Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) Ph.Eur., 13-valent

PREVENAR 13®

1. NAME OF THE MEDICINAL PRODUCT

PREVENAR13®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pneumococcal 13-valent Conjugate Vaccine is a sterile solution of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotype*s* 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated by reductive amination to non-toxic diphtheria CRM_{197} protein. The polysaccharides are chemically activated, and then covalently linked to the protein carrier CRM_{197} to form the glycoconjugate.

Individual conjugates are compounded, and then polysorbate 80 and aluminum phosphate are added to formulate the vaccine. The potency of the vaccine is determined by the quantity of the saccharide antigens and the saccharide-to-protein ratios in the individual glycoconjugates. Each 0.5 mL dose is formulated to contain 2.2 µg of each saccharide for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F and 4.4 µg of saccharide for serotype 6B, conjugated to CRM_{197} carrier protein, 0.02% polysorbate 80 and 0.125 mg of aluminum as aluminum phosphate adjuvant.

3. PHARMACEUTICAL FORM

Ready-to-use suspension for intramuscular injection.

Supplied as a pre-filled syringe. along with needles

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4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

For active immunization for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including sepsis, meningitis, bacteraemia, pneumonia and acute otitis media) in infants and children from 6 weeks to 5 years of age.

For active immunization for the prevention of Pneumonia and invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults of 50 years and older age group.

4.2 Posology and Method of Administration

For intramuscular use only

The dose is 0.5 mL given intramuscularly, with care to avoid injection into or near nerves and blood vessels. The preferred sites are the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in older children and adults. The vaccine should not be injected in the gluteal area.

Do not administer Prevenar13 intravascularly.

The vaccine should not be injected intradermally, subcutaneously or intravenously, since the safety and immunogenicity of these routes have not been evaluated.

Parenteral products should be inspected visually for particulate matter or discoloration prior to use (see section 6.6 Instructions for Use and Handling).

Data on the interchangeability of pneumococcal 7-valent conjugate vaccine or Prevenar13 with other pneumococcal conjugate vaccines containing a protein carrier different from CRM_{197} are not available.

It is recommended that infants who receive a first dose of Prevenar13 complete the vaccination course with Prevenar13.

Vaccination Schedule

Primary Immunization

For infants, the recommended immunization series of Prevenar13 consists of three doses of 0.5 mL each, at approximately 2-month intervals, followed by a fourth dose of 0.5 mL at 12-15 months of age. The customary age for the first dose is 2 months of age, but it can be given as young as 6 weeks of age. The recommended dosing interval is 4 to 8 weeks. The fourth (booster) dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.

For children who are beyond the age of routine infant schedule, the following Prevenar13 schedule applies:

Prevenar13 Vaccine Schedule for Previously Unvaccinated Children ≥7 Months of age	
Age at First Dose	Total Number of 0.5 mL Doses
7-11 months of age	3*
12-23 months of age	2†
≥24 months through 5 years of age (prior to the 6th birthday)	1
* 2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the second dose by at least 2 months. † 2 doses at least 2 months apart.	

Prevenar13 Schedule for Infants and Children Previously Vaccinated with Pneumococcal 7-valent Conjugate Vaccine (*Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F):

Prevenar13 contains the same 7 serotypes contained in pneumococcal 7-valent conjugate vaccine and is manufactured based on the same conjugate technology using the same carrier protein CRM_{197}. Children who have begun immunization with pneumococcal 7-valent conjugate vaccine may complete immunization by switching to Prevenar13 at any point in the schedule. In clinical trials, immunogenicity and safety profiles were comparable. Children 15 months through 5 years of age who are considered completely immunized, or with any incomplete pneumococcal 7-valent conjugate vaccine schedule may receive one dose of Prevenar13 to elicit immune responses to the six additional serotypes. The catch-up (supplemental) dose of Prevenar13 should be administered with an interval of at least 8 weeks after the final dose of pneumococcal 7-valent conjugate vaccine.i To ensure adequate protection against all 13 serotypes, children 15 to 23 months of age that received only a single dose of pneumococcal 7-valent conjugate vaccine before the age of 12 months, should receive 2 doses of Prevenar13 at least 2 months apart and separated from the first dose by at least 2 months.

Prevenar13 Schedule for Children 12 Months through 5 Years of Age Incompletely Vaccinated with Prevenar13:

For children 7 months through 5 years of age that have not received any prior doses of Prevenar13, see the Vaccine Schedule for Previously Unvaccinated Children ≥7 Months of Age.

Children who are considered incompletely vaccinated with Prevenar13 are children who have received 3 or fewer doses of Prevenar13 before 12 months of age and no Prevenar13 dose after 12 months of age or children who did not complete the recommended age appropriate vaccine schedule for previously unvaccinated children (see the Vaccine Schedule for Previously Unvaccinated Children ≥7 Months of Age).

For children 12 months through 5 years of age with any incomplete Prevenar13 schedule, the following schedule applies to complete the Prevenar13 immunization schedule:

Vaccine Schedule for Children 12 months through 5 years of Age Incompletely Vaccinated with Prevenar13		
Current age (months)	Previous Prevenar13 vaccination history	Total Number of 0.5 mL Doses
12-23 months	1 dose <12 months	2*
	2 or 3 doses <12 months	1†
24-71 months	Any incomplete schedule	1†
* Two doses at least 2 months apart and separated from the first dose by at least 2 months. † Separated from the previous dose by at least 2 months.		

The immune responses induced by this Prevenar13 schedule may result in lower antibody concentrations compared to antibody concentrations following four doses of Prevenar13 (given at 2, 4, 6 and 12 to 15 months).

Protective immunity to the six new serotypes in Prevenar13 requires age-appropriate dosing as described above.

Vaccination Schedule for Adults 50 years of Age and Older

Prevenar13 is to be administered as a single dose to adults 50 years and older including those previously vaccinated with a pneumococcal polysaccharide vaccine. The need for re-vaccination with a subsequent dose of Prevenar13 has not been established.

Pediatric Use

The safety and effectiveness of Prevenar13 in children below the age of 6 weeks or on or after the 6th birthday have not been established.

Geriatric Use

Prevenar13 has been shown to be safe and immunogenic in the geriatric population.

Of the 5,667 adults in the 6 studies of the clinical development program who received Prevenar13; 1,785 (31.5%) were 65 to 74 years of age, and 1,266 (22.3%) were 75 years of age and over. No clinically significant differences in safety or immunogenicity were observed between 65 to 74 year-old individuals and greater than 75 year-old individuals.

4.3 Contraindications

Hypersensitivity to any component of the vaccine, including diphtheria toxoid.

4.4 Special Warnings and Special Precautions for Use

Special Warnings

As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine (see section 4.8 Undesirable Effects).

Minor illnesses, such as mild respiratory infection, with or without low-grade fever, are not generally contraindications to vaccination. The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. The administration of Prevenar13 should be postponed in subjects suffering from acute severe febrile illness.

As with any intramuscular injection, Prevenar13 should be given with caution to infants, children or adults with thrombocytopenia or any coagulation disorder, or to those receiving anticoagulant therapy.

Prevenar13 will only protect against *Streptococcus pneumoniae* serotypes included in the vaccine, and will not protect against other microorganisms that cause invasive disease, pneumonia, or otitis media. This vaccine is not intended to be used for treatment of active infection.

As with any vaccine, Prevenar13 may not protect all individuals receiving the vaccine from pneumococcal disease. For the most recent epidemiological information in your country, you should consult with the relevant national organisation.

Precautions

Safety and immunogenicity data on Prevenar13 are not available for individuals in immunocompromised group (e.g., individuals with congenital or acquired splenic dysfunction, HIV infection, malignancy, nephrotic syndrome) and vaccination should be considered on an individual basis.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium free’.

Infants and children aged 6 weeks through 5 years

In clinical studies, Prevenar13 elicited an immune response to all thirteen serotypes included in the vaccine. The immune response for serotype 3 following the booster dose was not increased above the levels seen after the infant vaccination series; the clinical relevance of this observation regarding the induction of serotype 3 immune memory is unknown (see section 5.1 Pharmacodynamic Properties).

The proportions of functional antibody responders (OPA titres ≥1:8) to serotypes 1, 3 and 5 were high. However, the OPA geometric mean titres were lower than those against each of the remaining additional vaccine serotypes; the clinical relevance of this observation for protective efficacy is unknown (see section 5.1 Pharmacodynamic Properties).

Limited data have demonstrated that pneumococcal 7-valent conjugate vaccine (three-dose primary series) induces an acceptable immune response in infants with sickle cell disease with a safety profile similar to that observed in non-high-risk groups.

The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccine (PPV23) in children ≥24 months of age with sickle cell disease, asplenia, HIV infection, chronic illness, or who are otherwise immunocompromised. Data on sequential vaccination with Prevenar13 followed by 23-valent pneumococcal polysaccharide vaccine are not available; data on sequential vaccination with pneumococcal 7-valent conjugate vaccine followed by PPV23 are limited.

As with all injectable pediatric vaccines, the potential risk of apnea should be considered when administering the primary immunization series to premature infants. The need for monitoring for at least 48 hours after vaccination should be considered for very premature infants (born ≤30 weeks of gestation) who remain hospitalized at the time of the recommended administration. As the benefit of vaccination is high in this group of infants, vaccination should not be with-held or delayed.

For vaccine serotypes, protection against otitis media is expected to be lower than protection against invasive disease. As otitis media is caused by many organisms other than pneumococcal serotypes represented in the vaccine, protection against all otitis media is expected to be low (see section 5.1 Pharmacodynamic Properties).

When Prevenar13 is administered concomitantly with Infanrix hexa (DTPa-HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of Prevenar (7-valent) and Infanrix hexa (see section 4.8 Undesirable Effects). Increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of Prevenar 13 and Infanrix hexa (see section 4.8 Undesirable Effects).

Antipyretic treatment should be initiated according to local treatment guidelines for children with seizure disorders or with a prior history of febrile seizures and for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Different injectable vaccines should always be given at different injection-sites.

Infants and children aged 6 weeks to 5 years

Prevenar13 can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole-cell pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella. Clinical studies demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.

Previously, studies with pneumococcal 7-valent conjugate vaccine and rotavirus vaccines have demonstrated that the immune responses of the seven pneumococcal serotypes in pneumococcal 7-valent conjugate vaccine and the rotavirus vaccine were unaffected. It is not expected that any differences in immune response for the six additional serotypes or the rotavirus vaccine will be observed in Prevenar13.

In clinical trials, when Prevenar13 was given concomitantly, but at a different site/route, with rotavirus vaccine or hepatitis A vaccine, no change in the safety profiles for these infants was observed.

Data from a post-marketing clinical study evaluating the impact of prophylactic use of antipyretics (ibuprofen and paracetamol) on the immune response to Prevenar13 suggest that administration of paracetamol concomitantly or within the same day of vaccination may reduce the immune response to Prevenar13 after the infant series. Responses to the booster dose administered at 12 months were unaffected. The clinical significance of this observation is unknown.

Adults aged 50 years and older

Prevenar13 can be administered concomitantly with trivalent inactivated influenza vaccine (TIV).

In two studies conducted in adults aged 50-59 and 65 years and older, it was demonstrated that Prevenar13 may be given concomitantly with trivalent inactivated influenza vaccine (TIV). The responses to all three TIV antigens were comparable when TIV was given alone or concomitantly with Prevenar13.

When Prevenar13 was given concomitantly with TIV, the immune responses to Prevenar13 were lower compared to when Prevenar13 was given alone. The clinical significance of this is unknown.

Concomitant use with other vaccines has not been investigated.

Concomitant administration of Prevenar13 and 23-valent pneumococcal polysaccharide vaccine has not been studied. In clinical studies when Prevenar13 was given 1 year after 23-valent pneumococcal polysaccharide vaccine the immune responses were lower for all serotypes compared to when Prevenar13 was given to subjects not previously immunised with 23-valent pneumococcal polysaccharide vaccine. The clinical significance of this is unknown.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

There are no data from the use of pneumococcal 13-valent conjugate vaccine in pregnant women. Therefore, the use of Prevenar13 should be avoided during pregnancy.

Lactation

Safety during lactation has not been established. It is not known whether vaccine antigens or antibodies are excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3 Preclinical Safety Data).

4.7 Effects on Ability to Drive and Use Machine

Not relevant

4.8 Undesirable Effects

Infants and children aged 6 weeks to 5 years

The safety of the vaccine was assessed in 13 controlled-clinical trials where approximately 15,000 doses were given to 4,729 healthy infants in ages ranging from 6 weeks to 16 months of age. In all trials, Prevenar13 was co-administered with routine pediatric vaccines.

In a catch-up study, 354 children (7 months to 5 years of age) receiving at least one dose of Prevenar13 were also assessed for safety.

Adults aged 50 years and older

Safety was assessed in 6 clinical studies including 6,198 adults ranging in ages from 50 to 95 years. Prevenar13 was administered to 5,667 adults; 2,616 adults were aged 50 to 64 years and 3,051 adults 65 years and older. Of the Prevenar13 recipients 1,916 adults were previously vaccinated with PPSV23 at least 3 years prior, and 3,751 adults were PPSV23 unvaccinated. Frequencies shown below are for adults aged 50 to 64 years of age, and 65 and older. Subjects older than 65 years of age reported fewer events than younger adults, regardless of prior immunization status. Overall, the frequency categories were similar for both age groups.

Expected frequency of adverse reactions is presented in CIOMS frequency categories.

Very common: ≥10%
Common: ≥1% and <10%
Uncommon: ≥0.1% and <1%
Rare: ≥0.01% and <0.1%
Very rare: <0.01%

Adverse Reactions from Clinical Trials with Prevenar13

Infants and children aged 6 weeks to 5 years

These data are from clinical trials in which Prevenar13 was administered simultaneously with other routine childhood vaccines.

System Organ Class	Adverse Reaction
Metabolism and nutrition disorders	
Very common	Decreased appetite
Psychiatric disorders	
Very common	Irritability
Uncommon	Crying
Nervous system disorders	
Very common	Drowsiness/increased sleep; restless sleep/decreased sleep
Uncommon	Seizures (including febrile seizures)
Rare	Hypotonic–Hyporesponsive episode
Gastrointestinal disorders	
Common	Diarrhea; vomiting
Immune system disorders	
Rare	Hypersensitivity reaction including face edema, dyspnea, bronchospasm
Skin and subcutaneous tissue disorders	
Common	Rash

Uncommon	Urticaria or urticaria-like rash

General disorders and administration site conditions

Very common	Fever; any injection-site erythema, induration/swelling or pain/tenderness; injection-site erythema or duration/swelling 2.5 cm - 7.0 cm (after toddler dose and in older children [age 2 to 5 years]).
Common	Fever greater than 39°C; injection-site erythema or induration/swelling 2.5 cm - 7.0 cm (after infant series); injection-site pain/tenderness interfering with movement
Uncommon	Injection-site induration/swelling or erythema greater than 7.0 cm

Adults aged 50 years and older

System Organ Class	Adverse Reaction

Metabolism and nutrition disorders

Very common	Decreased appetite

Nervous system disorders

Very common	Headaches

Gastrointestinal disorders

Very common	Diarrhea
Common	Vomiting
Uncommon	Nausea

Immune system disorders

Uncommon	Hypersensitivity reaction including face edema, dyspnea, bronchospasm

Skin and subcutaneous tissue disorders

Very common	Rash

Musculoskeletal and connective tissue disorders

Very common	Generalized new/aggravated joint pain; generalized new/aggravated muscle pain

General disorders and administration site conditions

Very common	Chills; fatigue; vaccination-site erythema, vaccination site induration/swelling; vaccination-site pain/tenderness; limitation of arm movement
Common	Fever
Uncommon	Lymphadenopathy localized to the region of the vaccination site

Overall, no significant differences in frequencies of adverse reactions were noted if Prevenar13 was given to adults pre-vaccinated with PPSV23 or adults PPSV23 unvaccinated. Frequency categories for all adverse reactions of adults aged 50 to 64 years and adults ≥65 years of age were similar.

Solicited adverse reactions in adult studies with Prevenar13 and trivalent inactivated influenza vaccine

The safety of concomitant administration of Prevenar13 with trivalent inactivated influenza vaccine was assessed in 2 studies in PPSV23 unvaccinated adults.

Frequencies of local reactions in adults aged 50-59 years and in adults aged ≥65 years were similar after Prevenar13 was administered with trivalent inactivated influenza vaccine compared to Prevenar13 administered alone.

Higher frequency in some solicited systemic reactions was observed when Prevenar13 was administered concomitantly with trivalent inactivated influenza vaccine compared to trivalent inactivated influenza vaccine given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or Prevenar13 given alone (headache, fatigue, chills, decreased appetite, and joint pain).

Adverse reactions from Prevenar13 Post-marketing experience

Although the following adverse reactions were not observed in clinical trials, they are considered adverse drug reactions for Prevenar13 as they were reported in the post-marketing experience.

System Organ Class	Adverse Reaction
Blood and lymphatic system disorders	
	Lymphadenopathy localized to the region of the vaccination-site
Immune system disorders	
	Anaphylactic/anaphylactoid reaction including shock
Skin and subcutaneous tissue disorders	
	Angioneurotic edema; erythema multiforme
General disorders and administration site conditions	
	Vaccination-site dermatitis; vaccination-site urticaria; vaccination-site pruritus; flushing

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Overdose with Prevenar13 is unlikely due to its presentation as a pre-filled syringe and as a single dose vial. However, there have been reports of overdose with Prevenar13 defined as subsequent doses administered closer than recommended to the previous dose. In general, adverse events reported with overdose are consistent with those that have been reported with doses given in the recommended schedules of Prevenar13.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological class, therapeutic class

Vaccines

5.1 Pharmacodynamic Properties

Mode Of Action

Prevenar13 contains the 7 pneumococcal capsular polysaccharides that are in pneumococcal 7-valent conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F) plus 6 additional polysaccharides (1, 3, 5, 6A, 7F, 19A) all conjugated to CRM_{197} carrier protein. B-cells produce antibodies in response to antigenic stimulation via T-dependent and T-independent mechanisms. The immune response to most antigens is T-dependent and involves the collaboration of CD4+ T-cells and B-cells, recognizing the antigen in a linked fashion.CD4+ T-cells (T-helper cells) provide signals to B-cells directly through cell surface protein interactions, and indirectly through the release of cytokines. These signals result in proliferation and differentiation of the B-cells, and production of high-affinity antibodies. CD4+ T-cell signaling is a requisite for the generation of long-lived B-cells called plasma cells, which continuously produce antibodies of several isotypes (with an IgG component) and memory B-cells that rapidly mobilize and secrete antibodies upon re-exposure to the same antigen.

Bacterial capsular polysaccharides (PSs), while varied in chemical structure, share the common immunological property of being largely T-independent antigens. In the absence of T-cell help, PS-stimulated B-cells predominantly produce IgM antibodies; there is generally no affinity maturation of the antibodies, and no memory B-cells are generated. As vaccines, PSs are associated with poor or absent immunogenicity in infants less than 24 months of age and failure to induce immunological memory at any age. Conjugation of PSs to a protein carrier overcomes the T-cell-independent nature of PS antigens. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response and generation of B-cell memory. Conversion of *Streptococcus pneumoniae* PSs to a T-cell-dependent antigen by covalent coupling to the immunogenic protein carrier CRM_{197} enhances the antibody response, induces immune memory, and elicits booster responses on re-exposure in infants and young children to pneumococcal polysaccharides.

PHARMACODYNAMICS, CLINICAL EFFICACY

Disease Burden for Infants and Children

S. pneumoniae is an important cause of morbidity and mortality in persons of all ages worldwide. The organism causes invasive infections, such as bacteremia and meningitis, as well as pneumonia and upper respiratory tract infections, including otitis media and sinusitis. In children older than 1 month, *S. pneumoniae* is the most common cause of invasive disease. More than 90 different serotypes of *S. pneumoniae* have been identified, varying both by the composition of their seroreactive capsular polysaccharides and in their ability to cause disease, with the majority of invasive disease caused by relatively few serotypes. The relative frequencies of pneumococcal serotypes causing invasive disease in children vary geographically, but have been remarkably stable over time. In the US, the serotypes causing the majority of disease in the 1990s were the basis for the development of the pneumococcal 7-valent conjugate vaccine and included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

Prior to the introduction of the pneumococcal 7-valent conjugate vaccine, the incidence of IPD among children less than 2 years of age was approximately 180-200 cases/100,000/year, with an overall estimated case-fatality rate of 1.4%. The incidence of pneumococcal meningitis in this age group was estimated to be approximately 7-10 cases/100,000/year, with an associated mortality rate as high as 8%-25%. Of survivors, a significant proportion had serious sequelae, including developmental delay, seizure disorders, and deafness. Finally, while pneumonia is generally not considered to be invasive disease *per se*, it may be accompanied by bacteremia or may be complicated by local invasion into a normally sterile space with empyema; both of these invasive manifestations of pneumonia are more severe and carry considerably higher morbidity and mortality rates than do non-invasive pneumonia, even among children. Prior to the licensure of the pneumococcal 7-valent conjugate vaccine, the estimated incidence of pneumonia among children <2 years of age was 24/100,000. Children in group child care have an increased risk for invasive pneumococcal disease, as do immunocompromised individuals with neutropenia, asplenia, sickle cell disease, disorders of complement and humoral immunity, human immunodeficiency virus (HIV) infections or chronic underlying disease.

The pneumococcal 7-valent conjugate vaccine was licensed in the US in 2000, following a randomized, double-blinded clinical trial in a multiethnic population at Northern California Kaiser Permanente (NCKP) from October 1995 through August 20, 1998, in which 37,816 infants were randomized to receive either the pneumococcal 7-valent conjugate vaccine or a control vaccine (an investigational meningococcal group C conjugate vaccine [MnCC]) at 2, 4, 6, and 12-15 months of age. In this study, the efficacy of the pneumococcal 7-valent conjugate vaccine against invasive disease due to *S. pneumoniae* in cases accrued during this period was 100% in both the per-protocol and intent-to-treat analyses (95% CI, 75.4%-100% and 81.7%-100%, respectively). Data accumulated through an extended follow-up period to April 20, 1999, resulted in similar efficacy estimates of 97.3% in the per-protocol analysis and 94.4% in the intent-to-treat analysis. Since the vaccine's introduction, a 98% reduction in IPD caused by vaccine serotypes has been observed among children younger than 5 years of age through 2005, attesting to the high effectiveness of the pneumococcal 7-valent conjugate vaccine in routine use. While the effect of routine use of the pneumococcal 7-valent conjugate vaccine in infants and young children has been dramatic, with a near-total elimination of the serotypes contained in this vaccine, a proportional increase in other serotypes causing IPD has been observed (as an increasing percentage of residual disease). Specifically, while serotype 19A was the 9th most commonly isolated serotype causing IPD in the US prior to the introduction of the pneumococcal 7-valent conjugate vaccine, according to both CDC and independent surveillance, as of 2005, serotype 19A had become the predominant pneumococcal serotype causing IPD in US children, accounting for approximately 30%-45% of the residual IPD in 2005 in children <5 years of age. Compounding the issue of the predominance of emerging serotype 19A is that it is increasingly likely to be non-susceptible to commonly used 1st-line antimicrobial agents. Furthermore, approximately 52% of the serotyped IPD cases occurring in children <2 years of age in 2005 in the CDC's Active Bacterial Core surveillance were due to serotypes (19A, 7F, 3, 6A, and 5) included in Prevenar13. In various recent US surveys conducted by other investigators, more than 40% and up to 58% of residual IPD cases in pediatric subjects were caused by these 6 additional serotypes.

Epidemiologic observations in the US since the introduction of the pneumococcal 7-valent conjugate vaccine have shown that not only has invasive disease been significantly reduced among vaccinated children, especially that caused by serotypes included in the vaccine, but it has also been reduced both among persons older than 5 years of age (a population for whom the conjugate vaccine

is not routinely recommended) and among infants too young to be eligible for immunization. It is generally believed that the reduction in disease among unvaccinated people is the result of "herd immunity" or "indirect effect," a phenomenon that occurs via interruption of transmission of disease to otherwise susceptible populations, resulting in an observed reduction in disease overall; in this case, herd immunity is observed in unvaccinated populations due to the ability of the pneumococcal 7-valent conjugate vaccine to interrupt transmission of pneumococci from vaccinated children to their unvaccinated contacts. It is expected that there will be similar population responses related to Prevenar13 when used routinely.

The exact contribution of *S. pneumoniae* to childhood pneumonia is unknown, as it is often not possible to identify the causative organisms. In studies of children less than 5 years of age with community-acquired pneumonia (CAP), where diagnosis was attempted using serological methods, antigen testing, or culture data, 30% of cases were classified as bacterial pneumonia, and 70% of these (21% of total community-acquired pneumonia) were found to be due to *S. pneumoniae*, making it the most common bacterial cause of pneumonia in this age group. Observations since the introduction of the pneumococcal 7-valent conjugate vaccine, however, suggest that *S. pneumoniae*, and in particular those pneumococcal serotypes included in the vaccine, are responsible for a considerable burden of CAP among children, and that the pneumococcal 7-valent conjugate vaccine is effective in preventing CAP in children. In particular, reviews of hospital utilization databases in the US found a 39%-52.4% reduction in hospitalizations for all-cause pneumonia, and a 57.6%-65% reduction in hospitalizations coded as pneumococcal pneumonia, in children younger than 2 years of age. While uncomplicated pneumonia is generally considered non-invasive disease, pneumococcal pneumonia may be complicated by both bacteremia and locally invasive manifestations, including pleural empyema and pulmonary necrosis. Observations in the US since the introduction of the pneumococcal 7-valent conjugate vaccine suggest that complicated, invasive pneumonia may be increasing, and that these more severe manifestations of pneumonia are more likely to be associated with serotypes included in Prevenar13 (1, 3, 19A, and 7F); serotype 3 in particular has been associated with necrotizing pneumonia.

Streptococcus pneumoniae is also a major cause of non-invasive disease in children, particularly of acute otitis media (AOM). Acute otitis media (AOM) is a common childhood disease, with more than 60% of children experiencing an episode by one year of age, and more than 90% of children experiencing an episode by age 5. Prior to the US introduction of the pneumococcal 7-valent conjugate vaccine in the year 2000, approximately 24.5 million ambulatory care visits and 490,000 procedures for myringotomy with tube placement were attributed to otitis media annually. The peak incidence of AOM is 6 to 18 months of age. Otitis media is less common, but occurs, in older children. In a 1990 surveillance report by the Centers for Disease Control and Prevention (CDC), otitis media was the most common principal illness diagnosis in children 2-10 years of age. Complications of AOM include persistent middle-ear effusion, chronic otitis media, transient hearing loss, or speech delays and, if left untreated, may lead to more serious diseases, such as mastoiditis and meningitis. *S. pneumoniae* is an important cause of AOM. It is the bacterial pathogen most commonly isolated from middle-ear fluid, identified in 20% to 40% of middle-ear fluid cultures in AOM. Pneumococcal otitis media is associated with higher rates of fever and is less likely to resolve spontaneously than AOM due to either non-typeable *H. influenzae* or *M. catarrhali*s.

The efficacy of the pneumococcal 7-valent conjugate vaccine against otitis media was assessed in two clinical trials: a trial in Finnish infants at the National Public Health Institute and the pivotal efficacy trial in US infants at Northern California Kaiser Permanente (NCKP). The Finnish Otitis

Media (FinOM) trial was a randomized, double-blind trial in which 1,662 infants were equally randomized to receive either pneumococcal 7-valent conjugate vaccine or a control vaccine (Hepatitis B vaccine [Hep B]) at 2, 4, 6, and 12-15 months of age. In this study, parents of study participants were asked to bring their children to the study clinics if the child had respiratory infections or symptoms suggesting acute otitis media (AOM). If AOM was diagnosed, tympanocentesis was performed, and the middle-ear fluid was cultured. If *S. pneumoniae* was isolated, serotyping was performed; the primary endpoint was efficacy against AOM episodes caused by vaccine serotypes in the per-protocol population. In the NCKP trial, the efficacy of the pneumococcal 7-valent conjugate vaccine against otitis media was assessed from the beginning of the trial in October 1995 through April 1998. The otitis media analysis included 34,146 infants randomized to receive either the pneumococcal 7-valent conjugate vaccine (N=17,070), or the control vaccine (N=17,076), at 2, 4, 6, and 12-15 months of age. In this trial, no routine tympanocentesis was performed, and no standard definition of otitis media was used by study physicians. The primary otitis media endpoint was efficacy against all otitis media episodes in the per-protocol population.

The vaccine efficacy against AOM episodes due to vaccine serotypes assessed in the Finnish trial was 57% (95% CI, 44%-67%) in the per-protocol population and 54% (95% CI, 41%-64%) in the intent-to-treat population. The vaccine efficacy against AOM episodes due to vaccine-related serotypes (6A, 9N, 18B, 19A, 23A), also assessed in the Finnish trial, was 51% (95% CI: 27, 67) in the per-protocol population and 44% (95% CI: 20, 62) in the intent-to-treat population. There was a non-significant increase in AOM episodes caused by serotypes unrelated to the vaccine in the per-protocol population, suggesting that children who received the pneumococcal 7-valent conjugate vaccine appeared to be at increased risk of otitis media due to pneumococcal serotypes not represented in the vaccine, compared to children who received the control vaccine. However, vaccination with the pneumococcal 7-valent conjugate vaccine reduced pneumococcal otitis media episodes overall. In the NCKP trial, in which the endpoint was all otitis media episodes regardless of etiology, vaccine efficacy was 7% (95% CI, 4%-10%) and 6% (95% CI, 4%-9%), respectively, in the per-protocol and intent-to-treat analyses. Several other otitis media endpoints were also assessed in the two trials. Recurrent AOM, defined as 3 episodes in 6 months or 4 episodes in 12 months, was reduced by 9% in both the per-protocol and intent-to-treat populations (95% CI: 3%-15% in per-protocol and 95% CI: 4%-14% in intent-to-treat) in the NCKP trial; a similar trend was observed in the Finnish trial. The NCKP trial also demonstrated a 20% reduction (95% CI: 2, 35) in the placement of tympanostomy tubes in the per-protocol population and a 21% reduction (95% CI: 4, 34) in the intent-to-treat population. Data from the NCKP trial accumulated through an extended follow-up period to April 20, 1999, in which a total of 37,866 children were included (18,925 in the pneumococcal 7-valent conjugate vaccine group and 18,941 in the MnCC control group), resulted in similar otitis media efficacy estimates for all endpoints.

Similar to the experience with IPD, reductions in AOM have been observed in the US since the introduction of the pneumococcal 7-valent conjugate vaccine as a routine infant vaccine. Since diagnostic tympanocentesis is not routinely performed in the US, less information is available on shifts in the distribution of causative pneumococcal serotypes. However, results of several recent studies suggest that non-vaccine serotypes are also emerging as important causes of AOM or its complications in children (including mastoiditis, which now accounts for 12% of all IPD in the US Pediatric Multicenter Pneumococcal Surveillance Study, all of it caused in 2006-07 by serotype 19A), and that these are likely to be resistant to commonly used antimicrobial agents. Another series of pneumococcal isolates from tympanocentesis samples collected from 5 centers across the United

States identified serotype 3 most commonly, with a smaller percentage accounted for by serotypes 1 and 7.

Disease Burden for Adults

Streptococcus pneumoniae is a significant threat to world health. The World Health Organization (WHO) estimates that each year 1.6 million people die from pneumococcal disease, of which 600,000 to 800,000 are adults. Pneumococcal disease can be classified by the degree of bacterial invasion, which is predictive of complications and mortality. Invasive pneumococcal disease is defined by the isolation of pneumococcus from a normally sterile site, such as blood, cerebrospinal fluid, pleural fluid, or peritoneal fluid.

Pneumonia is the most common clinical presentation of pneumococcal disease in adults.

The reported incidence of community-acquired pneumonia (CAP) and IPD in Europe varies by country, increases with age from 50 years and is highest in individuals aged ≥65 years. *S. pneumoniae* is the most frequent cause of CAP, and is estimated to be responsible for approximately 30% of all CAP cases requiring hospitalisation in adults in developed countries.

Bacteraemic pneumonia (approximately 80% of IPD in adults), bacteraemia without a focus, and meningitis are the most common manifestations of IPD in adults.

Additional risk factors for serious pneumococcal disease include living circumstances and underlying medical conditions. Living conditions can increase the individual risk of pneumococcal disease, particularly residence in a nursing home or other long-term care facility. Significant medical risk conditions include: congenital or acquired immunodeficiency; sickle cell disease; asplenia; human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS); chronic heart, lung (including asthma), renal, or liver diseases; cancer; cerebrospinal fluid (CSF) leak; diabetes; chronic alcoholism or cigarette smoking; organ or hematopoietic cell transplantation; and cochlear implants. Among hospitalized patients in the United States, the all case fatality rate from IPD remains high (12%-16%) and is much higher in many subgroups including those with increased age, comorbidities, complications of IPD and admission to intensive care units. Despite advances in medical science over the last decades, there has been little change in mortality rates since penicillin's introduction.

The reported incidence of IPD worldwide ranges from 45 to 90 per 100,000. Prior to the introduction of the Prevenar into National Immunization Programs (NIP), the IPD incidence for Canadian adults aged 65 years and older ranged from 16 to 31 per 100,000, while for US residents of the same age, the IPD incidence ranged from 60 to 65 per 100,000 (with rates of 190/100,000 documented among members of the Navajo Nation). The IPD incidence for older Europeans in the same age group ranged from 41 in Sweden to 66 per 100,000 in Denmark, with a particularly high rate documented in the older age groups beyond 65 years, for instance, in the Netherlands or the UK. In the United States, a decrease in adult disease after the initiation of childhood vaccination has been noted, presumably due to reduction of pneumococcal colonization in infants and spread to susceptible adults (herd immunity). However, the incidence of IPD in adults, especially the elderly, has remained appreciably high ranging from 23 per 100,000 to 29.4 per 100,000. Although the incidence estimates among adults younger than 65 are lower than those among those older than 65, IPD represents a major public health burden among younger adults as well.

Pneumonia is one of the most common infectious diseases. In the United States, during 2006, over 4 million cases of pneumonia due to all causes were reported in adults. Rates of hospitalized CAP in Europe range from 200-260 per 100,000, with 75% of CAP cases being managed in the community.

Higher rates of CAP have been noted in the developing world, within specific genetic groups, in populations with lower socioeconomic status and in groups with less access to health care. Mortality from all-cause CAP range from 5%-15% and CAP contributes to a significant proportion of intensive care unit (ICU) admissions. Patients with pneumonia caused by *S. pneumoniae* tend to have more severe illness including greater likelihood of bacteremia, longer hospitalization, greater need for intensive care, and higher mortality. However, the incidence of non-bacteremic pneumonia caused by *S. pneumoniae* is more difficult to ascertain, because the causative pathogen is often not identified in the majority of cases despite aggressive efforts. Yet, *S. pneumoniae* is still the leading cause of community-acquired pneumonia accounting for 25%-35% of all cases requiring hospitalization and resulting in an overall case fatality rate of 12%.

While host factors, such as age and comorbid conditions contribute to the likelihood of IPD and poor outcomes, there has been increasing appreciation that pathogen virulence and antibiotic resistance play an important role. Although more than 90 different serotypes of *S. pneumoniae* have been identified human disease is caused by a relatively small group of serotypes possessing poorly defined virulence factors that allow them to cause disease. According to a meta-analysis of serotype-specific disease outcomes for patients with pneumonia, serotypes 3, 6A, 6B, 9N, and 19F were statistically significantly associated with increased mortality when compared to serotype 14, used as a reference. For serotypes 19A and 23F, there was a trend towards increased mortality which did not reach statistical significance. Despite some regional variations in rate and mortality, these observations appeared to be a relatively stable characteristic of the serotype and appeared to be independent of antibiotic resistance.

Antibiotic resistance increases the difficulty of initially treating some serotypes of *S. pneumoniae* with an effective antibiotic. Despite great geographic variability of serotype distribution and prevalence of antibiotic resistance, serotypes 6A, 6B, 9V, 14, 15A, 19F, 19A and 23F were most likely to demonstrate resistance to both penicillin and erythromycin.

Prevenar13 provides and immune response against prevalent strains of *S. pneumoniae* including those most likely to cause disease, be antibiotic resistant and result in poor outcomes.

Table 1: Mortality and Resistance of Selected Serotypes in Adults

Serotype	3	6A	6B	9N	9V	14	15A	19A	19F	23F
Mortality	+	+	+	+				+/-	+	+/-
Resistance		+	+		+	+	+	+	+	+

Prevenar13 Immunogenicity Clinical Studies in Infants and Children

The World Health Organization (WHO) has recommended a serum anti-capsular polysaccharide antibody concentration of 0.35 μg/mL measured one month after the primary infant series as a single antibody reference concentration to estimate the efficacy of new pneumococcal conjugate vaccines against IPD. This recommendation is largely based upon the observed correlation between immunogenicity and IPD efficacy from three placebo-controlled trials with either pneumococcal

7-valent conjugate vaccine or the investigational 9-valent CRM_{197} conjugate polysaccharide vaccine. This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis.

Immune Responses Following a Three-dose Primary Infant Series

Clinical trials have been conducted in a number of European countries, Canada and the US using a range of primary vaccination schedules. The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥0.35 µg/mL one month after a three-dose primary series in representative studies are presented below (Table 2).

Table 2: Percentage of Subjects with Pneumococcal Anti-capsular Polysaccharide IgG Antibody Concentrations ≥ 0.35 µg/mL One Month After the Infant Series

Serotype	**2, 3, 4 months Germany**	**2, 3, 4 months Poland**	**2, 4, 6 months Spain**	**2, 4, 6 months US**	**2, 4, 6 months US**	**2, 4, 6 months US**	**2, 4, 6 months US**	**2, 4, 6 months Canada**
					Lot 1	**Lot 2**	**Lot 3**	
	N=282-285	**N=106-128**	**N=261-273**	**N=249-252**	**N=387-399**	**N=398-413**	**N=387-404**	**N=272-277**
1	96.1	93.0	99.3	95.6	98.5	97.8	97.0	95.7
3	98.2	93.7	90.3	63.5	79.1	68.5	72.4	79.6
4	98.2	97.7	98.9	94.4	98.5	97.6	95.5	97.1
5	93.0	90.6	97.3	89.7	94.4	94.2	90.3	87.0
6A	91.9	85.2	97.4	96.0	98.2	98.1	95.5	96.4
6B	77.5	77.3	98.5	87.3	94.4	94.9	89.5	93.1
7F	98.6	100.0	100.0	98.4	99.7	99.8	99.0	98.6
9V	98.6	98.4	99.3	90.5	96.5	95.4	95.5	95.3
14	98.9	92.9	97.4	97.6	98.2	99.2	99.0	98.2
18C	97.2	96.1	98.1	96.8	98.0	97.8	95.8	96.4
19A	99.3	99.2	99.6	98.4	98.7	98.1	99.0	97.8
19F	95.8	98.4	99.3	98.0	99.2	97.8	97.5	98.5
23F	88.7	82.8	94.6	90.5	87.2	91.2	88.1	90.2

In Prevenar13 recipients, antipolysaccharide binding antibody IgG for each of the 13 serotypes has been demonstrated to be correlated with functional antibacterial opsonophagocytic activity (biologically-active antibody). Clinical trials also demonstrated that the response to Prevenar13 was non-inferior to that of pneumococcal 7-valent conjugate vaccine for all 13 serotypes using a set of pre-defined immunological non-inferiority criteria. Immune responses elicited by Prevenar13 to the 6 additional serotypes were quantitatively greater, for both polysaccharide-binding and opsonophagocytic antibodies, than the responses elicited by Prevenar13.

Immune Responses Following a Two-dose Primary Series

The immunogenicity after two doses in infants has been documented in four studies. The proportion of infants achieving a pneumococcal anti-capsular polysaccharide IgG concentration ≥0.35 µg/mL one month after the second dose ranged from 79.6% to 98.5% across 11 of the 13 vaccine serotypes. Smaller proportions of infants achieved this antibody concentration threshold for serotype 6B (27.9% to 58.4%) and 23F (55.8% to 68.6%). Compared to a three-dose infant series, pneumococcal anti-capsular polysaccharide IgG GMCs were lower after a two-dose infant series for most

serotypes. The clinical effectiveness of a two-dose primary series against acute otitis media or pneumonia has not been established.

Booster Responses Following Two-dose and Three-dose Primary Schedules

Post-booster antibody concentrations were higher for 12 serotypes than those achieved after the infant primary series, which is consistent with adequate priming (the induction of immunologic memory). For serotype 3, antibody concentrations following the infant primary series and booster dose were similar. Antibody responses to booster doses following two-dose or three-dose infant primary series were comparable for all 13 vaccine serotypes.

For children aged from 7 months to 5 years, age appropriate catch-up immunization schedules (as described in section Dosage and Administration) result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a three-dose primary series in infants.

Booster Responses to Prevenar13 Following a Three-dose Primary Infant Series of Pneumococcal 7-valent Conjugate Vaccine or Prevenar13

In a randomized, double-blind, active-control study in France (008) infants were randomly assigned to three groups in a 2:1:1 ratio: (1) Prevenar13 at 2, 3, 4 and 12 months or (2) pneumococcal 7-valent conjugate vaccine at 2, 3, 4 months followed by Prevenar13 at 12 months or (3) pneumococcal 7-valent conjugate vaccine at 2, 3, 4 and 12 months. Geometric mean concentrations of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes in the 3 groups are shown in Table 3. GMCs to the seven pneumococcal 7-valent conjugate vaccine serotypes did not differ in the 3 groups. Although the GMCs to the 6 additional serotypes in the pneumococcal 7-valent conjugate vaccine/Prevenar13 recipients were lower than those observed with the four dose Prevenar13 regimen (except for serotype 3), they were at least comparable to those of a three-dose primary series in infants in studies 004 and 3005. This comparison to infant series responses is similar to what was done with pneumococcal 7-valent conjugate vaccine to establish the immunization schedules in older infants and children.

Table 3: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) One Month After Vaccination					
Serotype	**13v/13v Post-toddler (008) N=233-236**	**7v/13v Post-toddler (008) N=108-113**	**7v/7v Post-toddler (008) N=111-127**	**13v Post-infant (004) N=249-252**	**13v Post-infant (3005) N=1172-1213**
1	4.08	1.83	0.04	2.03	1.78
3	0.99	1.32	0.10	0.49	0.56
4	4.20	4.04	4.85	1.31	1.46
5	3.30	1.14	0.53	1.33	1.24
6A	6.14	2.60	1.54	2.19	2.21
6B	8.99	10.33	9.63	2.10	2.51
7F	4.52	3.71	0.05	2.57	2.57
9V	2.59	2.29	3.24	0.98	1.09
14	9.52	7.81	10.83	4.74	5.09
18C	2.30	2.43	2.81	1.37	1.37
19A	9.50	5.33	3.98	2.07	1.91
19F	5.18	3.73	4.11	1.85	2.15
23F	3.01	3.12	3.69	1.33	1.18

Previously Unvaccinated Older Infants and Children

In an open-label study of Prevenar13 in Poland (3002), children 7 to 11 months of age, 12 to 23 months and ≥24 months through 5 years of age (prior to the 6th birthday) who were naive to pneumococcal conjugate vaccine, were given 3, 2, or 1 dose of Prevenar13 according to the age-appropriate schedules (see section 4.2 Posology and Method of Administration). Serum IgG concentrations were measured one month after the final dose in each age group and the data are shown in Table 4.

These age appropriate catch-up immunization schedules result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a three-dose primary series in infants.

Table 4: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) One Month After the Final Dose by Age Group			
Serotype	**7 to 11 months of age (N=83-84)**	**12 to 23 months of age (N=104-110)**	**≥24 months through 5 years of age (N=135-152)**
1	2.88	2.74	1.78
3	1.94	1.86	1.42
4	3.63	4.28	3.37
5	2.85	2.16	2.33
6A	3.72	2.62	2.96
6B	4.77	3.38	3.41
7F	5.30	5.99	4.92
9V	2.56	3.08	2.67
14	8.04	6.45	2.24
18C	2.77	3.71	2.56

19A	4.77	4.94	6.03
19F	2.88	3.07	2.53
23F	2.16	1.98	1.55

Simultaneous Administration with Other Vaccines in Infants and Children

In studies 004, 3005 and 3008 routine pediatric vaccines were administered at the same visit as Prevenar13. Immune responses to selected concomitant vaccine antigens were compared in infants receiving pneumococcal 7-valent conjugate vaccine and Prevenar13. The proportions of responders at pre-specified antibody levels are shown in Table 5. Responses to all antigens in Prevenar13 recipients were similar to those in pneumococcal 7-valent conjugate vaccine recipients and met formal criteria for non-inferiority. Varicella responses as measured by a commercial whole cell ELISA kit, designed to detect immunity after natural infection, were low in both groups, but there was no evidence of interference with the immune response by concomitantly administered Prevenar13.

Table 5: Subjects Achieving a Pre-specified Antibody Level for Concomitant Vaccines Antigens

Vaccine Name/Vaccine Antigen (Pre-specified Antibody Level)	**Prevenar13 %Responders (n^a/N^b)**	**Pneumococcal 7-valent Conjugate Vaccine %Responders (n^a/N^b)**
Pediarix (DTaP-IPV-HepB) Responses after the Three-dose Infant Series		
Dip (≥0.1 IU/mL)	95.7 (223/233)	96.1 (221/230)
Tet (≥0.1 IU/mL)	98.4 (181/184)	98.5 (193/196)
PT ≥16.5 EU/mL	94.1 (225/239)	95.0 (228/240)
FHA ≥40.5 EU/mL	96.7 (231/239)	95.0 (228/240)
PRN ≥26 EU/mL	93.7 (224/239)	95.8 (230/240)
Polio Type 1 (titer ≥1:8)	100.0 (183/183)	100.0 (187/187)
Polio Type 2 (titer ≥1:8)	98.9 (181/183)	99.5 (186/187)
Polio Type 3 (titer ≥1:8)	100.0 (182/182)	99.5 (186/187)
HBV ≥10.0 mIU/mL	100.0 (153/153)	100.0 (173/173)
ActHIB (PRP) Responses After the Infant Series		
Hib (PRP) (≥ 0.15 µg/mL)	97.9 (232/237)	97.8 (225/230)
Hib (PRP) (≥1.0 µg/mL)	77.6 (184/237)	78.3 (180/230)
Pentacel (DTaP-IPV-Hib) Responses After the Infant Series		
Hib (PRP) (≥0.15 µg/mL)	97.8 (266/272)	99.6 (265/266)
Hib (PRP)	81.6 (222/272)	84.6 (225/266)

Table 5: Subjects Achieving a Pre-specified Antibody Level for Concomitant Vaccines Antigens		
Vaccine Name/Vaccine Antigen (Pre-specified Antibody Level)	**Prevenar13 %Responders (n^a/N^b)**	**Pneumococcal 7-valent Conjugate Vaccine %Responders (n^a/N^b)**
(≥1.0 µg/mL)		
PT ≥12.0 EU/mL	98.6 (278/282)	96.0 (266/277)
FHA ≥20.0 EU/mL	99.3 (281/283)	95.7 (266/278)
PRN ≥7.0 EU/mL	96.8 (274/283)	96.0 (266/277)
FIM ≥4.0 EU/mL	93.6 (264/282)	95.3 (262/275)
PedvaxHIB (PRP-OMP) Responses at 12 to 15 Months Following Infant Series with ActHIB		
Hib (PRP) (≥0.15 µg/mL)	100.0 (230/230)	100.0 (214/214)
Hib (PRP) (≥1.0 µg/mL)	90.4 (208/230)	92.1 (197/214)
ProQuad (MMR-Varicella) Responses at 12 to 15 Months		
Measles (≥1.10 I.V.)	96.4 (213/221)	97.1 (204/210)
Mumps (≥1.10 I.V.)	76.5 (169/221)	72.9 (153/210)
Rubella (≥15 IU/mL)	91.9 (192/209)	90.7 (185/204)
Varicella (≥1.09 I.V.)	26.7 (59/221)	21.9 (46/210)
[a] Number of subjects achieving the pre-specified antibody level. [b] Number of subjects in the evaluable immunogenicity population.		

Efficacy study in adults 65 years and older

Efficacy against vaccine-type (VT) pneumococcal CAP and IPD was assessed in a large-scale randomised double-blind, placebo-controlled study (Community-Acquired Pneumonia Immunization Trial in Adults–CAPiTA) in the Netherlands. 84,496 subjects, 65 years and older received a single vaccination of either Prevenar 13 or placebo in a 1:1 randomization.

The CAPiTA study enrolled volunteers ≥65 years of age whose demographic and health characteristics may differ from those seeking vaccination.

A first episode of hospitalised, chest X-ray confirmed pneumonia was identified in about 2% of this population (n=1,814 subjects) of which 329 cases were confirmed pneumococcal CAP and 182 cases were VT pneumococcal CAP in the per protocol and modified intent to treat (mITT) populations. For the primary endpoint (per protocol population), there were 139 (49 Prevenar 13: 90 Placebo) first episodes of VT-CAP resulting in an efficacy of 45.56% (95.2% CI, 21.82-62.49; p=0.0006).

Efficacy was also demonstrated for the two secondary endpoints in the per protocol population. For the non-bacteraemic/non-invasive (NB/NI) pneumococcal CAP secondary endpoint, there were 93 (33 Prevenar 13: 60 Placebo) first episodes of NB/NI VT pneumococcal CAP resulting in an efficacy of 45.00% (95.2% CI, 14.21-65.31; p=0.0067). For the IPD secondary endpoint, there were 35 (7 Prevenar 13: 28 Placebo) first episodes of VT-IPD, resulting in an efficacy of 75.00% (95.2% CI, 41.06-90.87; p=0.0005).

The duration of protective efficacy against a first episode of VT pneumococcal CAP, NB/NI VT pneumococcal CAP, and VT-IPD extended throughout the 4-year study.

The study was not designed to demonstrate efficacy in subgroups, and the number of subjects ≥85 years of age was not sufficient to demonstrate efficacy in this age group.

Prevenar13 Immunogenicity Clinical Trials in Adults

An antipolysaccharide binding antibody IgG level to predict protection against invasive pneumococcal disease or non-bacteremic pneumonia has not been defined for adults. However, non-clinical and clinical data support functional antibody, measured by opsonophagocytic activity (OPA) antibody assay, as a contributor to protection against pneumococcal disease. The OPA antibody assay provides an *in vitro* measurement of the ability of serum antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant *in vivo* mechanisms of protection against pneumococcal disease. OPA antibody titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%. Pivotal trials for Prevenar13 were designed to show that functional OPA antibody responses for the Prevenar13 serotypes are non-inferior and for some serotypes superior to the common serotypes in the currently licensed pneumococcal polysaccharide vaccine (PPSV23).

Serotype-specific OPA antibody geometric mean titers (GMTs) measured 1 month after each vaccination were calculated. Non-inferiority between vaccines was defined as the lower bound of the 2-sided, 95% confidence interval (CI) for the ratio of the GMTs (GMR) greater than 0.5 (2-fold criterion); statistically significantly greater responses were defined as the lower bound of the 2-sided 95% CI for the GMR greater than 1.

The response to the additional serotype 6A, which is unique to Prevenar13 but not in PPSV23 was assessed by demonstration of a 4-fold increase in the specific OPA antibody titer above pre-immunization levels. Superiority of the response for Prevenar13 was defined as the lower bound of the 2-sided, 95% CI for the difference in percentages of adults achieving a 4-fold increase in OPA antibody titer greater than zero. For comparison of OPA antibody GMTs, a statistically greater response for serotype 6A was defined as the lower bound of the 2-sided 95% CI for the GMR greater than 2.

Five phase 3 clinical trials were conducted in a number of European countries and in the US evaluating the immunogenicity of Prevenar13 in different age groups, and in individuals who were either not previously vaccinated (PPSV23 unvaccinated) with PPSV23 or had received one or more doses of PPSV23 (PPSV23 pre-vaccinated).

Each study included healthy adults and immunocompetent adults with stable underlying conditions including chronic cardiovascular disease, chronic pulmonary disease, renal disorders, diabetes mellitus, chronic liver disease including alcoholic liver disease, and alcoholism because it is known

that these are common conditions in adults that increase risk of serious pneumococcal community-acquired pneumonia and invasive pneumococcal disease.

Two (2) pivotal non-inferiority trials were conducted in which Prevenar13 response was compared to PPSV23 immune response, one in PPSV23 unvaccinated adults aged 50-64 years (6115A1-004), and one in PPSV23 pre-vaccinated adults aged ≥70 years (6115A1-3005). One study (6115A1-3000) in PPSV23 pre-vaccinated adults collected safety data only. Two studies (6115A1-3001 and 6115A1-3008) assessed the concomitant administration of Prevenar13 with seasonal trivalent inactivated influenza vaccine (TIV).

Clinical trials conducted in adults not previously vaccinated with PPSV23

In an active-controlled modified[1] double-blind clinical trial (6115A1-004) of Prevenar13 in the US, PPSV23-unvaccinated adults aged 60 to 64 years were randomly assigned (1:1) to receive Prevenar13 or PPSV23. In addition, adults aged 50 to 59 years were enrolled and received one dose of Prevenar13 (open-label). ([1]Modified double-blind means that the site staff dispensing and administering the vaccine were unblinded, but all other study personnel including the principal investigator and subject were blinded.)

The OPA antibody responses elicited by Prevenar13 were non-inferior to those elicited by PPSV23 for the 12 serotypes in common to both vaccines. In addition, 8 of the serotypes in common exhibited a statistically significantly greater immune response after Prevenar13 compared with after PPSV23.

For serotype 6A, which is unique to Prevenar13, the proportions of adults with a 4-fold increase after Prevenar13 (88.5%) were significantly greater than after PPSV23 (39.2%) in PPSV23-unvaccinated adults aged 60-64 years. OPA antibody GMTs for serotype 6A were statistically significantly greater after Prevenar13 compared with after PPSV23.

The OPA antibody responses elicited by Prevenar13 in adults aged 50-59 years were non-inferior to the Prevenar13 responses in adults aged 60-64 years for all 13 serotypes. In addition, 9 of the 13 serotypes exhibited a statistically significantly greater immune response in adults aged 50-59 years compared with adults aged 60-64 years.

This clinical trial demonstrated that the immune responses elicited by Prevenar13 are non-inferior and for most serotypes statistically significantly greater than PPSV23. In addition, the immune responses in adults aged 50-59 years were non-inferior and for most serotypes statistically significantly greater than those observed in adults aged 60-64 years. In adults aged 60-64 years, antibody levels one year after vaccination were greater after Prevenar13 compared to antibody levels after PPSV23 for 7 of 12 serotypes in common. In adults aged 50-59 years, antibody levels one year after vaccination with Prevenar13 were greater for 12 of 13 serotypes compared to vaccination with Prevenar13 in 60-64 year olds.

Table 6: OPA Antibody GMTs in PPSV23-Unvaccinated Adults Aged 50-59 Years Given Prevenar13; and in Adults Aged 60-64 Years Given Prevenar13 or PPSV23[a,b]

	Prevenar13	Prevenar13	PPSV 23	Prevenar13 50-59 Relative to 60-64 Years		Prevenar13 Relative to PPSV 23, 60-64 Years	
Serotype	**50-59 Years N=350-384 GMT**	**60-64 Years N=359-404 GMT**	**60-64 Years N=367-402 GMT**	**GMR**	**95% CI**	**GMR**	**95% CI**
1	200	146	104	1.4	(1.08, 1.73)	1.4	(1.10, 1.78)
3	91	93	85	1.0	(0.81, 1.19)	1.1	(0.90, 1.32)
4	2833	2062	1295	1.4	(1.07, 1.77)	1.6	(1.19, 2.13)
5	269	199	162	1.4	(1.01, 1.80)	1.2	(0.93, 1.62)
6A[†]	4328	2593	213	1.7	(1.30, 2.15)	12.1	(8.63, 17.08)
6B	3212	1984	788	1.6	(1.24, 2.12)	2.5	(1.82, 3.48)
7F	1520	1120	405	1.4	(1.03, 1.79)	2.8	(1.98, 3.87)
9V	1726	1164	407	1.5	(1.11, 1.98)	2.9	(2.00, 4.08)
14	957	612	692	1.6	(1.16, 2.12)	0.9	(0.64, 1.21)
18C	1939	1726	925	1.1	(0.86, 1.47)	1.9	(1.39, 2.51)
19A	956	682	352	1.4	(1.16, 1.69)	1.9	(1.56, 2.41)
19F	599	517	539	1.2	(0.87, 1.54)	1.0	(0.72, 1.28)
23F	494	375	72	1.3	(0.94, 1.84)	5.2	(3.67, 7.33)

GMT, Geometric Mean Titer.
GMR, Geometric Mean Ratio.
[†] 6A is a serotype unique to Prevenar13 but not contained in PPSV23.
[a] Non-inferiority was defined for the 12 common serotypes in cohort 1 and for the 13 serotypes in cohort 2 as the lower limit of the 2-sided 95% CI for GMT ratio (Prevenar13/PPSV23) greater than 0.5.
[b] For serotype 6A, which is unique to Prevenar13, a statistically significantly greater response was defined for analysis in cohort 1 as the lower limit of the 2-sided 95% CI for the GMT ratio (Prevenar13/PPSV23) greater than 2.

Clinical Trials Conducted in Adults Previously Vaccinated with PPSV23 (pre-vaccinated)

In a phase 3 active-controlled, modified double-blind clinical trial (6115A1-3005) of Prevenar13 in the US and Sweden, PPSV23-prevaccinated adults aged ≥70 years who had received one dose of PPSV23 ≥5 years prior were randomly assigned (1:1) to receive either Prevenar13 or PPSV23.

The OPA antibody responses elicited by Prevenar13 were non-inferior for the 12 serotypes in common to those elicited by PPSV23 when the vaccines were administered at a minimum of 5 years after PPSV23. In addition, 10 of the serotypes in common exhibited a statistically significantly greater immune response after Prevenar13 compared with after PPSV23.

For serotype 6A, which is unique to prevenar13, proportions of adults with a 4-fold increase after prevenar13 (71.1%) was significantly greater than after PPSV23 (27.3%) in PPSV23-pre-vaccinated

adults aged ≥70 years. OPA antibody GMTs for serotype 6A were statistically significantly greater after Prevenar13 compared with after PPSV23.

This clinical trial demonstrated that in adults aged ≥70 years and pre-vaccinated with PPSV23 ≥5 years prior, vaccination with Prevenar13 elicited non-inferior immune responses as compared with re-vaccination with PPSV23.

Table 7: OPA Antibody GMTs in PPSV23-Previously Vaccinated Adults Aged ≥70 Years Given Prevenar13 or PPSV23[a,b]

Serotype	**Prevenar13** N=400-426	**PPSV23** N=395-445	**Prevenar13 Relative to PPSV23**	
	GMT	GMT	GMT Ratio	(95% CI)
1	81	55	1.5	(1.17, 1.88)
3	55	49	1.1	(0.91, 1.35)
4	545	203	2.7	(1.93, 3.74)
5	72	36	2.0	(1.55, 2.63)
6A[†]	903	94	9.6	(7.00, 13.26)
6B	1261	417	3.0	(2.21, 4.13)
7F	245	160	1.5	(1.07, 2.18)
9V	181	90	2.0	(1.36, 2.97)
14	280	285	1.0	(0.73, 1.33)
18C	907	481	1.9	(1.42, 2.50)
19A	354	200	1.8	(1.43, 2.20)
19F	333	214	1.6	(1.17, 2.06)
23F	158	43	3.7	(2.69, 5.09)

GMT, Geometric Mean Titer.
[†] 6A is a serotype unique to Prevenar13 but not contained in PPSV23.
[a] For the 12 common serotypes, non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMT ratio (Prevenar13/PPSV23) greater than 0.5.
[b] For serotype 6A, which is unique to Prevenar13, a statistically significantly greater response was defined as the lower limit of the 2-sided 95% CI for the GMT ratio (Prevenar13/PPSV23) greater than 2.

Clinical Trials to Assess Prevenar13 Given with Seasonal Trivalent Inactivated Influenza Vaccine (TIV) in Adults

Two randomized, double-blind clinical trials evaluated the immunogenicity of Prevenar13 given with TIV (A/H1N1, A/H3N2, and B strains) in adults who were PPSV23 unvaccinated aged 50-59 years and in adults ≥65 years.

Each clinical trial compared concomitant administration of Prevenar13 and TIV (administered in opposite arms) with [1] TIV given with placebo and [2] with Prevenar13 given alone. Group 1 received Prevenar13 given with TIV, followed one month later by placebo; Group 2 received TIV given with placebo, followed one month later by Prevenar13.

A phase 3 randomized, double-blind clinical trial (6115A1-3001) of Prevenar13 given with TIV in adults aged 50-59 years who were PPSV23 unvaccinated in the US assessed the immune responses of TIV when TIV was given with Prevenar13 compared with TIV given with placebo (in the following called TIV alone).

A phase 3 randomized, double-blind clinical trial (6115A1-3008) of Prevenar13 given with TIV in adults aged ≥65 years who were PPSV23 unvaccinated in Europe assessed the immune responses of TIV when TIV was given with Prevenar13 compared with TIV given with placebo.

Immune responses elicited by TIV were measured by haemagglutination inhibition (HAI) assays one month after TIV vaccination. The immune responses were measured as the proportion of adults achieving a ≥4-fold increase in HAI titer (responder) for each TIV strain 1 month after vaccination. The non-inferiority criterion was achieved for each vaccine antigen if the lower limit of the 95% CI for the difference in proportions of responders was >-10%.

The studies also assessed the immune responses of Prevenar13 when Prevenar13 was given with TIV compared with Prevenar13 given alone. The immune responses elicited by Prevenar13 were measured by ELISA IgG GMC one month after Prevenar13 vaccination. The non-inferiority criterion was achieved if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (Prevenar13 and TIV relative to Prevenar13 alone) was >0.5 (2-fold criterion).

TIV immune responses 50-59 years of age: The immune responses were similar after Prevenar13 given concomitantly with TIV compared to TIV alone. Non-inferiority was met for all 3 TIV strains after Prevenar13 given concomitantly with TIV compared to TIV alone (Table 8).

TIV immune responses in ≥65 years of age: The immune responses were similar after Prevenar13 given concomitantly with TIV compared to TIV alone. Non-inferiority was met for A/H1N1 and B-strains but not for A/H3N2 with a lower limit of the 95% CI of -10.4% (Table 9).

Table 8: Proportion of Participants Aged 50–59 Years with a ≥4-fold Increase in HAI Titer after

TIV	TIV + Prevenar13		TIV + Placebo		Difference
HAI	n/N	%(95% CI)	n/N	%(95% CI)	%(95% CI)
A/H1N1	445/530	84.0 (80.6, 87.0)	431/531	81.2 (77.6, 84.4)	2.8 (-1.8, 7.4)
A.H3N2	377/530	71.1 (67.1, 75.0)	369/531	69.5 (65.4, 73.4)	1.6 (-3.9, 7.2)
B	321/530	60.6 (56.3, 64.8)	320/531	60.3 (56.0, 64.5)	0.3 (-5.6, 6.2)

Table 9: Proportion of Participants Aged ≥65 Years with a ≥4-fold Increase in HAI Titer after TIV with Prevenar13 and TIV with Placebo

TIV	TIV + Prevenar13		TIV + Placebo		Difference
HAI	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
A/H1N1	440/548	80.3 (76.7, 83.5)	429/546	78.6 (74.9, 81.9)	1.7 (-3.1, 6.5)
A/H3N2	316/545	58.0 (53.7, 62.2)	341/545	62.6 (58.4, 66.6)	-4.6 (-10.4, 1.3)
B	286/548	52.2 (47.9, 56.4)	295/546	54.0 (49.7, 58.3)	-1.8 (-7.8, 4.1)

Prevenar13 immune responses in 50-59 year olds: Non-inferiority was met for all serotypes (Table 10).

Prevenar13 immune responses in ≥65 year olds: Non-inferiority was met for all serotypes except serotype 19F. The lower limit of the 95% CI of the GMR for 19F was 0.49 [criterion 0.5] (Table 11).

Table 10: Pneumococcal IgG GMC 1 Month After Prevenar13 and TIV; and 1 Month After Prevenar13 (Given 1 month After Placebo and TIV) for Participants 50-59 Years[a,b]

Serotype	**Post-dose 1 Prevenar13 + TIV (N = 247-294)**	**Post-dose 2 Prevenar13* (N = 247-289)**	**Vaccine Comparison**
	GMC, µg/mL	GMC, µg/mL	Ratio (95% CI)
1	4.05	5.45	0.74 (0.58, 0.95)
3	1.15	1.46	0.79 (0.66, 0.93)
4	2.35	3.41	0.69 (0.55, 0.87)
5	6.03	7.18	0.84 (0.67, 1.05)
6A	5.78	6.70	0.86 (0.70, 1.06)
6B	7.58	10.09	0.75 (0.60, 0.93)
7F	8.14	10.57	0.77 (0.63, 0.95)
9V	4.96	6.97	0.71 (0.59, 0.86)
14	10.77	14.05	0.77 (0.60, 0.98)
18C	9.65	13.49	0.72 (0.58, 0.88)
19A	16.80	18.84	0.89 (0.74, 1.08)
19F	6.13	7.13	0.86 (0.67, 1.10)
23F	7.17	8.54	0.84 (0.66, 1.08)

GMC, Geometric Mean Concentration.
Given 4 weeks after placebo and TIV.
[a] Antibody measured by a standardized ELISA.
[b] The non-inferiority criterion was achieved if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (Prevenar13 and TIV relative to Prevenar13 alone) was >-0.5 (2-fold criterion).

Table 11: Pneumococcal IgG GMC 1 Month After Prevenar13 and TIV; and 1 Month After Prevenar13 (Given 1 month After Placebo and TIV) for Participants ≥65 Years[a,b]

Serotype	**Post-dose 1 Prevenar13 + TIV (N = 247-294)**	**Post-dose 2 Prevenar13* (N = 247-289)**	**Vaccine Comparison**
	GMC, µg/mL	GMC, µg/mL	Ratio (95% CI)
1	2.52	3.20	0.79 (0.60, 1.04)
3	1.08	1.15	0.94 (0.78, 1.13)
4	2.15	3.24	0.66 (0.51, 0.87)
5	4.74	6.90	0.69 (0.55, 0.86)
6A	4.61	6.10	0.76 (0.61, 0.94)
6B	6.24	6.43	0.97 (0.75, 1.25)
7F	7.63	9.04	0.84 (0.67, 1.07)
9V	4.97	6.21	0.80 (0.63, 1.02)
14	8.95	12.44	0.72 (0.53, 0.97)
18C	8.88	11.07	0.80 (0.64, 1.01)

19A	11.93	17.10	0.70 (0.56, 0.87)
19F	4.78	7.39	0.65 (0.49, 0.85)
23F	5.82	6.11	0.95 (0.71, 1.27)

GMC, Geometric Mean Concentration.
Given 4 weeks after placebo and TIV.
[a] Antibody measured by a standardized ELISA.
[b] The non-inferiority criterion was achieved if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (Prevenar13 and TIV relative to Prevenar13 alone) was >-0.5 (2-fold criterion).

Prevenar13 may be administered concomitantly with the seasonal trivalent inactivated influenza vaccine (TIV).

When Prevenar13 was given concomitantly with TIV, the immune responses to TIV were similar to the responses when TIV was given alone.

When Prevenar13 was given concomitantly with TIV, the immune responses to Prevenar13 were lower compared to when Prevenar13 was given alone. The clinical significance of this is unknown.

5.2 Pharmacokinetic Properties

Not applicable.

5.3 Preclinical Safety Data

A repeated dose intramuscular (5 IM doses) rabbit toxicity study of pneumococcal 13-valent conjugate vaccine resulted in the generation of serotype-specific antibody responses and did not demonstrate any significant local or systemic adverse effects. In addition, there were no significant adverse findings in a single-dose IM local tolerance study in rabbits.

In single-dose subcutaneous (SC) safety pharmacology studies of pneumococcal 13-valent conjugate vaccine in rats or monkeys, there were no effects on central nervous, respiratory, or cardiovascular systems. In repeated dose (7 SC doses) toxicity studies in rats and monkeys, no significant adverse effects were observed. In addition, in a repeated dose (5 SC doses) toxicity study in juvenile rats, no significant adverse effects were observed.

A reproductive toxicity study in female rabbits shows that I.M administration of Prevenar13 prior to mating and during gestation did not affect fertility embryo/fetal development, or post-natal development

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Aluminum Phosphate IP, Sodium chloride IP, -, Succinic acid IP, Polysorbate 80 IP, Water for injection IP.

6.2 Incompatibilities

The vaccine is not to be mixed with other vaccines/products in the same syringe.

6.3 Shelf-life

36 months

6.4 Special Precautions for Storage

Store refrigerated at 2°C to 8°C.

Do not freeze. Discard if the vaccine has been frozen.

Store in original package.

Applies to pre-filled syringe only.

6.5 Nature and Contents of Container

0.5 mL suspension for Injection in pre-filled syringe (Type I glass) with a plunger rod (polypropylene) and the syringe packaging may include a hypodermic needle

6.6 Instructions for Use and Handling

Prevenar13 is a suspension containing an adjuvant. The vaccine should be shaken well to obtain a homogeneous white suspension prior to expelling air from the syringe, and should be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise.

Keep out of reach of children

Manufactured by:
John Wyeth & Brother Ltd.
New Lane, Havant,
Hampshire,
PO9 2NG, UK.

Imported and Marketed in India by:
Pfizer Limited
The Capital- A Wing,
1802, 18th Floor,
Plot No. C-70, G Block,
Bandra Kurla Complex,
Bandra (East),
Mumbai 400 051,
India.

[i] CSR-76155, Version 1.0, Interim Report: A phase 3, open-label trial evaluating the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine in healthy children aged 15 months to 17 years in the United States, 11-Dec-2009.