1. NAME OF THE MEDICINAL PRODUCT

Prevenar 13 suspension for injection
Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 mL) contains:

Pneumococcal polysaccharide serotype 1[1]	2.2 µg
Pneumococcal polysaccharide serotype 3[1]	2.2 µg
Pneumococcal polysaccharide serotype 4[1]	2.2 µg
Pneumococcal polysaccharide serotype 5[1]	2.2 µg
Pneumococcal polysaccharide serotype 6A[1]	2.2 µg
Pneumococcal polysaccharide serotype 6B[1]	4.4 µg
Pneumococcal polysaccharide serotype 7F[1]	2.2 µg
Pneumococcal polysaccharide serotype 9V[1]	2.2 µg
Pneumococcal polysaccharide serotype 14[1]	2.2 µg
Pneumococcal polysaccharide serotype 18C[1]	2.2 µg
Pneumococcal polysaccharide serotype 19A[1]	2.2 µg
Pneumococcal polysaccharide serotype 19F[1]	2.2 µg
Pneumococcal polysaccharide serotype 23F[1]	2.2 µg

[1]Conjugated to 32 µg CRM_{197} carrier protein and adsorbed on aluminium phosphate (0.125 mg aluminium).

Excipients with known effect
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
The vaccine is a homogeneous white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children 6 weeks through 17 years of age

Active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks to 17 years of age (prior to 18th birthday). See sections 4.4 and 5.1 for information on protection against specific *pneumococcal* serotypes.

The use of Prevenar 13 should be determined on the basis of official recommendations taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different geographical areas.

Adults 18 years through 49 years of age

Active immunisation for the prevention of invasive disease and pneumonia caused by *S. pneumoniae* in adults ≥18 to 49 years of age.

Adults 50 years of age and older

Active immunisation for the prevention of pneumonia and invasive disease caused by *S. pneumoniae*.

The need for re-vaccination with a subsequent dose of Prevenar 13 has not been established. For specific guidelines, please refer to local recommendations.

The use of Prevenar 13 should be determined on the basis of official recommendations taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different geographical areas.

4.2 Posology and method of administration

Method of administration

The vaccine should be given by intramuscular injection 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 (vastus lateralis muscle) in infants or the deltoid muscle of the upper arm in older children and adult. The vaccine should not be injected in the gluteal area. Do not administer Prevenar 13 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.

Data on the interchangeability of pneumococcal 7-valent conjugate vaccine or Prevenar 13 with other pneumococcal conjugate vaccines containing a protein carrier different from CRM_{197} are not available.

Pediatric population

The safety and effectiveness of Prevenar 13 in children below the age of 6 weeks have not been established.

Posology

The immunisation schedules for Prevenar 13 should be based on official recommendations.

Infants and children aged 6 weeks to 5 years

It is recommended that infants who receive a first dose of Prevenar 13 complete the vaccination course with Prevenar 13.

Infants aged 6 weeks-6 months

Three-dose primary series
The recommended immunisation series consists of four doses, each of 0.5 mL. The primary infant series consists of three doses, with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. The fourth (booster) dose is recommended between 12 and 15 months of age.

Unvaccinated children ⩾7 months of age

Infants aged 7-11 months
Two doses, each of 0.5 mL, with an interval of at least 1 month between doses. A third dose is recommended in the second year of life.

Children aged 12-23 months
Two doses, each of 0.5 mL, with an interval of at least 2 months between doses.

Children aged 2-17 years
One single dose of 0.5 mL.

Prevenar 13 schedule for preterm infants (<37 weeks gestation)

In preterm infants, the recommended immunisation series consists of 4 doses, each of 0.5 mL. The primary infant series consists of 3 doses, with the first dose given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as 6 weeks of age. The fourth (booster) dose is recommended at approximately 12 months of age.

Prevenar 13 vaccine schedule for infants and children previously vaccinated with Pneumococcal 7-valent conjugate vaccine (*S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F)

Prevenar 13 contains the same 7 serotypes contained in pneumococcal 7-valent conjugate vaccine, using the same carrier protein CRM_{197}.

Infants and children who have begun immunisation with pneumococcal 7-valent conjugate vaccine may switch to Prevenar 13 at any point in the schedule.

Young children (12-59 months) completely immunized with pneumococcal 7-valent conjugate vaccine
Young children who are considered completely immunised with pneumococcal 7-valent conjugate vaccine should receive one dose of 0.5 mL of Prevenar 13 to elicit immune responses to the 6 additional serotypes. This dose of Prevenar 13 should be administered at least 8 weeks after the final dose of pneumococcal 7-valent conjugate vaccine (see section 5.1).

Children 5-17 years

Children 5 to 17 years of age may receive a single dose of Prevenar 13 if they have been previously vaccinated with one or more doses of pneumococcal 7-valent conjugate vaccine. This dose of Prevenar 13 should be administered at least 8 weeks after the final dose of pneumococcal 7-valent conjugate vaccine (see section 5.1).

Adults ⩾18 years of age, and the elderly

Prevenar 13 is to be administered as a single dose to adults 18 years and older including those previously vaccinated with a pneumococcal polysaccharide vaccine.

The need for re-vaccination with a subsequent dose of Prevenar 13 has not been established. For specific guidelines, please refer to local recommendations.

Special populations

Individuals who may be at higher risk of pneumococcal infection (e.g., individuals with sickle cell disease or HIV infection) including those previously vaccinated with 1 or more doses of 23-valent pneumococcal polysaccharide vaccine (PPSV23) may receive at least 1 dose of Prevenar 13.

In individuals with a hematopoietic stem cell transplant (HSCT), the recommended immunisation series consists of 4 doses of Prevenar 13, each of 0.5 mL. The primary series consists of 3 doses, with the first dose given 3 to 6 months after HSCT and with an interval of at least 1 month between doses. A booster dose is recommended 6 months after the third dose (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients (see section 6.1), or to diphtheria toxoid.

As with other vaccines, the administration of Prevenar 13 should be postponed in subjects suffering from acute, severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

4.4. Special warnings and precautions for use

4.4.1 Special warnings

Prevenar 13 must not be administered intravascularly.

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 4.9).

The administration of Prevenar 13 should be postponed in subjects suffering from acute severe febrile illness.

As with any intramuscular injection, Prevenar 13 should be given with caution to infants, children or adults with thrombocytopenia or any coagulation disorder, or to those receiving anticoagulant therapy, but may be given subcutaneously if the potential benefit clearly outweighs the risks (see section 5.1).

Prevenar 13 will only protect against *S. pneumoniae* serotypes included in the vaccine, and will not protect against other microorganisms that cause invasive disease, pneumonia, or otitis media. As with any vaccine, Prevenar 13 may not protect all individuals receiving the vaccine from pneumococcal disease.

Individuals with impaired immune responsiveness, whether due to the use of immuno-suppressive therapy, a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have reduced antibody response to active immunisation.

Safety and immunogenicity data on Prevenar 13 are not available for individuals in immunocompromised groups (e.g., individuals with malignancy or nephrotic syndrome) and vaccination should be considered on an individual basis.

Infants and children aged 6 weeks to 5 years

In clinical studies, Prevenar 13 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).

The proportions of functional antibody responders (opsonophagocytic activity (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).

Limited data have demonstrated that pneumococcal 7-valent conjugate vaccine (3-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 (see section 5.1).

Children younger than 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series (see section 4.2). The use of pneumococcal conjugate vaccine does not replace the use of PPSV23 in children ≥2 years of age with conditions (such as sickle cell disease, asplenia, HIV infection, chronic illness, or those who are immunocompromised) placing them at higher risk for invasive disease due to *S. pneumoniae*. Whenever recommended, children at risk who are ≥24 months of age and already primed with Prevenar 13 should receive PPSV23. The interval between the 13-valent pneumococcal conjugate vaccine (Prevenar 13) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of PPSV23 to unprimed children or to children primed with Prevenar 13 might result in hyporesponsiveness to further doses of Prevenar 13.

The potential risk of apnea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very premature infants (born ≤30 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.

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).

When Prevenar 13 is administered concomitantly with Infanrix hexa (DTPa-HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of pneumococcal 7-valent conjugate vaccine and Infanrix hexa (see section 4.9).

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.

4.4.2 Precautions

Safety and immunogenicity data on Prevenar 13 are not available for individuals in immunocompromised groups (e.g., individuals with malignancy or nephrotic syndrome) and vaccination should be considered on an individual basis.

Infants and children aged 6 weeks to 5 years

- Limited data have demonstrated that pneumococcal 7-valent conjugate vaccine (3-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 PPSV23 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 Prevenar 13 followed by PPSV23 vaccine are not available; data on sequential vaccination with pneumococcal 7-valent conjugate vaccine followed by PPSV23 are limited.
- As with all injectable pediatric vaccines, the potential risk of apnea should be considered when administering the primary immunisation 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 withheld or delayed.
- When Prevenar 13 is administered concomitantly with Infanrix hexa (DTaP HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of pneumococcal 7-valent conjugate vaccine and Infanrix hexa (see section 4.9).

4.5 Interaction with other medicinal products and other forms of interaction

Different injectable vaccines should always be given at different vaccination sites.

Infants and children aged 6 weeks to 5 years

Prevenar 13 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 A, hepatitis B, meningococcal serogroup C, measles, mumps, rubella, varicella, and rotavirus.

Prevenar 13 can also be given concomitantly between 12-23 months of age with the tetanus toxoid conjugated meningococcal polysaccharide serogroups A, C, W and Y vaccine.

Data from a post-marketing clinical study evaluating the impact of prophylactic use of antipyretics on the immune response to Prevenar 13 suggest that concomitant administration of paracetamol may reduce the immune response to Prevenar 13 after the infant series. Responses to the booster dose administered at 12 months were unaffected. The clinical significance of this observation is unknown.

Children and adolescents 6 to 17 years of age

In children and adolescents, there are no data on the concomitant administration of Prevenar 13 with human papillomavirus vaccine (HPV), meningococcal protein conjugate vaccine (MCV4), or tetanus, diphtheria and acellular pertussis vaccine (Tdap).

Adults 18 to 49 years of age

No data are available regarding concomitant use with other vaccines.

Adults 50 years and older

Prevenar 13 can be administered concomitantly with trivalent or quadrivalent inactivated influenza vaccine (TIV or QIV) (see section 5.1).

In two studies conducted in adults aged 50-59 and 65 years and older, it was demonstrated that Prevenar 13 may be given concomitantly with TIV. The responses to all three TIV antigens were

comparable when TIV was given alone or concomitantly with Prevenar 13.

When Prevenar 13 was given concomitantly with TIV, the immune responses to Prevenar 13 were lower compared to when Prevenar 13 was given alone. The clinical significance of this is unknown.

Concomitant use with other vaccines has not been investigated.

Different injectable vaccines should always be given at different vaccination sites.

Concomitant administration of Prevenar 13 and PPSV23 has not been studied. In clinical studies when Prevenar 13 was given 1 year after PPSV23, the immune responses were lower for all serotypes compared to when Prevenar 13 was given to subjects not previously immunised with PPSV23. The clinical significance of this is unknown.

4.6 Pregnancy and lactation

Safety during pregnancy has not been established.

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

4.7 Geriatric use

Prevenar 13 has been shown to be safe and immunogenic in the geriatric population (see section 5.1).

Of the 48,806 adults in the 7 studies (6115A1-004, 6115A1-3005, 6115A1-3010, 6115A1-3000, 6115A1-3001, 6115A1-3008, 6115A1-3006) of the clinical development program who received Prevenar 13, 30,793 (63.1%) were 65-74 years of age, and 14,498 (29.7%) were 75 years of age and over. No clinically significant differences in safety or immunogenicity were observed between 65-74-year-old individuals and greater than 75-year-old individuals.

4.8 Effects on ability to drive and use machines

Prevenar 13 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.9 “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.9 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, Prevenar 13 was co-administered with routine paediatric vaccines (see section 4.5).

In a catch-up study, 354 children (7 months to 5 years of age) receiving at least one dose of Prevenar 13 were also assessed for safety.

Children and adolescents 5 to 17 years of age

Safety was evaluated in 592 healthy children and adolescents, including those with asthma who may be predisposed to pneumococcal infection. Two hundred and ninety-four (294) children aged 5 to <10 years had previously been immunised with at least one dose of pneumococcal 7-valent conjugate vaccine and 298 children aged 10 to 17 years had not previously been vaccinated with a

pneumococcal vaccine.

Additional information in special populations

Children and adolescents with sickle cell disease, HIV infection or a hematopoietic stem cell transplant had similar frequencies of adverse reactions as children and adolescents 2-17 years of age, except that headaches, vomiting, diarrhea, pyrexia, fatigue, arthralgia and myalgia were very common.

Adults ≥18 years and the elderly

Safety was assessed in 7 clinical studies including 91,593 adults ranging in ages from 18 to 101 years. Prevenar 13 was administered to 48,806 adults; 2,616 (5.4%) aged 50 to 64 years and 45,291 (92.8%) aged 65 years and older. One of the 7 studies included a group of adults (n=899) ranging from 18 to 49 years who received Prevenar 13 and who were not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Of the Prevenar 13 recipients 1,916 adults were previously vaccinated with 23-valent pneumococcal polysaccharide vaccine at least 3 years prior to study vaccination, and 46,890 were 23-valent pneumococcal polysaccharide vaccine unvaccinated.

A trend to lower frequency of adverse reactions was associated with increasing age; adults >65 years of age (regardless of prior pneumococcal vaccination status) reported fewer adverse reactions than younger adults, with adverse reactions generally most common in adults, 18-29 years of age.

Overall, the frequency categories were similar for all age groups, with the exception of vomiting which was very common (≥1/10) in adults aged 18-49 years and common (≥1/100 to <1/10) in all other age groups, and pyrexia was very common in adults aged 18-29 years and common in all other age groups. Severe vaccination-site pain/tenderness and severe limitation of arm movement was very common in adults 18-39 years and common in all other age groups.

Additional information in special populations

Adults with HIV infection had similar frequencies of adverse reactions as adults 50 years of age and older, except that fever and vomiting were very common and nausea was common.

Adults with a hematopoietic stem cell transplant have similar frequencies of adverse reactions as adults 18 years and older, except that fever and vomiting were very common.

Adverse reactions reported in clinical trials or from the post-marketing experience are listed in the following table per body system and per frequency, and this is for all age groups. The frequency is defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (≤1/10,000).

Adverse reactions from clinical trials with Prevenar 13

Infants and children aged 6 weeks to 5 years

These data are from clinical trials in which Prevenar 13 was administered simultaneously with other routine childhood vaccines.

Table 1: Adverse Reactions Table				
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**
Immune System Disorders				Hypersensitivity reaction including face edema, dyspnea, bronchospasm
Metabolism and Nutrition Disorders	Decreased appetite			
Psychiatric Disorders	Irritability		Crying	
Nervous System Disorders	Drowsiness/increased sleep; restless sleep/decreased sleep		Seizures (including febrile seizures)	Hypotonic-hyporesponsive episode
Gastrointestinal Disorders		Diarrhea; vomiting		
Skin and Subcutaneous Tissue Disorders		Rash	Urticaria or urticaria-like rash	
General Disorders and Administration Site Conditions	Fever; any vaccination-site erythema, induration/swelling or pain/tenderness; Vaccination-site erythema or induration/swelling 2.5 cm - 7.0 cm (after toddler dose and in older children [age 2 to 5 years])	Fever greater than 39°C; vaccination-site erythema or induration/swelling 2.5 cm - 7.0 cm (after infant series); vaccination-site pain/tenderness interfering with movement	Vaccination-site induration/swelling or erythema greater than 7.0 cm	

Children and adolescents aged 5-17 years

The most common adverse reactions in children and adolescents 5-17 years of age were:

Table 2: Adverse Reactions Table		
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**
Metabolism and Nutrition Disorders	Decreased appetite	
Psychiatric Disorders	Irritability	
Nervous System Disorders	Drowsiness/increased sleep, restless sleep/decreased sleep	Headache
Gastrointestinal Disorders		Diarrhea; vomiting
Skin and Subcutaneous Tissue Disorders		Rash; urticaria or urticaria-like rash
General Disorders and Administration Site Conditions	Any vaccination-site erythema, induration/swelling, or pain/tenderness, vaccination-site tenderness (including impaired movement)	Fever

Other adverse events observed in other age groups may also be applicable in this age group but due to the small sample size in this study (6096A1-3011) were not seen.

Adults ≥18 years and the elderly

Table 3: Adverse Reactions Table			
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**
Immune System Disorders			Hypersensitivity reaction including face edema, dyspnea, bronchospasm
Metabolism and Nutrition Disorders	Decreased appetite		
Nervous System Disorders	Headache		
Gastrointestinal Disorders	Diarrhea; vomiting (in adults aged 18-49 years)	Vomiting (in adults aged 50 years and over)	Nausea
Skin and Subcutaneous Tissue Disorders	Rash		
Musculoskeletal, Connective Tissue and Bone Disorders	Generalized new/aggravated joint pain; generalized new/aggravated muscle pain		
General Disorders and Administration Site Conditions	Chills; fatigue; vaccination-site erythema, vaccination-site induration/swelling; vaccination-site pain/tenderness (severe vaccination-site pain/tenderness very common in adults aged 18 to 39 years); limitation of arm movement (severe limitation of arm movements very common in adults aged 18 to 39 years)	Fever (very common in adults aged 18 to 29 years)	Lymphadenopathy localized to the region of the vaccination site

Overall, no significant differences in frequencies of adverse reactions were noted if Prevenar 13 was given to adults pre-vaccinated with PPSV23 or adults PPSV23 unvaccinated. Frequency categories for all adverse reactions of adults aged 50-64 years and adults ≥65 years of age were similar.

Solicited adverse reactions in adult studies with Prevenar 13 and TIV

The safety of concomitant administration of Prevenar 13 with TIV 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 Prevenar 13 was administered with TIV compared to Prevenar 13 administered alone.

Higher frequency in some solicited systemic reactions was observed when Prevenar 13 was administered concomitantly with TIV compared to TIV given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or Prevenar 13 given alone (headache, fatigue, chills, decreased appetite, and joint pain).

Adverse reactions from Prevenar 13 post-marketing experience

Although the following adverse drug reactions were not observed in the clinical trials, they are considered adverse drug reactions for Prevenar 13 as they were reported in the post-marketing experience.

Because these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

Table 4: Adverse Reactions Table	
System Organ Class	**Frequency Not Known (cannot be estimated from available data)***
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	Angioedema; erythema multiforme
General Disorders and Administration Site Conditions	Vaccination-site dermatitis; vaccination-site urticaria; vaccination-site pruritus; flushing
*ADR identified post-marketing.	

Apnea in very premature infants (≤30 weeks of gestation) (see section 4.4).

4.10 Overdose

Overdose with Prevenar 13 is unlikely due to its presentation as a pre-filled syringe. However, in infants and children there have been reports of overdose with Prevenar 13 defined as subsequent doses administered closer than recommended to the previous dose. In general, adverse reactions reported with overdose are consistent with those that have been reported with doses given in the recommended schedules of Prevenar 13.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pneumococcal vaccines; ATC code: J07AL02.

Mechanism of action

Prevenar 13 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 *S. pneumoniae* PSs to a T-cell-dependent antigen by covalent coupling to the immunogenic protein carrier CRM_{197} enhances the antibody

response and induces immune memory. This has been demonstrated to elicit booster responses on re-exposure in infants and young children to pneumococcal polysaccharides.

Clinical trials data on 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.

Prior to the introduction of the pneumococcal 7-valent conjugate vaccine, the incidence of invasive pneumococcal disease (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 IPD, as do individuals with asthma, diabetes mellitus, immunocompromised individuals with neutropenia, asplenia, sickle cell disease, disorders of complement and humoral immunity, human immunodeficiency virus (HIV) infection or chronic underlying disease.

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 <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 CAP) 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. 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.

Burden of disease in infants and children aged 6 weeks to 5 years

Acute otitis media (AOM) is a common childhood disease with different aetiologies. Bacteria can be responsible for 60%-70% of clinical episodes of AOM. *S. pneumoniae* is one of the most common causes of bacterial AOM worldwide. *S. pneumoniae* is also a major cause of non-invasive disease in children, particularly of acute otitis media (AOM). AOM is a common childhood disease, with more than 60% of children experiencing an episode by 1 year of age, and more than 90% of children experiencing an episode by age 5. The peak incidence of AOM is 6-18 months of age. Otitis media is less common, but occurs, in older children. 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%-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.

Prevenar 13 is estimated to cover over 90% of serotypes causing antibiotic-resistant IPD.

Burden of disease in children and adolescents aged 6 to 17 years

In children and adolescents aged 6 to 17 years, the incidence of pneumococcal disease is low, however, there is an increased risk of morbidity and mortality in those with underlying co-morbidities.

Disease Burden for Adults

S. 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. IPD is defined by the isolation of pneumococcus from a normally sterile site, such as blood, cerebrospinal fluid, pleural fluid, or peritoneal fluid. In adults, the major clinical presentations of IPD are meningitis, bacteremia, or bacteremic pneumonia. Pneumonia without bacteremia is the most common serious manifestation of non-IPD.

Burden of disease in adults aged 50 years and older

The incidence of invasive pneumococcal disease (IPD) in adults increases with age from 50 years, risk factors (smoking status or alcohol use), and underlying co-morbidities (chronic cardiovascular disease, chronic pulmonary disease including asthma, renal disorders, diabetes mellitus, and chronic liver disease including alcoholic liver disease). Bacteraemic pneumonia, bacteraemia without a focus, and meningitis are the most common manifestations of IPD in adults aged 50 years or older. Based on surveillance data, the pneumococcal serotypes in Prevenar 13 may be responsible for at least 50% - 76% (depending on country) of IPD in adults aged over 50 years. Approximately 80% of IPD in adults is bacteraemic pneumonia.

Adults older than 50 years of age, especially those older than 65 years of age, are at increased risk for developing pneumococcal infections and are more likely to develop IPD with its associated increased mortality, morbidity and complications. Additional risk factors for serious pneumococcal disease include living circumstances and underlying medical conditions which may also concern younger adults, e.g., 18 years and above. 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); malignant hematological diseases, 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. Despite advances in medical science over the last decades, there has been little change in mortality rates since penicillin’s introduction.

Pneumonia is one of the most common infectious diseases and the most common clinical presentation of pneumococcal disease in adults. *S. pneumoniae* is the most frequent cause of CAP, and is estimated to be responsible for approximately 30% of all CAP cases requiring hospitalization in adults in developed countries. The incidence of non-bacteremic pneumonia caused by *S. pneumoniae* is difficult to ascertain, because the causative pathogen is not identified in the majority of cases. 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. As for IPD, the risk of pneumococcal pneumonia increases with age from 50 years and is highest in individuals aged ≥65 years of age. Risk also increases with chronic underlying medical conditions, specifically, anatomical or functional asplenia, diabetes mellitus, asthma, chronic cardiovascular, pulmonary, kidney or liver disease, and it is highest in those who are immune-suppressed, such as those with malignant haematological diseases or HIV infection.

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 antimicrobial 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 antimicrobial resistance.

Antimicrobial 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 antimicrobial resistance, serotypes 6A, 6B, 9V, 14, 15A, 19F, 19A and 23F were most likely to demonstrate resistance to both penicillin and erythromycin.

Prevenar 13 provides an immune response against prevalent strains of *S. pneumoniae* including those most likely to cause disease, be antimicrobial resistant, and result in poor outcomes.

Table 5: Mortality and Resistance of Selected Serotypes in Adults

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

Prevenar 13 Immunogenicity Clinical Studies in Infants and Children

The protective efficacy of Prevenar 13 against IPD has not been studied. The World Health Organization (WHO) has recommended a serum anti-capsular polysaccharide antibody concentration of 0.35 µg/mL measured 1 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 3 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 3-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, including two randomized non-inferiority studies (Germany [006] and US [004]). In these two studies, the immune responses were compared using a set of non-inferiority criteria including the percentage of subjects with serum anti-polysaccharide serotype specific IgG ≥0.35 µg/mL 1 month after the primary series and the comparison of IgG geometric mean concentrations (ELISA GMC in addition, functional antibody titres (OPA) between subjects receiving Prevenar 13 and Prevenar were compared. For the six additional serotypes, these values were compared with the lowest response among all of the common serotypes in the Prevenar recipients.

The non-inferiority immune response comparisons for study 006 based on the proportion of infants achieving anti-polysaccharide IgG concentrations ≥0.35 µg/mL, are shown in Table 6 below. Results for study 004 were similar. Prevenar 13 non-inferiority (lower bound of the 95% CI for the difference in percentage of responders at 0.35 µg/mL between groups was >-10%) was demonstrated for all 7 common serotypes, except for serotype 6B in study 006 and serotypes 6B and 9V in study 004, which missed by a small margin. All seven common serotypes met pre-defined non-inferiority criteria for IgG ELISA GMCs. Prevenar 13 elicited comparable, although slightly lower, antibody levels than Prevenar for the 7 common serotypes. The clinical relevance of these differences is not known.

Non-inferiority was met for the 6 additional serotypes based on the proportion of infants achieving antibody concentrations ≥0.35 µg/mL and comparison of IgG ELISA GMCs in study 006 and was met for 5 out of the 6 serotypes, with the exception of serotype 3 for study 004. For serotype 3, the percentage of Prevenar 13 recipients with serum IgG ≥0.35 µg/mL were 98.2% (study 006) and 63.5% (study 004).

Table 6: Comparison of Subjects Achieving a Pneumococcal Anti-polysaccharide IgG Antibody Concentration ⩾0.35 µg/mL after Dose 3 of the Infant Series – Study 006

Serotypes	Prevenar 13 (N = 282-285) n (%)	7-valent Prevenar (N = 277-279) n (%)	Difference (95% CI)
7-valent Prevenar Serotypes			
4	280 (98.2)	274 (98.2)	0.0 (-2.5, 2.6)
6B	220 (77.5)	242 (87.1)	-9.6 (-16.0, -3.3)
9V	281 (98.6)	269 (96.4)	2.2 (-0.4, 5.2)
14	281 (98.9)	272 (97.5)	1.5 (-0.9, 4.1)
18C	277 (97.2)	273 (98.6)	-1.4 (-4.2, 1.2)
19F	272 (95.8)	266 (96.0)	-0.3 (-3.8, 3.3)
23F	252 (88.7)	248 (89.5)	-0.8 (-6.0, 4.5)
Additional Serotypes in Prevenar 13			
1	274 (96.1)	242 (87.1)*	9.1 (4.5, 13.9)
3	277 (98.2)	242 (87.1)	11.2 (7.0, 15.8)

Table 6: Comparison of Subjects Achieving a Pneumococcal Anti-polysaccharide IgG Antibody Concentration ⩾0.35 µg/mL after Dose 3 of the Infant Series – Study 006			
Serotypes	**Prevenar 13 (N = 282-285) n (%)**	**7-valent Prevenar (N = 277-279) n (%)**	**Difference (95% CI)**
5	264 (93.0)	242 (87.1)	5.9 (0.8, 11.1)
6A	260 (91.9)	242 (87.1)	4.8 (-0.3, 10.1)
7F	281 (98.6)	242 (87.1)	11.5 (7.4, 16.1)
19A	283 (99.3)	242 (87.1)	12.2 (8.3, 16.8)
*The serotype in Prevenar with the lowest percent response rate was 6B in study 006 (87.1%).			

Prevenar 13 elicited functional antibodies to all 13 vaccine serotypes in studies 004 and 006. For the 7 common serotypes, there were no differences between groups in the proportion of subjects with OPA titres ≥1:8. For each of the seven common serotypes, >96% and >90% of the Prevenar 13 recipients reached an OPA titre ≥1:8 one month after the primary series in studies 006 and 004, respectively. For each of the 6 additional serotypes, Prevenar 13 elicited OPA titres ≥1:8 in 91.4% to 100% of vaccines one month after the primary series in studies 004/006. The functional antibody (OPA) geometric mean titres for serotypes 1, 3 and 5 were lower than the titres for each of the other additional serotypes; the clinical relevance of this observation for protective efficacy is unknown.

The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥0.35 µg/mL 1 month after a 3-dose primary series in representative studies are presented below (Table 7).

Table 7: Percentage of Subjects with Pneumococcal Anti-capsular Polysaccharide IgG Antibody Concentrations ≥0.35 µg/mL 1 Month After the Infant Series								
Serotype	**2, 3, 4 months Germany (6096A1-006)**	**2, 3, 4 months Poland (6096A1-3000 Manufacturing)**	**2, 4, 6 months Spain (6096A1-501)**	**2, 4, 6 months US (6096A1-004)**	**2, 4, 6 months US Lot 1 (6096A1-3005)**	**2, 4, 6 months US Lot 2 (6096A1-3005)**	**2, 4, 6 months US Lot 3 (6096A1-3005)**	**2, 4, 6 months Canada (6096A1-3008)**
	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 Prevenar 13 recipients, anti-polysaccharide binding IgG antibody 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 Prevenar 13 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 Prevenar 13 to the 6 additional serotypes were quantitatively greater, for both polysaccharide-binding and opsonophagocytic antibodies, than the responses elicited by pneumococcal 7-valent conjugate vaccine.

Immune responses following a 2-dose infant primary series

The immunogenicity after 2 doses in infants has been documented in 4 studies. The proportion of infants achieving a pneumococcal anti-capsular polysaccharide IgG concentration ≥0.35 μg/mL 1 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%) for all studies using a 2-,4-month regimen, compared to 58.4% for serotype 6B and 68.6% for 23F for a study using a 3-,5-month regimen. After the booster dose, all vaccine serotypes including 6B and 23F had immune responses consistent with adequate priming with a 2-dose primary series. In a UK study, the functional antibody (OPA) responses were comparable for all serotypes including 6B and 23F in the Prevenar and Prevenar 13 arms after the primary series at two and four months of age and after the booster dose at 12 months of age. For Prevenar 13 recipients, the proportion of responders with an OPA titre ≥1:8 was at least 87% following the infant series, and at least 93% following the booster dose. The OPA geometric mean titres for serotypes 1, 3 and 5 were lower than the titres for each of the other additional serotypes; the clinical relevance of this observation is unknown. Compared to a 3-dose infant series, pneumococcal anti-capsular polysaccharide IgG GMCs were lower after a 2-dose infant series for most serotypes. The clinical effectiveness of a 2-dose primary series against AOM or pneumonia has not been established.

Booster responses following 2-dose and 3-dose primary infant series

Following the booster dose, antibody concentrations increased from the pre-booster level for all 13 serotypes. Post-booster antibody concentrations were higher for 12 serotypes than those achieved after the infant primary series. These observations are consistent with adequate priming (the induction of immunologic memory). For serotype 3, antibody concentrations following the infant primary series and booster dose were similar; the clinical relevance of this observation regarding the induction of serotype 3 immune memory is unknown.

Antibody responses to booster doses following 2-dose or 3-dose infant primary series were comparable for all 13 vaccine serotypes.

For children aged 7 months to 5 years, age appropriate catch-up immunisation schedules (as described in section 4.2) 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 3-dose primary series in infants.

Antibody persistence and immunological memory were evaluated in a study in healthy children who received a single dose of Prevenar 13 at least 2 years after they had been previously immunised with either 4 doses of Prevenar, a 3-dose infant series of Prevenar followed by Prevenar 13 at 12 months of age, or 4 doses of Prevenar 13.

The single dose of Prevenar 13, in children approximately 3.4 years of age regardless of previous vaccination history with Prevenar or Prevenar 13, induced a robust antibody response for both the 7 common serotypes and the 6 additional serotypes in Prevenar 13.

Since the introduction of 7-valent Prevenar in 2,000, pneumococcal disease surveillance data have not shown that the immunity elicited by Prevenar in infancy has waned over time.

Booster Responses to Prevenar 13 Following a 3-Dose Primary Infant Series of Pneumococcal 7-valent Conjugate Vaccine or Prevenar 13

In a randomized, double-blind, active-control study in France (6096A1-008) infants were randomly assigned to 3 groups in a 2:1:1 ratio: (1) Prevenar 13 at 2, 3, 4 and 12 months or (2) pneumococcal 7-valent conjugate vaccine at 2, 3, and 4 months followed by Prevenar 13 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 8. GMCs to the 7 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/Prevenar 13 recipients were lower than those observed with the 4-dose Prevenar 13 regimen (except for serotype 3), they were at least comparable to those of a 3-dose primary series in infants in studies (6096A1-004) and (6096A1-3005). 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 8: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) 1 Month After Vaccination

Serotype	13v/13v Post-toddler (6096A1-008) N = 233-236	7v/13v Post-toddler (6096A1-008) N = 108-113	7v/7v Post-toddler (6096A1-008) N = 111-127	13v Post-infant (6096A1-004) N = 249-252	13v Post-infant (6096A1-3005) 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

Preterm Infants (B1851037 [6096A1-4001])

Safety and immunogenicity of Prevenar 13 given at 2, 3, 4 and 12 months was assessed in 100 prematurely born infants (Estimated Gestational Age [EGA] mean, 31 weeks; range, 26 to 36 weeks) and compared with 100 infants born at term (EGA mean, 39 weeks; range, 37 to 42 weeks). More than 85% of subjects in the preterm group in the evaluable immunogenicity population achieved a pneumococcal polysaccharide IgG binding antibody concentration ≥0.35 µg/mL 1 month after the infant series for all serotypes except serotypes 5 (71.7%), 6A (82.7%), and 6B (72.7%) in the preterm group. For these 3 serotypes, the proportion of responders among preterm infants was significantly lower than among term infants. One month after the toddler dose, evidence of priming was observed as the proportion of subjects in each group in the evaluable toddler immunogenicity population achieving this same antibody concentration threshold was >97%, except for serotype 3 (70.6% in preterm infants and 79.3% in term infants). In general, serotype-specific IgG GMCs were lower for preterm infants than term infants.

During study B1851037, immune response to concomitantly administered vaccines was not assessed and therefore, data are not available from this study.

Prevenar (7-valent vaccine) protective efficacy in infants and children

The efficacy of the pneumococcal 7-valent conjugate vaccine against otitis media was assessed in 2 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 infection or symptoms suggesting 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 2 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.

The efficacy results from these trials (for invasive pneumococcal disease, pneumonia, and acute otitis media) are presented below (Table 9).

Table 9: Summary of Efficacy of 7-valent Prevenar[1]			
Test	**N**	**VE[2]**	**95% CI**
NCKP: Vaccine-serotype IPD[3]	30,258	97%	85, 100
NCKP: Clinical pneumonia with abnormal chest X-ray	23,746	35%	4, 56
NCKP: Acute Otitis Media (AOM)[4]	23,746		
Total episodes		7%	4, 10
Recurrent AOM (3 episodes in 6 months, or 4 episodes in 1 year)		9%	3, 15
Recurrent AOM (5 episodes in 6 months, or 6 episodes in 1 year)		23%	7, 36
Tympanostomy tube placement		20%	2, 35
FinOM: AOM	1,662		
Total episodes		6%	-4, 16
All pneumococcal AOM		34%	21, 45
Vaccine-serotype AOM		57%	44, 67

[1]Per protocol.
[2]Vaccine efficacy.
[3]October 1995 to April 20, 1999.
[4]October 1995 to April 30, 1998.

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-pneumococcal 7-valent conjugate 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 2006-2007 by serotype 19A, and that these non-pneumococcal 7-valent conjugate vaccine serotypes 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.

Prevenar (7-valent) effectiveness

The effectiveness (both direct and indirect effect) of 7-valent Prevenar against pneumococcal disease has been evaluated in both three-dose and two-dose primary infant series immunisation programmes, each with booster doses (Table 10). Following the widespread use of Prevenar, the incidence of IPD has been consistently and substantially reduced. An increase in the incidence of IPD cases caused by serotypes not contained in Prevenar, such as 1, 7F and 19A, has been reported in some countries. Surveillance will continue with Prevenar 13, and as countries update their surveillance data, information in this table may change.

Using the screening method, serotype specific effectiveness estimates for 2 doses under the age of 1 year in the UK were 66% (29, 91%) and 100% (25, 100%) for serotype 6B and 23F, respectively.

Table 10: Summary of Effectiveness of 7-valent Prevenar for Invasive Pneumococcal Disease			
Country (year of introduction)	**Recommended schedule**	**Disease reduction, %**	**95% CI**
UK (England & Wales)[1] (2006)	2, 4, +13 months	Vaccine serotypes: Two doses under age 1: 85%	49, 95%
USA (2000) Children <5[2] Persons ⩾65[3]	2, 4, 6, +12-15 months	 Vaccine serotypes: 98% All serotypes: 77% Vaccine serotypes: 76% All serotypes: 38%	 97, 99% 73, 79% NA NA
Canada (Quebec)[4] (2004)	2, 4, +12 months	All serotypes: 73% Vaccine serotypes: 2-dose infant series: 99% Completed schedule:100%	NA 92, 100% 82, 100%
[1]Children <2 years of age. Calculated vaccine effectiveness as of June 2008 (Broome method). [2]2005 data. [3]2004 data. [4]Children <5 years of age. January 2005 to December 2007. Complete effectiveness for routine 2+1 schedule not yet available.			

Effectiveness of Prevenar in a 3+1 schedule has also been observed against acute otitis media and pneumonia since its introduction in a national immunisation programme. In a retrospective evaluation of a large US insurance database, AOM visits were reduced by 42.7%, and prescriptions for AOM by 41.9%, in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997-99). In a similar analysis, hospitalisations and ambulatory visits for all-cause pneumonia were reduced by 52.4% and 41.1%, respectively. For those events specifically identified as pneumococcal pneumonia, the observed reductions in hospitalisations and ambulatory visits were 57.6% and 46.9%, respectively, in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997-99). While direct cause-and-effect cannot be inferred from observational analyses of this type, these findings suggest that Prevenar plays an important role in reducing the burden of mucosal disease (AOM and pneumonia) in the target population.

Previously unvaccinated older infants and children

In an open-label study of Prevenar 13 in Poland (6096A1-3002), children 7-11 months of age, 12-23 months and ≥24 months to 5 years of age (prior to the 6th birthday) who were naive to pneumococcal conjugate vaccine, were given 3, 2 or 1 dose of Prevenar 13 according to the age-appropriate schedules (see section 4.2). Serum IgG concentrations were measured 1 month after the final dose in each age group and the data are shown in Table 11.

These age appropriate catch-up immunisation 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 3-dose primary series in infants.

Table 11: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) 1 Month After Vaccination (in Study 6096A1-3002)			
Serotype	**7-11 months of age (N = 83-84)**	**12-23 months of age (N = 104-110)**	**⩾24 months to 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 6096A1-004, 6096A1-3005, and 6096A1-3008, routine pediatric vaccines were administered at the same visit as Prevenar 13. Immune responses to selected concomitant vaccine antigens were compared in infants receiving pneumococcal 7-valent conjugate vaccine and Prevenar 13. The proportion of responders at pre-specified antibody levels are shown in Table 12. Responses to all antigens in Prevenar 13 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 Prevenar 13.

Table 12: Subjects Achieving a Pre-specified Antibody Level for Concomitant Vaccine Antigens (in Study 6096A1-004, Study 6096A1-3005, and Study 6096A1-3008)

Vaccine Name/Vaccine Antigen (Pre-specified Antibody Level)	Prevenar 13 % Responders (n^a/N^b)	Pneumococcal 7-valent Conjugate Vaccine % Responders (n^a/N^b)
Pediarix (DTaP-IPV-HepB) Responses After the 3-dose Infant Series		
Dip (i0.1 IU/mL)	95.7 (223/233)	96.1 (221/230)
Tet (et1 IU/mL)	98.4 (181/184)	98.5 (193/196)
PT ⩾T.5 EU/mL	94.1 (225/239)	95.0 (228/240)
FHA ⩾HA0 EU/mL	96.7 (231/239)	95.0 (228/240)
PRN ⩾RN 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 ⩾BV5 mIU/mL	100.0 (153/153)	100.0 (173/173)
ActHIB (PRP) Responses After the Infant Series		
Hib (PRP) (ib (P µg/mL)	97.9 (232/237)	97.8 (225/230)
Hib (PRP) (ib (µg/mL)	77.6 (184/237)	78.3 (180/230)
Pentacel (DTaP-IPV-Hib) Responses After the Infant Series		
Hib (PRP) (ib (P µg/mL)	97.8 (266/272)	99.6 (265/266)
Hib (PRP) (ib (µg/mL)	81.6 (222/272)	84.6 (225/266)
PT ⩾T.6 EU/mL	98.6 (278/282)	96.0 (266/277)
FHA ⩾HA0 EU/mL	99.3 (281/283)	95.7 (266/278)
PRN ⩾RN7 EU/mL	96.8 (274/283)	96.0 (266/277)
FIM ⩾IM0 EU/mL	93.6 (264/282)	95.3 (262/275)
PedvaxHIB (PRP-OMP) Responses at 12-15 Months Following Infant Series with ActHIB		
Hib (PRP) (ib (P µg/mL)	100.0 (230/230)	100.0 (214/214)
Hib (PRP) (ib (µg/mL)	90.4 (208/230)	92.1 (197/214)
ProQuad (MMR-Varicella) Responses at 12-15 Months		
Measles (easle I.V.)	96.4 (213/221)	97.1 (204/210)
Mumps (umps(I.V.)	76.5 (169/221)	72.9 (153/210)
Rubella	91.9 (192/209)	90.7 (185/204)

Table 12: Subjects Achieving a Pre-specified Antibody Level for Concomitant Vaccine Antigens (in Study 6096A1-004, Study 6096A1-3005, and Study 6096A1-3008)		
Vaccine Name/Vaccine Antigen (Pre-specified Antibody Level)	**Prevenar 13 % Responders (n^a/N^b)**	**Pneumococcal 7-valent Conjugate Vaccine % Responders (n^a/N^b)**
(ube IU/mL)		
Varicella (arice 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.		

Additional Prevenar (7-valent) immunogenicity data: children with sickle cell disease

The immunogenicity of Prevenar has been investigated in an open-label, multicenter study in 49 infants with sickle cell disease. Children were vaccinated with Prevenar (3 doses one month apart from the age of 2 months), and 46 of these children also received a 23-valent pneumococcal polysaccharide vaccine at the age of 15-18 months. After primary immunisation, 95.6% of the subjects had antibody levels of at least 0.35 µg/mL for all seven serotypes found in Prevenar. A significant increase was seen in the concentrations of antibodies against the seven serotypes after the polysaccharide vaccination, suggesting that immunological memory was well established.

Children and adolescents 5-17 years of age

In Study 6096A1-3011 in the US, in children 5 to <10 years of age previously vaccinated with at least 1 dose of pneumococcal 7-valent conjugate vaccine, and in pneumococcal vaccine-naïve children and adolescents 10-17 years of age 1 dose of Prevenar 13 elicited immune responses to all 13 serotypes.

In children 5 to <10 years of age, serum IgG concentrations for the 7 common serotypes 1 month after administration of a single dose of Prevenar 13 vaccination (Study 6096A1-3011) were non-inferior (i.e., the lower limit of the 2-sided 95% CI for the geometric mean ratio [GMR] of >0.5) to those elicited by the fourth dose of pneumococcal 7-valent conjugate at 12-15 months of age (Study 6096A1-3005). In addition, IgG concentrations elicited by a single dose of Prevenar 13 for the 6 additional serotypes in children 5 to <10 years of age were non-inferior to those elicited by the fourth dose of Prevenar 13 at 12-15 months of age (Study 6096A1-3005) as shown in Tables 13 and 14.

Table 13: Comparison of Pneumococcal IgG GMCs (µg/mL) for the 7 Common Serotypes After a Single Dose of Prevenar 13 (Study 6096A1-3011) Relative to Pneumococcal 7-valent Conjugate Vaccine After the Fourth Dose (Study 6096A1-3005)[a]

	Vaccine Group (as Enrolled/Randomized)							
	Prevenar 13 5 to <10 Years of Age (Study 6096A1-3011)			Pneumococcal 7-valent Conjugate Vaccine 12-15 Months of Age (Study 6096A1-3005)				
Serotype	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	Ratio[e]	(95% CI[f])
Common								
4	169	8.45	(7.24, 9.87)	173	2.79	(2.45, 3.18)	3.03	(2.48, 3.71)
6B	171	53.56	(45.48, 63.07)	173	9.47	(8.26, 10.86)	5.66	(4.57, 6.99)
9V	171	9.51	(8.38, 10.78)	172	1.97	(1.77, 2.19)	4.83	(4.10, 5.70)
14	169	29.36	(24.78, 34.78)	173	8.19	(7.31, 9.18)	3.58	(2.93, 4.39)
18C	171	8.23	(7.13, 9.51)	173	2.33	(2.05, 2.65)	3.53	(2.91, 4.29)
19F	171	17.58	(14.95, 20.67)	173	3.31	(2.87, 3.81)	5.31	(4.29, 6.58)
23F	169	11.26	(9.79, 12.95)	173	4.49	(3.86, 5.23)	2.51	(2.04, 3.08)

[a] Evaluable immunogenicity population.
[b] n = Number of subjects with a determinate antibody concentration for the specified serotype.
[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMCs after the fourth dose for pneumococcal 7-valent conjugate vaccine (Study 6096A1-3005).
[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
[e] Ratio of GMCs: Prevenar 13 (Study 6096A1-3011) to pneumococcal 7-valent conjugate vaccine (Study 6096A1-3005).
[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Prevenar 13 (Study 6096A1-3011) – pneumococcal 7-valent conjugate vaccine (Study 6096A1-3005)).
Note – ClinicalTrials.gov NCT numbers are as follows: (Study 6096A1-3011) NCT00761631, (Study 6096A1-3005) NCT00444457.

Table 14: Comparison of Pneumococcal IgG GMCs (µg/mL) for Additional 6 Serotypes after A Single Dose of Prevenar 13 (Study 6096A1-3011) Relative to Prevenar 13 in Study 6096A1-3005 after Fourth Dose (in Study 6096A1-3005)[a]

	Vaccine Group (as Enrolled/Randomized)							
	Prevenar 13 (5 to <10 years) (Study 6096A1-3011)			Prevenar 13 (12-15 Months) (Study 6096A1-3005)				
Serotype	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	Ratio[e]	(95% CI[f])
Additional								
1	171	3.57	(3.05, 4.18)	1068	2.90	(2.75, 3.05)	1.23	(1.07, 1.42)
3	171	2.38	(2.07, 2.74)	1065	0.75	(0.72, 0.79)	3.17	(2.78, 3.62)
5	171	5.52	(4.82, 6.32)	1068	2.85	(2.72, 2.98)	1.94	(1.71, 2.20)
6A	169	21.51	(18.15, 25.51)	1063	7.11	(6.78, 7.46)	3.03	(2.64, 3.47)
7F	170	6.24	(5.49, 7.08)	1067	4.39	(4.18, 4.61)	1.42	(1.24, 1.62)
19A	170	17.18	(15.01, 19.67)	1056	8.44	(8.05, 8.86)	2.03	(1.78, 2.32)

[a] Evaluable immunogenicity population.
[b] n = Number of subjects with a determinate antibody concentration for the specified serotype.
[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMCs after fourth dose for Prevenar 13 (Study 6096A1-3005).
[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
[e] Ratio of GMCs: Prevenar 13 (Study 6096A1-3011) to Prevenar 13 (Study 6096A1-3005).
[f] CIs for the ratio are back transformations of a confidence interval based on the student t distribution for the mean difference of the logarithms of the measures (Prevenar 13 (Study 6096A1-3011) – Prevenar 13 (Study 6096A1-3005)).
Note – ClinicalTrials.gov NCT numbers are as follows: (Study 6096A1-3011) NCT00761631, (Study 6096A1-3005)

Table 14: Comparison of Pneumococcal IgG GMCs (µg/mL) for Additional 6 Serotypes after A Single Dose of Prevenar 13 (Study 6096A1-3011) Relative to Prevenar 13 in Study 6096A1-3005 after Fourth Dose (in Study 6096A1-3005)[a]

	Vaccine Group (as Enrolled/Randomized)							
	Prevenar 13 (5 to <10 years) (Study 6096A1-3011)			Prevenar 13 (12-15 Months) (Study 6096A1-3005)				
Serotype	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	Ratio[e]	(95% CI[f])

NCT00444457.

In children and adolescents 10 to 17 years of age OPA GMTs 1 month after vaccination were non-inferior (i.e., the lower limit of the 2-sided 95% CI for the GMR of >0.5) to OPA GMTs in the 5 to <10 year-old group for 12 of the 13 serotypes (except for serotype 3), as shown in Table 15.

Table 15: Comparison of Pneumococcal OPA GMTs After Vaccination, Prevenar 13 (10-17 years) Relative to Prevenar 13 (5 to <10 years) in Study 6096A1-3011[a]

	Vaccine Group							
	Prevenar 13 (10-17 years)			Prevenar 13 (5 to <10 years)				
Serotype	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	Ratio[e]	(95% CI[f])
Common								
4	188	6912	(6101.2, 7831.4)	181	4629	(4017.2, 5334.3)	1.5	(1.24, 1.80)
6B	183	14224	(12316.4, 16427.3)	178	14996	(13164.1, 17083.1)	0.9	(0.78, 1.15)
9V	186	4485	(4001.1, 5027.5)	180	4733	(4203.3, 5328.4)	0.9	(0.80, 1.12)
14	187	6894	(6028.3, 7884.0)	176	4759	(4120.4, 5497.0)	1.4	(1.19, 1.76)
18C	182	6263	(5436.4, 7215.1)	175	8815	(7738.2, 10041.0)	0.7	(0.59, 0.86)
19F	184	2280	(1949.4, 2667.6)	178	1559	(1293.3, 1878.9)	1.5	(1.15, 1.86)
23F	187	3808	(3354.7, 4322.6)	176	3245	(2818.8, 3735.5)	1.2	(0.97, 1.42)
Additional								
1	189	319	(271.2, 376.0)	179	187	(160.4, 218.6)	1.7	(1.36, 2.13)
3	181	114	(100.4, 129.4)	178	202	(180.9, 226.3)	0.6	(0.48, 0.67)
5	183	336	(270.3, 417.6)	178	491	(426.3, 565.3)	0.7	(0.53, 0.89)
6A	182	9928	(8457.0, 11654.8)	178	7514	(6350.8, 8890.7)	1.3	(1.05, 1.67)
7F	185	6584	(5829.4, 7435.5)	178	10334	(9099.0, 11736.8)	0.6	(0.53, 0.76)
19A	187	1276	(1131.7, 1439.0)	180	1180	(1047.5, 1329.4)	1.1	(0.91, 1.28)

[a] Evaluable immunogenicity population.
[b] n = Number of subjects with a determinate antibody titer for the specified serotype.
[c] Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
[e] Ratio of GMTs: Prevenar 13 (10-17 years) to Prevenar 13 (5 to <10 years).
[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures [Prevenar 13 (10-17 years) – Prevenar 13 (5 to <10 years)].

Prevenar 13 Effectiveness

Invasive Pneumococcal Disease

Four years after the introduction of Prevenar as a two dose primary series plus booster dose in the second year of life and with a 94% vaccine uptake a 98% (95% CI 95; 99) reduction of disease caused by the 7 vaccine serotypes was reported in England and Wales. Subsequently, four years following the switch to Prevenar 13, the additional reduction in incidence of IPD due to the 7 serotypes in Prevenar ranged from 76% in children less than 2 years of age to 91% in children 5-14 years of age. The serotype specific reductions for each of the 5 additional serotypes in Prevenar 13 (no cases of serotype 5 IPD were observed) by age group are shown in Table 16 and ranged from 68% (serotype 3) to 100% (serotype 6A) for children less than 5 years of age. Significant incidence reductions were also observed in older age groups who had not been vaccinated with Prevenar 13 (indirect effect).

Table 16: Serotype Specific Number of Cases and Incidence Reductions of IPD in 2013/14 Compared to 2008/09-2009/10 (2008/10) by Age in England and Wales

	<5 years of age			**5 to 64 years of age**			**≥65 years of age**		
	2008-10§	2013/14§	% Incidence reduction (95% CI*)	2008-10§	2013/14§	% Incidence reduction (95% CI*)	2008-10§	2013/14§	% Incidence reduction (95% CI*)
Additional serotypes covered by Prevenar 13									
1	59 (54)	5 (5)	91% (98%; 68%)**	458 (382)	77 (71)	83% (88%; 74%)**	102 (89)	13 (13)	87% (94%; 72%)**
3	26 (24)	8 (8)	68% (89%; 6%)	178 (148)	73 (68)	59% (72%; 38%)**	256 (224)	143 (146)	44% (57%; 27%)**
6A	10 (9)	0 (0)	100% (100%; 62%)**	53 (44)	5 (5)	90% (97%; 56%)**	94 (82)	5 (5)	95% (99%; 81%)**
7F	90 (82)	8 (8)	91% (97%; 74%)**	430 (361)	160 (148)	63% (71%; 50%)**	173 (152)	75 (77)	56% (70%; 37%)**
19A	85 (77)	7 (7)	91% (97%; 75%)**	225 (191)	104 (97)	54% (65%; 32%)**	279 (246)	97 (99)	65% (75%; 53%)**

§ Corrected for proportion of samples serotyped, missing age, denominator compared with 2009/10, and for the trend in total invasive pneumococcal disease up to 2009/10 (after which no trend correction was applied).

* 95% CI inflated from a Poisson interval based on over-dispersion of 2·1 seen from modelling of 2000-06 pre-Prevenar all IPD data.

** p<0·005 to cover 6A where p=0.002.

Otitis Media (OM)

In a two dose primary series plus booster dose in the second year of life the impact of Prevenar 13 on OM was documented in a population based active surveillance system in Israel with tympanocentesis culturing of middle ear fluid in children less than 2 years of age with OM. Following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently Prevenar 13 there was a decline in incidence of 96% of OM for the pneumococcal 7-valent conjugate vaccine serotypes plus serotype 6A and a decline in incidence of 85% for the additional serotypes 1, 3, 5, 7F, and 19A in Prevenar 13.

In a prospective, population-based, long-term surveillance study conducted in Israel between 2004 and 2015 following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently Prevenar 13, reductions of non-pneumococcal bacteria isolated from children <3 years of age with OM were 75% for all NTHi cases, and 81% and 62% for cases of OM due to *M. catarrhalis* and *S. pyogenes*, respectively.

Pneumonia

In a multicenter observational study in France comparing the periods before and after the switch from pneumococcal 7-valent conjugate vaccine to Prevenar 13, there was 16% reduction in all community acquired pneumonia (CAP) cases in emergency departments in children 1 month to 15 years of age. Reductions were 53% ($p<0.001$) for CAP cases with pleural effusion and 63% ($p<0.001$) for microbiologically confirmed pneumococcal CAP cases. In the second year after the introduction of Prevenar 13 the total number of CAP cases due to the 6 additional vaccine serotypes in Prevenar 13 was reduced by 74% (27 to 7 isolates).

In an ongoing surveillance system (2002 to 2013) to document the impact of pneumococcal 7-valent conjugate vaccine and subsequently Prevenar 13 on CAP in children less than 5 years in Southern Israel using a 2 dose primary series with a booster dose in the second year of life, there was a reduction of 68% (95% CI 73; 61) in outpatient visits and 32% (95% CI 39; 22) in hospitalizations for alveolar CAP following the introduction of Prevenar 13 when compared to the period before the introduction of pneumococcal 7-valent conjugate vaccine was introduced.

While direct cause-and-effect cannot be inferred from observational analyses of this type, these findings suggest that Prevenar plays an important role in reducing the burden of mucosal disease (AOM and pneumonia) in the target population.

Reduction of Antimicrobial Resistance (AMR)

Following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently Prevenar 13, a reduction in AMR has been shown as a result of direct reduction of serotypes and clones associated with AMR from the population (including 19A), reduction of transmission (herd effects), and reduction in the use of antimicrobial agents.

In a double–blind, randomized, controlled study in Israel comparing pneumococcal 7-valent conjugate vaccine and Prevenar 13 that reported the acquisition of *S. pneumoniae,* reductions of serotypes 19A, 19F, and 6A not susceptible to either penicillin, erythromycin, clindamycin, penicillin plus erythromycin, or multiple drugs (≥3 antibiotics) ranged between 34% and 62% depending on serotype and antibiotic.

Analyses of data from the United States Centers for Disease Control and Prevention evaluated temporal trends for four antibiotic classes and showed that compared to 2009 (the last year of pneumococcal 7-valent conjugate vaccine use in the US, following which it was replaced with Prevenar 13), by 2013 the annual incidence of IPD due to pneumococci non-susceptible to macrolides, cephalosporins, penicillins, and tetracyclines had decreased by 63%, 81%, 83%, and 81%

in children less than 5 years of age and 24%, 49%, 57%, and 53% in persons 65 years of age and older.

Prevenar 13 Effect on Nasopharyngeal Carriage

In a surveillance study in France in children presenting with AOM, changes in nasopharyngeal (NP) carriage of pneumococcal serotypes were evaluated following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently Prevenar 13. Prevenar 13 significantly reduced NP carriage of the 6 additional serotypes (and serotype 6C) combined and individual serotypes 6C, 7F, 19A when compared with pneumococcal 7-valent conjugate vaccine. A reduction in carriage was also seen for serotype 3 (2.5% vs. 1.1%; p = 0.1). There was no carriage of serotypes 1 or 5 observed.

The effect of pneumococcal conjugate vaccination on NP carriage was studied in a randomized double-blind study (6096A1-3006) in which infants received either Prevenar 13 or pneumococcal 7-valent conjugate vaccine at 2, 4, 6 and 12 months of age in Israel. Prevenar 13 significantly reduced newly identified NP acquisition of the 6 additional serotypes (and serotype 6C) combined and of individual serotypes 1, 6A, 6C, 7F, 19A when compared with pneumococcal 7-valent conjugate vaccine. There was no reduction seen in serotype 3 and for serotype 5 the colonization was too infrequent to assess impact. For 6 of the remaining 7 common serotypes, similar rates of NP acquisition were observed in both vaccine groups; for serotype 19F a significant reduction was observed.

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.

Efficacy of Prevenar 13 in preventing a first episode of VT pneumococcal CAP (the primary endpoint of the study) and the two secondary endpoints was demonstrated as shown in Table 17.

Table 17: Vaccine Efficacy (VE) in Primary and Secondary Endpoints of the CAPiTA Study (per protocol population)

Efficacy Endpoint	Cases			VE (%) (95.2% CI)	p-value
	Total	Prevenar 13 group	Placebo group		
Primary endpoint					
First episode of confirmed VT pneumococcal CAP	139	49	90	45.56 (21.82, 62.49)	0.0006
Secondary endpoints					
First episode of confirmed NB/NI[1] vaccine type pneumococcal CAP	93	33	60	45.00 (14.21, 65.31)	0.0067
First episode of VT-IPD[2]	35	7	28	75.00 (41.06, 90.87)	0.0005

[1]NB/NI – non-bacteraemic/non-invasive.
[2]VT-IPD – vaccine-type invasive pneumococcal disease.

The protective efficacy of Prevenar 13 against a first episode of VT pneumococcal CAP, VT NB/NI pneumococcal CAP, and VT-IPD was evident shortly after vaccination and was sustained throughout the duration of the study.

A post-hoc analysis was used to estimate the following public health outcomes against clinical CAP (as defined in the CAPiTA study, and based on clinical findings regardless of radiologic infiltrate or etiologic confirmation): vaccine efficacy, incidence rate reduction and number needed to vaccinate (Table 18):

Table 18: Public Health Outcomes Against Clinical CAP* (modified intent-to-treat population)

	Vaccine efficacy % (95% CI)	Incidence rate reduction[1] (95% CI)	Number needed to vaccinate[2]
All episodes analysis	8.1 (-0.6, 16.1)	72.2 (-5.3, 149.6)	277
First episode analysis	7.3 (-0.4, 14.4)	53.0 (-2.7, 108.7)	378

* Patients with at least 2 of the following: Cough; purulent sputum, temperature >38°C or <36.1°C; pneumonia (auscultatory findings); leukocytosis; C-reactive protein value >3 times the upper limit of normal; hypoxemia with a partial oxygen pressure <60 mm Hg while breathing room air.
[1] per 100,000 person-years of follow-up.
[2] based on a 5-year duration of protection.

Although CAPiTA was not powered to demonstrate serotype specific VE, an evaluation of clinical CAP data was performed for serotypes with at least 10 outcomes in the placebo group. VE (95% CI) for the five evaluated serotypes against first clinical CAP episodes were: serotype 1, 20.0% (-83.1% to 65.8%); serotype 3, 61.5% (17.6% to 83.4%); serotype 6A, 33.3% (-58.6% to 73.2%); serotype 7F, 73.3% (40.5% to 89.4%); and serotype 19A, 45.2% (-2.2% to 71.5%).

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.

Prevenar 13 Immunogenicity Clinical Trials in Adults

An anti-polysaccharide binding antibody IgG level to predict protection against IPD or non-bacteremic pneumonia has not been defined for adults. However, non-clinical and clinical data support functional antibody, measured by OPA assay, as a contributor to protection against pneumococcal disease. OPA 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 titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%. Pivotal trials for Prevenar 13 were designed to show that functional OPA antibody responses for the Prevenar 13 serotypes are non-inferior and for some serotypes superior to the common serotypes in the currently licensed PPSV23.

Serotype-specific OPA 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) >0.5 (2-fold criterion); statistically significantly greater responses were defined as the lower bound of the 2-sided 95% CI for the GMR >1.

The response to the additional serotype 6A, which is unique to Prevenar 13 but not in PPSV23 was assessed by demonstration of a 4-fold increase in the specific OPA titer above pre-immunization

levels. Superiority of the response for Prevenar 13 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 titer greater than zero. For comparison of OPA GMTs, a statistically greater response for serotype 6A was defined as the lower bound of the 2-sided 95% CI for the GMR >2.

Five (5) Phase 3 clinical trials (6115A1-004, 6115A1-3005, 6115A1-3010, 6115A1-3001, 6115A1-3008) were conducted in a number of European countries and in the US evaluating the immunogenicity of Prevenar 13 in different age groups, and in individuals who were either not previously vaccinated (PPSV23 unvaccinated) with PPSV23 or had received 1 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 CAP and IPD.

Two (2) pivotal non-inferiority trials were conducted in which Prevenar 13 response was compared to PPSV23 immune response, 1 in PPSV23 unvaccinated adults aged 50-64 years (6115A1-004), and 1 in PPSV23 pre-vaccinated adults aged ≥70 years (6115A1-3005). One (1) study (6115A1-3000) in PPSV23 pre-vaccinated adults collected safety data only. Two (2) studies (6115A1-3001 and 6115A1-3008) assessed the concomitant administration of Prevenar 13 with seasonal TIV.

Clinical trials conducted in adults not previously vaccinated with PPSV23

In an active-controlled modified[1] double-blind clinical trial (6115A1-004) of Prevenar 13 in the US, PPSV23-unvaccinated adults aged 60-64 years were randomly assigned (1:1) to receive Prevenar 13 or PPSV23. In addition, adults aged 18-49 years (with age sub-groups 18-29 years, 30-39 years, 40-49 years) and 50-59 years were enrolled and received 1 dose of Prevenar 13 (open-label).

The OPA antibody responses elicited by Prevenar 13 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 Prevenar 13 compared with after PPSV23.

For serotype 6A, which is unique to Prevenar 13, the proportions of adults with a 4-fold increase after Prevenar 13 (88.5%) were significantly greater than after PPSV23 (39.2%) in PPSV23-unvaccinated adults aged 60-64 years. OPA GMTs for serotype 6A were statistically significantly greater after Prevenar 13 compared with after PPSV23.

The OPA responses elicited by Prevenar 13 in adults aged 50-59 years were non-inferior to the Prevenar 13 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 Prevenar 13 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.

[11] 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.

In adults aged 60-64 years, antibody levels 1 year after vaccination were greater after Prevenar 13 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 Prevenar 13 were greater for 12 of 13 serotypes compared to vaccination with Prevenar 13 in 60-64 years old.

Table 19: OPA GMTs in PPSV23 Unvaccinated Adults Aged 50-59 Years Given Prevenar 13; and in Adults Aged 60-64 Years Given Prevenar 13 or PPSV23 (in Study 6115A1-004)[a,b]

	Prevenar 13	**Prevenar 13**	**PPSV23**	**Prevenar 13, 50-59 Relative to 60-64 Years**		**Prevenar 13 Relative to PPSV23, 60-64 Years**	
	50-59 Years N = 350-384	**60-64 Years** N = 359-404	**60-64 Years** N = 367-402				
Serotype	GMT	GMT	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 Prevenar 13 but not contained in PPSV23.
[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR greater than 0.5. Statistically significantly greater responses were defined as the lower bound of the 2-sided 95% CI for the GMR greater than 1.
[b] For serotype 6A, which is unique to Prevenar 13, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR greater than 2.

Table 20 shows OPA GMTs 1-month after vaccination in subjects 18-29 years of age, 30-39 years of age, and 40-49 years of age given a single dose of Prevenar 13. It also shows a comparison of OPA GMTs in subjects 18-49 years of age and 60-64 years of age.

Table 20: OPA GMTs in Adults Aged 18-49 Years and Adults Aged 60-64 Years (in Study 6115A1-004) Given Prevenar 13[a,b]

	18-29 Years N = 276-290	**30-39 Years N = 276-288**	**40-49 Years N = 279-290**	**18-49 Years N = 836-866**	**60-64 Years N = 359-404**	**18-49 Years Relative to 60-64 Years**	
Serotype	**GMT[b]**	**GMT[b]**	**GMT[b]**	**GMT[b]**	**GMT[b]**	**GMR**	**(95% CI[c])**
1	409	353	305	353	146	2.4	(2.03, 2.87)
3	112	93	72	91	93	1.0	(0.84, 1.13)
4	7152	4589	3229	4747	2062	2.3	(1.92, 2.76)
5	567	375	271	386	199	1.9	(1.55, 2.42)
6A	8476	6131	3626	5746	2593	2.2	(1.84, 2.67)
6B	14134	10180	6571	9813	1984	4.9	(4.13, 5.93)
7F	3741	3276	2792	3249	1120	2.9	(2.41, 3.49)
9V	5086	3208	2292	3339	1164	2.9	(2.34, 3.52)
14	4452	2919	2049	2983	612	4.9	(4.01, 5.93)
18C	5240	3841	3171	3989	1726	2.3	(1.91, 2.79)
19A	2162	1504	1209	1580	682	2.3	(2.02, 2.66)
19F	2251	1507	1076	1533	517	3.0	(2.44, 3.60)
23F	2954	1606	814	1570	375	4.2	(3.31, 5.31)

Table 20: OPA GMTs in Adults Aged 18-49 Years and Adults Aged 60-64 Years (in Study 6115A1-004) Given Prevenar 13[a,b]

Serotype	18-29 Years N = 276-290 GMT[b]	30-39 Years N = 276-288 GMT[b]	40-49 Years N = 279-290 GMT[b]	18-49 Years N = 836-866 GMT[b]	60-64 Years N = 359-404 GMT[b]	GMR	18-49 Years Relative to 60-64 Years (95% CI[c])

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.
[b] Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR greater than 1.
[c] Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures.

In adults aged 18-49 years, OPA GMTs to all 13 serotypes in Prevenar 13 were non-inferior to the Prevenar 13 responses in adults aged 60-64 years. For 12 serotypes, immune responses were related to age, with adults aged 18-49 years showing statistically significantly greater responses than adults aged 60-64 years. Similarly, statistically significantly greater responses for 12 serotypes were observed for adults in age subgroups 18-29 years, 30-39 years and 40-49 years compared with adults aged 60-64 years. OPA GMTs were highest in adults aged 18-29 years and lowest in adults aged 60-64 years.

One (1) year after vaccination with Prevenar 13, OPA titers had declined compared to titers measured 1 month after vaccination ranging from 23 to 2948; however, OPA titers for all serotypes remained higher than levels measured at baseline ranging from 5 to 186.

Immune responses in special populations

Individuals with the conditions described below have an increased risk of pneumococcal disease.

Sickle cell disease

An open-label single-arm study (6096A1-3014 [B1851013]) with 2 doses of Prevenar 13 given 6 months apart was conducted in 158 children and adolescents ≥6 to <18 years of age with sickle cell disease who were previously vaccinated with 1 or more doses of PPSV23 at least 6 months prior to enrollment. After the first vaccination, Prevenar 13 elicited antibody levels measured by both IgG GMCs and OPA GMTs that were statistically significant higher when compared to levels prior to vaccination. After the second dose immune responses were comparable to the ones after the first dose. One (1) year after the second dose, antibody levels measured by both IgG GMCs and OPA GMTs were higher than levels prior to the first dose of Prevenar 13, except the IgG GMC for serotype 3 that was similar.

Additional pneumococcal 7-valent conjugate vaccine immunogenicity data: children with sickle cell disease

The immunogenicity of pneumococcal 7-valent conjugate vaccine has been investigated in an open-label, multicenter study (0887X1-100722) in 49 infants with sickle cell disease. Children were vaccinated with pneumococcal 7-valent conjugate vaccine (3 doses 1 month apart from the age of 2 months), and 46 of these children also received a PPSV23 at the age of 15-18 months. After primary immunisation, 95.6% of the subjects had antibody levels of >0.35 μg/mL for all 7 serotypes found in pneumococcal 7-valent conjugate vaccine. A significant increase was seen in the concentrations of antibodies against the 7 serotypes after PPSV23, suggesting that immunological memory was well established.

HIV infection

Children and adults not previously vaccinated with a pneumococcal vaccine

In study 6115A1-3002 (B1851021), HIV-infected children and adults (CD4 ≥200 cells/µL, viral load <50,000 copies/mL and free of active AIDS-related illness) not previously vaccinated with a pneumococcal vaccine received 3 doses of Prevenar 13. As per general recommendations, a single dose of PPSV23 was subsequently administered. Vaccines were administered at 1 month intervals. Immune responses were assessed in 259-270 evaluable subjects approximately 1 month after each dose of vaccine. After the first dose, Prevenar 13 elicited antibody levels, measured by both IgG GMCs and OPA GMTs that were statistically significantly higher when compared to levels prior to vaccination. After the second and third dose of Prevenar 13, immune responses were similar or higher than those after the first dose.

Adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine

In study 6115A1-3017 (B1851028), immune responses were assessed in 329 HIV-infected adults ≥18 years of age (CD4+ T-cell count ≥200 cells/µL and viral load <50,000 copies/mL) previously vaccinated with PPSV23 administered at least 6 months prior to enrollment. Subjects received 3 doses of Prevenar 13, at enrollment, 6 months and 12 months after the first dose of Prevenar 13. After the first vaccination, Prevenar 13 elicited antibody levels measured by both IgG GMCs and OPA GMTs that were statistically significant higher when compared to levels prior to vaccination. After the second and third dose of Prevenar 13, immune responses were comparable or higher than those after the first dose. Subjects who received two or more previous doses of PPSV23 showed a similar immune response compared with subjects who received a single previous dose.

Hematopoietic stem cell transplant

In study 6115A1-3003 (B1851022), children and adults with an allogeneic HSCT at ≥2 years of age received 3 doses of Prevenar 13 with an interval of at least 1 month between doses. The first dose was administered at 3 to 6 months after HSCT. A fourth (booster) dose of Prevenar 13 was administered 6 months after the third dose. As per general recommendations, a single dose of PPSV23 was administered 1 month after the fourth dose of Prevenar 13. Immune responses as measured by IgG GMCs were assessed in 168-211 evaluable subjects approximately 1 month after vaccination. Prevenar 13 elicited increased antibody levels after each dose of Prevenar 13. Immune responses after the fourth dose of Prevenar 13 were significantly increased for all serotypes compared with after the third dose.

Clinical trials conducted in adults previously vaccinated with PPSV23 (pre-vaccinated)

In a Phase 3 active-controlled, modified[2] double-blind clinical trial (6115A1-3005) of Prevenar 13 in the US and Sweden, PPSV23 pre-vaccinated adults aged ≥70 years who had received 1 dose of PPSV23 ≥5 years prior were randomly assigned (1:1) to receive either Prevenar 13 or PPSV23.

The OPA antibody responses elicited by Prevenar 13 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 Prevenar 13 compared with after PPSV23.

For serotype 6A, which is unique to Prevenar 13, proportions of adults with a 4-fold increase after Prevenar 13 (71.1%) was significantly greater than after PPSV23 (27.3%) in PPSV23-pre-vaccinated adults aged ≥70 years. OPA GMTs for serotype 6A were statistically significantly greater after Prevenar 13 compared with after PPSV23.

[2] 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.

This clinical trial demonstrated that in adults aged ≥70 years and pre-vaccinated with PPSV23 ≥5 years prior, vaccination with Prevenar 13 shows an improved immune response as compared to re-vaccination with PPSV23.

Table 21: OPA GMTs in PPSV23 Previously Vaccinated Adults Aged ≥70 Years (in Study 6115A1-3005) Given Prevenar 13 or PPSV23[a,b]

Serotype	Prevenar 13 N=400-426 GMT	PPSV23 N=395-445 GMT	Prevenar 13 Relative to PPSV23	
			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 Prevenar 13 but not contained in PPSV23.
[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR greater than 0.5. Statistically significantly greater responses defined as the lower bound of the 2-sided 95% CI for the GMR greater than 1.
[b] For serotype 6A, which is unique to Prevenar 13, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR greater than 2.

Clinical trials to assess Prevenar 13 given with seasonal TIV in adults

Two (2) randomized, double-blind clinical trials (6115A1-3001 and 6115A1-3008) evaluated the immunogenicity of Prevenar 13 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 Prevenar 13 and TIV (administered in opposite arms) with [1] TIV given with placebo and [2] with Prevenar 13 given alone. Group 1 received Prevenar 13 given with TIV, followed 1 month later by placebo; Group 2 received TIV given with placebo, followed 1 month later by Prevenar 13.

A Phase 3 randomized, double-blind clinical trial (6115A1-3001) of Prevenar 13 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 Prevenar 13 compared with TIV given with placebo (in the following called TIV alone).

A Phase 3 randomized, double-blind clinical trial (6115A1-3008) of Prevenar 13 given with TIV to adults aged ≥65 years who were PPSV23 unvaccinated in Europe assessed the immune responses of TIV when TIV was given with Prevenar 13 compared with TIV given with placebo.

Immune responses elicited by TIV were measured by haemagglutination inhibition (HAI) assays 1 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 Prevenar 13 when Prevenar 13 was given with TIV compared with Prevenar 13 given alone. The immune responses elicited by Prevenar 13 were

measured by ELISA IgG GMC 1 month after Prevenar 13 vaccination. The non-inferiority criterion was achieved if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (Prevenar 13 and TIV relative to Prevenar 13 alone) was >0.5 (2-fold criterion).

TIV immune responses 50-59 years of age: The immune responses were similar after Prevenar 13 given concomitantly with TIV compared to TIV alone. Non-inferiority was met for all 3 TIV strains after Prevenar 13 given concomitantly with TIV compared to TIV alone (Table 22).

TIV immune responses in ≥65 years of age: The immune responses were similar after Prevenar 13 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 23).

Table 22: Proportion of Participants Aged 50–59 Years with a ≥4-Fold Increase in HAI Titer After TIV with Prevenar 13 and TIV with Placebo (in Study 6115A1-3001)

TIV HAI	TIV + Prevenar 13		TIV + Placebo		Difference
	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 23: Proportion of Participants Aged ≥65 Years with a ≥4-Fold Increase in HAI Titer After TIV with Prevenar 13 and TIV with Placebo (in Study 6115A1-3008)

TIV HAI	TIV + Prevenar 13		TIV + Placebo		Difference
	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)

Prevenar 13 immune responses in 50-59 years old: Non-inferiority was met for all serotypes (Table 24).

Table 24: Pneumococcal IgG GMC 1 Month After Prevenar 13 and TIV; and 1 Month After Prevenar 13 (Given 1 Month After Placebo and TIV) for Participants 50-59 Years (in Study 6115A1-3001)[a,b]

	Post-dose 1 Prevenar 13 + TIV (N = 247-294)	Post-dose 2 Prevenar 13* (N = 247-289)	Vaccine Comparison
Serotype	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 (Prevenar 13 and TIV relative to Prevenar 13 alone) was >0.5 (2-fold criterion).

Prevenar 13 immune responses in ≥65 years old: 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 25).

Table 25: Pneumococcal IgG GMC 1 Month After Prevenar 13 and TIV; and 1 Month After Prevenar 13 (Given 1 Month After Placebo and TIV) for Participants ≥65 Years (in Study 6115A1-3008)[a,b]

	Post-dose 1 Prevenar 13 + TIV (N = 247-294)	**Post-dose 2 Prevenar 13*** (N = 247-289)	**Vaccine Comparison**
Serotype	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 (Prevenar 13 and TIV relative to Prevenar 13 alone) was >0.5 (2-fold criterion).

Prevenar 13 may be administered concomitantly with seasonal TIV.

When Prevenar 13 was given concomitantly with TIV, the immune responses to TIV were similar to the responses when TIV was given alone.

When Prevenar 13 was given concomitantly with TIV, the immune responses to Prevenar 13 were lower compared to when Prevenar 13 was given alone. The clinical significance of this is unknown.

Clinical trial to assess Prevenar 13 given with seasonal QIV in adults

A randomized, double-blind post-marketing study evaluated the immunogenicity of Prevenar 13 given with inactivated QIV (Fall 2014/Spring 2015 Fluzone, A/H1N1, A/H3N2, B/Brisbane, and B/Massachusetts strains) in PPSV23 previously vaccinated adults aged ≥50 years conducted in the US. One group received Prevenar 13 and QIV concurrently, followed approximately 1 month later by placebo. The other group received QIV and placebo concurrently, followed approximately 1 month later by Prevenar 13.

The antibody responses elicited by Prevenar 13 were measured as OPA GMTs 1 month after Prevenar 13 vaccination. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI for the

OPA GMT ratios (Prevenar 13 + QIV relative to Prevenar 13 alone) was >0.5. Prevenar 13 mcOPA antibody responses met non-inferiority for all 13 serotypes after Prevenar 13 was given concomitantly with QIV compared to Prevenar 13 given alone (Table 26).

Table 26: Pneumococcal OPA GMTs 1 Month After Prevenar 13 and QIV and 1 Month After Prevenar 13 (Given 1 Month After Placebo and QIV)

	Prevenar 13 + QIV (n^a=412-425)	**Prevenar 13** (n^a=405-419)	**Vaccine Comparison**
Serotype	GMT[b]	GMT[b]	Ratio[c] (95% CI[d])
1	75	83	0.9 (0.74, 1.12)
3	41	49	0.8 (0.70, 0.98)
4	587	824	0.7 (0.55, 0.91)
5	97	101	1.0 (0.78, 1.18)
6A	953	1413	0.7 (0.53, 0.85)
6B	867	1041	0.8 (0.64, 1.08)
7F	651	670	1.0 (0.83, 1.14)
9V	699	838	0.8 (0.69, 1.00)
14	574	760	0.8 (0.62, 0.92)
18C	713	865	0.8 (0.64, 1.06)
19A	337	390	0.9 (0.72, 1.04)
19F	324	360	0.9 (0.71, 1.14)
23F	278	364	0.8 (0.56, 1.03)

Abbreviations: GMT = geometric mean titer; OPA = opsonophagocytic activity.
a. n = Number of subjects with a determinate OPA titer to the given serotype.
b. GMTs were calculated using all subjects with available data for the specified blood draw.
c. Ratio of GMTs (Prevenar 13+QIV/placebo to placebo+QIV/Prevenar 13) was calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.
d. CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (Prevenar 13+QIV/placebo – placebo+QIV/Prevenar 13).

Antibody responses elicited by QIV were measured by HAI 1 month after QIV vaccination. The immune responses were measured as HAI GMTs for each QIV strain 1 month after vaccination. Non-inferiority was demonstrated for each vaccine antigen if the lower limit of the 2-sided 95% CI for the GMT ratio of the HAI titer was >0.5. Non-inferiority was demonstrated for each of the 4 QIV strains after Prevenar 13 was given concomitantly with QIV compared with QIV given alone (Table 27).

Table 27: HAI GMTs 1 Month After Prevenar 13 With QIV and Placebo With QIV

	Prevenar 13 +QIV n^a=427	**Placebo+QIV n^a=430**	**Vaccine Comparison**	
Strain	**GMT[b]**	**GMT[b]**	**Ratio[c]**	**(95% CI[d])**
A/H1N1	115	113	1.0	(0.88, 1.18)
A/H3N2	226	196	1.2	(1.01, 1.32)
B/Brisbane	28	26	1.1	(0.95, 1.24)
B/Massachusetts	45	43	1.0	(0.90, 1.21)

Abbreviations: GMT = geometric mean titer; HAI = hemagglutination inhibition assay.
a. n = Number of subjects with a determinate HAI titer to the given strain.
b. GMTs were calculated using all subjects with available data for the specified blood draw.
c. Ratio of GMTs (Prevenar 13+QIV/placebo to placebo+QIV/Prevenar 13) was calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.
d. CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (Prevenar 13+QIV/placebo – placebo+QIV/Prevenar 13).

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not available for vaccines.

5.3 Preclinical safety data

A repeated-dose intramuscular (5 IM doses) rabbit toxicity study of Prevenar 13 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 Prevenar 13 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 showed that IM administration of Prevenar 13 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

Sodium chloride
Succinic acid
Polysorbate 80
Water for injections

For adjuvant, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

Refer to the outer packaging

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C).
Do not freeze.

Prevenar 13 has been shown to be stable at temperatures of up to 25°C for 4 days. These data are not recommendations for shipping or storage, but may guide decisions for use in case of temporary temperature excursions.

6.5 Nature and contents of container

0.5 mL suspension for injection in pre-filled syringe (Type I glass) with a plunger stopper (latex-free chlorobutyl rubber) and protective-tip cap (latex-free isoprene bromobutyl rubber).

Pack size of 1 pre-filled syringe with needle.

6.6 Special precautions for disposal

During storage, a white deposit and clear supernatant can be observed.

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.

No special requirements for disposal.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York, USA

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