody concentration was < LLOQ, then the post-vaccination antibody concentration was ≥ LLOQ, (2) If pre-vaccination antibody concentration was ≥ 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.
Subset 1 consisted of subjects receiving Rotarix™ (Italy and Sweden); Subset 2 consisted of subjects receiving RotaTeq™ (Finland). Subjects received PR5I / INFANRIX™ hexa + Prevenar 13™ at 2, 4 and 11 to 12 mos; Rotarix™ at 2 and 4 mos (Subjects in Subset 1); RotaTeq™ at 2, 4 and 5 mos (Subjects in Subset 2). The first dose of RotaTeq™ given at 2 mos can be received prior to enrollment to the study according to the protocol.
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 subjects included in the analysis, PP-RW = Per-protocol-Revised Windows (defined as a blood draw sample window of Days 28 to 51 following Dose 2 or the toddler dose), PRN = Pertactin, PT = Pertussis toxoid, s = Number of responders.

Table 34. Summary of Anti-PRP Response by Time and Vaccination Group (PP-RW Population)

Time Point	Endpoint	Vaccination Group			
		PR5I		INFANRIX™ hexa	
		n	Observed Response (95% CI) [1]	n	Observed Response (95% CI) [1]
One Month Postdose 2	% with titer ≥ 1.0 µg/mL (s/n)	609	72.91 (444/609) (69.19, 76.40)	592	26.69 (158/592) (23.17, 30.45)
	% with titer ≥ 0.15 µg/mL (s/n)	609	96.55 (588/609) (94.78, 97.85)	592	77.87 (461/592) (74.31, 81.15)
	GMT	609	2.38 (2.13, 2.67)	592	0.46 (0.41, 0.51)
Pre-Toddler Dose	% with titer ≥ 1.0 µg/mL (s/n)	593	50.08 (297/593) (45.98, 54.18)	572	10.31 (59/572) (7.95, 13.10)
	% with titer ≥ 0.15 µg/mL (s/n)	593	91.40 (542/593) (88.85, 93.53)	572	48.08 (275/572) (43.91, 52.26)
	GMT	593	0.94 (0.85, 1.04)	572	0.17 (0.16, 0.19)
One Month After the Toddler Dose	% with titer ≥ 1.0 µg/mL (s/n)	454	89.87 (408/454) (86.72, 92.49)	478	91.00 (435/478) (88.07, 93.41)
	% with titer ≥ 0.15 µg/mL (s/n)	454	99.56 (452/454) (98.42, 99.95)	478	99.37 (475/478) (98.18, 99.87)
	GMT	454	4.43 (3.97, 4.94)	478	7.76 (6.81, 8.85)

[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.
Subset 1 consisted of subjects receiving Rotarix™ (Italy and Sweden); Subset 2 consisted of subjects receiving RotaTeq™ (Finland). Subjects received PR5I / INFANRIX™ hexa + Prevenar 13™ at 2, 4 and 11 to 12 mos; Rotarix™ at 2 and 4 mos (Subjects in Subset 1); RotaTeq™ at 2, 4 and 5 mos (Subjects in Subset 2). The first dose of RotaTeq™ given at 2 mos can be received prior to enrollment to the study according to the protocol.
CI = Confidence interval, GMT = Geometric mean titer, mos = Months, n = Number of subjects included in the analysis, PP-RW = Per-protocol-Revised Windows (defined as a blood draw sample window of Days 28 to 51 following Dose 2 or the toddler dose), PRP = Polyribosylribitol phosphate, s = Number of responders.

(d) Non-Inferiority Analysis Regarding Concomitant Use of PR5I and Rotarix at One Month Postdose 2

Non-inferiority analysis regarding the concomitant use of PR5I and Rotarix one month Postdose 2 based on the PP-RW population is provided for Subset 1 in Table 35. The anti-rotavirus IgA GMT ratio (PR5I group/ INFANRIX hexa group) one month Postdose 2 was 0.80 (95% CI: 0.54 to 1.20; p-value = 0.011); the lower limit of the 2-sided 95% CI for GMT ratio (PR5I group / INFANRIX hexa group) was > 0.50 indicating that the non-inferiority criterion was met. Similar findings were observed for the PP-OW and the FAS populations.

Table 35. Analysis of Non-Inferiority Regarding GMT for Rotarix at One Month Postdose 2 When Administered Concomitantly with PR5I/INFANRIX hexa (PP-RW Population, Subset 1) (Protocol 008)

		PR5I (N=193)		INFANRIX™ hexa (N=194)					
Antigen	Endpoint	n	Estimated GMT [1]	n	Estimated GMT [1]	GMT Ratio [1] (95% CI)	NI Margin	One-Sided P-Value [1]	Conclusion: Non-inferiority Criterion Met/Not Met
Rotavirus IgA	GMT	160	94.40	171	117.46	0.80 (0.54, 1.20)	0.50	0.011	Met

[1] The estimates for GMT, GMT ratio (PR5I group / INFANRIX™ hexa group), 95% CI and p-value were based on an ANCOVA model with natural log-transformed post vaccination titre as the response variable, and vaccination group, natural log-transformed prevaccination titre, country as explanatory variables. The missing prevaccination titres are imputed by a multiple imputation method and used in the ANCOVA analysis.
Subset 1 consisted of subjects receiving Rotarix™ (Italy and Sweden); Subset 2 consisted of subjects receiving RotaTeq™ (Finland). Subjects received PR5I / INFANRIX™ hexa + Prevenar 13™ at 2, 4 and 11 to 12 mos; Rotarix™ at 2 and 4 mos (Subjects in Subset 1); RotaTeq™ at 2, 4 and 5 mos (Subjects in Subset 2). The first dose of RotaTeq™ given at 2 mos could have been received prior to enrollment to the study according to the protocol.
ANCOVA = Analysis of covariance, CI = Confidence interval, GMT = Geometric mean titre, 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 a blood draw sample window of Days 28 to 51 following Dose 2 or the Toddler dose).

Discussion on Study 008

The study outline and conduct were adequate to assess the immunogenicity of PR5I and its non-inferiority to INFANRIX hexa, when given to healthy infants at 2, 4 and 11-12 months of age.

The immunogenicity data also support the administration of PR5I with licensed peadiatric vaccines (i.e. RotaTeq, Prevenar 13, and ProQuad).

The data from this study indicates slightly lower immune responses towards most PR5I antigens using the 2, 4 months infant series followed by a toddler dose at 11 to 12 months, as compared to the 2, 3 and 4 months followed by a toddler dose at 12 months used in study 007.

The main conclusion regarding immunogenicity findings in the study were the following:

- Acceptable response rates to all antigens contained in PR5I were elicited at one month following the Toddler dose.
- PR5I was non-inferior to INFANRIX hexa regarding the response rates to antigens contained in both vaccines at one month after the Toddler dose.
- Immune responses to Rotarix in subjects who received it concomitantly with either PR5I or INFANRIX hexa met the non-inferiority criterion.
- PR5I was superior to INFANRIX hexa regarding the response rates to PRP antigen (% ≥ 1.0 µg/mL) at one month Postdose 2. Nevertheless, response rates to PRP antigen were lower than those observed at one month postdose 3 in study 007, which used the 2, 3, 4 infant schedule. Although dose response rates and PRP GMTs in study 008 were lower in the PR5I group than in the INFANRIX hexa group following the toddler dose, the difference between the two vaccination groups was less pronounced than observed in study 007.
- Anti-HBs antibody responses were somewhat weaker than observed in study 007. Reverse cumulative distribution curves showed a trend towards lower anti Hepatitis B immune responses in

the PR5I versus INFANRIX hexa groups. Similar differences was not observed in the in the 007 study. It is unclear whether the somewhat lower immune response for the PR5I group would have any clinical significance since the immunological memory persist beyond the detection of antibodies and the persistence of anti-HBs antibodies may therefore not be the most appropriate surrogate of long term protection. The long term persistence of anti-HBs immunity may need to be evaluated in future studies.

- One month post dose 2 and one month post toddler dose, pertussis FHA and PRN response rates were lower with 95% confidence intervals not overlapping. FHA and PRN GMT were about 50% lower. Prior to the Toddler dose, the pertussis response rates for all shared antigens (PT, FHA, PRN) were lower in the PR5I compared to the Infanrix hexa group (see Table 33). For FHA and PRN, the GMT (8.09 and 6.53, respectively) returned to levels very close to the pre-vaccine GMT (6.41 and 4.57, respectively).
- After the Toddler dose, the pertussis antibody response rates were similar in the PR5I and Infanrix hexa groups for all shared antigens (PT, FHA, PRN). A slightly lower response rate was observed to the FHA antigen, but was still within the non-inferiority margin.
- One month post dose 2 the response rates and GMTs of IPV1 and IPV3 were lower. However, after the Toddler dose the response rates to all three poliovirus antigens were very similar between both groups.

The possible clinical relevance of the trends toward lower immune responses following the 2, 4 and 11-12 month dosing regimen, and potential consequences for dosing recommendations was assessed during the procedure and is discussed further in the following sections.

2.5.2.1. Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36. Summary of Efficacy for trial 007

Title: A Phase III Randomized, Double-Blind, Active-Comparator Controlled Clinical Trial to Study the Safety, Tolerability, and Immunogenicity of V419/PR5I in Healthy Infants When Given at 2, 3, 4, and 12 Months.		
Study identifier	V419/007	
Design	Phase III Randomized, Double-Blind (operating under in-house and third party blinding procedures) , Active-Comparator, Controlled Clinical Trial to Study the Safety, Tolerability, and Immunogenicity of PR5I (PR5I) in Healthy Infants (46 to 74 days of age at enrollment) When Given at 2, 3, 4, and 12 Months.	
	Duration of main phase:	26-May-2011 to 13-Mar-2013

<table>
<tr><td>Hypothesis</td><td colspan="3">Primary Hypotheses :
1. Acceptability of the vaccine-induced antibody response rates to polyribosylribitol phosphate (PRP), diphtheria, tetanus, inactivated poliovirus (IPV) Type 1, IPV Type 2, and IPV Type 3 at one month after the third dose of PR5I and to all antigens contained in PR5I at one month after the Toddler dose of PR5I.
2. Immunologic Non-inferiority of PR5I to INFANRIX hexa is considered to be demonstrated if the subjects have :
- Non-inferior response rates against PRP, diphtheria, tetanus, IPV1, IPV2, and IPV3 at one month after the third dose of PR5I, assessed by seroprotection rates.
- Non-inferior response rates against pertussis antigens (PT, FHA and PRN) at one month after the Toddler dose of PR5I, assessed by seroresponse rates.
- Non-inferior response rates against HBsAg at one month after the Toddler dose of
PR5I, assessed by the seroprotection rate.
Secondary Hypotheses :
Immunogenicity of ProQuad in subjects who receive it concomitantly with PR5I is acceptable and non-inferior to the responses observed in subjects who receive ProQuad concomitantly with INFANRIX hexa at one month after the Toddler dose of PR5I or the Control.</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">PR5I group</td><td>Received PR5I, Prevenar 13, and RotaTeq at 2, 3, and 4 months followed by PR5I and ProQuad at 12 months, and Prevenar 13 and ProQuad at 13 months.
Number randomized : n=611</td></tr>
<tr><td colspan="2">INFANRIX hexa group</td><td>Received INFANRIX hexa, Prevenar 13, and RotaTeq at 2, 3, and 4 months, followed by INFANRIX hexa and ProQuad at 12 months, and Prevenar 13 and ProQuad at 13 months.
Number randomized : n=606</td></tr>
<tr><td rowspan="3">Endpoints and definitions</td><td rowspan="2">Co-Primary endpoints</td><td>Seroresponse rates (%)</td><td>1.Antibody responses rates to PRP, diphtheria, tetanus, IPV1, IPV2 and IPV3 one month after the third dose of PR5I and antibody responses to all antigens contained in PR5I one month after the Toddler dose of PR5I.
The statistical criteria require that, for all of the PR5I antigens, the lower limit of the 2-sided 95% confidence interval (CI) for the response rate (%) is greater than the predetermined lower limit (P0) as defined in Table 6.</td></tr>
<tr><td>Seroresponse rates (%)</td><td>2. The endpoints for the primary hypothesis of non-inferiority of PR5I were antibody responses rates to antigens that are common to both PR5I and INFANRIX hexa and included PRP, diphtheria, tetanus, IPV1, IPV2 and IPV3 one month after the third dose of PR5I and pertussis and HBsAg one month after the Toddler dose of PR5I.</td></tr>
<tr><td>Secondary endpoints</td><td>Seroresponse rates (%)
95% CI for single group proportion</td><td>The endpoints for the non-inferiority and acceptability of ProQuad concomitantly administered with the Toddler dose of PR5I were antibody response rates at one month after the concomitant administration of ProQuad and the Toddler dose of PR5I.</td></tr>
</table>

	Two PP populations, PP-Revised Windows (PP-RW) and PP-Original Windows (PP-OW), were used in this study. PP-RW was defined as the PP population using 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 blood draw sample window of Days 28 to 44 following Dose 3 or the Toddler dose. The success of the hypothesis test will be based on the results from the PP-RW population. 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 for each serology time point.

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Two PP populations, PP-Revised Windows (PP-RW) and PP-Original Windows (PP-OW), were used in this study. PP-RW was defined as the PP population using 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 blood draw sample window of Days 28 to 44 following Dose 3 or the Toddler dose. The success of the hypothesis test will be based on the results from the PP-RW population.			
Primary endpoint	The endpoints for the primary hypothesis of acceptability of PR5I were antibody responses to PRP, diphtheria, tetanus, IPV1, IPV2 and IPV3 one month after the third dose of PR5I and antibody responses to all antigens contained in PR5I one month after the Toddler dose of PR5I. The endpoints for the primary hypothesis of non-inferiority of PR5I were antibody responses to antigens that are common to both PR5I and INFANRIX hexa and included PRP, diphtheria, tetanus, IPV1, IPV2 and IPV3 one month after the third dose of PR5I and pertussis and HBsAg one month after the Toddler dose of PR5I.			
Descriptive statistics and estimate variability	***PR5I Antigen Responses rates One Month PostDose 3 (PP-RW Population)***			
	Strain	**PRP**		
	Treatment group	PR5I	INFANRIX hexa	
	Number of subjects	550	521	
	% with titre ≥ 0.15 µg/mL	98.36	86.99	
	95% CI	<96.92,99.25>	(83.75,89.72)	
	Strain	**Diphtheria**		
	Treatment group	PR5I	INFANRIX hexa	
	Number of subjects	542	517	
	% with titre ≥ 0.01 IU/mL	99.82	99.81	
	95% CI	(98.98,100.00)	(98.93,100.00)	
	Strain	**Tetanus**		
	Treatment group	PR5I	INFANRIX hexa	

	Number of subjects	538	519	
	% with titre ≥ 0.01 IU/mL	100.00	100.00	
	95% CI	(99.32,100.00)	(99.29,100.00)	
	Strain	**IPV1**		
	Treatment group	PR5I	INFANRIX hexa	
	Number of subjects	547	528	
	% with Neutralizing Ab ≥ 1:8 dilution	100.00	99.81	
	95% CI	(99.33,100.00)	(98.95,100.00)	
	Strain	**IPV2**		
	Treatment group	PR5I	INFANRIX hexa	
	Number of subjects	547	530	
	% with NAb ≥ 1:8 dilution	99.82	99.62	
	95% CI	(98.99,100.00)	(98.64,99.95)	
	Strain	**IPV3**		
	Treatment group	PR5I	INFANRIX hexa	
	Number of subjects	545	525	
	% with NAb ≥ 1:8 dilution	100.00	100.00	
	95% CI	(99.33,100.00)	(99.30,100.00)	
	Antigen Responses One Month <u>Post Toddler Dose</u> (PP-RW Population) ***PR5I Antigen Responses One Month <u>Post Toddler dose</u> (PP-RW Population)***			
	Strain	**HBsAg**		
	Treatment group	PR5I	INFANRIX hexa	
	Number of subject	551	531	
	% with titre ≥ 10mIU/mL	99.64	99.06	
	95% CI	(98.70,99.96)	(97.82,99.69)	
	Strain	**Pertussis-PT**		
	Treatment group	PR5I	INFANRIX hexa	
	Number of subject	543	523	

	% seroresponse *	99.82	98.49	
	95% CI	(98.96,100.00)	(97.01,99.34)	
	Strain	**Pertussis-FHA**		
	Treatment group	PR5I	INFANRIX hexa	
	Number of subject	542	524	
	% seroresponse *	97.23	99.81	
	95% CI	(95.48,98.44)	(98.94,100.00)	
	Strain	**Pertussis-PRN**		
	Treatment group	PR5I	INFANRIX hexa	
	Number of subject	543	523	
	% seroresponse *	98.90	98.86	
	95% CI	(97.61,99.59)	(97.52,99.58)	
	* Notes on % seroresponse *	Pertussis seroresponse Postdose 3 was defined as follows: (1) If prevaccination antibody concentration was < LLOQ, then the postvaccination antibody concentration was ≥ LLOQ, (2) If prevaccination antibody concentration was ≥ LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. Pertussis seroresponse Post Toddler dose was defined as follows: (1) If prevaccination antibody concentration was < 4 x LLOQ, then the postvaccination antibody concentration was ≥ 4 x LLOQ, (2) If prevaccination antibody concentration was ≥ 4 x LLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels.		
Effect estimate per comparison	Primary endpoint **PRP** % with titre ≥ 0.15 µg/mL One Month Post Dose 3	Comparison groups	PR5I Group, INFANRIX hexa group	
		Rate difference (NI Margin: -10%)	11.37	
		95% CI	(8.44,14.68)	
		P-value	<0.001	
	Primary endpoint **Diphtheria** % with titre ≥ 0.01 IU/mL One Month Post Dose 3	Comparison groups	PR5I Group, INFANRIX hexa group	
		Rate difference (NI Margin: -10%)	-0.00	
		95% CI	(-0.95,0.96)	
		P-value	<0.001	
	Primary endpoint **Tetanus**	Comparison groups	PR5I Group, INFANRIX hexa group	

	% with titre ≥ 0.01 IU/mL One Month Post Dose 3	Rate difference (NI Margin: -5%)	0.00
		95% CI	(-0.71,0.74)
		P-value	<0.001
	Primary endpoint **IPV1** % with Neutralizing Ab ≥ 1:8 dilution One Month Post Dose 3	Comparison groups	PR5I Group, INFANRIX hexa group
		Rate difference (NI Margin: -5%)	0.19
		95% CI	(-0.51,1.07)
		P-value	<0.001
	Primary endpoint **IPV2** % with Neutralizing Ab ≥ 1:8 dilution One Month Post Dose 3	Comparison groups	PR5I Group, INFANRIX hexa group
		Rate difference (NI Margin: -5%)	0.19
		95% CI	(-0.69,1.21)
		P-value	<0.001
	Primary endpoint **IPV3** % with Neutralizing Ab ≥ 1:8 dilution One Month Post Dose 3	Comparison groups	PR5I Group, INFANRIX hexa group
		Rate difference (NI Margin: -5%)	0.00
		95% CI	(-0.70,0.73)
		P-value	<0.001
	Primary endpoint **HBsAg** % with titre ≥ 10mIU/mL One Month Post Toddler dose	Comparison groups	PR5I Group, INFANRIX hexa group
		Rate difference (NI Margin: -10%)	0.58
		95% CI	(-0.49,1.85)
		P-value	<0.001
	Primary endpoint **PT** % seroresponse * One Month Post Toddler dose	Comparison groups	PR5I Group, INFANRIX hexa group
		Rate difference (NI Margin: -10%)	1.33
		95% CI	(0.32,2.86)
		P-value	<0.001
	Primary endpoint **FHA** % seroresponse * One Month Post Toddler dose	Comparison groups	PR5I Group, INFANRIX hexa group
		Rate difference (NI Margin: -10%)	-2.59
		95% CI	(-4.39,-1.29)
		P-value	<0.001
	Primary endpoint **PRN** % seroresponse * One Month Post Toddler dose	Comparison groups	PR5I Group, INFANRIX hexa group
		Rate difference (NI Margin: -10%)	0.03
		95% CI	(-1.40,1.52)
		P-value	<0.001

Notes	The lower limit of the 2-sided 95% CI for the group difference (PR5I group minus INFANRIX hexa group) was above the pre-specified non-inferiority margin regarding all pre-specified endpoints, indicating that the PR5I group was non-inferior to the INFANRIX hexa group. Furthermore, the group difference regarding anti-PRP ≥ 0.15 µg/mL one month Postdose 3 was 11.37% (95% CI: 8.44% to 14.68%; p < 0.001) with its entire 95% CI above 0, suggesting a superior anti-PRP response elicited by PR5I Postdose 3 compared to INFANRIX Postdose 3.

Table 37. Summary of efficacy for trial 008

Title: A Phase III Randomized, Double-blind, Active-Comparator Controlled Clinical Trial to Study the Safety, Tolerability and Immunogenicity of PR5I in Healthy Infants When Given at 2, 4, and 11 to 12 Months / Protocol No: 008-04 (country-specific protocol for Finland) and 008-05 (country-specific protocol for Italy and Sweden)			
Study identifier	V419 Prot. No. 008-04 (Finland) V419 Prot. No. 008-05 (Italy, Sweden)		
Design	Randomized, Double-blind, Active-Comparator Controlled Clinical Trial		
	Duration of main phase:		23-Nov-2011 (FPE) to 09-Oct-2013 (LPLV)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Non-inferiority		
Treatments groups	PR5I		2+1 dose schedule at 2,4+12 Months n=656 randomized
	Infanrix hexa		2+1 dose schedule at 2,4+12 Months n=659 randomized
	Subset 1 consisted of subjects receiving Rotarix (Italy and Sweden); **Subset 2** consisted of subjects receiving RotaTeq (Finland). Subjects received PR5I / Infanrix hexa + Prevenar 13 at 2, 4 and 11 to 12 months; Rotarix at 2 and 4 months (Subjects in Subset 1); RotaTeq at 2, 4 and 5 months (Subjects in Subset 2). The first dose of RotaTeq given at 2 months can be received prior to enrollment to the study according to the protocol.		
Endpoints and definitions	Primary endpoint	Response rate (%)	Subjects who receive PR5I at 2, 4, and 11 to 12 months have an **acceptable** response rate to all PR5I-contained antigens at **one month after the Toddler dose** of PR5I. The statistical criteria require that, for each of the PR5I antigens, the lower limit of the 2-sided 95% CI is greater than the predetermined lower limit (P0) as defined in Table 6

	Secondary endpoint 1	Response rate (%)	At **one month after the second dose**, the anti-PRP response (% ⩾ 1.0 µg/mL) elicited by PR5I is **non-inferior** to that elicited by Infanrix hexa. The statistical criteria require that the lower limit of the 2-sided 95% CI of the differences in rates (PR5I group minus Infanrix hexa group) is > -0.10. Conditional upon acceptance of Secondary Hypothesis #1, the anti-PRP response (% ⩾ 1.0 µg/mL) elicited by PR5I is **superior** to that elicited by Infanrix hexa at one month after the second dose of PR5I or Infanrix hexa. The statistical criteria require that the lower limit of the 2-sided 95% CI of the differences in rates (PR5I group minus Infanrix hexa group) is > 0.
	Secondary endpoint 2	Response rate (%)	When compared with subjects who receive Infanrix hexa at 2, 4, and 11 to 12 months, the subjects who received PR5I at 2, 4, and 11 to 12 months must have: **- non-inferior** response rates against PRP, HBsAg, diphtheria, tetanus, IPV Type 1, IPV Type 2, and IPV Type 3 at **one month after the Toddler dose** of PR5I, assessed by seroprotection rates. **- non-inferior** response rates against pertussis-pertussis-PT), pertussis-FHA, and pertussis-pertactin PRN at **one month after the Toddler dose** of PR5I, assessed by seroresponse rates. 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 Infanrix hexa group) is greater than the prespecified margin (- δ) as defined.
	Secondary endpoint 3	GMT ratio	The **immunogenicity of Rotarix** in subjects who receive it concomitantly with PR5I as an infant series at 2 and 4 months is **non-inferior** to the responses observed in subjects who receive Rotarix concomitantly with the Control at **one month after the second dose** of PR5I/Infanrix hexa. The statistical criteria require that the lower limit of the 2-sided 95% CI of the anti-rotavirus immunoglobulin A (IgA) GMT ratio (PR5I/Infanrix hexa) is > 0.50.
(data not shown in this table)	*Tertiary endpoint 1*	*Response rate (%)*	*The anti-PRP response (% ⩾0.15 µg/mL) elicited by PR5I **before the Toddler dose** (~12 months) is **superior** to that elicited by Infanrix hexa at the same time point. The statistical criteria require that the lower limit of the 2-sided 95% CI of the differences in rates (PR5I group minus Infanrix hexa group) is > 0.*
	Tertiary endpoint 2	GMT	GMTs for all Antigens in PR5I and Infanrix hexa at **One Month Postdose 2**

(data not shown in this table)	*Tertiary endpoint 3*	*GMT*	*GMTs for Rotavirus Antigens at **One Month Postdose 2***
(data not shown in this table)	*Tertiary endpoint 4*	*GMT*	*GMTs for all Antigens in PR5I and Infanrix hexa at **One Month After the Toddler Dose***
(data not shown in this table)	*Tertiary endpoint 5*	*GMT*	*Subjects with Titres ≥ 0.1 IU/mL and ≥ 1.0 IU/mL for Diphtheria and Tetanus After the Toddler Dose*

Results and Analysis

Analysis description	**Primary Analysis**		
Primary endpoint	**Analysis of Acceptability of PR5I Antigen Responses**		
Analysis population and time point description	PR5I Group **One Month After the Toddler Dose** (PP-RW Population)		
Descriptive statistics and estimate variability	Treatment group		**PR5I**
	Number of vaccinated subjects		638
Effect estimate per comparison	Primary endpoint (**PRP**)	Response rate % with titre ≥ 1.0 µg/mL	89.87
		95% CI	**86.72**, 92.49
		P-value	<0.001
		Predetermined LL	75% (**Met**)
	Primary endpoint (**HBsAg**)	Response rate % with titre ≥ 10mIU/mL	98.14
		95% CI	**96.21**, 99.25
		P-value	<0.001
		Predetermined LL	90% (**Met**)
	Primary endpoint (**Diphteria**)	Response rate % with titre ≥ 0.1 IU/mL	98.64
		95% CI	**97.35**, 99.41
		P-value	<0.001
		Predetermined LL	80% (**Met**)
	Primary endpoint (**Tetanus**)	Response rate % with titre ≥ 0.1 IU/mL	99.83
		95% CI	**99.06**, 100.00
		P-value	<0.001
		Predetermined LL	90% (**Met**)
	Primary endpoint (**PT**)	Pertussis seroresponse	99.12
		95% CI	**97.95**, 99.71
		P-value	<0.001
		Predetermined LL	75% (**Met**)
	Primary endpoint (**FHA**)	Pertussis seroresponse	97.42
		95% CI	**95.78**, 98.55
		P-value	<0.001
		Predetermined LL	75% (**Met**)
	Primary endpoint	Pertussis seroresponse	98.28

	(**FIM**)	95% CI	**96.86**, 99.17
		P-value	<0.001
		Predetermined LL	75% (**Met**)
	Primary endpoint (**PRN**)	Pertussis seroresponse	96.91
		95% CI	**95.16**, 98.16
		P-value	<0.001
		Predetermined LL	75% (**Met**)
	Primary endpoint (**IPV1**)	Response rate % with NAb ≥ 1:8 dilution	99.32
		95% CI	**98.28**, 99.82
		P-value	<0.001
		Predetermined LL	90% (**Met**)
	Primary endpoint (**IPV2**)	Response rate % with NAb ≥ 1:8 dilution	99.83
		95% CI	**99.06**, 100.00
		P-value	<0.001
		Predetermined LL	90% (**Met**)
	Primary endpoint (**IPV3**)	Response rate % with NAb ≥ 1:8 dilution	99.49
		95% CI	**98.52**, 99.90
		P-value	<0.001
		Predetermined LL	90% (**Met**)
Analysis description	**Secondary Analysis**		
Secondary endpoint 1	**Analysis of Non-Inferiority Regarding PRP Antigen Response**		
Analysis population and time point description	**One Month Postdose 2 (5 Months of age)** (PP-RW Population)		
Descriptive statistics and estimate variability	Treatment group		**PR5I** / **Infanrix hexa**
	Number of randomized subject		649 / 651
	Number of vaccinated subject		609 / 592
	PRP Response rate % with titre ≥ 1.0 µg/mL		72.86 / 26.66
	Secondary endpoint (**PRP**)	Comparison groups	**PR5I minus Infanrix hexa**
		Estimated Difference %	46.20
		95% CI	**41.05**, 51.06
		P-value	<0.001
		NI margin	-10% (**Met**)
		Superiority	LL>0% (**Met**)
Secondary endpoint 2	**Analysis of Non-Inferiority Regarding PR5I Antigen Response**		
Analysis population and time point description	**One Month After the Toddler Dose (12-13 Months of age)** (PP-RW Population)		
	Treatment group		**PR5I** / **Infanrix hexa**

	Number of randomized subject		638	642
	Number of vaccinated subject		454	478
	PRP Response rate % with titre ≥ 1.0 µg/mL		89.80	91.06
	Secondary endpoint (**PRP**)	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	-1.27	
		95% CI	**-5.13**, 2.52	
		P-value	<0.001	
		NI margin	-10% (**Met**)	
	Treatment group		**PR5I**	**Infanrix hexa**
	Number of randomized subject		638	642
	Number of vaccinated subject		377	391
	HBsAg % with titre ≥ 10 mIU/mL		98.14	98.73
	Secondary endpoint (**HBsAg**)	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	-0.59	
		95% CI	**-2.66**, 1.35	
		P-value	<0.001	
		NI margin	-10% (**Met**)	
	Treatment group		**PR5I**	**Infanrix hexa**
	Number of randomized subject		638	642
	Number of vaccinated subject		590	578
	Diphtheria % with titre ≥ 0.1 IU/mL		98.62	99.83
	Secondary endpoint (**Diphteria**)	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	-1.21	
		95% CI	**-2.54**, -0.22	
		P-value	<0.001	
		NI margin	-10% (**Met**)	
	Treatment group		**PR5I**	**Infanrix hexa**
	Number of randomized subject		638	642
	Number of vaccinated subject		589	577
	Tetanus % with titre ≥ 0.1 IU/mL		99.83	100
	Secondary endpoint (**Tetanus**)	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	-0.17	
		95% CI	**-0.95**, 0.50	
		P-value	<0.001	
		NI margin	-5% (**Met**)	
	Treatment group		**PR5I**	**Infanrix hexa**
	Number of randomized subject		638	642
	Number of vaccinated subject		566	561

	PT % seroresponse		99.11	99.64
	Secondary endpoint (**PT**)	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	-0.54	
		95% CI	**-1.75**, 0.49	
		P-value	<0.001	
		NI margin	-10% (**Met**)	
	Treatment group		**PR5I**	**Infanrix hexa**
	Number of randomized subject		638	642
	Number of vaccinated subject		582	571
	FHA % seroresponse		97.40	99.13
	Secondary endpoint (**FHA**)	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	-1.73	
		95% CI	**-3.47**, -0.26	
		P-value	<0.001	
		NI margin	-10% (**Met**)	
	Treatment group		**PR5I**	**Infanrix hexa**
	Number of randomized subject		638	642
	Number of vaccinated subject		582	572
	PRN % seroresponse		96.86	98.28
	Secondary endpoint (**PRN**)	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	-1.42	
		95% CI	**-3.42**, 0.39	
		P-value	<0.001	
		NI margin	-10% (**Met**)	
	Treatment group		**PR5I**	**Infanrix hexa**
	Number of randomized subject		638	642
	Number of vaccinated subject		591	580
	IPV1 % with NAb ≥ 1:8 dilution		99.32	99.83
	Secondary endpoint (**IPV1**)	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	-0.51	
		95% CI	**-1.59**, 0.34	
		P-value	<0.001	
		NI margin	-5% (**Met**)	
	Treatment group		**PR5I**	**Infanrix hexa**
	Number of randomized subject		638	642
	Number of vaccinated subject		591	579
	IPV2 % with NAb ≥ 1:8 dilution		99.83	100
	Secondary endpoint	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	-0.17	

	(**IPV2**)	95% CI	**-0.96**, 0.49	
		P-value	<0.001	
		NI margin	-5% (**Met**)	
	Treatment group		**PR5I**	**Infanrix hexa**
	Number of randomized subject		638	642
	Number of vaccinated subject		590	579
	IPV3 % with NAb ≥ 1:8 dilution		99.49	99.65
	Secondary endpoint (**IPV3**)	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	-0.16	
		95% CI	**-1.20**, 0.82	
		P-value	<0.001	
		NI margin	-5% (**Met**)	
Secondary endpoint 3	**Analysis of Non-Inferiority Regarding Rotarix Antigen Response**			
Analysis population and time point description	**One Month Postdose 2 (5 Months of age)** (PP-RW Population, Subset 1)			
	Treatment group		**PR5I**	**Infanrix hexa**
	Number of randomized subject		193	194
	Number of vaccinated subject		160	171
	Estimated GMT		94.40	117.46
	Secondary endpoint (**Rotavirus IgA**)	Comparison groups	**PR5I minus Infanrix hexa**	
		Estimated Difference %	0.80	
		95% CI	**0.54**, 1.20	
		P-value	0.011	
		NI margin	>0.50 (**Met**)	
	Acceptability criteria The lower limit of the 2-sided 95% CI for the response rate (%) was greater than the predetermined lower limit regarding all prespecified endpoints, indicating that the PR5I group met the response rate acceptability criteria. **Pertussis seroresponse** The pertussis seroresponse was defined as follows: (1) If pre-vaccination antibody concentration was < LLOQ, then the post-vaccination antibody concentration was ≥ LLOQ, (2) If pre-vaccination antibody concentration was ≥ LLOQ, then the post-vaccination antibody concentration was ≥ pre-vaccination levels. The pre-vaccination level was defined as the antibody titre at pre- Dose 1.			
Analysis description	**Tertiary Analysis**			
Tertiary endpoint	**Analysis of GMTs for all Antigens in PR5I and Infanrix hexa**			
Analysis population and time point description	**One Month Postdose 2 (5 Months of age)** (PP-RW Population)			
			PR5I	**Infanrix hexa**
	Number of vaccinated subject		609	592

	Antigen	**Anti-PRP**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subjects	609	592
	GMT	2.38	0.46
	95% CI	2.13, 2.67	0.41, 0.51
	Antigen	**Anti-HBsAg**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subject	319	329
	GMT	225.50	343.48
	95% CI	195.8, 259.71	287.53, 410.33
	Number of analyzed subject	319	329
	% with titre ≥ 10 mIU/mL	98.12	96.35
	95% CI	95.95, 99.31	93.72, 98.10
	Antigen	**Anti-Diphteria**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subject	584	567
	GMT	0.08	0.09
	95% CI	0.08, 0.09	0.08, 0.10
	Number of analyzed subject	584	567
	% with titre ≥ 0.01 IU/mL	98.29	99.47
	95% CI	96.87, 99.18	98.46, 99.89
	Antigen	**Anti-Tetanus**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subject	578	561
	GMT	0.47	0.48
	95% CI	0.45 to 0.50	0.45 to 0.51
	Number of analyzed subject	578	561
	% with titre ≥ 0.01 IU/mL	100	100
	95% CI	99.36, 100	99.34, 100
	Antigen	**Anti-PT**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subject	598	586
	GMT	113.10	92.44
	95% CI	107.11, 119.42	88.14, 96.96
	Number of analyzed subject	574	571
	% seroresponse	98.08	98.95

	95% CI	96.60, 99.04	97.73, 99.61
	Antigen	**Anti-FHA**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subject	597	583
	GMT	44.52	86.55
	95% CI	42.16, 47.01	82.06, 91.29
	Number of analyzed subject	590	578
	% seroresponse	88.98	96.54
	95% CI	86.17, 91.39	94.71, 97.87
	Antigen	**Anti-PRN**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subject	600	586
	GMT	37.84	78.27
	95% CI	34.07, 42.03	71.53, 85.65
	Number of analyzed subject	593	582
	% seroresponse	80.27	91.58
	95% CI	76.83, 83.40	89.02, 93.71
	Antigen	**Anti-FIM**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subject	606	587
	GMT	231.69	3.45
	95% CI	214.28, 250.52	3.16, 3.77
	Number of analyzed subject	597	577
	% seroresponse	93.30	4.33
	95% CI	90.99, 95.17	2.82, 6.33
	Antigen	**Anti-IPV1**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subject	601	582
	GMT	65.31	88.07
	95% CI	56.79, 75.11	76.10, 101.92
	Number of analyzed subject	601	582
	IPV1 % with NAb ≥ 1:8 dilution	93.84	96.39
	95% CI	91.61, 95.63	94.54, 97.75
	Antigen	**Anti-IPV2**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subject	600	581

	GMT	92.46	88.95
	95% CI	79.07, 108.13	76.12, 103.95
	Number of analyzed subject	600	581
	IPV2 % with NAb ≥ 1:8 dilution	98	97.42
	95% CI	96.53, 98.96	95.78, 98.55
	Antigen	**Anti-IPV3**	
	Treatment group	**PR5I**	**Infanrix hexa**
	Number of analyzed subject	595	578
	GMT	76.60	105.28
	95% CI	66.03, 88.85	90.47, 122.52
	Number of analyzed subject	595	578
	IPV3 % with NAb ≥ 1:8 dilution	92.94	95.16
	95% CI	90.58, 94.87	93.07, 96.76

2.5.3. Analysis performed across trials (pooled analyses)

The primary vaccination schedules used in clinical studies are: 2, 4 months of age without hepatitis B vaccination at birth; 2, 3, 4 months of age without hepatitis B vaccination at birth; 2, 4, 6 months of age with and without hepatitis B vaccination at birth. The booster dose in clinical studies was given at 11-12 months after a 2-dose primary series or at 12 months of age after a 3-dose primary series vaccination. Results obtained for each component of the vaccine are summarised across studies in Table 38 and Table 39.

Table 38. Seroprotection/Seroconversion Rates One Month After the Primary Vaccination Series

Antibody Thresholds	**Two doses**	**Three doses**	
	2-4 months	**2-3-4 months**	**2-4-6 months**
	N = 319-609 %	**N = 498-550 %**	**N = 2455-2696 %**
Anti-diphtheria (≥ 0.01 IU/mL)	98.3	99.8	99.8
Anti-tetanus (≥ 0.01 IU/mL)	100.0	100.0	100.0
Anti-PT (vaccine response)[a]	98.1	99.4	98.9
Anti-FHA (vaccine response)[a]	89.0	89.0	88.1
Anti-PRN (vaccine response)[a]	80.3	86.7	84.0
Anti-FIM (vaccine response)[a]	93.3	97.2	90.0
Anti-Polio type 1 (≥ 1:8 dilution)	93.8	100.0	100.0
Anti-Polio type 2 (≥ 1:8 dilution)	98.0	99.8	100.0

Anti-Polio type 3 (≥ 1:8 dilution)		92.9	100.0	100.0
Anti-HBs Ag (≥ 10 IU/mL)	With hepatitis B vaccination at birth	/	/	99.8
	Without hepatitis B vaccination at birth	98.1	97.8	97.8[b]
Anti-PRP (≥ 0.15 µg/mL)		96.6	98.4	98.1

[a]Vaccine response: If pre-Dose 1 antibody concentration < lower limit of quantification (LLOQ), then the post-vaccination series antibody concentration was ≥ LLOQ; if pre-Dose 1 antibody concentration ≥ LLOQ, then the post-vaccination series antibody concentration was ≥ pre-Dose 1 levels.

[b]N=89 subjects from a separate study

Table 39. Seroprotection/Seroconversion Rates One Month After Booster Vaccination

Antibody Thresholds		**Booster at 11 -12 months of age, after 2-dose primary series**	**Booster at 12 months of age after 3-dose primary series**
		N = 377-591 **%**	**N = 439-551** **%**
Anti-diphtheria (≥ 0.1 IU/mL)		98.6	99.8
Anti-tetanus (≥ 0.1 IU/mL)		99.8	100.0
Anti-PT (vaccine response)[a]		99.1	99.8
Anti-FHA (vaccine response)[a]		97.4	97.2
Anti-PRN (vaccine response)[a]		96.9	99.3
Anti-FIM (vaccine response)[a]		98.3	99.6
Anti-Polio type 1 (≥ 1:8 dilution)		99.3	99.8
Anti-Polio type 2 (≥ 1:8 dilution)		99.8	100.0
Anti-Polio type 3 (≥ 1:8 dilution)		99.5	100.0
Anti-HBs Ag (≥ 10 mIU/mL)[b]		98.1	99.6
Anti-PRP	(≥ 0.15 µg/mL)	99.6	99.5
	(≥ 1.0 µg/mL)	89.9	95.0

[a] Vaccine response: If pre-Dose 1 antibody concentration < LLOQ, then post-booster antibody concentration should be ≥ LLOQ; If pre-Dose 1 antibody concentration ≥ LLOQ, then the post-booster antibody concentration should be ≥ pre-Dose 1 levels.

[b] Did not receive hepatitis B vaccine at birth

2.5.4. Clinical studies in special populations

Specific studies in special populations were not carried out.

Premature infants

Premature infants were not excluded from the Phase 3 studies. The gestational age was not collected. As the number of subjects identified as premature ("Premature baby", "Premature delivery" and/or "Low birth weight baby") is small compared to the overall study population, immunogenicity information is provided descriptively. No formal statistical comparisons were planned between PR5I and control within premature infants, or between the premature infant groups and the studies as a whole.

In the Phase 3 studies, a total of 111 subjects in the PR5I group and 49 subjects in the Control group had medical history terms consistent with prematurity.

Overall, although the numbers are small, the data indicate that a high percentage of premature infants mounted protective immune responses to antigens that have a well-defined correlate of protection. A high percentage also achieved protocol-defined vaccine response against pertussis.

Ethnicity

The studies have been performed in several European countries, which is considered a sufficient justification of the applicability of the available study data to the European population.

Immunocompromised infants

Immunocompromised infants were excluded from studies. This aspect is added as missing information in the Risk Management Plan (see further below).

2.5.5. Supportive studies

Study 005

- **Study design**

Study V419-005 served as a pivotal immunogenicity study in the US. The study design assessed the safety, tolerability, and immunogenicity of PR5I compared to the component vaccine control(s) (US standard-of-care) when given as an infant series 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).

The **comparator arm** of the study represented the current standard-of-care in the USA with PENTACEL administered as an infant series at 2, 4, and 6 months, with RECOMBIVAX HB administered separately at 2 and 6 months. The infant series of PR5I and PENTACEL was followed by a Toddler dose of DAPTACEL (Sanofi Pasteur Ltd) and Hib conjugate vaccine at 15 months of age. PedvaxHIB (PRP-OMPC conjugate, Merck) completed the PR5I infant series and ActHIB (PRP-TT conjugate, Sanofi Pasteur Ltd) completed PENTACEL to preserve antigenic continuity throughout the Hib vaccination series. However, PedvaxHIB is alum adjuvanted whereas ActHIB is not.

A PR5I regimen was compared to a 4-dose regimen of PENTACEL in a separate study (V419-006).

The **concomitant administration** of standard-of-care, licensed pediatric vaccines (Prevnar 13 and RotaTeq) with PR5I or the component vaccine Control(s) was evaluated in all study participants. The response rates to the PR5I antigens were compared to the component vaccine Control(s) to provide information on the compatibility of PR5I when given concomitantly with both Prevnar 13 and RotaTeq during the infant series. Additionally, the immunogenicity of concomitant RotaTeq was evaluated in this study. The immunogenicity of concomitant administration with Prevnar 13 was evaluated in another study in the Phase III program (V419-006).

This study was to provide evidence of immune protection after the complete infant vaccination series for hepatitis B to be consistent with the medical need for protection against hepatitis B exposure. This study was also to provide immunogenicity data in the presence of a birth dose of a monovalent hepatitis B vaccine, which represents the standard-of-care in the USA.

- **Primary analysis**

Non-inferiority criteria of the PR5I antigen responses and GMTs one month post-primary series were met for all PR5I antigens except for FHA GMTs.

Non-inferiority criteria of the PR5I antigen responses and GMTs one month post-Toddler dose were met for all PR5I antigens, although this has not been defined as a primary analysis.

Non-inferiority criteria of the pertussis antigen responses and GMTs one month post-Toddler dose were met for all pertussis antigens (PT, FHA, PRN, FIM).

Acceptability criteria of the IPV antigen responses in the PR5I group one month post-primary series were met for IPV 1, IPV2 and IPV3.

The results were consistent in the PP-RW, PP-OW and FAS populations.

PR5I is not used in a post-toddler/booster dose in study 005, but Daptacel is administered as booster, and the separate Hib-containing vaccine used for the booster dose varies between the two groups: PedvaxHiB is used as booster at 15 months in the PR5I group, and ActHIB is used as booster in the control group. Analyses of post-toddler endpoint for PRP/Hib are thus difficult to interpret because the immune responses post-booster result from the combined effect of four different vaccines (PR5I or Pentacel as primary series, PedvaxHiB or ActHIB as booster).

One month post-primary series the FHA GMTs are lower in the PR5I group than in the control group, and as a result the primary endpoint for FHA GMTs is not met in the primary analysis of US pivotal study 005. Likewise, the pre-toddler dose GMT for FHA in the PR5I group returned to pre-vaccination levels, i.e 6.3 and 6.9 for pre-toddler and pre-vaccination GMT respectively, and was twice higher before the toddler dose in the control group (13.2), suggesting a more rapid waning after a primary series of PR5I compared to the comparator, as the same vaccine (DAPTACEL) was used for boosting the pertussis response (data not shown in this report). A similar observation was made in the EU pivotal studies 007 and 008 in the tertiary analysis, respectively, although non-inferiority criteria were not defined.

One month post-Toddler dose, the non-inferiority criteria for pertussis were met.

The proportion of subjects with anti-PRP ≥ 1.0 µg/mL one month after the Toddler dose (indicative of long-term protection for Hib) was about 95% for both PR5I and control, whereas PR5I GMTs were inferior.

Study 006

PR5I is not used in a post-toddler/booster dose in study 006, but the vaccine used as booster (Pentacel) is the same in the two groups. Analyses of post-toddler endpoint (secondary objective for pertussis and tertiary for all antigens) can thus be meaningful to compare the priming effect of PR5I and the comparator, because the two groups receive the same vaccine as booster.

PR5I induced an acceptable immune response against all disease antigens contained in PR5I except for FHA.

The immune response to a 3-dose infant series of PR5I was comparable to vaccination with a licensed Control regimen for all prespecified endpoints, except for the GMT of the FHA antigen.

PR5I includes polyribosylribitol phosphate (PRP) conjugated to outer membrane protein complex of Neisseria meningitidis (OMPC) that elicits a rapid immune response to Hib. The subjects in the PR5I group of Protocol 006 received PRP-OMPC for 3 infant doses as contained in PR5I, and a Toddler dose of PRP-T (Tetanus Toxoid conjugate) as contained in PENTACEL. Based on known kinetics of antibody responses to stand-alone PRP-OMPC Hib vaccines (as contained in PR5I) and combination PRP-T Hib vaccines (as contained in INFANRIX hexa and PENTACEL), higher PRP seroprotection rates and GMT are expected after the initial doses for PRP-OMPC Hib vaccines but higher post-Toddler dose GMT are expected for PRP-T Hib vaccines.

The Hib literature shows that “mixed regimens” in which initial doses of PRP-OMPC are followed by other types of Hib conjugate vaccines (including PRP-T), resulted in the highest post-vaccination GMT.

The response to the primary series is consistent with the anti-PRP GMT results of P007. However, the response to the booster dose is higher in study 006 than in study 007. In study 007, both primary series and booster used PR5I and the responses to the booster dose were lower than with the comparator (Infanrix Hexa). This reinforces the interest to boost with a vaccine containing another Hib component.

The study’s outline and conduct were adequate to show consistency of the three batches of PR5I. Comparative immunogenicity (seroprotection/seroconversion) of three batches investigated show no significant differences and equivalence between the different PR5I batches was concluded for all valences.

The primary and secondary immunogenicity findings demonstrated lot consistency and support the administration of PR5I as a 3-dose infant series given to healthy infants at 2, 4, and 6 months of age . PR5I induced an immune response against all disease antigens. However, one of the two non-inferiority criteria with a control vaccine were not met for two pertussis antigens (one endpoint each): GMT response to 3-dose primary series for FHA and GMT response to a toddler dose of Pentacel for PRN.

The immunogenicity data also support the administration of PR5I with licensed pediatric vaccines, including PCV 13 (Prevenar 13).

Furthermore, the immunogenicity findings demonstrate that a 3-dose infant series of PR5I can be followed by a Toddler dose of a pertussis-containing vaccine to complete the 4-dose pertussis vaccination series.

Study PRI01C

PRI01C was designed to assess the safety, tolerability, and immunogenicity of PR5I administered at 2, 3, and 4 months of age when given concomitantly with licensed meningococcal serogroup C conjugate vaccines (NeisVac-C or Menjugate). (UK Vaccination schedule)

A number of meningococcal vaccines are either available or are in development but in Europe only monovalent meningococcal serogroup C conjugate (MCC) vaccines are licensed for infants, either as a tetanus toxoid (TT) conjugated vaccine (MCC-TT) or as a CRM197 conjugated vaccine (MCC-CRM).

At the time of the study implementation, in the UK, the childhood vaccination schedule was an accelerated 3-dose primary series of a pentavalent (DTaP-IPV-PRP) vaccine at 2, 3, and 4 months of age, the second and third doses being given concomitantly with a MCC vaccine, with a booster dose of a combined Hib-MCC vaccine at 12 months of age. A pneumococcal conjugate vaccine (PCV) (a CRM197 conjugated vaccine) is also administered at 2 and 4 months of age with a booster dose at 12 months of age. This unique and specific primary vaccination schedule used in the UK (not in other EU countries) was not covered by the initial PR5I Phase III clinical program.

The introduction of universal hepatitis B vaccination of infants in the UK would only be considered with a multivalent combination vaccine. At the time of study implementation, DT5aP-based combinations were currently recommended by the Joint Committee on Vaccination and Immunisation.

Interference has been previously observed between MCC vaccines (TT or CRM197 conjugate) and Hib-containing paediatric vaccine (e.g. Pediacel® [PRP-TT conjugate]). Therefore to facilitate the potential future introduction of PR5I in the UK, its administration within the current childhood vaccination schedule and in particular when given concomitantly with MCC vaccines was to be evaluated.

In addition, the immune responses following a booster dose with a Hib-MCC vaccine (TT conjugate, Menitorix®) given at 12 months of age was also required to confirm that adequate protection against these 2 diseases was still observed about 8 months after the concomitant administration with PR5I. Since the study implementation, the UK vaccination calendar was changed on 01-JUN- 2013.

Indeed 1 dose of MCC is now recommended at 3 months of age, still followed by a booster dose of a combined Hib-MCC vaccine at 11-12 months of age. Because this study includes evaluation of MCC antibody response 1 month after the first dose of MCC administered at 3 months of age, it still remains relevant for the new British schedule.

- **Study Design**

This was an open-label, randomized Phase III study conducted in healthy infants (46 to 74 days of age at enrollment) at 11 study centers across the UK. Eligible subjects were randomized in a 1:1 ratio to receive PR5I at 2 months of age and concomitantly with either NeisVac-C or Menjugate at 3 and 4 months of age. Additionally, subjects in both groups received the same other concomitant vaccines: Prevenar 13 at 2 and 4 months of age and Menitorix (Haemophilus type b and Meningococcal group C conjugate vaccine), Prevenar 13 and MMRVAXPRO at 12 months of age as part of the study.

The vaccination period lasted 10 months and was split in 2 parts: Part I and Part II.

Part I referred to the infant doses.

Part II referred to the booster/Toddler dose.

- **Results**

Results based on the Part II FAS were comparable for Hib but not for MCC results. Seroresponse and GMT to MCC were much higher pre-booster (12 months) in the MCC-TT group compared to the MCC-CRM group, suggesting a more rapid waning after the primary doses in the MCC-CRM group (40.4% ≥1:8 at 12 months).

This may have a clinical impact as it is an age with the highest incidence of meningococcal invasive disease. GMTs were higher in the MCC-TT than in the MCC-CRM group at 13 months of age after the booster dose as they were post-dose 1 and post-dose 2.

The present immunogenicity and safety findings support the administration of PR5I as a 3-dose primary series given to healthy infants at 2, 3, and 4 months of age concomitantly with MCC vaccine. The present findings also demonstrate that a 3-dose infant series of PR5I can be followed by a toddler dose of a combined Hib-MCC vaccine.

In healthy infants who received a accelerated 3-dose primary series at 2, 3, and 4 months of age with PR5I, the second and third doses given concomitantly with a MCC vaccine followed by a booster dose with a combined Hib-MCC vaccine at 12 months of age together with routine PCV-13 and MMR vaccinations, the following conclusions can be drawn:

- Post primary series, the post-Dose 2 SPR against MCC was acceptable for both the MCC-TT and MCC-CRM vaccines. Whatever the MCC vaccine used, the SPRs against MCC were high (titres ≥1:8 dil) after 2 doses (≥99.1%) but also after 1 dose (≥96.4%); SPRs were also high (≥97.3%) and comparable after the booster dose. However, post-dose 1 and post-dose 2 GMTs were higher in the MCC-TT than in the MCC-CRM group.; these differences persisted at 12 months of age before the booster dose, and a much lower seroresponse (titres ≥1:8) was observed in the MCC-CRM group (40.4% vs. 83.1% in the MCC-TT group), suggesting a more rapid waning after the primary series. The differences in GMT also persisted at 13 months of age after the booster dose.
- PR5I induced a robust immune response against all disease antigens. Post-primary series, the SPR against Hib response was acceptable for the combined vaccine groups. The immune response was comparable to the responses observed in the pivotal controlled study 007 which compared the accelerated 3-dose primary series with PR5I to a licensed control vaccine.

Study PRI02C

The study report of Study PRI02C, ongoing at the time of the MAA submission, was submitted with the Responses to the D120 List of Questions.

PRI02C was an open-label, single arm, multi-centre study designed to assess the immunogenicity and the safety of a mixed vaccination schedule that includes PR5I at 2 and 6 months of age and Pediacel at 4 months of age in Spain.

Subjects received a 3-dose primary series with PR5I at 2 and 6 months of age and Pediacel at 4 months of age (mixed schedule), the first and second doses given concomitantly with one dose of meningococcal serogroup C TT-conjugate (MCC-TT) (NeisVac-C), together with one dose of pneumococcal polysaccharide conjugate vaccine (Prevenar 13) and one dose of pentavalent combination live vaccine of five human-bovine reassortant rotavirus strains (RotaTeq), and the third dose with RotaTeq. The vaccination period lasted around 4 months.

Co-primary objectives

- To demonstrate that the mixed schedule induces acceptable responses for hepatitis B (% of subjects with an anti-HBs titre ≥ 10 mIU/mL) one month after the third dose of the mixed schedule (i.e. at Month 7).

- To demonstrate that the mixed schedule induces acceptable responses for Haemophilus influenzae type b (Hib) (% of subjects with an anti-polyribosylribitol phosphate [PRP] titre ≥ 0.15 μg/mL) one month after the third dose of the mixed schedule (i.e. at Month 7).

Secondary Objectives

Immunogenicity

- To describe the antibody response to all PR5I antigens: hepatitis B, Hib (PRP), diphtheria and tetanus toxoids, pertussis (5aP: pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN] and fimbriae [FIM] types 2&3) and inactivated poliovirus (IPV1, IPV2, IPV3) antigens one month after completion of the mixed schedule (i.e. at Month 7).
- To describe the antibody response to meningococcal serogroup C conjugate (MCC) vaccine one month after the second dose of MCC vaccine when used concomitantly with the mixed schedule.

Safety

- To describe the safety profile after each dose and any dose of study vaccines administered.

The acceptability was demonstrated if the two-sided 95% Confidence Interval (CI) around the post-vaccination response rate excluded rates equal to or lower than 90% for hepatitis B and 80% for Hib. The success of the study required that both co-primary objectives were achieved (i.e. for hepatitis B and for Hib).

No formal hypotheses were to be tested, neither for the secondary immunogenicity objectives, nor for the secondary safety objectives.

Treatments

Table 40. Schedule of vaccine administration and blood sampling

Visit	1	2	3	4	5
Age	~2 months 46 to 74 days of age	~4 months 120 days of age ±7 days	~5 months 28 to 44 days after previous vaccinations	~6 months 180 days of age ±10 days	~7 months 28 to 44 days after previous vaccinations
	PR5I + NeisVac-C® + Prevenar 13® + RotaTeq®	Pediacel® + NeisVac-C® + Prevenar 13®+ RotaTeq®		PR5I+ RotaTeq®	
Blood Sample			BS1		BS2

Results

Outcomes and estimation

Primary endpoint

The analysis of acceptability of HBs and Hib (PRP) antigen responses (i.e. proportion of subjects with an anti-HBs titre ≥ 10 mIU/mL and with an anti-PRP titre ≥ 0.15 mcg/mL, respectively) one month post-dose 3 of the mixed schedule based on the PR5I PPS is provided in Table 41.

The lower bound of the 2-sided 95% CI of the response rate for HBs and Hib (PRP), one month after the third dose of the mixed schedule, were respectively 97.2% and 99.0%, i.e. greater than the pre-specified acceptability thresholds (respectively 90% and 80%).

The results based on the FAS were similar.

Table 41. Analysis of acceptability of HBs and Hib (PRP) antigen responses one month post-dose 3 of the mixed schedule – PR5I Per Protocol Set (N=370)

Antigen	Endpoint	n	Alpha	Point estimate ([1-alpha]%CI)[1]	Lower bound limit for acceptability	Conclusion: acceptability criterion
HBs	% with titre ≥10 mIU/mL	369	0.05	365 (98.9%) [97.2;99.7]	90%	Met
PRP	% with titre ≥0.15 µg/mL	365	0.05	365 (100.0%) [99.0;100.0]	80%	Met
N: Number of subject vaccinated, n: number of subjects, CI: Confidence interval. [1] 95% CI for the response rate calculation is based on the exact method of D.COLLETT.						

The co-primary endpoints have been met; therefore the mixed schedule would induce an acceptable post-dose 3 response rate for hepatitis B and for Hib.

Secondary endpoint

- Descriptive Statistics for Post-Dose 3 Immunogenicity of PR5I/Pediacel given at 2, 4 and 6 Months of Age

Table 42. Summary of PR5I/Pediacel antigen response post-dose 3 of the mixed schedule – PR5I Per Protocol set (N=370)

Antigen	Endpoint	n	Observed response	[95% CI] [1]
HBsAg (mIU/mL)	GMT	369	1054.97	[911.49;1221.03]
PRP (µg/mL)	% with titres ≥1.0	365	348 (95.3%)	[92.6;97.3]
	GMT		8.00	[7.17;8.93]
Diphtheria (IU/mL)	% with titres ≥0.01	359	359 (100.0%)	[99.0;100.0]
	% with titres ≥0.1	359	331 (92.2%)	[88.9;94.8]
	GMT		0.47	[0.42;0.52]
Tetanus (IU/mL)	% with titres ≥0.01	350	350 (100.0%)	[99.0;100.0]
	% with titres ≥0.1	350	350 (100.0%)	[99.0;100.0]
	GMT		2.44	[2.31;2.59]
Pertussis				
PT (EU/mL)	GMT	349	107.46	[101.55;113.71]
FHA (EU/mL)	GMT	349	67.09	[62.38;72.15]
PRN (EU/mL)	GMT	349	56.46	[51.60;61.78]
FIM 2&3 (EU/mL)	GMT	349	360.99	[332.58;391.82]
Poliovirus Type 1 (dil)	% with titres ≥1:8	356	356 (100.0%)	[99.0;100.0]
	GMT		663.97	[588.10;749.62]
Poliovirus Type 2 (dil)	% with titres ≥1:8	356	356 (100.0%)	[99.0;100.0]
	GMT		1198.93	[1051.90;1366.51]
Poliovirus Type 3 (dil)	% with titres ≥1:8	356	356 (100.0%)	[99.0;100.0]
	GMT		764.64	[664.70;879.61]

n = number of subjects included in the analysis. CI = confidence interval
Mixed schedule: PR5I at 2 and 6 months of age (first and second dose) and Pediacel® at 4 months of age (third dose); first and second doses given concomitantly with one dose of meningococcal serogroup C conjugate (MCC) (NeisVac-C®), one dose of pneumococcal polysaccharide conjugate vaccine (Prevenar 13®), and one dose of pentavalent combination live vaccine of five human-bovine reassortant rotavirus strains (RotaTeq®); third dose given with RotaTeq®. Moreover, subjects had received one dose of monovalent hepatitis B vaccine at birth.
[1] The 95% CI for response rate is based on the exact binomial method by D. COLLETT. The 95% CI for GMT is based on the Student's t-distribution of the natural log-transformed antibody titre.

- Descriptive statistics for Post-Dose 2 Immunogenicity of MCC Given at 2 and 4 Months of Age

One month after the second dose of MCC vaccine administered at 2 and 4 months of age, the response rate (i.e. the proportion of subjects with an anti MCC titre ≥ 1:8 dil) was 99.2%. The anti-MCC GMT was 739.63 dil. The results based on the FAS were consistent with those of the MCC PPS.

Table 43. Summary of MCC antigen response post-dose 2 of MCC vaccine – MCC per protocol set (N=375)

MCC (dil)	n	Observed response	(95% CI)[1]
% with titres ≥1: 8	375	372 (99.2%)	[97.7;99.8]
GMT		739.63	[659.94;828.96]

CI: Confidence interval. N: Number of subject vaccinated, n: number of subjects included in the analysis.
Mixed schedule: PR5I at 2 and 6 months of age (first and second dose) and Pediacel® at 4 months of age (third dose); first and second doses given concomitantly with one dose of meningococcal serogroup C conjugate (MCC) (NeisVac-C®), one dose of pneumococcal polysaccharide conjugate vaccine (Prevenar 13®), and one dose of pentavalent combination live vaccine of five human-bovine reassortant rotavirus strains (RotaTeq®); third dose given with RotaTeq®. Moreover, subjects had received one dose of monovalent hepatitis B vaccine at birth
[1] The 95% CI for the response rate calculation is based on the exact method of D. COLLETT. The 95% CI for GMT is based on the t-distribution of the log transformed antibody titre.

In another study that applied concomitant vaccination with a MenC-TT vaccine, Study PRI01C, an acceptability threshold of 90% for the lower bound limit of the 95% confidence interval was prespecified. Although no formal hypotheses were tested for the secondary immunogenicity objectives, the lower bound of

the 2-sided 95% CI of the SPR to MCC one month after 2 doses of MCC vaccine (95.0%) was greater than 90% (i.e. the prespecified acceptability threshold), demonstrating that the SPR for MCC vaccine was acceptable.

Table 44. Analysis of Acceptability of MCC Antigen Responses One Month Postdose 2 of MCC Vaccine When Given Concomitantly With PR5I (Per Protocol Set - Part I - N=236) (Study PRI01C)

Vaccine group	Endpoint	s/n	Alpha	Point estimate ([1-alpha]% CI) [1]	Lower bound limit	Conclusion: acceptability criterion met/not met
MCC-TT	% with titre ≥1:8 dil	121/121	0.050	100 [97.0, 100]	90%	Met
MCC-CRM	% with titre ≥1:8 dil	108/109	0.050	99.1 [95.0, 100]	90%	Met

CI = confidence interval, s/n = number of subjects with the response / number of subjects included in the analysis
[1] CI is calculated based on an exact binomial method by D. COLLETT.
Source: Listing 16.2.6.a

Table 45. Vaccine administration by vaccination group (Study PRI01C)

Group	Vaccine Administered		Visit 1 2 months	Visit 2 3 months	Visit 3 4 months	Visit 5 12 months
MCC-TT (n=141)	Test vaccines	PR5I	X	X	X	
		MCC-TT vaccine		X	X	
		Hib-MCC vaccine				X
	Routine vaccines	PCV-13	X		X	X
		MMR vaccine				X
MCC-CRM (n=143)	Test vaccines	PR5I	X	X	X	
		MCC-CRM vaccine		X	X	
		Hib-MCC vaccine				X
	Routine vaccines	PCV-13	X		X	X
		MMR vaccine				X

Each 0.5 mL dose of vaccine was injected via intramuscular (IM) route.
Test vaccines:
PR5I: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, *Haemophilus influenzae* b (Hib) conjugate [Meningococcal Outer Membrane Protein Complex], and hepatitis B (recombinant) vaccine.
MCC-TT vaccine: meningococcal group C polysaccharide conjugate vaccine to tetanus toxoid
MCC-CRM vaccine: meningococcal group C conjugate vaccine to CRM-197
Hib-MCC vaccine: *Haemophilus influenzae* type b and Meningococcal group C conjugate vaccine
Routine vaccines:
PCV-13: pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)
MMR vaccine: measles, mumps and rubella vaccine

Table 46. Summary of MCC Antigen Responses per Dose (Per Protocol Set - Part I - N=236) in Study PRI01C in the UK

		MCC-TT (N=125)		MCC-CRM (N=111)		Total (N=236)	
Time point	Endpoint	s/n	Observed response [95% CI] [1]	s/n	Observed response [95% CI] [1]	s/n	Observed response [95% CI] [1]
Post-dose 1 of MCC vaccine	% with titres ≥1:8 dil	102/102	100 [96.4, 100]	81/84	96.4 [89.9, 99.3]	183/186	98.4 [95.4, 99.7]
	% with titres ≥1:128 dil	100/102	98.0 [93.1, 99.8]	71/84	84.5 [75.0, 91.5]	171/186	91.9 [87.0, 95.4]
	GMT		1353.0 [1058.4, 1729.6]		285.0 [201.5, 403.1]		669.6 [530.2, 845.6]
	n missing		23		27		50
Post-dose 2 of MCC vaccine	% with titres ≥1:8 dil	121/121	100 [97.0, 100]	108/109	99.1 [95.0, 100]	229/230	99.6 [97.6, 100]
	% with titres ≥1:128 dil	120/121	99.2 [95.5, 100]	108/109	99.1 [95.0, 100]	228/230	99.1 [96.9, 99.9]
	GMT		2024.7 [1689.8, 2425.9]		1077.4 [847.5, 1369.8]		1501.5 [1288.8, 1749.3]
	n missing		4		2		6

CI = confidence interval; n = number of subjects included in the analysis; s = number of subjects with the response
[1] The 95% CI for response rate is based on the exact binomial method by D. COLLETT. The 95% CI for GMT is based on the t-distribution of the natural log-transformed antibody titre.
Source: Listing 16.2.6.a

Although no formal acceptability test was performed, the seroresponse rate for the MenC-TT vaccine (NeisVac-C) met the acceptability criteria set in another study, and is therefore considered acceptable.

Differences were observed in GMT values observed after 2 doses of NeisVac-C (MenC-TT) with higher value in PRI01C study in the UK (2024.7 (dil)) compared to PRI02C study (739.63 (dil)) in Spain. For both studies, the proportion of subjects with an anti-MCC titre (SBA titre) ≥ 1:8 dil (i.e. seroprotection rate) was similar and above 99%. Concomitant use of other pediatric vaccines in Spain, such as PCV13 and rotavirus vaccine, could have contributed to the lower GMTs observed in Spain. These findings are consistent with those reported in the literature for concomitant administration of MCC-TT with TT-containing combination vaccines.

Additional analysis on pertussis antigens

In order to further support the immunological data package of PR5I, the Applicant was requested to provide i) a post-hoc efficacy bridging of PR5I immunogenicity data for all antigens to Daptacel immunogenicity data obtained from the Sweden I Efficacy trial: PR5I immunogenicity data in a 3-dose schedule (2, 4, 6) in studies 005 and 006 compared to Daptacel immunogenicity data in a 3-dose schedule (2, 4, 6) in the Sweden I Efficacy trial (of note, this was not a retesting exercise but a comparison with historical data); ii) post-hoc non-inferiority testing results of studies 005, 006, 007 and 008 for all antigens post-primary and post-booster; iii) an efficacy bridging of PR5I immunogenicity data in a 2-dose schedule (2-4) in study 008 to the immunogenicity data of a similar vaccine for which clinical efficacy in a 2-dose schedule is established (Sweden II trial).

i) The Sweden I Efficacy trial was a 4-arm, randomized, double-blind, controlled study, conducted in 14 study centers in Sweden and compared the following vaccines: DT (Swedish standard of care), CLI DTP (whole cell pertussis), DTaP2 and DTaP5 (Daptacel), administered to infants at 2, 4 and 6 months of age. The Sweden I immunogenicity results included in the post-hoc analyses below focus on those obtained for Daptacel, given the similarity in vaccine formulation with the DTaP5 portion of PR5I for diphtheria, tetanus

and pertussis antigens but for lower PT and FHA antigen content in Daptacel (10 and 5 mcg/dose, resp.). This study was conducted by the Swedish Institute for Infectious Disease Control.

The Sweden I trial demonstrated that the absolute efficacy of Daptacel compared to the DT control was 85% (95% CI: 81; 89) in relation to the WHO Case Definition for infants (typical pertussis defined as ≥ 21 consecutive days of paroxysmal cough and laboratory or culture-confirmed B. pertussis) who received 3 doses of vaccine. For mild disease (defined as ≥ 1 day of paroxysmal cough and laboratory confirmed pertussis), the VE for Daptacel was 78% (95% CI: 73; 83).

A post-hoc, descriptive comparison analysis of GMTs and Vaccine response rates (as defined in the Phase III PR5I studies) for PR5I pertussis antigen responses in P005 and Daptacel responses in Sweden I are shown in Table 47.

Table 47. Post-hoc non-inferiority comparisons for pertussis antigens postdose 3 (P005 PR5I vs. Daptacel in Sweden I)

Antigen	Endpoint	PR5I		Daptacel™ (Sweden I)		GMTR or Rate Difference (95% CI)
		N	% or GMT (n/N or 95% CI)	N	% or GMT† (n/N or 95% CI)	
PT	GMT	810	110.40 (105.78, 115.21)	178	49.38 (44.74, 54.50)	2.24 (2.01, 2.49)
	Vaccine response	796	98.12 (781/ 796)	178	97.75 (174/178)	0.36 (-1.49, 3.82)
FHA	GMT	810	48.17 (45.68, 50.80)	178	34.09 (30.81, 37.73)	1.41 (1.26, 1.58)
	Vaccine response	796	87.31 (695/ 796)	178	92.70 (165/178)	-5.39 (-9.36, -0.18)
PRN	GMT	808	56.22 (51.93, 60.85)	178	116.53 (102.69, 132.24)	0.48 (0.42, 0.56)
	Vaccine response	794	79.35 (630/ 794)	178	97.75 (174/178)	-18.41 (-21.81,-14.32)
FIM	GMT	809	235.62 (221.43, 250.73)	178	351.09 (301.64, 408.65)	0.67 (0.57, 0.79)
	Vaccine response	796	90.20 (718/ 796)	178	97.19 (173/178)	-6.99 (-9.88, -3.03)

N = number of subjects in the analysis, n = number of subjects with vaccine response. The postdose 3 vaccine response was defined as (1) If prevaccination antibody concentration was < 4xLLOQ, then the postvaccination antibody concentration was ≥ 4xLLOQ, (2) If prevaccination antibody concentration was ≥ 4xLLOQ, then the postvaccination antibody concentration was ≥ prevaccination levels. The prevaccination level was defined as the antibody titer at pre-Dose 1.
† Laboratory testing performed at the Swedish Institute for Infectious Disease Control. LLOQ for the Swedish lab was set at 1 for all pertussis antigens (PT/FHA/PRN/FIM)
The estimates for the response rate and rate difference (PR5I Group minus Control Group) were based on the method by Miettinen and Nurminen. The estimates for GMT ratio (PR5I Group/Control Group) are based on two-sample t-test with different variances and a degrees-of-freedom approximated by Satterthwaite method.

The analysis shows that the PR5I pertussis responses in P005 had slightly higher vaccine response rates for PT (rate difference 95% CI included 0, difference not significant), marginally lower vaccine response rates for

FHA, significantly lower response rates for PRN, and lower vaccine response rates for FIM, as compared to Daptacel Sweden I responses. However vaccine response rates FIM were in excess of 90% for PR5I. The PR5I GMTs were over 2-fold higher for PT, 1.4-fold higher for FHA, 0.48-fold for PRN, and 0.67-fold for FIM, as compared to Daptacel Sweden I GMTs.

The P006 results are similar to those in P005.

Additionally, the Applicant provided data on the anti-pertussis GMTs observed in a pivotal European Pediacel trial (A5I16), utilizing a 3-dose priming schedule administered to study participants at 2, 3 and 4 months of age.

To further demonstrate efficacy, the comparability of pertussis efficacy observed in Sweden I and that inferred from the immunogenicity studies of a pentavalent DTaP5-IPV-Hib vaccine (Pediacel) was calculated using the correlates of protection model developed by Storsaeter et al. and applied by Kohberger et al. in order to bridge immunogenicity to protection of pertussis disease. The estimated vaccine efficacy of Pediacel following primary series in study A5I16 was 83.0% (95% CI: 70.0; 94.8). The overall estimated vaccine efficacy of Pediacel, following primary series (2 or 3 doses of the vaccine administered in infancy, using 2/3/4, 2/4/6 or 3/5 schedule) was between 79.6% and 83.2%.

In summary, the overall post-primary series pertussis immunogenicity data for PR5I in studies P005 and P006, following a 3-dose schedule in infants, show comparable PT response rates but lower FHA, PRN and FIM response rates to those observed in Sweden I and in Pediacel pivotal trials.

ii) Non-inferiority testing results of studies 005, 006, 007 and 008 for all antigens post-primary and post-booster. The Applicant provided immunogenicity non-inferiority analyses for all antigens post-primary as well as a visual presentation thereof. The post-booster comparisons of all antigens were presented for study 008 (2-dose) and limited to the pertussis antigens for the other studies.

Some of these analyses were performed as primary or secondary endpoint in the pivotal US and EU trials, whereas other analyses (pertussis post-primary, GMT comparisons, comparisons of all antigens post-primary to Infanrix hexa in the 2-dose schedule) were performed post-hoc and should therefore be interpreted with caution. In summary, it was noted that the pertussis data were similar across studies and vaccination schedules (2-dose, 3-dose). In general, PT GMTs are superior and PT response rates are similar to control, whereas FHA and PRN GMTs and response rates are weaker or inferior to control.

Although the exact contribution of the individual pertussis antigens to protection is not well understood, PT is considered to play a key role in establishing protection against clinical pertussis. The PT data are therefore reassuring. Nevertheless, the immune responses against all pertussis antigens of PR5I do not indicate that PR5I would be superior to the current vaccines. A similar vaccine efficacy is anticipated based on the PT data, but a lesser vaccine efficacy cannot be excluded based on the weaker or inferior FHA and PRN data.

iii) Efficacy bridging of PR5I immunogenicity data in a 2-dose schedule (2-4) in study 008 to the immunogenicity data of a similar vaccine for which clinical efficacy in a 2-dose schedule is established (Sweden II trial). Study 008 (2 doses) demonstrated lower immune responses to most antigens compared to study 007 (3 doses). Therefore a post-hoc analysis to assess non-inferiority of immune responses for PR5I antigens vs. Infanrix hexa after primary vaccination (post-dose 2) was requested during the procedure, using the same non-inferiority margins as used for the post-toddler dose analysis. Non-inferiority could not be demonstrated for FHA/PRN/IPV1 antigens and IPV3 was nearly inferior.

To further investigate this, the Applicant was requested to explore an efficacy bridging of PR5I immunogenicity data in a 2-dose schedule (2-4) in study 008 to the immunogenicity data of a similar vaccine for which clinical efficacy in a 2-dose schedule is established (Sweden II trial).

Sweden II was a 4-arm, randomized, double-blind, controlled study, conducted in 24 study centers in Sweden, which compared the relative efficacy and immunogenicity of the following DTP vaccines: a whole cell pertussis formulation (DTPwc, Wellcome), a 2-component acellular pertussis formulation (DTaP2, SKB), a 3-component acellular pertussis formulation (DTaP3, Chiron) and a 5-component acellular pertussis formulation (HCPDT, Sanofi Pasteur). These vaccines were administered to infants at either 2, 4 and 6 months of age or at 3, 5 and 12 months of age. The study was conducted by the Swedish Institute for Infectious Disease Control.

The Sweden II trial demonstrated that the relative protective efficacies (using the 3, 5 and 12 month schedule) against culture-confirmed pertussis, irrespective of duration, for HCPDT was high (Relative Risk (RR) = 0.85, 95%CI: 0.41; 1.79) and similar compared to DTPwc. Responses to the PRN and FHA antigens were lower (between 80 and 90%) than those demonstrated with HCPDT (>95%). Responses to the PT and FIM antigens were similar to those demonstrated with HCPDT, with PT response >95% for both vaccines.

Additional analysis on Hib antigen

After the primary series, PR5I was superior to control (Infanrix hexa, Pentacel/Recombivax HB) in terms of response rates against the Hib antigen. Because the PRP antigen is conjugated to the strongly immunogenic OMPC conjugate in PR5I, but conjugated to the lesser immunogenic TT in the control vaccines, a superior priming response with PR5I is reasonable.

However, this primary superiority was not reproduced after the booster dose. In contrast, in both study 007 and 008 the comparison test favored Infanrix hexa although non-inferiority is formally demonstrated. The Applicant argued that, considering that 90-95% of PR5I vaccinees (study 007 and 008) achieved a titre of > 1.0 µg/ml, indicative of long-term protection, after the toddler dose and the high vaccination coverage in Europe, the somewhat lower post-toddler dose anti-Hib titres induced by PR5I are not likely to negatively affect Hib disease burden in Europe. The applicant's response was considered acceptable.

The vaccine effectiveness (VE) of the hexavalent vaccines (Hexavac and Infanrix hexa) against invasive Hib disease was monitored in Germany during 5 years in the period 2001-2005 (Kalies et al., 2008). For children having an incomplete primary series, the VE was 68.4% (95% CI: 19.0 to 87.6), but when receiving a second year dose while not being fully immunised, VE was 100.0% (95% CI: 0.0 to 100.0). These data are encouraging since they indicate that, with the current vaccines, the booster dose provides optimal protection even if less than 3 priming doses were given (second year dose, but not fully immunised), which reflects in part the real life setting and/or a 2-dose priming schedule.

Table 4 Vaccine effectiveness of *H. influenzae* type b immunisation with DTaP–IPV–HB/Hib on children born from 8/2000 to 12/2004 in Germany

Completeness of vaccination schedule	Number of cases	Parameter estimate (ß)	S.E.	Vaccine effectiveness[a]	95% CI
No vaccination	19	Reference	–	Reference	–
Incomplete primary series	6	−1.1511	0.4795	68.4%	19.0–87.6
Full primary series	5	−2.3402	0.5698	90.4%	70.6–96.8
Second year dose, but not fully immunised	0	−16.7638	0.4399	100.0%	0.0–100.0[b]
Full immunisation	0	−16.7399	0.4273	100.0%	52.7–100.0[b]

Estimates, S.E. and vaccine effectiveness from Cox regression model and robust variance estimates for completeness of vaccination schedule.
[a] $(1 - e^{\beta}) \times 100\%$.
[b] Binominal exact confidence intervals.

Reference: Kalies et al., Effectiveness of hexavalent vaccines against invasive Haemophilus influenzae type b disease: Germany's experience after 5 years of licensure. Vaccine. 2008, 26:2545-52.

OMPC-conjugated Hib-antigens have been used before in the US as a stand-alone vaccine, but PR5I is the first hexavalent, fully liquid vaccine that contains the PRP-OMPC Hib-antigen. The pharmacodynamics of this newly combined vaccine in terms of long-term Hib protection are therefore difficult to estimate based on vaccine effectiveness of current PRP-TT combination vaccines.

PR5I is non-inferior compared to the control vaccines in terms of post-booster Hib responses indicative of long-term protection (anti-PRP ≥ 1.0 µg/mL) but the response rates in the 2-dose and 3-dose schedule are slightly lower (90-95%) which is somehow unexpected in view of the strong OMPC-conjugate in PR5I.

It is anticipated that the impact on clinical protection will be nihil or minimal.

The CHMP therefore agrees that monitoring of vaccine failure reports through routine postmarketing surveillance is anticipated to be sufficient to alleviate concerns regarding duration of protection of the Hib antigen in Vaxelis.

In addition, the protective efficacy of PR5I in the prevention of invasive Hib diseases is expected to be similar to that obtained with a monovalent PRP-OMPC vaccine in a randomized, double-blind, placebo-controlled study involving 3486 Native American (Navajo) infants (the Protective Efficacy Trial). Following the primary 2-dose regimen, the protective efficacy was 93% (95% confidence interval [C.I.] 57-98%). In this study, 91% and 59% of vaccinated subjects developed anti-PRP antibody >0.15 µg/mL and >1.0 µg/mL, respectively. Efficacy for the follow-up period of two years and nine months following the last dose, was 96.6% (95% C.I., 72.2-99.9%) in children under 18 months of age and 100% (95% C.I., 23.5-100) in children over 18 months of age. In a phase III study conducted in Europe with Vaxelis given as a 2-dose primary series at 2 and 4 months of age, a high proportion of Vaxelis recipients developed early seroprotective anti-Hib responses (97% and 73% subjects developed anti-PRP antibody ≥ 0.15 µg/mL and ≥ 1.0 µg/mL, respectively).

Additional data on of Hepatitis B Antigen

Data on protective efficacy of the hepatitis B component of PR5I is available in neonates born of mothers positive for both HBsAg and HBeAg (a core-associated antigenic complex which correlates with high infectivity). The estimated efficacy in prevention of chronic hepatitis B infection was 95% as compared to the infection rate in unvaccinated historical controls.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Two main studies that compared PR5I with Infanrix hexa were submitted in the application:

- Study 007 (BE, FI, DE): safety and immunogenicity in a 3-dose primary schedule followed by a booster dose in the second year of life: 2,3,4+12 Month [3+1], concomitant RV5, PCV13, MMRV;
- Study 008 (FI, IT, SE): safety and immunogenicity study in 2-dose primary schedule followed by a booster dose in the second year of life: 2,4+12 Month [2+1], concomitant RV2 or RV5, PCV13;

In addition, four supportive studies were provided. Two US pivotal studies compared PR5I to the US standard of care, Pentacel and RecombivaxHB.

- 005 (US pivotal): 2,4,6+15 Month [3+1], concomitant RV5 and PCV13;
- 006 (US pivotal): 2,4,6+15 Month [3+1], concomitant RV5 and PCV13;
- PRI01C (UK): 2,3,4+12 Month [3+1], concomitant MenC-TT or MenC-CRM, PCV13, MMR;
- PRI02C (ES): 2,4,6 Months [3+0], mixed hexavalent-pentavalent-hexavalent schedule with PR5I at 2 and 6 Months and Pediacel at 4 Months of age, concomitant MenC-TT, PCV13, RV5.

Overall the clinical studies were adequately conducted and were based on demonstrating acceptability or non-inferiority of the immune responses after either primary and booster vaccination or both.

For pertussis, acceptability and non-inferiority endpoints for these antigens were evaluated after the 12-month dose in the EU pivotal studies, because it was considered that the vaccination series for pertussis is not complete until after the toddler dose. However immunogenicity after the primary series should be collected as of relevance. Indeed non-inferiority comparisons after the priming doses were determined post-hoc.

The EU pivotal studies compare PR5I with Infanrix hexa in a 3+1 and 2+1 vaccination schedule, including concomitant administration of PCV13 and rotavirus vaccine RV5 or RV2.

Different thresholds are used in different studies to define seroprotection rates for PRP, diphtheria and tetanus, due to different regulatory requirements in the US and the EU.

Of note, PCV13 (Prevenar 13) was coadministered with PR5I in the EU pivotal studies, hence all immunogenicity data take into account the coadministration, even if there is no formal study to formally assess the extent of the potential impact of PCV on PR5I immunogenicity. The only study including a control arm without the concomitant administration with PCV (Prevenar), study 004, did not perform a formal comparison of groups and thus could not conclude on the potential interference between administration of PCV7 and PR5I, however descriptive results were indicative of no interference (see further below). Concomitant administration with other PCV vaccines such as PCV10 (Synflorix) was not studied, although these data would be useful in view of PCV10 being implemented in several national immunisation programme across Europe.

Efficacy data and additional analyses

PR5I elicits acceptable immune responses to all antigens as demonstrated by the EU pivotal studies, with the exception of FHA pertussis antigen post-primary series:

Post-primary series (5 Months of age)

- non-inferiority of D, T, IPV, Hib antigen response compared to Infanrix hexa (Study 007)
- superiority of Hib PRP antigen response compared to Infanrix hexa (Study 007, 008)
- acceptable seroresponses to D, T, IPV, Hib antigens (Study 007)

Post-booster (ca. 12 Months of age)

- acceptable seroresponses to all PR5I antigens (Study 007, 008)
- non-inferiority pertussis antigen and HepB response compared to Infanrix hexa (Study 007, 008)
- non-inferiority of all PR5I response compared to Infanrix hexa (Study 008)

Seroresponse to the Hib PRP-OMPC antigen is superior to both controls used, Pentacel/Recombivax and Infanrix hexa, after the primary series but similar or slightly lower after the booster dose.

Nevertheless, seroresponse to the pertussis FHA and PRN antigens was systematically weaker in both EU and US pivotal studies as demonstrated by:

- GMT non-inferiority compared to Pentacel/Recombivax HB not met for FHA GMTs post-primary series (primary endpoint: Study 005, secondary endpoint: 006)
- GMT non-inferiority compared to Pentacel/Recombivax HB not met for PRN GMTs post-booster (secondary endpoint: 006)
- lower FHA and PRN seroresponses compared to Infanrix hexa (95% CI not overlapping) post-primary series (tertiary analysis) (Study 007)
- lower seroresponse compared to Pentacel post-primary series (no formal comparison made but 14% difference in seroresponse rate to FHA compared to the concomitant Prevenar-PR5I group) (Study 006)
- In most studies comparing PR5I versus comparator, GMTs of FHA and PRN were considerably lower. In the 2+1 dose schedule (2,4+12) and the 3+1 dose schedule (2,3,4+12) the titres reached about half the value of the titres reached with Infanrix hexa for all time points, and lower seroresponse rates with non-overlapping 95%CI were observed after the primary series. In the 2+1 dose schedule (2,4+12), the immunogenicity non-inferiority could not be demonstrated in a post-hoc analysis for pertussis antigens FHA and PRN and polio antigen IPV1, in addition to a low IPV3 response one month after the 2 doses (hence in 5 months infants), compared to Infanrix hexa. Although the clinical relevance of these data remain uncertain in the absence of a correlate of protection, complementing the primary vaccination scheme with a booster dose in the second year of life is important.

Concerning a potential role of the concomitant administration of PCV in these lower responses, Study 004 overall supports the co-administration of Prevenar with PR5I since pre-specified immunogenicity criteria were met. In addition the hepatitis B component elicited acceptable anti hepatitis B immune responses.

Additional analysis on pertussis antigens

i) Post-hoc non-inferiority comparisons were made between PR5I immunogenicity data of studies 005 and 006 and Daptacel immunogenicity data obtained in the Sweden I Efficacy trial, in which 85% vaccine efficacy

of Daptacel was demonstrated. These exploratory analyses show that PR5I is similar to Daptacel in terms of PT response, but weaker or inferior in terms of FHA, PRN and FIM response. In the absence of pre-specified efficacy bridging criteria and an established correlate for protection, it is impossible to conclude on PR5I vaccine efficacy based on these data. The similar PT response is encouraging in terms of protection against pertussis, although the exact contribution of the individual pertussis antigens to protection is not well understood.

Post-hoc efficacy bridging analyses are to be interpreted with caution due to different vaccines compositions, smaller sample sizes, different regions with different epidemiology, different timing, type of data comparison (i.e. with historical data, no retesting done) and since bridging criteria were not prespecified. These analyses can therefore only be exploratory as to the clinical significance of the observed immunogenicity of PR5I.

The Applicant also provided GMT data of Pediacel from the A5I16 pivotal trial. Vaccine efficacy of Pediacel has been estimated earlier through modelling at 83% in study A5I16 and between 79.6 - 83.2% when using various primary series (using the Storsaeter model). The GMT data are difficult to interpret because no formal statistical comparison parameter is calculated. A visual interpretation shows similar post-dose 3 GMTs for PT (overlapping 95% CI) and higher post-dose 3 GMTs for FHA, PRN and FIM (not overlapping 95% CI) for PR5I compared to Pediacel.

ii) Concerning the post-hoc non-inferiority analysis across trials, it was seen in general that PT GMTs are higher and PT response rates are similar to control, whereas FHA and PRN GMTs and response rates are weaker than control. Although the exact contribution of the individual pertussis antigens to protection is not well understood, PT is considered to play a key role in establishing protection against clinical pertussis. The PT data are therefore reassuring. Nevertheless, the immune responses against all pertussis antigens of PR5I do not indicate that PR5I would be superior to the current vaccines. A similar vaccine efficacy is anticipated based on the PT data, but a lesser vaccine efficacy cannot be excluded based on the weaker FHA and PRN data.

iii) The Applicant was requested to explore an efficacy bridging of PR5I immunogenicity data in a 2-dose schedule (2-4) in study 008 to the immunogenicity data of a similar vaccine for which clinical efficacy in a 2-dose schedule is established (Sweden II trial). The post-hoc efficacy bridging with the HCPDT vaccine in the Sweden II study confirms earlier results of the original data package in that adequate PT response but inferior PRN and FHA response after only 2 priming doses are observed. However this data should be interpreted with cautions due to the limitations of the analysis. Overall, as mentioned, there are some uncertainties with the 2-dose schedule –whose clinical relevance is unknown- which will be reflected in section 5.1 of the SmPC, but the dose recommendation should not be impacted.

2.5.7. Conclusions on the clinical efficacy

PR5I includes 5 acellular pertussis components: PT, FHA, PRN, FIM2 and FIM3. These are all included in Pentacel as part of the standard of care in the US, and in Daptacel and Pediacel.

The primary endpoints were met in all studies; in particular regarding PT and FIM similar response rates and higher GMTs were observed both post-primary and post-booster in comparison to control vaccines containing these antigens. Lower FHA, PRN, IPV1 and IPV3 immune responses were observed after a 2-dose primary schedule (2-4 months), and lower FHA and PRN immune responses were observed after a 3-dose primary schedule. Pertussis response rates are similar to the control vaccine for all pertussis antigens after the

booster dose, but FHA GMT remain lower regardless of the primary schedule. Although the clinical relevance of these data remain uncertain, complementing the primary vaccination scheme with a booster dose in the second year of life as recommended seems necessary. The clinical implications of this finding might be further elucidated by monitoring of vaccine failure through routine surveillance, also in light of the increasing incidence of pertussis disease worldwide, in particular among young infants.

PR5I is the first hexavalent vaccine that contains the Hib PRP antigen conjugated to OMPC in a fully liquid formulation. This antigen demonstrates higher immune response rates after the primary series than the tetanus toxoid conjugated PRP antigen, but comparable or lower response rates after the booster dose.

Overall the efficacy of the vaccine is demonstrated in the proposed indication in infants and toddlers above the age of 6 weeks (see also section 2.10 on the discussion related to the indication).

2.6. Clinical safety

Patient exposure

The safety data across the 2 Phase III randomized, comparator-controlled, blinded clinical EU-based studies (Protocols 007 and 008) as well as across Protocols 004, 005, 006, 007, 008 and PRI01C were pooled in order to perform a comprehensive analysis of the safety of PR5I in a large population.

In total, 16,226 doses were administered to infants and toddlers.

Adverse events

All adverse events

The 2 vaccination groups were similar with respect to the safety parameters measured.

Table 48. Analysis of Clinical Adverse Event Summary after any Dose Vaccination (all subjects of treated population) (Protocols 007 and 008)

	PR5I (N=1263)		INFANRIX™ hexa (N=1264)		Difference [3, 4]	
	n	Estimated Rate (%) [4]	n	Estimated Rate (%) [4]	Estimate	(95% CI)
Subjects in population	1263		1262			
Number of subjects:						
With no adverse event	10	(0.8)	7	(0.6)	0.2	(-0.4, 1.0)
With one or more adverse events (Day 1 to Day 15)	1253	(99.2)	1254	(99.4)	-0.2	(-0.9, 0.5)
Injection-site adverse events (Day 1 to Day 15)	1155	(91.4)	1130	(89.5)	1.9	(-0.4, 4.2)
Solicited injection-site adverse events (Day 1 to Day 5)	1144	(90.6)	1121	(88.8)	1.7	(-0.6, 4.1)
Systemic adverse events (Day 1 to Day 15)	1247	(98.7)	1251	(99.1)	-0.4	(-1.3, 0.4)
Solicited systemic adverse events (Day 1 to Day 5)	1239	(98.1)	1242	(98.4)	-0.3	(-1.4, 0.7)
Unsolicited systemic adverse events (Day 1 to Day 15)	795	(62.9)	777	(61.6)	1.2	(-2.4, 4.9)
With vaccine-related adverse events (Day 1 to Day 15) [1]	1251	(99.1)	1247	(98.8)	0.2	(-0.6, 1.1)
Injection-site adverse events (Day 1 to Day 15)	1155	(91.4)	1130	(89.5)	1.9	(-0.4, 4.2)
Solicited injection-site adverse events (Day 1 to Day 5)	1144	(90.6)	1121	(88.8)	1.7	(-0.6, 4.1)
Systemic adverse events (Day 1 to Day 15)	1230	(97.4)	1230	(97.5)	-0.1	(-1.3, 1.2)
Solicited systemic adverse events (Day 1 to Day 5)	1226	(97.1)	1227	(97.2)	-0.1	(-1.5, 1.2)
Unsolicited systemic adverse events (Day 1 to Day 15)	482	(38.1)	440	(34.9)	3.2	(-0.5, 6.8)
With serious adverse events (Day 1 to Day 15)	22	(1.7)	20	(1.6)	0.1	(-0.9, 1.2)
With serious adverse events [2]	29	(2.3)	32	(2.5)	-0.3	(-1.5, 1.0)
With serious vaccine-related adverse events [1]	4	(0.3)	4	(0.3)	0.0	(-0.5, 0.5)
Who died	0	(0.0)	0	(0.0)	0.0	(-0.3, 0.3)
Discontinued due to an adverse event	1	(0.1)	8	(0.6)	-0.6	(-1.2, -0.1)
Discontinued due to a vaccine-related adverse event [1]	0	(0.0)	5	(0.4)	-0.4	(-0.9, -0.1)
Discontinued due to a serious adverse event	1	(0.1)	3	(0.2)	-0.2	(-0.6, 0.2)
Discontinued due to a serious vaccine-related adverse event [1]	0	(0.0)	2	(0.2)	-0.2	(-0.6, 0.1)

Solicited injection-site Adverse events

There were statistically significant differences observed in the percent of subjects with injection-site erythema and injection-site swelling in the PR5I group as compared to the Control group (table 49).

For severe injection site erythema (>5.0 cm), severe injection site pain, and severe injection site swelling (>5.0 cm) the analysis shows that for injection-site erythema and swelling >5 cm, the incidence was numerically higher for subjects receiving PR5I as compared to Control. The difference was not statistically significant for severe injection-site swelling (95% CI includes 0), and it was marginally significant for severe injection-site erythema (95% CI 0.2 to 3.3). The overall incidence of severe injection-site erythema and swelling >5 cm was low (<5%), and of brief duration, similar between PR5I and Control. These are expected reactions with either similar or marginally higher incidence between PR5I and Control.

Table 49. 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 dose of vaccination (All subjects as treated population) (Protocols 007 and 008)

	PR5I (N=1263)		INFANRIX™ hexa (N=1264)		Difference [1] [2]	
	n	Estimated Rate (%) [2]	n	Estimated Rate (%) [2]	Estimate	(95% CI)
Subjects in population	1263		1262			
With one or more solicited injection-site adverse events [n (%)]	1113 (88.1%)		1073 (85.0%)			
With no solicited injection-site adverse event [n (%)]	150 (11.9%)		189 (15.0%)			
Injection site erythema	869	(68.8)	785	(62.2)	6.6	(2.9, 10.3)
Injection site pain	928	(73.5)	894	(70.8)	2.6	(-0.9, 6.1)
Injection site swelling	718	(56.8)	644	(51.0)	5.8	(1.9, 9.7)

Table 50. Analysis Number (%) of subjects with any Solicited Injection-Site Adverse Events Related to PR5I or Control by Maximum Size / Intensity (Incidence >0% in one or more vaccination groups) Day 1 to Day 5 following any dose vaccination (All Subjects Treated Population) (Protocols 007 and 008)

		PR5I (N=1263)		Control (N=1264)		Total (N=2527)	
	Intensity Grading	n	(%)	n	(%)	n	(%)
Subjects in population		1263		1262		2525	
Injection site erythema	Total	869	(68.8)	785	(62.2)	1654	(65.5)
	< 2.5 cm	644	(51.0)	594	(47.1)	1238	(49.0)
	≥ 2.5 to ≤ 5.0 cm	163	(12.9)	151	(12.0)	314	(12.4)
	> 5.0 cm	62	(4.9)	40	(3.2)	102	(4.0)
Injection site pain	Total	928	(73.5)	894	(70.8)	1822	(72.2)
	Mild	408	(32.3)	486	(38.5)	894	(35.4)
	Moderate	396	(31.4)	341	(27.0)	737	(29.2)
	Severe	124	(9.8)	67	(5.3)	191	(7.6)
Injection site swelling	Total	718	(56.8)	644	(51.0)	1362	(53.9)
	< 2.5 cm	458	(36.3)	421	(33.4)	879	(34.8)
	≥ 2.5 to ≤ 5.0 cm	201	(15.9)	182	(14.4)	383	(15.2)
	> 5.0 cm	58	(4.6)	41	(3.2)	99	(3.9)
	Unknown	1	(0.1)	0	(0.0)	1	(0.0)

For studies 007 and 008 combined, the Applicant provided the proportion of subjects and their 95% confidence intervals for severe injection site erythema (>5.0 cm), severe injection site pain, and severe injection site swelling (>5.0 cm), all being solicited adverse events, and for both the PR5I and the control group. Differences in proportion with their 95% confidence interval were also provided.

The proportions and their 95% CIs are provided in Table 86-1 and the difference in proportion in Table 86-2.

Table 86-1
Number (%) of Subjects with Severe (>5cm) Injection-Site Erythema and Swelling Related to PR5I or Control
Day 1 to Day 5 Following Any Dose Vaccination
(All Subjects as Treated Population)
(Protocols 007 and 008)

	PR5I (n=1263)		Control (n=1262)	
AE Term	s	Percent (95% CI)	s	Percent (95% CI)
Injection site erythema	62	4.9 (3.8, 6.2)	40	3.2 (2.3, 4.3)
Injection site swelling	58	4.6 (3.5, 5.9)	41	3.2 (2.3, 4.4)
n = Number of subjects in the population, s = Number of subjects with AE				

Table 86-2
Analysis of Severe (>5cm) Injection-Site Erythema and Swelling Related to PR5I or Control
Day 1 to Day 5 Following Any Dose Vaccination
(All Subjects as Treated Population)
(Protocols 007 and 008)

	PR5I (n=1263)		Control (n=1262)		Difference (PR5I - Control) [1]	
AE Term	s	Estimated Rate (%) [1]	s	Estimated Rate (%) [1]	Estimate	(95% CI)
Injection site erythema	62	(4.9)	40	(3.2)	1.7	(0.2, 3.3)
Injection site swelling	58	(4.6)	41	(3.3)	1.3	(-0.2, 2.9)
[1] Estimated rate, difference and 95% CI are based on Miettinen & Nurminen method stratified by study sample sizes. n = Number of subjects in the population, s = Number of subjects with AE.						

The analysis shows that for injection-site erythema and swelling >5 cm, the incidence was numerically higher for subjects receiving PR5I as compared to Control. The difference was not statistically significant for injection-site swelling (95% CI includes 0), and it was marginally significant for injection-site erythema (95% CI 0.2 to 3.3). The overall incidence of injection-site erythema and swelling >5 cm was low (<5%), and of brief duration, similar between PR5I and Control. As these are expected reactions with either similar or marginally higher incidence between PR5I and Control, the clinical significance of the analysis is low.

Based on these further statistical analysis for severe injection site erythema (>5.0 cm), severe injection site pain, and severe injection site swelling (>5.0 cm), it can be concluded that these expected reactions occur with similar or marginally higher incidence between PR5I and Control.

Unsolicited injection-site adverse events

No statistically significant differences were observed with these unsolicited injection-site adverse events between the two vaccination groups.

Solicited Systemic Adverse Events

In protocols 007 and 008 combined, 72.7% of children in the PR5I group and 70.1% of children in the Infanrix hexa group experienced pyrexia (difference 2.5% [-1.0, 6.1]). The occurrence of sever systemic adverse events is presented in table 51.

Table 51. Analysis Number (%) of subjects with severe solicited systemic adverse event (incidence >0% in one or more vaccination groups) Day 1 to Day 5 following any dose vaccination (All subjects treated population) (Protocols 007 and 008)

	Intensity	PR5I n=1263	Control n=1262	Total n=2525
All solicited systemic AEs	Severe	278 (22.0%)	223 (17.7%)	501 (19.8%)
Crying	Severe	178 (14.1%)	127 (10.1%)	305 (12.1%)
Decreased appetite	Severe	25 (2.0%)	20 (1.6%)	45 (1.8%)
Irritability	Severe	98 (7.8%)	70 (5.5%)	168 (6.7%)
Pyrexia	Severe	47 (3.7%)	44 (3.5%)	91 (3.6%)
Somnolence	Severe	27 (2.1%)	31 (2.5%)	58 (2.3%)
Vomiting	Severe	3 (0.2%)	14 (1.1%)	17 (0.7%)

Similar results were observed across Protocols 004, 005, 006, 007, 008, and PRI01C, with the exception of pyrexia which was reported in 56.8% of the subjects in the PR5I group and 47.4% of the subjects in the Control group [estimated difference: 9.4% (95% CI: 6.7, 12.0)]. Most events of pyrexia were mild to moderate in intensity and of short duration (2 days or less) with a low percentage (2.1% and 2.5% of PR5I and Control group, respectively) being reported severe in intensity (temperature ≥39.5°C). The increased rate of pyrexia as compared to control in the PR5I recipients across the Phase IIb and Phase III studies was driven mainly by the higher incidence of pyrexia observed in the U.S. studies (Protocols 005 and 006) as compared to PENTACEL.

Solicited temperature elevation

If the elevated temperature was part of an intercurrent illness, then it was not captured as an adverse event of pyrexia; therefore, the rates of elevated temperature are slightly higher as compared to pyrexia. The severity rating scale for elevated temperature was the same as for pyrexia (mild: temperatures between ≥38°C to ≤38.4°, moderate: ≥38.5°C to ≤39.4°C, and severe: ≥39.5°C).

Table 52. Analysis Analysis of subjects with temperature by severity Day 1 to Day 5 following any dose vaccination (All subjects as treated population) (Protocols 007 and d008)

	PR5I (N=1263)		Control (N=1264)		Difference [5] [6]	
	n	Estimated Rate (%) [6]	n	Estimated Rate (%) [6]	Estimate	(95% CI)
Subjects in analysis population [1]	1263		1262			
Subjects with temperature data [2] [n (%)]	1256 (99.4%)		1257 (99.6%)			
Subjects with no temperature data [n (%)]	7 (0.6%)		5 (0.4%)			
Maximum Temperature (All Routes [3]):						
< 38.0 °C	334	(26.6)	373	(29.7)	-3.1	(-6.6, 0.4)
≥ 38.0 °C and < 38.5 °C (Mild)	464	(36.9)	433	(34.4)	2.5	(-1.3, 6.2)
≥ 38.5 °C and < 39.5 °C (Moderate)	411	(32.7)	409	(32.5)	0.2	(-3.5, 3.9)
≥ 39.5 °C (Severe)	47	(3.7)	42	(3.3)	0.4	(-1.1, 1.9)
Maximum Temperature (Rectal [4]):						
< 38.0 °C	320	(25.5)	357	(28.4)	-2.9	(-6.4, 0.6)
≥ 38.0 °C and < 38.5 °C (Mild)	450	(35.8)	430	(34.2)	1.6	(-2.1, 5.3)
≥ 38.5 °C and < 39.5 °C (Moderate)	407	(32.4)	401	(31.9)	0.5	(-3.2, 4.2)
≥ 39.5 °C (Severe)	43	(3.4)	41	(3.3)	0.2	(-1.3, 1.6)

Across Protocols 004, 005, 006, 007, and 008, a statistically significant higher proportion of subjects in the PR5I group (61.2%) as compared to the Control group (52.7%) reported fever (defined as temperature ≥38.0°C, rectal) based on daily temperature measurements Day 1 to 5 post-vaccination. The statistically significant difference appears to be driven by the U.S. studies (Protocols 005 and 006) where the difference in fever rate between PR5I and Control was greater than in the EU studies. The comparator used in Protocols 004, 005, and 006 was PENTACEL and the comparator used in the Protocol 007 and 008 was INFANRIX hexa. The overall rate of severe fever (temperature ≥39.5°C) was generally low in both vaccination groups (≤3% across the 5 studies combined), similar to the data in Protocols 007 and 008.

Unsolicited systemic adverse events

In studies 007 and 008, the most frequent unsolicited systemic adverse events reported were pyrexia (15.5% in the PR5I group and 14.2% in the INFANRIX hexa group), diarrhoea (13.8% in the PR5I group and 12.1% in the INFANRIX hexa group), and rhinitis (8.8% in the PR5I group and 10.0% in the INFANRIX hexa group). There were no statistically significant differences observed between the PR5I group and the INFANRIX hexa group for these events.

Across Protocols 004, 005, 006, 007, 008 and PRI01C, 49.7% versus 53.2% of subjects respectively experienced one or more unsolicited systemic adverse events in the PR5I group versus those in the Control group. While there were slightly higher rates of body temperature increased (0.7, 95% CI: 0.1, 1.2), diarrhoea (1.5, 95% CI: 0.1, 2.8), and decreased appetite (0.7, 95% CI: 0.1, 1.3), in the PR5I group compared to the Control group in the global safety population, these small differences are not considered to be clinically meaningful.

Serious adverse event / deaths / other significant events

SAEs were collected at various time points across studies as the protocols were designed to collect all SAEs occurring to any subject from the time the consent was signed through the protocol-specific reporting period (e.g., Day 1 to 14 post-vaccination) and all SAEs that were either a death or considered by an investigator to

be possibly, probably, or definitely vaccine related which occurred at any time during the study. The protocols did differ in the periods of time following vaccination during which all SAEs were collected (without regard to causality), with longer periods in US studies as per US guidance. However, the protocols for all of these studies provide clear instruction that the investigator was to assess and assign causality to each adverse event according to criteria defined in the protocol and report the causality in the clinical eCRF (electronic clinical report form). Therefore, for all of the protocols, SAEs occurring throughout the study were assessed for relatedness, and additional information collected if considered vaccine-related, regardless of timing in relation to vaccination. The CHMP found this approach acceptable.

Vaccine related Serious adverse events

Vaccine-related serious adverse events after any vaccination were reported in 4 subjects (0.3%) in the PR5I group and 4 subjects (0.3%) in the INFANRIX hexa group across Protocols 007 and 008 (table 53). Of the 4 subjects who reported a vaccine-related serious adverse event in the PR5I group, only 3 events (i.e., febrile convulsion, prolymphocytic leukaemia, idiopathic thrombocytopenic purpura) were related to PR5I; 1 subject had gastroenteritis that was considered related to RotaTeq only.

Table 53. Analysis Subjects with Serious adverse events related to PR5I or Control (All vaccinated Subjects)

Serious AE	Vaccine administered	Dose	Post-dose day
Protocols 007 and 008			
Febrile convulsion	PR5I, Prevenar 13, Rotateq	3	6
Idiopathic Thrombocytopenic purpura	PR5I, Prevenar 13	Toddler	5
Prolymphocytic leukemia	PROQUAD, Prevenar 13 (Group PR5I)	Toddler	151
Pyrexia & swollen tongue	INFANRIX hexa, Prevenar 13, Rotateq	1	1
Kawasaki's disease	INFANRIX hexa, Prevenar 13, Rotateq	1	9
Injection site abcess	INFANRIX hexa, Prevenar 13	Toddler	30
Convulsion	INFANRIX hexa, Prevenar 13, Rotarix	2	3
Protocols 004, 005, 006, and PRI01C			
Hypotonia	PR5I, Prevenar	2	1
Apparent life threatening event	PR5I, Prevenar, RotaTeq	1	1
Pyrexia	PR5I, Prevenar 13, RotaTeq	1	1
Pyrexia	PR5I, Prevenar 13, RotaTeq	1	1
Pyrexia	PR5I, Prevenar 13, RotaTeq	1	2
Abdominal Pain & crying	PR5I, MCC-TT-MCC-CRM	2	3
Febrile convulsion	PENTACEL, Prevenar 13 (Group PR5I-006)	Toddler	1
Febrile convulsion	PENTACEL, Prevenar	Toddler	5
Pyrexia	PENTACEL, Prevenar 13	Toddler	1

Across Protocols 004, 005, 006, 007, 008, and PRI01C, nine subjects reported a serious adverse event related to PR5I and the concomitant vaccines; 3 additional subjects had serious adverse events (i.e., intussusception, diarrhea, and gastroenteritis) related only to RotaTeq.

Serious adverse events of pyrexia and febrile convulsions/convulsions

In Protocols 007 and 008, there were a total of four reports of febrile convulsion or convulsion (two in each vaccination group) that were considered serious within Days 1 to 15; two of which were vaccine-related (one in each vaccination group). The subject in the PR5I group who experienced a vaccine-related febrile convulsion also had concurrent viral gastroenteritis and respiratory tract infection. The convulsion ended spontaneously after 5-10 minutes.

Deaths

In total, 7 deaths were reported among subjects in Protocols 005 and 006. No deaths were reported during the study in Protocols 004, 007, 008 and PRI01C. Deaths occurred in 6 out of 5223 subjects in the PR5I group (0.1%) and 1 out of 2295 subjects in the Control group (0.0%). None of the deaths were considered to be related to the study vaccinations.

Table 54. Listing of subjects with adverse events leading to deaths (All vaccinated Subjects) (Protocols OO5 and 006)

Deaths	Vaccine administered	Dose	Diagnosis (days)
Postural asphyxia	PR5I, Prevenar 13, Rotateq	2	42
Hydrocephalus	PR5I, Prevenar 13, Rotateq	2	1 (death after 11 months)
Death (undetermined cause)	PR5I, Prevenar 13, Rotateq	1	44
Sepsis (Group A streptococcus)	PR5I, Prevenar 13, Rotateq	1	2
Sudden infant death syndrome	PR5I, Prevenar 13, Rotateq	2	10
Sudden infant death syndrome	PR5I, Prevenar 13, Rotateq	1	49
Pneumonia + complications	PENTACEL, Prevenar 13, RotaTeq, mpHBV	1	26

Laboratory findings

No safety laboratory evaluations were performed in the conduct of the clinical studies in support of the safety assessment.

Safety in special populations

Premature and/or low birth weight infants

A total of 160 subjects (111 (2.1%) in the PR5I group and 49 (2.1%) in the Control group) in Protocols 004, 005, 006, 007, 008, and PRI01C were identified as “premature infants”.

Table 55. Clinical adverse event summary after any dose vaccination in premature infants (All subjects of treated population) (Protocols 004, 005, 006, 007 and 008 and PRI01C)

	PR5I (N=111)		Control (N=49)		Total (N=160)	
	n	(%)	n	(%)	n	(%)
Subjects in population	110		49		159	
Number of subjects:						
With no adverse event	1	(0.9)	4	(8.2)	5	(3.1)
With one or more adverse events (Day 1 to Day 15)	107	(97.3)	43	(87.8)	150	(94.3)
Injection-site adverse events (Day 1 to Day 15)	83	(75.5)	37	(75.5)	120	(75.5)
Solicited injection-site adverse events (Day 1 to Day 5)	83	(75.5)	37	(75.5)	120	(75.5)
Systemic adverse events (Day 1 to Day 15)	106	(96.4)	42	(85.7)	148	(93.1)
Solicited systemic adverse events (Day 1 to Day 5)	104	(94.5)	41	(83.7)	145	(91.2)
Unsolicited systemic adverse events (Day 1 to Day 15)	46	(41.8)	17	(34.7)	63	(39.6)
With vaccine-related adverse events (Day 1 to Day 15) [1]	104	(94.5)	43	(87.8)	147	(92.5)
Injection-site adverse events (Day 1 to Day 15)	83	(75.5)	37	(75.5)	120	(75.5)
Solicited injection-site adverse events (Day 1 to Day 5)	83	(75.5)	37	(75.5)	120	(75.5)
Systemic adverse events (Day 1 to Day 15)	101	(91.8)	41	(83.7)	142	(89.3)
Solicited systemic adverse events (Day 1 to Day 5)	101	(91.8)	40	(81.6)	141	(88.7)
Unsolicited systemic adverse events (Day 1 to Day 15)	13	(11.8)	5	(10.2)	18	(11.3)
With serious adverse events (Day 1 to Day 15)	2	(1.8)	2	(4.1)	4	(2.5)
With serious adverse events[2]	5	(4.5)	6	(12.2)	11	(6.9)
With serious vaccine-related adverse events[1]	0	(0.0)	1	(2.0)	1	(0.6)
Who died	0	(0.0)	1	(2.0)	1	(0.6)
Discontinued due to an adverse event	0	(0.0)	1	(2.0)	1	(0.6)
Discontinued due to a vaccine-related adverse event [1]	0	(0.0)	1	(2.0)	1	(0.6)
Discontinued due to a serious adverse event	0	(0.0)	1	(2.0)	1	(0.6)
Discontinued due to a serious vaccine-related adverse event [1]	0	(0.0)	1	(2.0)	1	(0.6)

Other factors

No statistical hypothesis tests were performed on of race, ethnicity, gender, and premature birth. Although there were some numerical differences noted in race and ethnicity groups, there were no findings of clinical significance when the safety data were reviewed with regard to the aforementioned baseline characteristics.

Safety related to drug-drug interactions and other interactions

No interactions with drugs were investigated.

Regarding concomitant vaccinations, the CHMP considered the need to include information to the SmPC about the much higher frequency of fever and severe fever (>39.5°C) in patients receiving PR5I and concomitant pneumococcal conjugate vaccine. Phase III studies conducted with PR5I were not designed as a comparison of PR5I with or without the use of pneumococcal conjugate vaccine. Since all subjects received as part of the trial design pneumococcal conjugate vaccine, it is not possible based on the available clinical data to determine an increased frequency rate of pyrexia for PR5I when given concomitantly with pneumococcal conjugate vaccine in comparison to PR5I given alone. However, observations made across studies indicate that PR51 in combination with Prevenar 13 (concomitant) for the toddler dose induces a higher rate of fever (pyrexia) than other combinations (PR5I + ProQuad). The uncertainties that follow comparison of results between different studies are acknowledged. Still, the rate of pyrexia after a dose of PR51 and Prevenar 13 to toddlers is higher compared to study 007 where a combination of PR51 and ProQuad was used to toddlers and the studies 005/006 where other vaccines where used for toddlers (DAPTACEL, PENTACEL, Prevenar 13, ActHIB/PedvaxHIB).

Study	% pyrexia infant dose	Time point and Vaccines	% pyrexia toddler dose	Time point and Vaccines
008	33.1	2 months PR51+ INFANRIX Hexa + Rotarix/RotaTeq	**52.5**	11-12 months PR51+ Prevenar 13
007	36.1	2 months PR51+ INFANRIX Hexa+ RotaTeq	36.6	12 months PR51+ ProQuad
005	17.0	2 months PR51+Prevenar 13+ RotaTeq	26.0	15 months DAPTACEL+Prevenar 13 +PedvaxHIB
006	18.6	2 months PR51+Prevenar 13+ RotaTeq	20.9	15 months PENTACEL+Prevenar 13

While the rate of pyrexia is the same at 2 months infant dose and toddler dose in study 007, the toddler dose has much higher rate of fever compared to the 2 months infant dose in study 008. Also, in study 008 the total dosage regimen is 3 doses while it is 4 doses in study 007. Similar trend is seen for severe pyrexia. Therefore, data on fever rates across studies support the trend of substantially higher fever rates for the combination of PR51 and Prevenar 13 given to toddlers. This information was deemed important to be included in the SmPC section 4.4, 4.5 and 4.8.

The rates of all fever ⩾38.0 and severe fever ⩾39.5 for both infant and toddler doses were not available for vaccine-related pyrexia on a per-dose basis within the study database. Therefore, for the SmPC the CHMP agreed to utilize the objective temperature data which provides the requested information, but this is a

change in method compared to showing the rates of vaccine-related pyrexia. The rates of fever are very similar regardless of method.

Discontinuation due to adverse events

Of the 9 out of 2525 subjects (0.4%) who discontinued due to an adverse event in Protocol 007 and 008 combined, 8 were in the INFANRIX hexa group. The one subject in the PR5I group discontinued due to an unrelated serious adverse event (congenital heart disease).

2.6.1. Discussion on clinical safety

The Methods to collect safety data, including the Vaccine Report Card (VRC), are acceptable. The magnitude of the database is acceptable as per CHMP guideline on vaccine development (EMEA/CHMP/VWP/164653/05). No sub-population has been studied. In particular, specific safety issues are not ruled out for infants and toddlers with chronic pathologies. However, preterm infants were not excluded from the dataset at enrolment and more than 100 children have been enrolled. Although no safety issue has been identified in this group, the monitoring of those infants is desirable after the marketing of the vaccine.

All subjects (n=7557) in the studies received concomitant routine vaccinations, therefore the systemic adverse events reported in the PR5I and control groups included those of the concomitant vaccines. PR5I is highly reactogenic and nearly all subjects reported some local and systemic reaction after a dose.

A total of 85% of infants and toddlers receiving PR5I reported injection site reactions. The majority of reactions were mild or moderate and transient, and few continued after 1 week. Injection site pain was most frequent (71%). In the PR5I group, 6.8 % of subjects reported severe pain compared with 5.4% in the control groups. Injection site erythema and swelling were significantly more frequent in the PR5I group than the control with a difference in the range of 3-6%.

Among the infant doses the first dose seems to give more injection site reactions, while the second dose gives the highest frequency of fever. The rate of solicited injection site reactions and fever are higher after the toddler dose than the infant doses.

Solicited systemic adverse events were reported in 95% of subjects that received PR5I after any vaccine dose. Irritability was the most frequent systemic event (84%).

The unfavourable effects observed in the clinical studies are comparable to those of the licensed comparators vaccines. PR5I has a slightly higher injection-site associated reactogenicity as compared to Infanrix hexa, but comparable incidences of elevated temperature (≥ 38.0 °C). Several occurrences of severe pyrexia (≥ 39.5 °C) were nevertheless reported in the PR5I group.

Overall, the safety profile of PR5I is similar to the comparator vaccines. Nevertheless, differences in the occurrence of safety events were observed in the following cases

- Among solicited injection-site adverse events, erythema and swelling were more frequent in the PR5I group compared to the INFANRIX hexa groups (studies 007 and 008), essentially after the first dose of the vaccine; however based on further statistical analysis for severe injection site erythema (>5.0 cm), severe injection site pain, and severe injection site swelling (>5.0 cm) it can be concluded that these expected reactions occur with similar or marginally higher incidence between PR5I and Control.

Concerning fever, a higher overall rate of fever was observed in the EU study pool although antipyretic use did not appear to differ significantly between the study pools. Concerning possible explanations for the large

difference in absolute rate of fever in the EU and US studies, these include additional dosing and concomitant use of PR5I and MMRV.

Systematic variation in adverse event score across studies performed in the EU vs. US was seen and possible explanations considered. Indeed despite consistent safety data collection practices across the Phase III program a slightly higher rate of non-serious, unsolicited systemic reactions was observed in the EU study pool as compared to the overall global study pool. The reason is unknown, but the difference is not considered to be clinically significant since the higher rates were noted for both PR5I and Control, and the events were not serious.

It was also noted that estimates in proportions in analysis tables, e.g. concerning all crying and all pyrexia, were different than their corresponding observed proportions related to study vaccines or control because the estimates were adjusted by their study sample size weight.

Only few serious vaccine-related adverse events were reported across the studies but several occurrence of serious pyrexia were reported in the PR5I group. Seven deaths were reported and all were considered to be unrelated to the vaccine. Two deaths in the PR5I group were attributed to sudden infant death syndrome. Considering the number of infants in the PR5I groups, this level of occurrence is not unexpected but unexpected deaths after vaccination should be monitored after the marketing of the vaccine. Particularly, the CHMP agreed to apply standard practices for routine pharmacovigilance activities for monitoring adverse events in infants born prematurely and with unexpected deaths notified shortly after vaccination.

Bexsero is a vaccine against meningococcal disease caused by Neisseria meningitides group B indicated for the same age group as PR5I. Bexsero contains outer membrane vesicles from Neisseria meningitides group B while PR5I contains PRP conjugated to an outer membrane complex also from Neisseria meningitides group B. As both components have a potential to induce fever, the additional potential risk in the case the two vaccines are administered concomitantly was considered. The Applicant presented data on fever rates for another vaccine for infants that contain the same OMPC components as PR51. Compared to other similar vaccine products the OMPC component does not seem to induce more fever. The CHMP therefore agree that at this stage there is no reason to expect higher fever rates, if PR51 is given concomitantly with Bexsero, than what is described for each of the products.

In study 008 where PR5I was administered concomitantly with Prevenar 13 (PCV13) as a booster dose of both vaccines, fever $\geq$ 38.0° C was reported in 54.3% of infants, compared to 33.1% to 40.7% of infants during the primary series. Fever $\geq$ 39.5° C was observed in 3.7% of children (post-booster) and 0.2% to 0.8% of children (post-primary) receiving PR5I with PCV13. Almost all fevers after primary and booster doses were mild or moderate (<39.5° C) and transient (duration of $\leq$ 2 days). This was reflected in sections 4.4, 4.5 and 4.8.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of PR5I is similar to the comparator vaccines and is considered acceptable in the proposed indication. The most common ADRs for PR5I are decreased appetite, somnolence, vomiting, crying/irritability, fever and injections sites reactions (erythema, pain, swelling). These ADR have been included in the SmPC with a frequency of >1/10 (very common).

No major safety concern has been identified.

There is no data above 15 months of age. The safety data generated from the clinical studies can however be supportive for the use of PR5I in toddlers greater than 15 months of age, e.g. in the catch-up scenario (see also Uncertainty in the knowledge about the unfavourable effects, further below).

In the post-marketing period, further information will be generated by means of routine pharmacovigilance on the tolerability of the vaccine in infant population presenting chronic conditions, in pre-term infants and in infants who unexpectedly died after vaccination.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable. The PRAC endorsed the PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Important identified risks	None
Important potential risks	Hypersensitivity including anaphylactic reactions Convulsion, including febrile convulsion Hypotonic-hyporesponsive episode Encephalopathy/Encephalitis Apnoea (in premature infants less than or equal to 28 weeks gestation) Extensive swelling of the vaccinated limb
Missing information	Infants less than 6 weeks of age Premature infants less than 28 weeks of gestation at the time of birth Immunocompromised patients Use in children > 15 months of age Duration of protection with pertussis antigens

Pharmacovigilance plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation plan

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important identified risks		
None		
Important potential risks		
Hypersensitivity including anaphylactic reactions	The potential of hypersensitivity including anaphylactic reactions associated with the use of Vaxelis is described in the SmPC (section 4.3 Contraindications: not to use the vaccine in patients with hypersensitivity to any component of the vaccine; SmPC section 4.4 Special warnings and precautions for use: appropriate medical treatment and supervision should be readily available to minimize the risk).	None
Convulsions, including febrile convulsion	The potential for convulsions, including febrile convulsions associated with the use of Vaxelis is described in the SmPC (section 4.4 Special warnings and precautions for use and section 4.8/c Undesirable effects/Description of selected adverse reactions), patients who have had a history of convulsions including febrile convulsions should be closely followed up.	None
Hypotonic-hyporesponsive episode	The potential for hypotonic-hyporesponsive episodes associated with the use of Vaxelis is described in the SmPC (section 4.8/c Undesirable effects/Description of selected adverse reactions) (section 4.4 Special warnings and precautions for use)	None
Encephalopathy/ Encephalitis	The potential for encephalopathy/encephalitis associated with the use of Vaxelis is described in the SmPC (section 4.3 Contraindications), and information on not to use the vaccine in patients with encephalopathy of unknown aetiology, occurring within 7 days following prior vaccination with a pertussis containing vaccine is provided to the prescriber to minimize the risk.	None
Apnoea (in premature infants less than or equal to 28 weeks gestation)	The potential for apnoea (in premature infants ≤28 weeks gestation) associated with the use of Vaxelis is described in the SmPC (section 4.4 Special warnings and precautions for use and 4.8/d Undesirable effects/other Special Populations).	None
Extensive limb swelling	The potential for extensive limb swelling associated with the use of components or constituents of Vaxelis is described in the SmPC (section 4.8/c Undesirable effects/Description of selected adverse reactions).	None
Missing information		
Infants less than 6 weeks of age	The SmPC (section 4.1 Therapeutic indications) states that Vaxelis is indicated in infants and toddlers for primary and booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae* type b (Hib) from 6 weeks of age. Vaxelis has not been studied in infants less than 6 weeks of age and is not indicated for this population.	None
Premature infants less than 28 weeks of gestation at the time of birth	The SmPC (section 4.4 Special warnings and precautions for use) states that limited data from pre-term newborn infants in clinical trials indicate that Vaxelis can be given to premature infants. However, a lower immune response may be observed and the level of clinical protection is unknown. The potential risk of apnoea in premature infants less than 28 weeks of gestation at the time of birth described in the SmPC section 4.4 Special warnings and precautions for use and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	immunization series to very premature infants (born on or less than 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.	
Immunocompromised patients	The SmPC section 4.4 Special warnings and precautions for use states that the immunogenicity of the vaccine may be reduced by immunosuppressive treatment or immunodeficiency. It is recommended to postpone vaccination until the end of such treatment or disease. Nevertheless, vaccination of individuals with chronic immune deficiency such as HIV infection is recommended even if the antibody response may be limited.	None
Use in children> 15 months of age	The SmPC section 4.2 Posology and method of administration states that the safety and efficacy of Vaxelis in infants less than 6 weeks of age have not been established as no data are available. SmPC sections 4.8 and 5.1 state that the safety and immunogenicity of Vaxelis in children over 15 months of age has not been studied in clinical trials	None
Duration of protection with pertussis antigens	None	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

During evaluation, the Applicant was asked to consider data obtained with similar vaccines (hexa-penta-quadrivalent) with a particular focus on the safety and age indication of the paediatric diphtheria dosage in children above the age of 2 years, for which a waiver was granted. The Applicant clarified that DTaP and DTaP-IPV vaccines, which contain quantities of diphtheria toxoid similar to the amounts in Vaxelis, are registered in multiple countries for use from infancy through 6 years of age. Two DTaP-IPV vaccines are registered in Europe for use through 12 years of age. Routine pharmacovigilance data provide reassurance of acceptable safety profiles when these vaccines are administered to children beyond 2 years of age.

The CHMP found these considerations could be acceptable to extrapolate use of the vaccine in emergency catch-up vaccinations of older children (in accordance with official recommendations), but not sufficiently robust to identify a specific age cut off for an indication above 2 years of age. Hence based on the above the following indication was agreed:

Section 4.1

Vaxelis (DTaP-HB-IPV-Hib) is indicated for primary and booster vaccination in infants and toddlers from the age of 6 weeks against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib)~~up to the fifth birthday~~.

The use of Vaxelis should be in accordance with official recommendations.

Lack of data above 15 months of age was described in sections 4.2 (based on the SmPC Guideline), 4.8 and 5.1 for clarity to the prescribers.

In section 4.4 and 4.5 the following warning on co-administration was included:

Data from a clinical study indicate that, when Vaxelis is co-administered with pneumococcal conjugate vaccine (PCV13), the rate of fever is higher following the booster dose in the second year of life compared to the primary series. Almost all fevers were mild or moderate (<39.5° C) and transient (duration of ≤ 2 days). (See section 4.8).

Likewise in section 4.8:

In a clinical study where Vaxelis was administered concomitantly with Prevenar 13 (PCV13) as a booster dose of both vaccines, fever ≥ 38.0° C was reported in 54.3% of children, compared to 33.1% to 40.7% of children during the primary series. Fever ≥ 39.5° C was observed in 3.7% of children (post-booster) and 0.2% to 0.8% of children (post-primary) receiving Vaxelis with PCV13 (see sections 4.4 and 4.5). Almost all fevers after primary and booster doses were mild or moderate (<39.5° C) and transient (duration of ≤ 2 days).

Of note, the rates were not available for vaccine-related pyrexia on a per-dose basis within the study database. Therefore, the Applicant proposed to utilize the objective temperature data which means a change in method from showing the rates of vaccine-related pyrexia. The rates of fever are very similar regardless of method.

In section 5.1 the following information was included to summarise some uncertainties related to the pertussis immune responses:

Regarding PT and FIM, similar response rates and higher GMCs were observed both post-primary and post-booster in comparison to control vaccines. Lower FHA, PRN, IPV1 and IPV3 immune responses were observed after a 2-dose primary schedule (2-4 months), although the clinical relevance of these data remain uncertain. Pertussis response rates are similar to the control vaccine for all pertussis antigens after the booster dose.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Hexyon. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vaxelis (DIPHTHERIA, TETANUS, PERTUSSIS (ACELLULAR, COMPONENT), HEPATITIS B (RDNA), POLIOMYELITIS (INACT.) AND HAEMOPHILUS TYPE B

CONJUGATE VACCINE (ADSORBED)) is included in the additional monitoring list as it is a biological product that is authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

PR5I is a hexavalent paediatric combination vaccine for primary and booster immunization of infants and toddlers. It is designed to provide active immunization against diseases caused by *Corynebacterium diphtheria*, *Clostridium tetani*, *Bordetella pertussis*, poliovirus types 1, 2, and 3, Hib, and hepatitis B virus, i.e. to protect against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and invasive disease due to Haemophilus influenza type b. World-wide these diseases still causes significant morbidity and death, but in most developed countries, extensive immunization programs have made these diseases rare. The target populations are infants and toddlers from the age of 6 weeks.

Clinical trial data available from 6 studies that randomised a total of 7557 participants demonstrated that PR5I is immunogenic and achieves a satisfactory immune response for all antigens in children at about one year of age, hence after completing both the primary vaccination -regardless of infant vaccination scheme (2-3-4, 2-4-6, 2-4 months) - and a booster vaccination in toddlers at 11 to 12 months. The non-inferiority criteria were met when PR5I post-booster seroresponse rates were compared with Infanrix hexa post-booster seroresponse rates.

Available data also support the use of PR5I, exclusively in the infant vaccination series, with a combination of other licensed vaccines covering the same range of antigens for the booster dose in toddlers.

When including studies conducted in the US, the clinical data covers the major ethnicities found within the EU, although these were not equally represented in the studied subjects.

PR5I elicited more robust immune responses than the comparator vaccine with respect to the response rates to PRP antigen following the infant series at one month post-dose 2, or one month post-dose 3 indicating early protection against Hib.

The pertussis data are similar across studies and vaccination schedules (2-dose, 3-dose). In general, PT GMTs are superior and PT response rates are similar to control, whereas FHA and PRN GMTs and response rates are weaker than control. Although the exact contribution of the individual pertussis antigens to protection is not clear, PT is considered to play a key role in establishing protection against clinical pertussis. The PT data are therefore reassuring.

Limited available immunogenicity data (from 160 participants including the control arm) also support that PR5I can be administered to premature infants.

Overall, the Phase III studies demonstrated that PR5I can be administered with rotavirus vaccines (i.e. RotaTeq and Rotarix), with pneumococcal conjugate vaccines (i.e. Prevenar (7-valent) and Prevenar 13),

with measles, mumps, rubella and varicella vaccine (i.e. ProQuad), and with meningococcal type C vaccines (i.e. NeisVac-C or Menjugate), with little to no impact on the immunogenicity profile of PR5I or the licensed paediatric vaccines. However, the immune response to Rotarix antigens was lower -yet formally non-inferior- in the PR5I group compared to the Infanrix hexa group.

Uncertainty in the knowledge about the beneficial effects

Vaccines of this type are licensed based on comparative data of immunogenicity and non-inferiority testing to known licensed vaccines. Protective antibody levels have been established for some (e.g. hepatitis B) but are lacking for others (e.g. pertussis). A theoretical uncertainty therefore remains that for such antigen, the measured antibody level might not be protective in real life, although this is unlikely.

Lower FHA, PRN, IPV1 and IPV3 immune responses were observed after 2 doses of PR5I.

The Applicant performed several post-hoc efficacy bridging analyses comparing the immunogenicity of PR5I with Daptacel based on the Sweden I Efficacy Trial, which showed 85.2% vaccine efficacy against pertussis. A similar vaccine efficacy is anticipated based on the PT data, but a lesser vaccine efficacy cannot be excluded based on the weaker FHA and PRN data. The clinical implications of this finding are currently not clear and complementing the primary vaccination scheme with the recommended booster dose in the second year of life is important, in particular because the period between primary and booster dose coincides with the period of clinical vulnerability for pertussis, i.e. in an infant's first year of life, and in light of the current increase in pertussis disease in Europe.

Uncertainty remains on whether the protection rates and persistence of protection are expected to be comparable to similar vaccines or combinations of vaccines. Following the booster dose at 12 months, PR5I is non-inferior compared to the control vaccines in terms of post-booster Hib responses indicative of long-term protection (anti-PRP $\geq$ 1.0 μg/mL); the response rates in the 2-dose and 3-dose schedule are slightly lower than the control but remain around 90% (90-95%). The clinical consequence of this is unknown. Although it is anticipated that the impact on clinical protection is likely to be minimal, if any, more rapid waning of immunity or a negative effect on carriage/transmission rates cannot be excluded. Monitoring of vaccine failure reports through routine post-marketing surveillance is anticipated to be sufficient to alleviate concerns regarding duration of protection of the Hib antigen in PR5I.

The Applicant did not perform formal comparison of groups and thus could not conclude on the potential interference between administration of licensed pediatric vaccines such as PCV vaccine and PR5I.

Concomitant use has been tested with a number of other licensed vaccines currently in use for infant routine immunisation in the EU (RotaTeq, Rotarix, ProQuad, and NeisVac-C and Menjugate). However, several countries may in the near future also include immunisation against Meningococcal group B in the routine vaccination program. Concomitant use of PR5I together with the meningococcal group B vaccine Bexsero may need to be addressed in future studies. There are no data with PR5I in immunosuppressed or immunocompromised infants, but vaccine failure will be monitored through post marketing surveillance.

There are also no data with PR5I in children above the age of 15 months as PR5I has not been studied in this population. Although not explicitly studied in the PR5I clinical development program, the use of PR5I in children greater than 15 months of age (e.g. in catch up scenarios) is supported by clinical evidence of the immunogenicity of similar pertussis vaccines, however it is difficult to define a specific age cut off when appropriate booster vaccines should be considered. This limitation is reflected in the SmPC (sections 4.2 and 5.1).

There are no data with PR5I in children born to mothers who received maternal antenatal booster immunisation with aP-containing vaccine. A number of European countries (including UK, Belgium, The Netherlands, and some regions of Spain) have introduced maternal TdaP vaccination during pregnancy to help prevent mortality in infants too young to be vaccinated (WHO Position paper on pertussis, August 2015). However, recent data from the UK (Ladhani et al., 2015) and Belgium (Maertens et al., personal communication) show subsequent blunting of pertussis antigen responses after the primary series.

Data concerning the vaccine efficacy in malnutritioned or premature infants and in infants presenting chronic conditions are limited. While Phase III studies did not exclude premature infants, gestational age and weight were not collected and only descriptive immunogenicity information has been provided. Data available showed that the immune responses to PR5I in these infants were generally similar to those of the overall study population. However, a lower immune response may be observed and the level of clinical protection is unknown.

Risks

Unfavourable effects

Overall, the safety profile of PR5I is similar to the comparator vaccines or to the co-administration of a pentavalent and a monovalent HepB vaccine (Pentacel/RecombivaxHB) administered for primary series and booster vaccination in infants and toddlers. The overall safety profile is considered acceptable in the proposed indication. The most common ADRs for PR5I are decreased appetite, somnolence, vomiting, crying/irritability and injections sites reactions (erythema, pain, swelling). These ADR have been included in the SmPC with a frequency of >1/10 (very common).

No major safety concern has been identified.

Among the infant doses the first dose seems to give more injection site reactions, while the second dose gives the highest frequency of fever. The rate of solicited injection site reactions and fever are higher after the toddler dose than the infant doses.

When PR5I was administered concomitantly with Prevenar 13 (PCV13) (booster dose), fever ≥ 38.0° C was reported in 54.3% of children, compared to 33.1% to 40.7% of children during the primary series. Fever ≥ 39.5° C was observed in 3.7% of children (post-booster) and 0.2% to 0.8% of children (post-primary) receiving PR5I with PCV13 (see sections 4.4 and 4.5). Almost all fevers after primary and booster doses were mild or moderate (<39.5° C) and transient (duration of ≤ 2 days.

Uncertainty in the knowledge about the unfavourable effects

Although the sample size is sufficiently high for demonstrating uncommon adverse reactions, uncertainty remains about the incidence of very rare adverse events. An increase of rare syndromes cannot be ruled out with the presented database and good pharmacovigilance is therefore crucial.

The indication is limited to infants and toddlers from the age of 6 weeks. There are no data on subjects above 15 months. With respect to safety, the adverse event profile seen in infants receiving PR5I is generally similar to that observed with licensed vaccines such as PENTACEL (data from Protocols 005 and 006) and INFANRIX hexa (data from Protocols 007 and 008). The safety data generated from the clinical studies can be supportive for the use of PR5I in toddlers greater than 15 months of age, e.g. in the catch-up scenario.

There is limited data in immunosuppressed and premature infants, and this has been reflected in the SmPC.

The rate of fever after vaccination varies with study, study vaccines, vaccine dose, however the rate was equal for PR5I and comparator (EU studies).

As both PR5I and Bexsero have components (OMPC) known to have a potential to induce fever, the additional potential risk of fever in the case the two vaccines are administered concomitantly was considered. Based on the data presented on other similar vaccine products, the OMPC component does not seem to induce more fever in concomitant vaccination. The CHMP therefore considers that at this stage, although there is no data for PR5I, there is no reason to expect higher fever rates if PR51 is given concomitantly to Bexsero vs. what is described for each individual product.

The following important potential risks were identified: hypersensitivity including anaphylactic reactions; convulsions, including febrile convulsion; hypotonic-hyporesponsive episode; encephalopathy/Encephalitis; apnoea (in premature infants less than or equal to 28 weeks gestation); extensive limb swelling.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Effects table

Table 56. Effects Table for PR5I for the primary and booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Hib in infants and toddlers from the age of 6 weeks

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Immunogenicity **post-primary** 2,3,4 Mth series 3-dose	Immunogenicity of Hib PRP *95% CI* Diphteria Tetanus Polio IPV1 Polio IPV2 Polio IPV3 Hepatitis B Pertussis PT *95% CI* Pertussis FHA *95% CI* Pertussis PRN *95% CI* Pertussis FIM antigens	% (95% CI)	 98.36 *96.92 ; 99.25* 99.82 100 100 99.82 100 97.84 99.48 *98.35 ; 99.88* 89.02 *86.03; 91.55* 86.74 *83.55 ; 89.52* 97.19	 86.99 *83.75;89.72* 99.81 100 99.81 99.62 100 96.07 98.62 *97.18;99.44* 96.65 *94.7 ; 98.04* 92.32 *89.65;94.48* (1.64)	HepB and pertussis seroresponse testing Postdose 3 is included only in tertiary analysis. A formal non-inferiority test is lacking for pertussis but data indicate lower FHA and PRN seroresponse rate and higher PT seroresponse rate. Overall similar results. Lower FHA, PRN, IPV1 and IPV3 immune responses are observed after 2 doses of PR5I, but the clinical impact thereof is unknown.	Study 007 Study 008
Immunogenicity **post-booster** 2,3,4 Mth series 3-dose	Immunogenicity of Hib PRP *95% CI* Diphteria Tetanus Polio IPV1 Polio IPV2 Polio IPV3 Hepatitis B Pertussis PT *95% CI*	% (95% CI)	 94.99 *92.51 ; 96.83* 100 100 100 100 99.81 99.06 99.82 *98.98 ; 100*	 97.69 *95.78;98.88* 99.84 *97.01;99.34*	A formal non-inferiority test is lacking for pertussis but data indicate lower FHA seroresponse rate, and lower Hib PRP seroresponse rate. Acceptability criteria were met for all PR5I	Study 007

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	Pertussis FHA *95% CI* Pertussis PRN *95% CI* Pertussis FIM antigens		97.23 *95.48; 98.44* 98.90 *97.61 ; 99.59* 99.61	99.81 *98.94;100* 98.85 *97.52;99.58* (4.73)	antigens. Non-inferiority criteria were met for all PR5I antigens.	Study 008
Unfavourable Effects						
Injection-site AE	Erythema	Proportion	68.8%	62.2%	Difference: 6.6% [2.9 – 10.3]	Study 007-008
	Swelling	Proportion	56.8%	51%	Difference: 5.8% [1.9 – 9.7]	Study 007-008
	Severe erythema (>5cm)	Proportion	4.9%	3.2%	No statistical test	Study 007-008
	Severe site pain	Proportion	9.8%	5.3%	No statistical test	Study 007-008
	Severe swelling (>5cm)	Proportion	4.6%	3.2%	No statistical test	Study 007-008
Systemic AE	Pyrexia	Proportion	72.7%	70.1%	Difference: 2.5% [-1.0 – 6.1] not significant	Study 007-008
	Moderate elevation T° (≥38.0-<39.5°C , rectal)	Proportion	24.6%	19.5%	Difference: 5.2% [2.9 – 7.3]	Study 004, 005, 006, 007, 008
	Severe elevation temperature (>39.5°C, rectal)	Proportion	2.9%	1.9%	Difference: 1.0% [0.1 – 1.7]	Study 004, 005, 006, 007, 008
	Febrile convulsion or convulsion (days 1 -15)	Event	n=5223 3 events	n=2295 3 events	No statistical test	Study 007-008

Benefit-risk balance

Importance of favourable and unfavourable effects

The primary goal of a new vaccine is to induce antibody levels above an established threshold, should one exist. This goal has been reached for all antigens included in PR5I after the booster dose at the age of 12 months in comparison to Infanrix hexa, and for PT and FIM, similar response rates and higher GMTs were observed both post-primary and post-booster in comparison to control vaccines containing these antigens. PR5I is the first hexavalent vaccine that contains the Hib PRP antigen conjugated to OMPC in a fully liquid formulation. This antigen demonstrates higher immune response rates after the primary series than the tetanus toxoid conjugated PRP antigen, but comparable or lower response rates after the booster dose. Lower FHA, PRN, IPV1 and IPV3 immune responses were observed after a 2-dose primary schedule (2-4 months), although the clinical relevance of these data remain uncertain. Pertussis response rates are similar to the control vaccine for all pertussis antigens after the booster dose.

Overall, PR5I induced similar solicited adverse events vs. the Control. Injection site erythema and swelling were significantly more frequent in the PR5I group than the control with a difference in the range of 3-6%.

The frequency of fever was high when PR5I was given concomitantly with other vaccines. Based on daily temperature measures 73.4% of infants receiving PR5I (any dose) reported fever, while the number was 70.3% for the comparator Infanrix hexa. The rate of serious adverse events specified as pyrexia, febrile convulsions and convulsions were low and this is reassuring. The slightly higher rate of fever after PR5I than control vaccine is thus considered to be of limited clinical relevance and clinically manageable.

The high frequency of local and systemic reactions when PR5I is given concomitantly with other childhood vaccines might, however, have an impact on the acceptability of future new combinations with other vaccines.

There are no other concerns regarding other unsolicited adverse events or serious adverse events and no deaths were considered to be related to the vaccination with PR5I.

Discussion on the benefit-risk balance

The proposed formulation of Vaxelis has shown to elicit immune response above predefined thresholds of protection for each antigen, for which a correlate of protection exists, and non-inferior to the antigens in Infanrix hexa after the booster dose. The clinical data available from 6 studies that randomised a total of 7557 participants showed that Vaxelis can be used for both primary and booster vaccination regardless of vaccination scheme (Infant vaccination series, 2-3-4, 2-4-6, 2-4 months) with a booster dose in toddlers at 11 to 12 months. The issues concerning the lower antibody responses against FHA/PRN (pertussis) and anti-PRP (Hib) (the latter post toddler GMT) should be monitored in the routine pharmacovigilance, in particular regarding the 2-dose schedule.

Regarding PR5I's safety profile, the unfavourable effects observed in the clinical studies are comparable to those of the licensed comparators vaccines.

Considering favourable and unfavourable effects based on the available non-clinical and clinical data presented for this submission, the CHMP is of the opinion that the benefit-risk balance is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Vaxelis in the prophylaxis of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib), in infants and toddlers from the age of 6 weeks, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0034/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.