SCHEDULING STATUS: **S2**

1. NAME OF THE MEDICINE

PREVENAR 20 suspension for injection in pre-filled syringe [pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0,5 mL) contains:

Pneumococcal polysaccharide serotype 1[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 3[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 4[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 5[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 6A[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 6B[1,2]	4,4 µg
Pneumococcal polysaccharide serotype 7F[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 8[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 9V[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 10A[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 11A[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 12F[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 14[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 15B[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 18C[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 19A[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 19F[1,2]	2,2 µg
Pneumococcal polysaccharide serotype 22F[1,2]	2,2 µg

Pneumococcal polysaccharide serotype 23F[1,2] 2,2 µg

Pneumococcal polysaccharide serotype 33F[1,2] 2,2 µg

[1]Conjugated to diptheria CRM_{197} carrier protein (approximately 51 µg per dose)

[2]Adsorbed on aluminium phosphate (0,125 mg aluminium per dose)

PREVENAR 20 is sugar-free.

For the 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

Active immunisation for the prevention of pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in individuals from 6 weeks of age and older.

PREVENAR 20 may not prevent disease caused by *S. pneumoniae* serotypes that are not contained in the vaccine

PREVENAR 20 should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology

The safety and efficacy of PREVENAR 20 in infants below 6 weeks of age have not been established. No data are available.

Infants and children 6 weeks to less than 5 years of age

It is recommended that infants who receive a first dose of PREVENAR 20 complete the vaccination course with PREVENAR 20.

Vaccination schedule in infants and children 6 weeks to 15 months of age	
3-dose series (two-dose primary series followed by a booster dose)	The recommended immunisation series for PREVENAR 20, given as part of a routine infant immunisation program, consists of three doses, each of 0,5 mL. The first dose is usually given at 2 months of age, with a second dose 2 months later. The first dose may be given as early as 6 weeks of age. The third (booster) dose is recommended between 11 and 15 months of age (see section 5.1).
4-dose series (three-dose primary series followed by a booster dose)	PREVENAR 20 may be given as a 4-dose series, 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 4 weeks between doses. The first dose may be given as early as 6 weeks of age. The fourth (booster) dose is recommended between 11 and 15 months of age (see section 5.1).
Preterm infants (less than 37 weeks of gestation)[a]	The recommended immunisation series for PREVENAR 20 consists of four doses, each of 0,5 mL. The primary infant series consists of three doses, with the first dose given at 2 months of age and with an interval of at least 4 weeks between doses. The first dose may be given as early as 6 weeks of age. The fourth (booster) dose is recommended between 11 and 15 months of age (see sections 4.4 and 5.1).

Vaccination schedule for infants and children less than 15 months of age transitioning from another pneumococcal conjugate vaccine[b]	
Prior vaccination with another pneumococcal conjugate vaccine	Infants and children who have begun immunisation with another pneumococcal conjugate vaccine may complete immunisation by transitioning to PREVENAR 20 at any point in the schedule.
Catch-up vaccination schedule for infants and children 7 months to less than 18 years of age	
Unvaccinated infants 7 to less than 12 months of age[a]	Two doses, each of 0,5 mL, with an interval of at least 4 weeks between doses. A third dose is recommended in the second year of life.
Unvaccinated children 12 to less than 24 months of age[a]	Two doses, each of 0,5 mL, with an interval of at least 8 weeks between doses.
Unvaccinated children 2 to less than 5 years of age[a]	One single dose of 0,5 mL.
Children 15 months to less than 5 years of age previously vaccinated with a pneumococcal conjugate vaccine	One single dose (0,5 mL). If a previous pneumococcal conjugate vaccine was administered, at least 8 weeks should elapse before administering PREVENAR 20 (see section 5.1).
Children 5 to less than 18 years of age regardless of prior pneumococcal conjugate vaccination	One single dose (0,5 mL). If a previous pneumococcal conjugate vaccine was administered, at least 8 weeks should elapse before administering PREVENAR 20 (see section 5.1).

Vaccination schedule for individuals 18 years of age and older

Individuals 18 years of age and older	PREVENAR 20 is to be administered as a single dose to individuals 18 years of age and older. The need for revaccination with a subsequent dose of PREVENAR 20 has not been established. No data on sequential vaccination with other pneumococcal vaccines or a booster dose are available for PREVENAR 20. Based on the clinical experience with Prevenar 13 (a pneumococcal conjugate vaccine consisting of 13 polysaccharide conjugates that are also in PREVENAR 20), if the use of 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23 [PPSV23]) is considered appropriate, PREVENAR 20 should be given first (see section 5.1).

[a]. In preterm and unvaccinated infants and children 7 months to less than 5 years of age, PREVENAR 20 is expected to perform similarly to Prevenar 13, a pneumococcal conjugate vaccine consisting of 13 polysaccharide conjugates that are also in PREVENAR 20.

[b]. The safety and immunogenicity of PREVENAR 20 administered to infants and children less than 15 months of age who have begun vaccination with another pneumococcal conjugate vaccine have not been established. However, safety and immunogenicity studies with a transition from a lower valent to higher valent pneumococcal conjugate vaccine are relevant to PREVENAR 20. Based on clinical experience and relevant randomised controlled trials, the recommended transition from a lower to a higher valent pneumococcal conjugate vaccine may be considered in guiding vaccination with PREVENAR 20 for infants and children who have not yet completed the infant vaccination series.

Special populations

There are no data with PREVENAR 20 in special populations.

However, safety and immunogenicity studies of Prevenar 13 have been conducted in adults and children at higher risk of pneumococcal infection including immunocompromised adults and children with human immunodeficiency virus (HIV) infection or haematopoietic stem cell transplant (HSCT), and children with sickle cell disease (SCD); these are relevant to PREVENAR 20, since the vaccines are manufactured and formulated similarly and contain 13 of the same polysaccharide conjugates.

Individuals at higher risk of pneumococcal infection, including those previously vaccinated with 1 or more doses of PPSV23, were recommended to receive at least 1 dose of Prevenar 13.

In individuals with a HSCT, the recommended immunisation series with Prevenar 13 consisted of 4 doses of 0,5 mL each. The primary series consisted of 3 doses, with the first dose given 3 to 6 months after HSCT and with an interval of at least 4 weeks between doses. A booster dose was recommended 6 months after the third dose (see section 5.1).

The recommended dosing of Prevenar 13 may be considered in guiding vaccination with PREVENAR 20 in high-risk populations. For immune responses to pneumococcal vaccines in immunocompromised individuals, see section 4.4. The use of PREVENAR 20 in special populations should be guided by official recommendations.

Method of administration

For intramuscular injection only.

Each vaccine is for single use in one patient only. Discard any residue.

PREVENAR 20 should be administered as soon as possible after being removed from refrigeration.

The dose (0,5 mL) of PREVENAR 20 should be administered intramuscularly preferably in the anterolateral aspect of the thigh (vastus lateralis muscle) in infants or the deltoid muscle of the upper arm in children and adults, with care to avoid injection into or near nerves and blood vessels. The vaccine should not be injected in the gluteal area. Do not inject PREVENAR 20 intravascularly.

For instructions on the preparation of the vaccine for administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section 6.1, or to diphtheria toxoid.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicines, the name and the batch number of the administered vaccine should be clearly recorded.

Hypersensitivity

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

Concurrent illness

Vaccination should be postponed in individuals 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.

Thrombocytopenia and coagulation disorders

The vaccine must be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration.

The risk of bleeding in patients with coagulation disorders needs to be carefully evaluated before intramuscular administration of any vaccine, and subcutaneous administration should be considered if the potential benefit clearly outweighs the risks.

Protection against pneumococcal disease

PREVENAR 20 may only protect against *Streptococcus pneumoniae* serotypes included in the vaccine and will not protect against other microorganisms that cause invasive disease, pneumonia or otitis media (OM). As with any vaccine, PREVENAR 20 may not protect all individuals receiving the vaccine from pneumococcal invasive disease, pneumonia or OM.

Immunocompromised individuals

Safety and immunogenicity data on PREVENAR 20 are not available for individuals in immunocompromised groups and vaccination should be considered on an individual basis.

Based on experience with pneumococcal vaccines, some individuals with altered immunocompetence may have reduced immune responses to PREVENAR 20.

Individuals with impaired immune response, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation. The clinical relevance of this is unknown.

Safety and immunogenicity data with Prevenar 13 are available for a limited number of individuals with HIV infection, SCD or with a HSCT (see sections 4.8 and 5.1).

In adults across all studied age groups, formal noninferiority criteria were met although numerically lower geometric mean titres (GMTs) were observed with PREVENAR 20 for most of the serotypes compared to

Prevenar 13 (see section 5.1) however the clinical relevance of this observation for immunocompromised individuals is unknown.

Paediatric population

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

Use in the elderly

No dose adjustment or special precautions are applicable to use in the elderly

Of the 4 263 adults in the 3 studies (B7471006, B7471007, B7471008) of the clinical development program who received PREVENAR 20, 668 (15,7 %) were 65 through 69 years of age, 398 (9,3 %) were 70 through 79 years of age, and 72 (1,7 %) were 80 years of age and older. PREVENAR 20 has been shown to be safe and immunogenic in the geriatric population regardless of prior pneumococcal vaccination (see Section 5.1 Pharmacodynamic properties).

Effects on laboratory tests

No data available.

Excipient

PREVENAR 20 contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

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

Do not mix PREVENAR 20 with other vaccines/medicines in the same syringe.

Paediatric population

In infants and children 6 weeks to less than 5 years of age, PREVENAR 20 can be administered concomitantly with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular pertussis, hepatitis B, *Haemophilus influenzae* type b, inactivated poliomyelitis, measles, mumps, rubella, and varicella vaccines. PREVENAR 20 has been safely administered with influenza and rotavirus vaccines.

Individuals 18 years of age and older

PREVENAR 20 may be administered concomitantly with influenza vaccine, adjuvanted (Fluad Quadrivalent [QIV]) and COVID-19 mRNA vaccine (Comirnaty [tozinameran]) (see Section 5.1).

It has been demonstrated in adults 50 years of age and older that Prevenar 13 may be administered concomitantly with the seasonal trivalent or quadrivalent inactivated influenza vaccine (TIV or QIV) with no interference with the immune responses to TIV or QIV. Safety and immunogenicity of Prevenar 13 are relevant to PREVENAR 20, since the vaccines are manufactured similarly and contain 13 of the same polysaccharide conjugates.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of PREVENAR 20 in pregnant women.

In an animal study where, female rabbits were administered the human dose (0,5 mL) of the vaccine intramuscularly 17 and 3 days prior to mating, and on gestation days 10 and 24, there were no effects on pregnancy, parturition, foetal abnormalities, or pup survival and growth. Serotype-specific antibodies against each of the 20 vaccine serotypes were detected in does, foetuses and pups.

Administration of PREVENAR 20 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breastfeeding

It is unknown whether PREVENAR 20 is excreted in human milk.

Fertility

No human data on the effect of PREVENAR 20 on fertility are available. PREVENAR 20 showed no adverse effects on mating or fertility in a combined fertility, embryofoetal development and pre/postnatal study in which female rabbits were administered the human dose (0,5 mL) of the vaccine intramuscularly 17 and 3 days prior to mating, and on gestation days 10 and 24.

4.7 Effects on ability to drive and use machines

PREVENAR 20 has no, or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Paediatric population

The safety of PREVENAR 20 was evaluated in 5 987 participants 6 weeks of age to less than 18 years of age in four randomised double-blind, active-controlled, clinical trials and one single-arm clinical trial (one Phase 2 and four Phase 3);

3 664 participants received at least 1 dose of PREVENAR 20 and 2 323 participants received Prevenar 13 (control vaccine).

Participants 6 weeks to less than 15 months of age

Clinical trials were conducted in healthy infants 6 weeks to less than 15 months of age using a 3-dose schedule (Phase 3 trial B7471012 [Study 1012]) or a 4-dose schedule (Phase 3 trials B7471011 and B7471013 [Study 1011 and 1013,] and the Phase 2 trial B7471003 [Study 1003]). In these infant trials, 5 156 participants received at least 1 dose of vaccine: 2 833 received PREVENAR 20 and 2 323 received Prevenar 13. Overall, approximately 90 % of participants in each group received all doses through the study-specified toddler dose. In all studies, local reactions and systemic events were collected after each dose and adverse events (AEs) were collected from the first dose through 1 month after the last infant vaccination and from the toddler dose through 1 month after the toddler dose in all studies. Serious adverse events were evaluated through 1 month after the last dose in Study 1012 and 6 months after the last dose in studies 1011, 1013 and 1003.

PREVENAR 20 was well tolerated when administered in a 3-dose and a 4-dose series, in the infant study populations with low rates of severe local reactions and systemic events, and most reactions resolving within 1 to 3 days. The percentages of participants with local reactions and systemic events after PREVENAR 20 were generally similar to those after Prevenar 13. Based on the infant data, the most frequently reported local reactions and systemic events after any dose of PREVENAR 20 were irritability, drowsiness, and pain at injection site. In these studies, PREVENAR 20 was co-administered or permitted to be administered with certain routine paediatric vaccines (see section 4.5).

Study 1012 was a pivotal, double-blind, randomised, active-controlled Phase 3 trial, in which 601 healthy infants, 2 months (≥ 42 to ≤ 112 days) of age and born at > 36 weeks of gestation received PREVENAR 20 in a 3-dose series. The most frequently reported adverse reactions (> 10 %) after any dose of PREVENAR 20 were irritability (71,0 % to 71,9 %), drowsiness/increased sleep (50,9 % to 61,2 %), pain at injection site (22,8 % to 42,4 %), decreased appetite (24,7 % to 39,3 %), redness at the injection site (25,3 % to 36,9 %), swelling at the injection site (21,4 % to 29,8 %), and fever ≥ 38,0℃ (8,9 % to 24,3 %). Most adverse reactions occurred within 1 to 2 days following vaccination and were mild or moderate in severity and of short duration (1 to 2 days).

Studies 1011, 1013 and 1003, were double-blind, randomised, active-controlled trials that included 2 232 healthy infants, vaccinated with PREVENAR 20 in a 4-dose series. The most frequently reported adverse reactions (> 10 %) observed after any dose of PREVENAR 20 in infants were irritability (58,5 % to 70,6 %), drowsiness/increased sleep (37,7 % to 66,2 %), pain at injection site (32,8 % to 45,5 %), decreased appetite (23,0 % to 26,4 %), redness at the injection site (22,6 % to 24,5 %) and swelling at the injection site (15,1 % to 17,6 %). Most adverse reactions were mild or moderate following vaccination and severe reactions were reported infrequently. In Study 1013, the local reactions and systemic events in the preterm subgroup (111 infants born at 34 to less than 37 weeks of gestation) were similar to or lower than the term infants in the study. In the preterm subgroup the frequency of any reported local reaction (31,7 % to 55,3 % in the PREVENAR 20 group and 37,9 % to 47,1 % in the Prevenar 13 group) and systemic event (65,0 % to 85,5 % in the PREVENAR 20 group and 59,4 % to 77,4 % in the Prevenar 13 group).

The frequency and severity of the adverse reactions in all infant clinical trials were generally similar in the PREVENAR 20 and Prevenar 13 groups.

Participants aged 15 months to less than 18 years of age

In the Phase 3 trial B7471014 (Study 1014), 831 participants 15 months to less than 18 years of age received a single dose of PREVENAR 20 in four age groups (209 participants 15 to less than 24 months of age; 216 participants 2 years to less than 5 years of age; 201 participants 5 years to less than 10 years age; and 205 participants 10 years to less than 18 years of age). The participants less than 5 years of age had received at least 3 prior doses of Prevenar 13.

The most frequently reported adverse reactions (> 10 %) observed after any dose of PREVENAR 20 in participants less than 2 years of age were irritability (61,8 %), pain at the injection site (52,5 %), drowsiness/increased sleep (41,7 %), redness at the injection site (37,7 %), decreased appetite (25,0 %), swelling at the injection site (22,1 %) and fever ≥ 38,0 °C (11,8 %). In participants aged 2 years and older, the most frequently reported adverse reactions were pain at the injection site (66,0 % to 82,9 %), muscle

pain (26,5 % to 48,3 %), redness at the injection site (15,1 % to 39,1 %), fatigue (27,8 % to 37,2 %), headache (5,6 % to 29,3 %), and swelling at the injection site (15,6 % to 27,1 %).

Adults 18 years of age and older

The safety of PREVENAR 20 was evaluated in 4 552 participants 18 years of age and older in six clinical trials (two Phase 1, one Phase 2, and three Phase 3), and 2 496 participants in the control groups.

In the Phase 3 trials, 4 263 participants received PREVENAR 20 which included 1 798 adults 18 through 49 years of age, 334 adults 50 through 59 years of age, and 2 131 adults 60 years of age and older (1 138 were 65 years of age and older). Of the Phase 3 PREVENAR 20 recipients, 3 639 were naïve to pneumococcal vaccines, 253 had previously received Pneumovax 23 (pneumococcal polysaccharide vaccine [23-valent]; PPSV23) (≥ 1 to ≤ 5 years prior to enrolment), 246 had previously received Prevenar 13 only (≥ 6 months prior to enrolment), and 125 had previously received Prevenar 13 followed by PPSV23 (the dose of PPSV23 ≥ 1-year prior to enrolment).

Participants in the Phase 3 trial B7471007 (Pivotal Study 1007) were evaluated for adverse events for 1 month after vaccination, and serious adverse events through 6 months after vaccination. This study included 447 participants 18 to 49 years of age, 445 participants 50 to 59 years of age, 1 985 participants 60 to 64 years of age, 624 participants 65 to 69 years of age, 319 participants 70 to 79 years of age, and 69 participants ≥ 80 years of age.

The most frequent adverse reactions (> 10 %) after vaccination with PREVENAR 20 in Phase 3 trials in adults ≥ 18 years of age were pain at the injection site (> 40 %), muscle pain (> 30 %), fatigue (> 20 %) and headache (> 10 %). A slightly lower frequency of reactogenicity events was associated with greater age.

In Study 1007 participants 18 to 59 years of age, the most commonly reported adverse reactions were pain at the injection site (> 70 %), muscle pain (> 50 %), fatigue (> 40 %), headache (> 30 %), and joint pain

and injection site swelling (> 10 %), while the most frequent in participants older than 60 years of age were pain at the injection site (> 50 %), muscle pain and fatigue (> 30 %), headache (> 20 %), and joint pain (> 10 %). These were usually mild or moderate in intensity and resolved within a few days after vaccination.

Tabulated summary of adverse reactions

Tabulated lists of adverse reactions from the infant Phase 2, Phase 3 clinical trials in paediatric and adult populations, and post-marketing experience are presented below.

Adverse reactions from clinical trials

As PREVENAR 20 contains the same 13 serotype-specific capsular polysaccharide conjugates and the same vaccine excipients as Prevenar 13, the adverse reactions already identified for Prevenar 13 have been adopted for PREVENAR 20.

Table 1 presents adverse reactions reported in the Phase 2 infant trial, and Phase 3 trials in paediatric and adult populations, based on the highest frequency among adverse events, local reactions, or systemic events, after vaccination in an PREVENAR 20 group or integrated dataset. The data from clinical trials in infants reflect PREVENAR 20 administered simultaneously with other routine childhood vaccines. In the case of adverse reactions reported in clinical trials of Prevenar 13, but not reported in PREVENAR 20 trials, the frequency is not known.

In clinical trials, the safety profile of PREVENAR 20 was similar to that of Prevenar 13. No new adverse reactions were identified as compared to Prevenar 13, and none of the reported serious adverse events were considered related to PREVENAR 20.

Frequencies are categorised 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), unknown (cannot be estimated from the available data).

Table 1: Tabulated Adverse Reactions From PREVENAR 20 Clinical Trials

System organ class	Adverse reactions	Frequency		
		Infants/ Children/ Adolescents		Adults
		6 weeks to less than 5 years of age	5 to less than 18 years of age	
Immune system disorders	Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm	Unknown[a]	-	Uncommon
Metabolism and nutrition disorders	Decreased appetite	Very common	Unknown[c]	Unknown[e]
Psychiatric disorders	Irritability	Very common	Unknown[c]	-
	Crying	Unknown[a]		-
Nervous system disorders	Drowsiness/ increased sleep	Very common	Unknown[c]	-
	Seizures (including febrile seizures)	Uncommon	-	-
	Hypotonic-hyporesponsive episode	Unknown[a]	-	-
	Restless sleep /decreased sleep	Unknown[a]	Unknown[c]	-
	Headache	-	Very common	Very Common
	Diarrhoea	Common	Unknown[c]	Uncommon[e]

System organ class	Adverse reactions	Frequency		
		Infants/ Children/ Adolescents		Adults
		6 weeks to less than 5 years of age	5 to less than 18 years of age	
Gastro-intestinal disorders	Nausea	-	-	Uncommon
	Vomiting	Common	Unknown[c]	Uncommon[e]
Skin and sub-cutaneous tissue disorders	Rash	Common	Unknown[c]	Uncommon[e]
	Angioedema	-	-	Uncommon
	Urticaria or urticaria-like rash	Uncommon	Uncommon	-
Mus-culoskeletal and connective tissue disorders	Muscle pain	-	Very common[d]	Very common
	Joint pain	-	Common[d]	Very common
General disorders and admini-stration site conditions	Fever (pyrexia)	Very common	Uncommon	Common
	Fever greater than 38,9°C	Common	-	-
	Fatigue	-	Very common[d]	Very common
	Vaccination-site erythema	Very common	Very common	Common[e]
	Vaccination-site induration/swelling	Very common	Very common	Common[e]
	Vaccination-site erythema or induration/swelling (> 2,0 – 7,0 cm)	Very common (after toddler dose and in older children	-	-

System organ class	Adverse reactions	Frequency		
		Infants/ Children/ Adolescents		Adults
		6 weeks to less than 5 years of age	5 to less than 18 years of age	
		[age 2 to < 5 years])		
		Common (after infant series)	-	-
	Vaccination-site erythema or induration/swelling (> 7,0 cm)	Uncommon	-	-
	Vaccination-site pain/tenderness	Very common	Very common	Very common
	Vaccination-site pain/tenderness causing limitation of limb movement	Common	Common	Unknown[e]
	Vaccination-site pruritus	-	-	Uncommon
	Lymphadenopathy	-	-	Uncommon
	Vaccination-site urticaria	-	-	Uncommon
	Chills	-	-	Uncommon[e]
	Vaccination-site hypersensitivity	Rare[b]	-	

System organ class	Adverse reactions	Frequency		
		Infants/ Children/ Adolescents		Adults
		6 weeks to less than 5 years of age	5 to less than 18 years of age	

a. Adverse reactions (ARs) reported in clinical trials with Prevenar 13 in infants and children 6 weeks to less than 5 years of age with frequencies of very common (restless sleep/decreased sleep), uncommon (crying), and rare (hypersensitivity reaction including face oedema, dyspnoea, bronchospasm; hypotonic-hyporesponsive episode).
b. AR not reported for Prevenar 13, although injection-site urticaria, injection-site pruritus, and injection-site dermatitis were reported in Prevenar 13 post-marketing experience.
c. ARs reported in clinical trials with Prevenar 13 in children and adolescents 5 to less than 18 years of age with frequencies of very common (decreased appetite; irritability; drowsiness/increased sleep; restless sleep/decreased sleep) and common (vomiting; diarrhoea; rash).
d. ARs reported only in clinical trials of PREVENAR 20 in children and adolescents 5 to less than 18 years.
e. Event reported from clinical trials in adults with Prevenar 13 with very common frequency (≥ 1/10). Decreased appetite and limitation of arm movement were not reported in the adult Phase 3 trials of PREVENAR 20; therefore, the frequency is not known.

Safety with concomitant vaccine administration in adults

When PREVENAR 20 was administered to adults aged ≥ 65 years together with the third (booster) dose of a COVID-19 mRNA vaccine (nucleoside modified), the tolerability profile generally resembled that of the COVID-19 mRNA vaccine (nucleoside modified) administered alone. There were a few differences in the safety profile when compared to administration of PREVENAR 20 alone. In the phase 3 trial B7471026 (Study 1026), pyrexia (13,0 %) and chills (26,5 %) were reported as “very common” with co-administration. There was also one report of dizziness (0,5 %) in the co-administration group.

Adverse reactions from post-marketing experience

Table 2 includes adverse experiences that have been spontaneously reported during the post-marketing use of Prevenar 13 in paediatric and adult populations, which may also occur with PREVENAR 20. The post-marketing safety experience with Prevenar 13 is relevant to PREVENAR 20, as PREVENAR 20 contains all components (polysaccharide conjugates and excipients) of Prevenar 13. These events were reported voluntarily from a population of uncertain size. Therefore, it is not possible to reliably estimate their frequency or to establish, for all events, a causal relationship to vaccine exposure.

Table 2. Adverse Reactions From Prevenar 13 post-marketing experience

System organ class	Adverse reactions
Blood and lymphatic system disorders	Lymphadenopathy localised 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

Events reported spontaneously in Prevenar 13 post-marketing experience; therefore, the frequencies could not be estimated from the available data and are considered as not known.

Additional information in special populations in studies with Prevenar 13

Participants 6 to < 18 years of age with HIV infection have similar frequencies of adverse reactions in Table 1, except fever (11 % to 19 %), joint pain (24 % to 42 %), vomiting (8 % to 18 %) which were very common. Adults ≥ 18 years of age with HIV infection have similar frequencies of adverse reactions in

Table 1, except for pyrexia (5 % to 18 %) and vomiting (8 % to 12 %) which were very common and nausea (< 1 % to 3 %) which was common.

Participants 2 to < 18 years of age with HSCT have similar frequencies of adverse reactions in Table 1, except vaccination-site pain causing limitation of limb movement (5 % to 15 %), vomiting (6 % to 21 %), diarrhoea (15 % to 32 %), and joint pain (25 % to 32 %) which were very common. Adults (≥ 18 years of age) with an HSCT have similar frequencies of adverse reactions in Table 1, except for pyrexia (4 % to 15 %), vomiting (6 % to 21 %), and diarrhoea (25 % to 36 %) which were very common.

Participants 6 to < 18 years of age with SCD have similar frequencies of adverse reactions in Table 1, except vaccination-site pain causing limitation of limb movement (11 % to 16 %), fever (21 % to 22 %), vomiting (13 % to 15 %), diarrhoea (13 % to 25 %), and joint pain (40 % to 45 %) which were very common.

Safety with concomitant vaccine administration in adults

The safety profile was similar when PREVENAR 20 was administered with or without influenza vaccine, adjuvanted (Fluad Quadrivalent [QIV]).

PREVENAR 20 administered together with COVID-19 mRNA vaccine (Comirnaty [tozinameran]) was observed to have a tolerability profile similar to COVID-19 mRNA vaccine (Comirnaty [tozinameran]) administered alone, and an overall safety profile consistent with PREVENAR 20 or COVID-19 mRNA vaccine (Comirnaty [tozinameran]) given alone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com.

4.9 Overdose

Overdose with PREVENAR 20 is unlikely due to its presentation as a pre-filled syringe. In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, pneumococcal vaccines; ATC code: J07AL02

Mechanism of action

Pneumococcal polysaccharide conjugate vaccine (20-valent) contains 20 pneumococcal capsular polysaccharides all conjugated to CRM_{197} carrier protein, which modifies the immune response to the polysaccharide from a T-cell independent response to a T-cell dependent response. The T-cell dependent response leads to both enhanced antibody response and generation of memory B cells, allowing for an anamnestic (booster) response on re-exposure to the bacteria.

Vaccination with Pneumococcal polysaccharide conjugate vaccine (20-valent) induces serum antibody production and immunologic memory against the serotypes contained within the vaccine. In adults, the levels of circulating antibodies, and in paediatric populations the serotype-specific levels, that correlate with protection against pneumococcal disease have not been clearly defined.

Protection against pneumococcal disease is conferred mainly by opsonophagocytic killing of *S. pneumoniae*. Pneumococcal polysaccharide conjugate vaccine (20-valent) generates functional antibodies as measured by opsonophagocytic activity (OPA). An opsonic antibody titre that is predictive of protection against invasive pneumococcal disease or pneumococcal pneumonia has not been established.

Disease burden for adults

S. pneumoniae (pneumococcus) is the most frequent bacterial cause of community-acquired pneumonia (CAP) and has been estimated to be responsible for approximately 30 % of all CAP cases requiring hospitalisation in adults in developed countries, with the majority of cases considered nonbacteraemic. In addition, bacteraemic pneumonia is the most common manifestation of invasive pneumococcal disease (IPD) (approximately 80 % of cases) in adults. Based on surveillance data, the pneumococcal serotypes in Pneumococcal polysaccharide conjugate vaccine (20-valent) may be responsible for at least 63 % to 76 % (depending on country) of IPD in older adults in Europe.

Pneumococcal polysaccharide conjugate vaccine (20-valent) effectiveness

No efficacy studies have been performed for Pneumococcal polysaccharide conjugate vaccine (20-valent), however the efficacy and effectiveness of Prevenar 13 are relevant to Pneumococcal polysaccharide conjugate vaccine (20-valent), since the vaccines are manufactured similarly and contain 13 of the same polysaccharide conjugates.

Approval of Pneumococcal polysaccharide conjugate vaccine (20-valent) for the paediatric population is based on comparing the totality of the immune responses in infants after receiving Pneumococcal polysaccharide conjugate vaccine (20-valent) to the immune responses after receiving Prevenar 13. The comparison, following the World Health Organization (WHO) guideline, included the percentage of participants with predefined IgG (immunoglobulin G) concentrations and IgG geometric mean concentrations (GMCs). This approach is largely based upon the observed relationship between immunogenicity and invasive pneumococcal disease (IPD) efficacy from 3 placebo-controlled trials with either Prevenar (7-valent pneumococcal conjugate vaccine) or the investigational 9-valent CRM197 conjugate polysaccharide vaccine conducted in Navajo and White Mountain Apache Indian infants (cluster randomised trial), infants in Soweto, South Africa, and infants in the Northern California Kaiser Permanente (NCKP) health organization in the United States (see Prevenar Efficacy and Prevenar 13 Effectiveness in Children below). The predefined IgG concentration corresponding to 0,35 µg/mL in the WHO enzyme-linked

immunosorbent assay (ELISA) is only applicable at the population level and cannot be used to predict individual or serotype-specific protection against IPD.

Immunogenicity data

Pneumococcal polysaccharide conjugate vaccine (20-valent) clinical trials in infants, children and adolescents

Two Phase 3 clinical trials (Study 1012, Study 1011) and one Phase 2 clinical trial (Study 1003) evaluated the immunogenicity of Pneumococcal polysaccharide conjugate vaccine (20-valent) in a 3-dose and 4-dose series in infants. One Phase 3 trial (Study 1014) of children 15 months to less than 18 years of age evaluated a single dose of PREVENAR 20.

Pneumococcal IgG immune responses following 3 doses of 3-dose vaccination series

In Study 1012, the immunogenicity of Pneumococcal polysaccharide conjugate vaccine (20-valent) was evaluated in infants when administered in a series of 2 infant doses and 1 toddler dose in infants enrolled from Europe and Australia. The study enrolled infants 2 months (≥ 42 to ≤ 112 days) of age and born at > 36 weeks of gestation. Participants were randomised (1:1) to receive either PREVENAR 20 or Prevenar 13 with the first dose given at 42 to 112 days of age, a second dose given approximately 2 months later, and the third dose given at approximately 11 to 12 months of age. Participants received concomitant vaccines at these visits.

Pneumococcal polysaccharide conjugate vaccine (20-valent) elicited immune responses, as assessed by the percentage of participants with predefined IgG concentrations, IgG GMCs and OPA GMTs for all 20 serotypes contained in the vaccine. The observed IgG GMCs and percentage of participants with predefined IgG concentrations 1 month after the third (last) dose of PREVENAR 20 were generally comparable to the Prevenar 13 group for the 13 matched serotypes and higher for the 7 additional serotypes (Table 3).

One month after the 2 infant doses the observed IgG GMCs were generally comparable for most serotypes to the Prevenar 13 group and the percentages of participants with predefined IgG concentrations for the 13 matched serotypes were generally lower in the Pneumococcal polysaccharide conjugate vaccine (20-valent) group than the Prevenar 13 group (Table 4). The immune responses to the additional 7 serotypes were higher in the Pneumococcal polysaccharide conjugate vaccine (20-valent) group than the Prevenar 13 group after the second dose.

Table 3. Percentages of participants with predefined pneumococcal igg concentrations and pneumococcal IgG GMCs (µg/mL) one month after dose 3 of a 3-dose series, study 1012[a]

	Percentages of participants with predefined igg concentrations[b]			**IgG GMCs**		
	Pneu-mococcal polysaccharide conjugate vaccine (20-valent) N[c] = 493-495	**Prevenar 13 N[c] = 501-502**	**Pneu-mococcal polysa-ccharide conjugate vaccine (20-valent) – Prevenar 13)**	**Pneu-mococcal polysa-ccharide conjugate vaccine (20-valent) N[c] = 493-495**	**Prevenar 13 N[c] = 501-502**	**Pneu-mococcal polysa-ccharide conjugate vaccine (20-valent)/ Prevenar 13**
	%	**%**	**% (95 % CI[d])**	**GMC[e]**	**GMC[e]**	**GMR[e] (95 % CI[e;])**
Serotypes						
1	97,2	98,2	-1,0 (-3,1; 0,9)	1,71	2,53	0,67 (0,60; 0,75)
3	82,6	93,2	-10,6 (-14,7; -6,7)	0,72	1,09	0,66 (0,59; 0,73)
4	99,2	99,2	0,0	4,11	5,36	0,77

	Percentages of participants with predefined igg concentrations[b]			IgG GMCs		
			(-1,4; 1,3)			(0,68; 0,87)
5	98,4	98,0	0,4 (-1,4; 2,2)	1,74	2,41	0,72 (0,64; 0,81)
6A	98,8	98,8	0,0 (-1,6; 1,5)	7,75	11,82	0,66 (0,57; 0,75)
6B	98,4	97,6	0,8 (-1,1; 2,7)	2,64	4,63	0,57 (0,48; 0,67)
7F	99,6	100,0	-0,4 (-1,5; 0,4)	3,61	4,93	0,73 (0,67; 0,80)
9V	99,2	98,8	0,4 (-1,0; 1,9)	3,68	5,04	0,73 (0,66; 0,81)
14	96,6	98,0	-1,5 (-3,7; 0,6)	4,52	5,66	0,80 (0,69; 0,92)
18C	99,2	98,2	1,0 (-0,5; 2,7)	2,71	3,61	0,75 (0,67; 0,84)
19A	99,6	99,6	0,0 (-1,1; 1,1)	4,51	5,49	0,82 (0,72; 0,93)
19F	99,6	99,4	0,2 (-0,9; 1,4)	6,19	8,08	0,77 (0,68; 0,87)
23F	96,4	97,2	-0,9 (-3,2; 1,4)	2,64	4,40	0,60 (0,52; 0,69)
Additional Serotypes						
8	99,2	3,6	95,6 (93,4; 97,1)	3,57	0,03	113,37 (100,05; 128,46)

	Percentages of participants with predefined igg concentrations[b]			IgG GMCs		
10A	97,8	1,6	96,2 (94,1; 97,6)	4,86	0,01	423,02 (372,25; 480,73)
11A	98,4	4,6	93,8 (91,3; 95,6)	3,74	0,02	229,66 (199,06; 264,96)
12F	96,6	0,2	96,4 (94,3; 97,7)	1,86	0,01	224,31 (204,73; 245,76)
15B	99,4	4,8	94,6 (92,3; 96,3)	13,09	0,02	527,47 (465,44; 597,77)
22F	99,2	1,4	97,8 (96,1; 98,8)	9,27	0,00	2 193,09 (1 908,27; 2 520,41)
33F	98,6	1,8	96,8 (94,8; 98,0)	6,37	0,01	530,53 (470,15; 598,66)

Abbreviations: CI = confidence interval; GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.

Note: Noninferiority for a matched serotype was concluded if the lower bound of the 2-sided 95 % CI for the percentage difference (Pneumococcal poly-saccharide conjugate vaccine (20-valent) - Prevenar 13) was > -10 % or the lower bound of the 2-sided 95 % CI for the GMR (Pneumococcal poly-saccharide conjugate vaccine (20-valent) to Prevenar 13) was > 0,5 for that serotype.

Note: Assay results below the LLOQ were set to 0,5 × LLOQ in the analysis.

a. Study 1012 was conducted in Europe and Australia.

b. The predefined IgG concentration was ≥ 0,35 µg/mL for all serotypes except for serotypes 5, 6B and 19A which were ≥ 0,23 µg/mL, ≥ 0,10 µg/mL and ≥ 0,12 µg/mL respectively.

c. N = Number of participants with valid IgG concentrations.

d. Two-sided CI based on the Miettinen and Nurminen method.

e. GMCs, GMRs and the associated 2-sided CIs were calculated by exponentiating the means and the mean differences (Pneumococcal poly-saccharide conjugate vaccine (20-valent) – Prevenar 13) of logarithm of the concentrations and the corresponding CIs (based on the Student's t distribution).

Table 4. Percentage of participants with predefined pneumococcal IgG concentrations and pneumococcal IgG GMCs (µg/mL) one month after dose 2 of a 3-dose series, study 1012[a]

	Percentages of participants with predefined IgG concentrations[b]			**IgG GMCs**		
	Pneumococcal polysaccharide conjugate vaccine (20-valent) N[c] = 564-567	**Prevenar 13 N[c] = 561-562**	**Pneu-mococcal poly-saccharide conjugate vaccine (20-valent) – Prevenar 13)**	**Pneu-mococcal poly-saccharide conjugate vaccine (20-valent)N[c] = 564-567**	**Prevenar 13 N[c] = 561-562**	**Pneumococcal polysaccharide conjugate vaccine (20-valent)/ Prevenar 13**
	%	**%**	**% (95 % CI[d,]) **	**GMC[e]**	**GMC[e]**	**GMR (95 % CI[e])**
Serotypes						
1	70,7	84,2	-13,5 (-18,3; -8,7)	0,57	0,93	0,61 (0,54; 0,69)
3	58,0	75,8	-17,9	0,41	0,58	0,71

	Percentages of participants with predefined IgG concentrations[b]			**IgG GMCs**		
	Pneumococcal polysaccharide conjugate vaccine (20-valent) N[c] = 564-567	**Prevenar 13 N[c] = 561-562**	**Pneu-mococcal poly-saccharide conjugate vaccine (20-valent) – Prevenar 13)**	**Pneu-mococcal poly-saccharide conjugate vaccine (20-valent)N[c] = 564-567**	**Prevenar 13 N[c] = 561-562**	**Pneumococcal polysaccharide conjugate vaccine (20-valent)/ Prevenar 13**
	%	**%**	**% (95 % CI[d,])**	**GMC[e]**	**GMC[e]**	**GMR (95 % CI[e])**
			(-23,2; -12,4)			(0,64; 0,79)
4	68,6	79,5	-11,0 (-16,0; -5,9)	0,55	0,92	0,60 (0,52; 0,69)
5	63,4	76,0	-12,6 (-17,8; -7,2)	0,34	0,56	0,60 (0,52; 0,70)
6A	59,5	73,7	-14,1 (-19,5; -8,6)	0,45	0,84	0,54 (0,45; 0,65)
6B	20,7	36,5	-15,8 (-21,0; -10,6)	0,03	0,06	0,51 (0,43; 0,61)
7F	87,6	90,2	-2,6	1,02	1,41	0,72

	Percentages of participants with predefined IgG concentrations[b]			**IgG GMCs**		
	Pneumococcal polysaccharide conjugate vaccine (20-valent) N[c] = 564-567	**Prevenar 13 N[c] = 561-562**	**Pneu-mococcal poly-saccharide conjugate vaccine (20-valent) – Prevenar 13)**	**Pneu-mococcal poly-saccharide conjugate vaccine (20-valent)N[c] = 564-567**	**Prevenar 13 N[c] = 561-562**	**Pneumococcal polysaccharide conjugate vaccine (20-valent)/ Prevenar 13**
	%	**%**	**% (95 % CI[d,])**	**GMC[e]**	**GMC[e]**	**GMR (95 % CI[e])**
			(-6,3; 1,1)			(0,64; 0,80)
9V	60,2	74,6	-14,3 (-19,7; -8,9)	0,45	0,77	0,59 (0,50; 0,69)
14	78,6	81,9	-3,3 (-7,9; 1,4)	1,05	1,28	0,82 (0,70; 0,96)
18C	71,0	76,5	-5,5 (-10,6; -0,4)	0,69	0,87	0,79 (0,67; 0,92)
19A	92,2	94,0	-1,7 (-4,8; 1,3)	0,67	1,13	0,59 (0,51; 0,69)
19F	94,3	95,7	-1,4 (-4,0; 1,2)	2,21	3,06	0,72 (0,64; 0,82)
23F	23,5	41,8	-18,3	0,13	0,25	0,52 (0,44; 0,62)

	Percentages of participants with predefined IgG concentrations[b]			**IgG GMCs**		
	Pneumococcal polysaccharide conjugate vaccine (20-valent) N[c] = 564-567	**Prevenar 13 N[c] = 561-562**	**Pneu-mococcal poly-saccharide conjugate vaccine (20-valent) – Prevenar 13)**	**Pneu-mococcal poly-saccharide conjugate vaccine (20-valent)N[c] = 564-567**	**Prevenar 13 N[c] = 561-562**	**Pneumococcal polysaccharide conjugate vaccine (20-valent)/ Prevenar 13**
	%	**%**	**% (95 % CI[d,])**	**GMC[e]**	**GMC[e]**	**GMR (95 % CI[e])**
			(-23,6; -12,9)			
Additional Serotypes						
8	96,5	2,9	93,6 (91,2; 95,4)	1.62	0,02	91,19 (81,19; 102,43)
10A	28,9	2,7	26,3 (22,4; 30,3)	0.16	0,02	8,38 (7,20; 9,76)
11A	94,2	2,0	92,2 (89,7; 94,2)	1.62	0,02	74,53 (65,99; 84,17)
12F	30,3	0,2	30,2 (26,5; 34,1)	0.15	0,01	17,91 (15,66; 20,48)
15B	94,3	8,5	85,8 (82,5; 88,5)	3.33	0,04	83,56 (71,77; 97,28)
22F	94,4	2,0	92,4 (89,9; 94,3)	2.25	0,01	337,08

	Percentages of participants with predefined IgG concentrations[b]			IgG GMCs		
	Pneumococcal polysaccharide conjugate vaccine (20-valent) N[c] = 564-567	Prevenar 13 N[c] = 561-562	Pneu-mococcal poly-saccharide conjugate vaccine (20-valent) – Prevenar 13)	Pneu-mococcal poly-saccharide conjugate vaccine (20-valent)N[c] = 564-567	Prevenar 13 N[c] = 561-562	Pneumococcal polysaccharide conjugate vaccine (20-valent)/ Prevenar 13
	%	%	% (95 % CI[d,])	GMC[e]	GMC[e]	GMR (95 % CI[e])
						(287,86; 394,72)
33F	46,8	2,7	44,2 (39,8; 48,5)	0.31	0,03	12,19 (10,55; 14,09)

Abbreviations: CI = confidence interval; GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation. Note: Noninferiority for a matched serotype was concluded if the lower bound of the 2-sided 95 % CI for the percentage difference (Pneumococcal polysaccharide conjugate vaccine (20-valent)– Prevenar 13) was > -10 % or the lower bound of the 2-sided 95 % CI for the GMR (Pneumococcal polysaccharide conjugate vaccine (20-valent) to Prevenar 13) was > 0,5 for that serotype. Note: Assay results below the LLOQ were set to 0,5 × LLOQ in the analysis.

a. Study 1012 was conducted in Europe and Australia.

b. The Predefined IgG concentration was ≥ 0,35 µg/mL for all serotypes except for serotypes 5, 6B and 19A which were ≥ 0,23 µg/mL, ≥ 0,10 µg/mL and ≥ 0,12 µg/mL respectively.

c. N = Number of participants with valid IgG concentrations.

d. Two-sided CI based on the Miettinen and Nurminen method.

	Percentages of participants with predefined IgG concentrations[b]			IgG GMCs		
	Pneumococcal polysaccharide conjugate vaccine (20-valent) N[c] = 564-567	Prevenar 13 N[c] = 561-562	Pneu-mococcal poly-saccharide conjugate vaccine (20-valent) – Prevenar 13)	Pneu-mococcal poly-saccharide conjugate vaccine (20-valent)N[c] = 564-567	Prevenar 13 N[c] = 561-562	Pneumococcal polysaccharide conjugate vaccine (20-valent)/ Prevenar 13
	%	%	% (95 % CI[d,])	GMC[e]	GMC[e]	GMR (95 % CI[e])

e. GMCs, GMRs and the associated 2-sided CIs were calculated by exponentiating the means and the mean differences (PREVENAR 20 – Prevenar 13) of the logarithm of the concentrations and the corresponding CIs (based on the Student's t distribution).

OPA responses after 2 and 3 doses in a 3-dose vaccination series of Pneumococcal polysaccharide conjugate vaccine (20-valent)

The OPA geometric mean titres (GMTs) for the 13 matched serotypes at 1 month after Dose 2 and 1 month after Dose 3 in the Pneumococcal polysaccharide conjugate vaccine (20-valent) group were generally similar to the observed OPA GMTs in the Prevenar 13 group for most serotypes. The observed OPA GMTs were lower for serotype 6B after Dose 2 and serotype 1 after Dose 3 in the PREVENAR 20 group. OPA GMTs were higher after Dose 3 than after Dose 2 for all serotypes. The observed OPA GMTs for the 7 additional serotypes, including serotypes 10A and 12F, both 1 month after the second dose and 1 month after the third dose were substantially higher in the Pneumococcal poly-saccharide conjugate vaccine (20-valent) group than those in the Prevenar 13 group (Table 5).

Table 5. Pneumococcal OPA GMTs One Month after Doses 2 and 3 in a 3-dose series, Study 1012[a]

	Pneumococcal poly-saccharide conjugate vaccine (20-valent) N[b] = 96 - 116 After Dose 2	Prevenar 13 N[b] = 97 - 118 After Dose 2	Pneumo-coccal poly-saccharide conjugate vaccine (20-valent) N[b] = 72 - 106 After Dose 3	Prevenar 13 N[b] = 92 - 109 After Dose 3
	GMT[c] (95 % CI[c])	**GMT[c] (95 % CI[c])**	**GMT[c] (95 % CI[c])**	**GMT[c] (95 % CI[c])**
Serotypes				
1	14 (12, 16)	23 (19, 28)	54 (43, 69)	101 (79, 129)
3	31 (26, 36)	40 (34, 47)	99 (84, 117)	129 (111, 150)
4	333 (270, 413)	391 (314, 486)	904 (752, 1 086)	992 (777, 1 266)
5	21 (18, 23)	27 (23, 31)	60 (50, 72)	82 (66, 101)
6A	347 (273, 441)	409 (318, 527)	1 101 (897, 1 350)	1304 (1 018, 1 671)
6B	54 (42, 71)	105 (76, 144)	537 (408, 706)	864 (664, 1 125)
7F	858 (736, 1 000)	895 (781, 1 027)	1 811 (1 553, 2 112)	2197 (1 905, 2 533)
9V	233 (182, 298)	285 (228, 358)	3 254 (2 596, 4 079)	4 544 (3 681, 5 610)
14	287 (215, 383)	360 (264, 489)	738 (606, 899)	926 (751, 1 142)
18C	588 (467, 741)	719 (590, 876)	1296 (1 048, 1 602)	1870 (1 489, 2 348)
19A	57 (43, 75)	91 (69, 121)	754 (627, 907)	707 (558, 896)

19F	97 (81, 116)	117 (94, 146)	183 (140, 237)	258 (192, 347)
23F	59 (42, 84)	68 (48, 96)	697 (530, 917)	975 (734, 1296)
Additional Serotypes				
8	164 (133, 203)	17 (15, 18)	1 398 (1 088, 1 796)	31 (25, 39)
10A	855 (610, 1199)	39 (34, 44)	3 403 (2 600, 4 455)	69 (52, 91)
11A	327 (253, 423)	49 (47, 51)	2 966 (2 212, 3 978)	66 (51, 85)
12F	4 788 (3 779, 6 067)	26 (23, 28)	5 501 (4 499, 6 725)	29 (25, 35)
15B	846 (605, 1 183)	17 (15, 19)	2 676 (1 948, 3 677)	23 (18, 30)
22F	4444 (3 666, 5 386)	10 (9, 11)	6 523 (4 848, 8 777)	17 (13, 24)
33F	2 373 (1 759, 3 202)	178 (163, 195)	1 1315 (8 107, 15 794)	708 (545, 920

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.

Note: Assay results below the LLOQ were set to 0,5 × LLOQ in the analysis.

Note: OPA titres were determined on serum from randomly selected subsets of participants assuring equal representation of both vaccine groups.

a. Study 1012 was conducted in Europe and Australia.

b. N = Number of participants with valid OPA titres.

c. GMTs and 2-sided CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student's t distribution).

Booster responses after the last dose in a 3-dose infant vaccination series

Pneumococcal polysaccharide conjugate vaccine (20-valent) immune responses show boosting in IgG GMCs and percentage of participants with a predefined IgG concentrations after Dose 3, that are higher than concentrations before Dose 3, and also increased relative to the levels after Dose 2, indicating that a memory response was elicited by the 2 infant doses. (see Tables 3 and 4). For all serotypes, the OPA responses also show a generally similar pattern of boosting as observed with the IgG responses, with priming evidenced by the robust OPA responses (geometric mean fold rise (GMFRs) and the percentages of participants with a ≥ 4-fold rise in OPA titres) from before to one month after Dose 3. In summary, Pneumococcal poly-saccharide conjugate vaccine (20-valent) elicits immune responses that are comparable to Prevenar 13 for the 13 matched serotypes and the 7 additional serotypes after the third (toddler) dose.

The totality of data show that a 3-dose series of Pneumococcal polysaccharide conjugate vaccine (20-valent) elicited immune responses expected to provide children protection against pneumococcal disease similar to that of Prevenar 13 for all 20 vaccine serotypes.

Immune responses following 3 and 4 doses in a 4-dose infant vaccination series

Clinical studies evaluating the immunogenicity of Pneumococcal polysaccharide conjugate vaccine (20-valent) in infants with a 4-dose series (3 infant doses and a toddler dose) at 2, 4, 6, and 12 to 15 months of age have been conducted in 2 randomised Phase 2 (Study 1003) and Phase 3 studies (Study 1011) in United States/Puerto Rico.

In Study 1011, healthy infants 2 months (≥ 42 to ≤ 98 days) of age at the time of consent and born at > 36 weeks of gestation, were enrolled. Participants were randomised (1:1) to receive either Pneumococcal polysaccharide conjugate vaccine (20-valent) or Prevenar 13 at approximately 2, 4, 6, and 12 to 15 months of age. At one month after the fourth dose, the IgG GMCs for Pneumococcal polysaccharide conjugate

vaccine (20-valent) were noninferior to Prevenar 13 for all 13 matched serotypes, and 7 additional serotypes to the lowest IgG GMC among the vaccine serotypes (excluding serotype 3) in the Prevenar 13 group based on a 2-fold noninferiority criterion. This was also the case for the IgG GMCs for Prevenar 13, 1 month after the third dose. The percentages of participants with predefined serotype-specific IgG concentrations one month after the third dose was met for 8 of the 13 serotypes and missed by small margins for 4 serotypes (serotypes 1, 4, 9V, and 23F) with a 10 % noninferiority criterion. Six of the 7 additional serotypes met the noninferiority criterion; serotype 12F missed the statistical noninferiority criterion. The IgG GMCs at both time points and percentages of participants with predefined IgG concentrations for all 7 additional serotypes, including serotype 12F, were much higher than the corresponding serotype responses in the Prevenar 13 group, consistent with statistically greater antibody levels based on the lower bounds of the nominal 2-sided 95 % confidence limits (not adjusted for multiplicity).

OPA GMTs for the 13 matched serotypes 1 month after Dose 3 and Dose 4 in the Pneumococcal polysaccharide conjugate vaccine (20-valent) group were generally numerically similar to the OPA GMTs in the Prevenar 13 group, and have similar distributions. The observed OPA GMTs were substantially higher for the 7 additional serotypes in the Pneumococcal polysaccharide conjugate vaccine (20-valent) group than the Prevenar 13 group.

Pneumococcal polysaccharide conjugate vaccine (20-valent) elicits IgG immune responses that are comparable to Prevenar 13 for the 13 matched serotypes and the 7 additional serotypes after 3 doses in infants and a fourth dose in toddlers. Pneumococcal polysaccharide conjugate vaccine (20-valent) also elicits functional antibody to all 20 serotypes that was observed 1 month after Dose 3 and 1 month after Dose 4. Pneumococcal polysaccharide conjugate vaccine (20-valent) immune responses also show boosting after Dose 4, indicating that a memory response was elicited by the 3 infant doses.

Children 15 months to less than 18 years of age (Study 1014)

In a multi-center, single-arm trial (Study 1014), participants were enrolled into the study by age group (approximately 200 participants per group) to receive a single dose Pneumococcal polysaccharide conjugate vaccine (20-valent) as described below.

Children 15 months to less than 5 years of age previously vaccinated with Prevenar 13

In 15 to less than 24 months and 2 years to less than 5 years age groups, participants had been previously vaccinated with 3 or 4 doses of Prevenar 13. Increases in IgG concentrations from before to 1 month after Pneumococcal polysaccharide conjugate vaccine (20-valent) were observed for all 20 vaccine serotypes in participants 15 months to less than 5 years of age with prior vaccination with Prevenar 13. The observed IgG GMFRs to the 7 additional serotypes ranged from 27,9 to 1847,7 and increases in IgG GMCs were observed in all 20 vaccine serotypes from before to 1 month after Pneumococcal polysaccharide conjugate vaccine (20-valent) (Table 6). In children 15 months to less than 24 months of age 83,2 % – 100,0 % had predefined IgG concentrations to 6 of the 7 additional serotypes, serotype 12F was 40,0 %.

Table 6: Pneumococcal IgG GMCs in participants 15 months to less than 5 years of age – before and 1 month after vaccination – evaluable immunogenicity population – Study 1014[a]

	≥ 15 to < 24 Months **N[b] = 186 - 190**		**≥2 to <5 Years** **N[b] = 179 - 183**	
	Before Vaccination **GMC[c] (95 % CI[c])**	**After Vaccination** **GMC[c] (95 % CI[c])**	**Before Vaccination** **GMC[c] (95 % CI[c])**	**After Vaccination** **GMC[c] (95 % CI[c])**
Serotypes				
1	0,43 (0,37; 0,49)	1,46 (1,28; 1,67)	0,20 (0,17; 0,24)	4,21 (3,62; 4,90)
3	0,14 (0,12; 0,16)	0,54 (0,47; 0,61)	0,08 (0,06; 0,10)	1,21 (1,04; 1,42)
4	0,61 (0,52; 0,72)	2,59 (2,27; 2,96)	0,30 (0,25; 0,37)	8,37 (7,28; 9,62)

	≥ 15 to < 24 Months N[b] = 186 - 190		≥2 to <5 Years N[b] = 179 - 183	
	Before Vaccination **GMC[c] (95 % CI[c])**	**After Vaccination** **GMC[c] (95 % CI[c])**	**Before Vaccination** **GMC[c] (95 % CI[c])**	**After Vaccination** **GMC[c] (95 % CI[c])**
5	0,43 (0,36; 0,50)	1,53 (1,32; 1,77)	0,18 (0,15; 0,22)	5,09 (4,32; 5,99)
6A	1,61 (1,38; 1,88)	7,59 (6,67; 8,63)	0,71 (0,58; 0,88)	31,99 (27,85; 36,75)
6B	0,85 (0,71; 1,02)	4,27 (3,69; 4,94)	0,52 (0,42; 0,63)	17,78 (15,43; 20,48)
7F	1,17 (1,03; 1,33)	3,53 (3,16; 3,94)	0,51 (0,44; 0,60)	6,42 (5,69; 7,24)
9V	0,71 (0,61; 0,83)	2,70 (2,35; 3,09)	0,35 (0,28; 0,42)	7,94 (6,83; 9,24)
14	1,53 (1,31; 1,79)	4,42 (3,82; 5,12)	0,66 (0,53; 0,81)	14,60 (12,44; 17,13)
18C	0,65 (0,55; 0,76)	2,69 (2,32; 3,12)	0,26 (0,21; 0,32)	7,07 (6,01; 8,32)
19A	0,47 (0,38; 0,58)	3,29 (2,89; 3,76)	0,52 (0,40; 0,68)	12,48 (10,76; 14,48)
19F	0,80 (0,67; 0,94)	4,16 (3,61; 4,79)	0,56 (0,44; 0,71)	12,50 (10,48; 14,91)
23F	0,96 (0,79; 1,18)	5,35 (4,55; 6,30)	0,90 (0,71; 1,15)	16,18 (13,75; 19,04)
Additional Serotypes				
8	0,04 (0,03; 0,05)	4,66 (4,17; 5,22)	0,05 (0,04; 0,06)	5,08 (4,45; 5,80)

	≥ 15 to < 24 Months N[b] = 186 - 190		≥2 to <5 Years N[b] = 179 - 183	
	Before Vaccination **GMC[c] (95 % CI[c])**	**After Vaccination** **GMC[c] (95 % CI[c])**	**Before Vaccination** **GMC[c] (95 % CI[c])**	**After Vaccination** **GMC[c] (95 % CI[c])**
10A	0,01 (0,01; 0,02)	1,23 (1,02; 1,48)	0,03 (0,02; 0,03)	2,76 (2,28; 3,34)
11A	0,03 (0,02; 0,03)	1,61 (1,40; 1,86)	0,06 (0,04; 0,08)	2,64 (2,25; 3,09)
12F	0,01 (0,01; 0,01)	0,22 (0,18; 0,27)	0,01 (0,01; 0,01)	0,38 (0,31; 0,46)
15B	0,02 (0,02; 0,03)	1,17 (0,97; 1,40)	0,05 (0,04; 0,07)	3,96 (3,12; 5,03)
22F	0,01 (0,00; 0,01)	9,57 (8,12; 11,29)	0,02 (0,01; 0,02)	12,46 (10,82; 14,35)
33F	0,02 (0,01; 0,02)	1,91 (1,60; 2,27)	0,04 (0,03; 0,05)	3,16 (2,63; 3,79)

Abbreviations: CI = confidence interval; GMC = geometric mean concentration; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.

Note: Assay results below the LLOQ were set to 0,5 × LLOQ in the analysis.

a. Study 1014 was conducted in the United States.

b. N = Number of participants with valid IgG concentrations at the given sampling time point.

c. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student's t distribution).

Children and adolescents 5 years to less than 18 years of age previously unvaccinated or vaccinated with Prevenar 13 or Prevenar

In the study, age groups 5 to less than 10 years and 10 to less than 18 years, participants could be unvaccinated or previously vaccinated with Prevenar 13 or Prevenar. Pneumococcal polysaccharide conjugate vaccine (20-valent) elicited robust IgG and OPA immune responses to the 20 vaccine serotypes after a single dose in participants 5 to less than 18 years of age. OPA GMFRs ranged from 11,5 to 499,0 to the 7 additional serotypes and increases in OPA GMTs were observed for all 20 vaccine serotypes (Table 7).

In summary, a single dose of Pneumococcal polysaccharide conjugate vaccine (20-valent) administered to children and adolescents 15 months to less than 18 years of age is expected to generate protective responses against pneumococcal disease due to the 7 additional serotypes, and to the 13 matched serotypes.

Table 7: Pneumococcal OPA GMTs in participants 5 to less than 18 years of age – before and 1 month after vaccination – evaluable immunogenicity population – Study 1014[a]

	≥ 5 to < 10 Years N[b]=76 - 175		**≥ 10 to < 18 Years N[b]=86 - 187**	
	Before Vaccination GMT[c] (95 % CI[c])	**After Vaccination GMT[c] (95 % CI[c])**	**Before Vaccination GMT[c] (95 % CI[c])**	**After Vaccination GMT[c] (95 % CI[c])**
Serotypes				
1	10 (9, 11)	548 (455, 660)	11 (9, 12)	396 (302, 519)
3	29 (22, 40)	155 (135, 178)	19 (14, 24)	105 (88, 124)
4	43 (27, 67)	2 328 (1942, 2789)	34 (22, 51)	2 290 (1822, 2878)
5	15 (15, 15)	385 (324, 458)	15 (15, 16)	216 (159, 294)
6A	74 (51, 106)	8 268 (6 617,	64 (44, 91)	9 434 (7616,

Table 7: Pneumococcal OPA GMTs in participants 5 to less than 18 years of age – before and 1 month after vaccination – evaluable immunogenicity population – Study 1014[a]

	≥ 5 to < 10 Years N[b]=76 - 175		≥ 10 to < 18 Years N[b]=86 - 187	
	Before Vaccination GMT[c] (95 % CI[c])	**After Vaccination GMT[c] (95 % CI[c])**	**Before Vaccination GMT[c] (95 % CI[c])**	**After Vaccination GMT[c] (95 % CI[c])**
		10 331)		11 686)
6B	156 (99, 244)	6 569 (5 367, 8 040)	237 (155, 363)	10 085 (8 263, 12 309)
7F	541 (410, 713)	3 981 (3 446, 4 598)	516 (381, 698)	3 326 (2 878, 3 843)
9V	410 (289, 580)	11 717 (9 262, 14 823)	469 (330, 667)	9 627 (7 492, 12 369)
14	246 (172, 353)	4 610 (3 688, 5 762)	97 (65, 145)	3925 (3153, 4885)
18C	152 (89, 261)	6766 (5585, 8197)	73 (45, 119)	3 617 (2 816, 4 645)
19A	117 (76, 181)	2 162 (1 786, 2 618)	66 (44, 100)	2 212 (1 801, 2 717)
19F	91 (66, 125)	1 095 (810, 1 479)	57 (44, 73)	551 (401, 757)
23F	87 (53, 145)	2 213 (1 751, 2 797)	46 (29, 73)	1 842 (1 391, 2 439)
Additional Serotypes				
8	34 (28, 42)	3 870 (3 302, 4 535)	35 (28, 43)	3125 (2 680, 3 642)
10A	745 (519, 1071)	21 102 (17 238, 25 833)	554 (395, 777)	17417 (14 301, 21 214)

Table 7: Pneumococcal OPA GMTs in participants 5 to less than 18 years of age – before and 1 month after vaccination – evaluable immunogenicity population – Study 1014[a]

	≥ 5 to < 10 Years N[b]=76 - 175		≥ 10 to < 18 Years N[b]=86 - 187	
	Before Vaccination GMT[c] (95 % CI[c])	**After Vaccination GMT[c] (95 % CI[c])**	**Before Vaccination GMT[c] (95 % CI[c])**	**After Vaccination GMT[c] (95 % CI[c])**
11A	1 347 (962, 1 887)	16 882 (13 650, 20 880)	765 (543, 1 076)	11 677 (9 751, 13 982)
12F	48 (38, 60)	23 860 (19 002, 29 959)	46 (36, 59)	20 250 (16 861, 24 320)
15B	79 (54, 115)	25 729 (19 647, 33 695)	45 (33, 61)	21496 (16697, 27672)
22F	259 (170, 394)	33 615 (26 198, 43130)	243 (161, 366)	27 922 (22 622, 34 463)
33F	3 334 (2 847, 3 905)	45 921 (36 768, 57 353)	2 895 (2 448, 3 424)	32 363 (26 219, 39 946)

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.

Note: OPA titres for all serotypes were determined on serum from randomly selected subsets of participants except for the 7 additional serotypes among participants ≥ 5 to < 18 years of age, which were determined from all available samples.

Note: Assay results below the LLOQ were set to 0,5 × LLOQ in the analysis.

a. Study 1014 was conducted in the United States.

b n = Number of participants with valid OPA titres at the given sampling time point.

c. GMTs and 2-sided CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student's t distribution).

Preterm infants

The safety and tolerability of PREVENAR 20 were evaluated in Study 1013, which included 111 late preterm infants (born at 34 to less than 37 weeks of gestational age) among the total study population. Participants were randomised to receive a 4-dose series of either Pneumococcal polysaccharide conjugate vaccine (20-valent) (N=77) or Prevenar 13 (N=34). Studies have not been specifically conducted to describe the immunogenicity of Pneumococcal polysaccharide conjugate vaccine (20-valent) in preterm infants. Based on experience with Prevenar and Prevenar 13, immune responses are elicited in preterm infants, although they may be lower than in term infants.

Prevenar 13 efficacy study in adults 65 years of age and older

The efficacy of Prevenar 13 against vaccine-type (VT) pneumococcal community-acquired pneumonia (CAP) and IPD was assessed in a randomised, double-blind, placebo-controlled study (CAPiTA) conducted over approximately 4 years in the Netherlands. A total of 84 496 subjects, 65 years and older, received a single dose of either Prevenar 13 or placebo in a 1:1 randomisation; 42 240 subjects were vaccinated with Prevenar 13 and 42 256 subjects were vaccinated with placebo.

The primary objective was to demonstrate the efficacy of Prevenar 13 in the prevention of a first episode of confirmed VT-CAP (defined as presence of ≥2 specified clinical criteria; chest X-ray consistent with CAP as determined by a central committee of radiologists; and positive VT-specific Urinary Antigen Detection assay (UAD) or isolation of VT *S. pneumoniae* from blood or other sterile site). The secondary objectives were to demonstrate the efficacy of Prevenar 13 in the prevention of a first episode of 1) confirmed non-bacteraemic/non-invasive (NB/NI) VT-CAP (an episode of VT-CAP for which the blood culture result and any other sterile site culture results were negative for *S. pneumoniae*) and 2) VT-IPD (the presence of *S. pneumoniae* in a sterile site).

Surveillance for suspected pneumonia and IPD began immediately after vaccination and continued through identification of a pre-specified number of cases. Subjects who had a CAP or IPD episode with symptom onset less than 14 days after vaccination were excluded from all analyses.

The median duration of follow up per subject was 3,93 years (0 – 4,95 years). Prevenar 13 demonstrated statistically significant vaccine efficacy (VE) in preventing first episodes of VT pneumococcal CAP, non-bacteraemic/non-invasive (NB/NI) VT pneumococcal CAP, and VT-IPD (Table 8).

Table 8. Vaccine efficacy for the primary and secondary endpoints of the CAPiTA study (per-protocol population)

Efficacy endpoint	Total number of episodes	Vaccine group		VE (%)	(95,2 % CI)	p-value
		Prevenar 13	Pla-cebo			
		n	n			
Primary endpoint						
First case of confirmed VT pneumococcal CAP	139	49	90	45,6	(21,8; 62,5)	0,0006
Secondary endpoints						
First episode of confirmed NB/NI VT pneumococcal CAP	93	33	60	45	(14,2; 65,3)	0,0067
First episode of VT-IPD	35	7	28	75	(41,1; 90,9)	0,00005

Abbreviations: CAP = community-acquired pneumonia; CAPiTA = Community-Acquired Pneumonia Immunisation Trial in Adults; CI = confidence interval; N = number of participants; NB/NI = non-bacteraemic/non-invasive; IPD = invasive pneumococcal disease; VE = vaccine efficacy; VT = vaccine-type.

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 (see Table 9).

Table 9. Vaccine efficacy against clinical CAP*

	Episodes		VE[a] % (95 % CI) (1-sided p-value)	Incidence per 100 000 PYO		IRR[b] (95 % CI)	NNV[c]
	Prevenar 13	Placebo		Prevenar 13	Placebo		
All episodes analysis	1 375	1 495	8,1 (-0,6; 16,1) (0,034)	819,1	891,2	72,2 (-5,3; 149,6)	277
First episode analysis	1 126	1 214	7,3 (-0,4; 14,4) (0,031)	670,7	723,7	53,0 (-2,7; 108,7)	378

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; IRR = incidence rate reduction; NNV = number needed to vaccinate; PYO = person-years of observation; VE = vaccine efficacy.

* Patients with at least 2 of the following: cough; purulent sputum, temperature > 38 °C or < 36,1 °C; pneumonia (auscultatory findings); leucocytosis; C-reactive protein value > 3 times the upper limit of normal; hypoxemia with a partial oxygen pressure < 60 mm Hg while breathing room air.

a. A Poisson regression model with random effects was used to calculate VE.

b. Per 100 000 person-years of observation. IRR is calculated as the incidence in the placebo group minus the incidence in the vaccine group and was mathematically equivalent to VE × the incidence in the placebo group.

c. Based on a 5-year duration of protection. NNV is not a rate but instead indicates the number of cases prevented for a given number of persons vaccinated. NNV also incorporates the length of the trial or duration of protection and is calculated as 1 divided by the product of the IRR and duration of protection (or length of trial) (= 1/[IRR × duration]).

Although CAPiTA was not powered to demonstrate serotype specific VE, an evaluation of clinical CAP data (as defined in the CAPiTA study and based on clinical findings regardless of radiologic infiltrate or etiologic confirmation) was performed in a post-hoc analysis 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 %).

Pneumococcal polysaccharide conjugate vaccine (20-valent) clinical trials in adults

Three Phase 3 clinical trials, B7471006, B7471007 and B7471008 (Study 1006, Study 1007, and Study 1008), were conducted in the United States and Sweden evaluating the immunogenicity of Pneumococcal polysaccharide conjugate vaccine (20-valent) in different adult age groups, and in participants who were either pneumococcal vaccine-naïve, or previously vaccinated with Prevenar 13, PPSV23, or both.

Each study included participants who were healthy or immunocompetent with stable underlying conditions, including chronic cardiovascular disease, chronic pulmonary disease, renal disorders, diabetes mellitus, chronic liver disease, and medical risk conditions and behaviours (e.g., smoking) that are known to increase the risk of serious pneumococcal pneumonia and IPD. In the pivotal study (Study 1007), these risk factors were identified in 34 %, 32 %, and 26 % of participants 60 years of age and over, 50 to 59 years of age, and 18 to 49 years of age, respectively. A stable medical condition was defined as a medical condition not requiring significant change in therapy in the previous 6 weeks (i.e., change to new therapy category due to worsening disease), or any hospitalization for worsening disease within 12 weeks before receiving the study vaccine.

In each study, immune responses elicited by Pneumococcal polysaccharide conjugate vaccine (20-valent) and the control pneumococcal vaccines were measured by an opsonophagocytic activity (OPA) assay. OPA assays measure functional antibodies to *S. pneumoniae*.

Table 10. Summary of Patient Demographics for Clinical Trials in Adults

Study #	**Study design**	**Dosage, route of administration**	**Study subjects (n)[a]**	**Demographics**
B7471007	Phase 3, multicenter, randomised, double-blind study with an age-based 3-cohort design	Cohort 1: One IM dose of Pneumococcal polysaccharide conjugate vaccine (20-valent)/Saline or Prevenar 13/23vPPV (Vaccination 1/ Vaccination 2) Cohorts 2 and 3: One IM dose of Pneumococcal polysaccharide conjugate vaccine (20-valent) or Prevenar 13	Cohort 1 (≥ 60 years) Pneumococcal polysaccharide conjugate vaccine (20-valent)/saline: 1507 Prevenar 13/23VPPV: 1490 Cohort 2 (50 - 59 years) Pneumococcal polysaccharide conjugate vaccine (20-valent): 334 Prevenar 13: 111 Cohort 3 (18-49 years) Pneumococcal polysaccharide conjugate vaccine (20-valent): 335 Prevenar 13: 112	Cohort 1: Sex: 1221 M/1776 F Age: mean (min/max): 64,6 (60/91) years Cohort 2: Sex: 181 M/264 F Age: mean (min/max): 54,9 (48[b]/59) years Cohort 3: Sex: 156 M/291 F Age: mean (min/max): 34,0 (18/60[b]) years

Study #	**Study design**	**Dosage, route of administration**	**Study subjects (n)[a]**	**Demographics**
B7471006	Phase 3, multicenter, randomised, open- label study with a 3-cohort design based on prior pneumococcal vaccination status	Cohort A: One IM dose of Pneumococcal polysaccharide conjugate vaccine (20-valent) or Prevenar 13 Cohort B: One IM dose of Pneumococcal polysaccharide conjugate vaccine (20-valent) or 23vPPV Cohort C: One IM dose of Pneumococcal polysaccharide conjugate vaccine (20-valent)	Cohort A: (prior vaccination with 23vPPV ≥1 year and ≤5 years) Pneumococcal polysaccharide conjugate vaccine (20-valent): 253 Prevenar 13: 122 Cohort B: (prior vaccination with Prevenar 13 ≥ 6 months) Pneumococcal polysaccharide conjugate vaccine (20-valent): 246 Prevenar 13: 127 Cohort C: (prior vaccination with Prevenar 13 followed by 23vPPV) Pneumococcal polysaccharide conjugate vaccine (20-valent): 125	Cohort A: Sex: 171 M/204 F Age: mean (min/max): 69,8 (65/84) years Cohort B: Sex: 167 M/206 F Age: mean (min/max): 70,7 (65/92) years Cohort C: Sex: 60 M/65 F Age: mean (min/max): 70.8 (65/81) years

Study #	Study design	Dosage, route of administration	Study subjects (n)[a]	Demographics
B7471008	Phase 3, multicenter, randomised, double-blind, lot consistency study with a 4-arm parallel design	One IM dose of Pneumococcal polysaccharide conjugate vaccine (20-valent) (Lot 1, 2 or 3) or Prevenar 13	18 - 49 years, pneumococcal vaccine naïve Pooled Pneumococcal polysaccharide conjugate vaccine (20-valent): 1463 Prevenar 13: 245	Pooled PREVENAR 20: Sex: 492 M/971 F Age: mean (min/max): 35.4 (18/49) years Prevenar 13: Sex: 101 M/144 F Age: mean (min/max): 35,0 (18/49) years

Abbreviations: M: male; F: female

a. Number of subjects vaccinated.

b. One subject was incorrectly enrolled in Cohort 3 (18-49 years of age) rather than Cohort 1 (≥ 60 years of age), and one subject was incorrectly enrolled in Cohort 2 (50 - 59 years of age) rather than Cohort 3 (18-49 years of age).

Comparison of immune responses of Pneumococcal polysaccharide conjugate vaccine (20-valent) to Prevenar 13 and 23vPPV in Pneumococcal vaccine naïve adults

In a randomised, active-controlled, double-blind non inferiority clinical trial (Pivotal Study 1007) of Pneumococcal polysaccharide conjugate vaccine (20-valent) in the United States and Sweden, pneumococcal vaccine naïve adults 18 years of age and older were enrolled into 1 of 3 cohorts based on their age at enrolment (18 to 49, 50 to 59, and ≥ 60 years of age) enrolment and randomised to receive either Pneumococcal polysaccharide conjugate vaccine (20-valent) or control. Participants 60 years of age and older were randomised (1:1 ratio) and received Pneumococcal polysaccharide conjugate vaccine (20-valent) (n = 1,507) followed 1 month later with saline placebo or Prevenar 13 (n = 1,490) followed 1 month later with 23vPPV. Participants 18 to 49 years of age and 50 to 59 years of age were randomly assigned (3:1 ratio) and received a dose of Pneumococcal polysaccharide conjugate vaccine (20-valent) (18 to 49 years of age: n = 335, 50 to 59 years of age: n = 334) or Prevenar 13 (18 to 49 years of age: n = 112, 50 to 59 years of age: n = 111).

Serotype-specific OPA geometric mean titres (GMTs) were measured before the first vaccination and 1 month after each vaccination. Non inferiority of immune responses, OPA GMTs 1 month after vaccination, with Pneumococcal polysaccharide conjugate vaccine (20-valent) to a control vaccine for a serotype was declared if the lower bound of the 2 sided 95 % confidence interval (CI) for the GMT ratio (Pneumococcal polysaccharide conjugate vaccine (20-valent)/Prevenar 13; Pneumococcal polysaccharide conjugate vaccine (20-valent) /23vPPV) for that serotype was greater than 0,5.

In adults 60 years of age and older, immune responses to all 13 matched serotypes elicited by Pneumococcal polysaccharide conjugate vaccine (20-valent) were non inferior to the immune responses to the serotypes elicited by Prevenar 13 1 month after vaccination. Immune responses to 6 out of the 7 additional serotypes induced by Pneumococcal polysaccharide conjugate vaccine (20-valent) were non inferior to the immune responses to these same serotypes induced by 23vPPV one month after vaccination.

The response to serotype 8 missed the pre-specified statistical non inferiority criterion (the lower bound of the 2 sided 95 % CI for the GMT ratio being 0,49 versus > 0,50) (Table 11). The clinical relevance of this single data point is unknown, particularly since supportive analyses for other serotype 8 endpoints showed favourable outcomes. These include 22,1 geometric mean fold rise (GMFR) from before vaccination to 1 month post-vaccination, for serotype 8 in the Pneumococcal polysaccharide conjugate vaccine (20-valent) group, 77,8 % of participants achieved a ≥ 4-fold rise in OPA titres from before vaccination to 1 month after vaccination, and 92,9 % of participants achieved OPA titres ≥ LLOQ 1 month after vaccination; these were within the corresponding ranges observed for the 13 serotypes in the Prevenar 13 control group.

Table 11.OPA GMTs 1 month after vaccination in adults 60 years of age and older given Pneumococcal polysaccharide conjugate vaccine (20-valent) compared to Prevenar 13 for the 13 matched serotypes and 23vPPV for the 7 additional serotypes (Study 1007)[a,b,c,d]

	Pneumococcal polysaccharide conjugate vaccine (20-valent) (N = 1157–1430)	Prevenar 13 (N = 1390–1419)	23vPPV (N = 1201–1319)	Vaccine comparison
	GMT[e]	GMT[e]	GMT[e]	GMT ratio[e] (95 % CI)[e]
Serotype				
1	123	154		0,80 (0,71; 0,90)
3	41	48		0,85 (0,78; 0,93)
4	509	627		0,81 (0,71; 0,93)
5	92	110		0,83 (0,74; 0,94)
6A	889	1 165		0,76 (0,66; 0,88)
6B	1 115	1 341		0,83 (0,73; 0,95)
7F	969	1 129		0,86 (0,77; 0,96)
9V	1 456	1 568		0,93 (0,82; 1,05)
14	747	747		1,00 (0,89; 1,13)
18C	1 253	1 482		0,85 (0,74; 0,97)
19A	518	645		0,80 (0,71; 0,90)
19F	266	333		0,80 (0,70; 0,91)
23F	277	335		0,83 (0,70; 0,97)
Additional Serotypes				
8	466		848	0,55 (0,49; 0,62)
10A	2 008		1 080	1,86 (1,63; 2,12)
11A	4 427		2 535	1,75 (1,52; 2,01)

Table 11.OPA GMTs 1 month after vaccination in adults 60 years of age and older given Pneumococcal polysaccharide conjugate vaccine (20-valent) compared to Prevenar 13 for the 13 matched serotypes and 23vPPV for the 7 additional serotypes (Study 1007)[a,b,c,d]

	Pneumococcal polysaccharide conjugate vaccine (20-valent) (N = 1157–1430)	Prevenar 13 (N = 1390–1419)	23vPPV (N = 1201–1319)	Vaccine comparison
	GMT[e]	GMT[e]	GMT[e]	GMT ratio[e] (95 % CI)[e]
12F	2 539		1717	1,48 (1,27; 1,72)
15B	2 398		769	3,12 (2,62; 3,71)
22F	3 666		1 846	1,99 (1,70; 2,32)
33F	5 126		3 721	1,38 (1,21; 1,57)

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N = number of participants; OPA = opsonophagocytic activity; 23vPPV = pneumococcal polysaccharide vaccine (23-valent).

a. Study 1007 was conducted in the United States and in Sweden.
b. Non-inferiority for a serotype was met if the lower bound of the 2-sided 95 % CI for the GMT ratio (ratio of PREVENAR 20/comparator) was greater than 0,5 (2-fold criterion for non-inferiority).
c. Assay results below the LLOQ were set to 0,5 × LLOQ in the analysis.
d. Evaluable immunogenicity population.
e. GMTs and GMT ratios as well as the associated 2-sided CIs were based on analysis of log-transformed OPA titres using a regression model with vaccine group, sex, smoking status, age at vaccination in years, and baseline log transformed OPA titres.

Immunogenicity in pneumococcal vaccine naïve adults 18 through 59 years of age

Immunogenicity in participants 18 through 59 years of age

In Study 1007, described above, participants 50 through 59 years of age and participants 18 through 49 years of age were randomly assigned (3:1 ratio) to receive 1 vaccination with Pneumococcal polysaccharide conjugate vaccine (20-valent) or Prevenar 13. Serotype-specific OPA GMTs were measured before vaccination and 1 month after vaccination. Higher immune responses were observed in younger adults compared with older adults. A non-inferiority analysis of Pneumococcal polysaccharide conjugate vaccine (20-valent) in the younger age group versus Pneumococcal polysaccharide conjugate vaccine (20-valent) in adults 60 through 64 years of age for a serotype was performed to support the indication in adults 18 through 49 years of age and 50 through 59 years of age. Non-inferiority was to be declared if the lower bound of the 2-sided 95 % CI for the GMT ratio (Pneumococcal polysaccharide conjugate vaccine (20-valent) in participants 18 through 49 years of age / 60 through 64 years of age and in 50 through 59 years of age / 60 through 64 years of age) for the 20 serotypes was > 0,5. Pneumococcal polysaccharide conjugate vaccine (20-valent) elicited immune responses to all 20 vaccine serotypes in both of the younger age groups that were non-inferior to responses in adults 60 through 64 years of age 1 month after vaccination (Table 12).

Table 12. Comparisons of OPA GMTs 1 Month After Pneumococcal polysaccharide conjugate vaccine (20-valent) in Participants 18 Through 49 or 50 Through 59 Years of Age to Participants 60 Through 64 Years of Age (Study 1007)[a,b,c,d]

	18–49 Years (N = 251 –317)	**60–64 Years (N = 765 – 941)**	**18–49 Years Relative to 60 – 64 Years**	**50–59 Years (N = 266 – 320)**	**60–64 Years (N = 765 – 941)**	**50–59 Years Relative to 60 –64 Years**
	GMT[e]	**GMT[e]**	**GMT Ratio[e] (95 % CI)[e]**	**GMT[e]**	**GMT[e]**	**GMT Ratio[e] (95 % CI)[e]**
Serotype						
1	163	132	1,23 (1,01; 1,50)	136	132	1,03 (0,84; 1,26)

Table 12. Comparisons of OPA GMTs 1 Month After Pneumococcal polysaccharide conjugate vaccine (20-valent) in Participants 18 Through 49 or 50 Through 59 Years of Age to Participants 60 Through 64 Years of Age (Study 1007)[a,b,c,d]

	18–49 Years (N = 251 –317)	60–64 Years (N = 765 – 941)	18–49 Years Relative to 60 – 64 Years	50–59 Years (N = 266 – 320)	60–64 Years (N = 765 – 941)	50–59 Years Relative to 60 –64 Years
	GMT[e]	GMT[e]	GMT Ratio[e] (95 % CI)[e]	GMT[e]	GMT[e]	GMT Ratio[e] (95 % CI)[e]
3	42	42	1,00 (0,87; 1,16)	43	41	1,06 (0,92; 1,22)
4	1 967	594	3,31 (2,65; 4,13)	633	578	1,10 (0,87; 1,38)
5	108	97	1,11 (0,91; 1,36)	85	97	0,88 (0,72; 1,07)
6A	3 931	1 023	3,84 (3,06; 4,83)	1 204	997	1,21 (0,95; 1,53)
6B	4 260	1 250	3,41 (2,73; 4,26)	1 503	1 199	1,25 (1,00; 1,56)
7F	1 873	1 187	1,58 (1,30; 1,91)	1 047	1 173	0,89 (0,74; 1,07)
9V	6 041	1 727	3,50 (2,83; 4,33)	1 726	1 688	1,02 (0,83; 1,26)
14	1 848	773	2,39 (1,93; 2,96)	926	742	1,25 (1,01; 1,54)
18C	4 460	1 395	3,20 (2,53; 4,04)	1 805	1 355	1,33 (1,06; 1,68)

Table 12. Comparisons of OPA GMTs 1 Month After Pneumococcal polysaccharide conjugate vaccine (20-valent) in Participants 18 Through 49 or 50 Through 59 Years of Age to Participants 60 Through 64 Years of Age (Study 1007)[a,b,c,d]

	18–49 Years (N = 251 –317)	60–64 Years (N = 765 – 941)	18–49 Years Relative to 60 – 64 Years	50–59 Years (N = 266 – 320)	60–64 Years (N = 765 – 941)	50–59 Years Relative to 60 –64 Years
	GMT[e]	GMT[e]	GMT Ratio[e] (95 % CI)[e]	GMT[e]	GMT[e]	GMT Ratio[e] (95 % CI)[e]
19A	1 415	611	2,31 (1,91; 2,81)	618	600	1,03 (0,85; 1,25)
19F	655	301	2,17 (1,76; 2,68)	287	290	0,99 (0,80; 1,22)
23F	1 559	325	4,80 (3,65; 6,32)	549	328	1,68 (1,27; 2,22)
Additional Serotypes						
8	867	508	1,71 (1,38; 2,12)	487	502	0,97 (0,78; 1,20)
10A	4 157	2 570	1,62 (1,31; 2,00)	2 520	2 437	1,03 (0,84; 1,28)
11A	7 169	5 420	1,32 (1,04; 1,68)	6 417	5 249	1,22 (0,96; 1,56)
12F	5 875	3 075	1,91 (1,51; 2,41)	3 445	3 105	1,11 (0,88; 1,39)
15B	4 601	3019	1,52 (1,13; 2,05)	3 356	2 874	1,17 (0,88; 1,56)
22F	7 568	4 482	1,69 (1,30; 2,20)	3 808	4 228	0,90 (0,69; 1,17)

Table 12. Comparisons of OPA GMTs 1 Month After Pneumococcal polysaccharide conjugate vaccine (20-valent) in Participants 18 Through 49 or 50 Through 59 Years of Age to Participants 60 Through 64 Years of Age (Study 1007)[a,b,c,d]

	18–49 Years (N = 251 –317)	60–64 Years (N = 765 – 941)	18–49 Years Relative to 60 – 64 Years	50–59 Years (N = 266 – 320)	60–64 Years (N = 765 – 941)	50–59 Years Relative to 60 –64 Years
	GMT[e]	GMT[e]	GMT Ratio[e] (95 % CI)[e]	GMT[e]	GMT[e]	GMT Ratio[e] (95 % CI)[e]
33F	7 977	5 693	1,40 (1,10; 1,79)	5 571	5 445	1,02 (0,81; 1,30)

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N = number of participants; OPA = opsonophagocytic activity; PPSV23 = pneumococcal polysaccharide vaccine (23-valent).

a. Study 1007 was conducted in the United States and in Sweden.
b. Non-inferiority for a serotype was met if the lower bound of the 2-sided 95 % CI for the GMT ratio (ratio of younger age group/60 through 64 years of age group) was greater than 0,5 (2-fold criterion for non-inferiority).
c. Assay results below the LLOQ were set to 0,5 × LLOQ in the analysis.
d. Evaluable immunogenicity population.
e. GMTs, GMT ratios, and the associated 2-sided CIs were based on analysis of log-transformed OPA titres using a regression model with age group, sex, smoking status, and baseline log transformed OPA titres. The comparisons between participants 18 through 49 years of age and participants 60 through 64 years of age and between participants 50 through 59 years of age and participants 60 through 64 years of age were based on separate regression models.

Immunogenicity of Pneumococcal polysaccharide conjugate vaccine (20-valent) in adults previously vaccinated with pneumococcal vaccine

A Phase 3 randomised, open-label clinical trial (Study 1006) described immune responses to Pneumococcal polysaccharide conjugate vaccine (20-valent) in adults 65 years of age and older previously vaccinated with 23vPPV, with Prevenar 13, or previously vaccinated with Prevenar 13 followed by 23vPPV. Participants in this study previously vaccinated with Prevenar 13 (Prevenar 13 only or followed by 23vPPV) were enrolled at sites in the United States and participants previously vaccinated with 23vPPV only were also enrolled from Swedish sites (35,5 % in that category).

Pneumococcal polysaccharide conjugate vaccine (20-valent) elicited immune responses to all 20 vaccine serotypes in adults 65 years of age and older with prior pneumococcal vaccination (Table 13). Immune responses were lower in subjects in both groups who received prior 23vPPV vaccinations.

Table 13. Pneumococcal OPA GMTs Before and 1 Month After Pneumococcal polysaccharide conjugate vaccine (20-valent) in Participants 65 Years of Age and Older With Prior Pneumococcal Vaccination (Study 1006)[a,b,c,d]

	Prior PPSV23 only		**Prior Prevenar 13 only**		**Prior Prevenar 13 and PPSV23**	
	Before vaccination (N = 208 – 247)	**After vaccination (N = 216 – 246)**	**Before vaccination (N = 210 - 243)**	**After vaccination (N = 201 – 243)**	**Before vaccination (N = 106 – 121)**	**After vaccination (N = 102 - 121)**
	GMT (95 % CI)[e]	**GMT (95 % CI)[e]**	**GMT (95 % CI)[e]**	**GMT (95 % CI)[e]**	**GMT (95 % CI)[e]**	**GMT (95 % CI)[e]**
Serotype						
1	24 (20, 28)	51 (42, 62)	34 (28, 41)	115 (96, 138)	42 (32, 56)	82 (61, 110)
3	13 (11, 15)	31 (27, 36)	15 (13, 18)	54 (47, 63)	20 (17, 25)	39 (32, 48)

Table 13. Pneumococcal OPA GMTs Before and 1 Month After Pneumococcal polysaccharide conjugate vaccine (20-valent) in Participants 65 Years of Age and Older With Prior Pneumococcal Vaccination (Study 1006)[a,b,c,d]

	Prior PPSV23 only		Prior Prevenar 13 only		Prior Prevenar 13 and PPSV23	
	Before vaccination (N = 208 – 247)	After vaccination (N = 216 – 246)	Before vaccination (N = 210 - 243)	After vaccination (N = 201 – 243)	Before vaccination (N = 106 – 121)	After vaccination (N = 102 - 121)
	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]
4	29 (23, 35)	150 (118, 190)	67 (53, 84)	335 (274, 410)	73 (53, 101)	194 (143, 262)
5	27 (24, 31)	63 (53, 75)	38 (32, 44)	87 (73, 104)	47 (37, 59)	83 (65, 108)
6A	57 (46, 70)	749 (577, 972)	125 (99, 158)	1081 (880, 1327)	161 (116, 224)	1085 (797, 1478)
6B	107 (86, 133)	727 (574, 922)	174 (138, 219)	1159 (951, 1414)	259 (191, 352)	1033 (755, 1415)
7F	156 (132, 184)	378 (316, 452)	210 (175, 251)	555 (467, 661)	206 (164, 258)	346 (277, 432)
9V	203 (171, 241)	550 (454, 667)	339 (282, 408)	1085 (893, 1 318)	352 (270, 459)	723 (558, 938)
14	212 (166, 270)	391 (315, 486)	282 (224, 356)	665 (554, 798)	336 (238, 473)	581 (434, 777)
18C	173 (137, 218)	552 (445, 684)	219 (177, 272)	846 (693, 1 033)	278 (209, 369)	621 (470, 821)

Table 13. Pneumococcal OPA GMTs Before and 1 Month After Pneumococcal polysaccharide conjugate vaccine (20-valent) in Participants 65 Years of Age and Older With Prior Pneumococcal Vaccination (Study 1006)[a,b,c,d]

	Prior PPSV23 only		Prior Prevenar 13 only		Prior Prevenar 13 and PPSV23	
	Before vaccination (N = 208 – 247)	After vaccination (N = 216 – 246)	Before vaccination (N = 210 - 243)	After vaccination (N = 201 – 243)	Before vaccination (N = 106 – 121)	After vaccination (N = 102 - 121)
	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]
19A	82 (66, 100)	239 (197, 288)	124 (100, 153)	365 (303, 440)	182 (141, 235)	341 (264, 439)
19F	61 (52, 71)	159 (131, 192)	89 (74, 107)	242 (199, 294)	120 (94, 154)	218 (168, 282)
23F	23 (18, 28)	152 (115, 199)	48 (37, 62)	450 (358, 566)	66 (46, 94)	293 (204, 420)
Additional Serotypes						
8	55 (45, 67)	212 (172, 261)	28 (24, 33)	603 (483, 753)	139 (99, 195)	294 (220, 392)
10A	212 (166, 269)	1012 (807, 1270)	141 (113, 177)	2005 (1586, 2 536)	400 (281, 568)	1580 (1 176, 2 124)
11A	510 (396, 656)	1473 (1 192, 1820)	269 (211, 343)	1908 (1 541, 2 362)	550 (386, 785)	1567 (1 141, 2 151)
12F	147 (112, 193)	1054 (822, 1 353)	53 (43, 65)	1763 (1 372, 2 267)	368 (236, 573)	1401 (1 002, 1 960)

Table 13. Pneumococcal OPA GMTs Before and 1 Month After Pneumococcal polysaccharide conjugate vaccine (20-valent) in Participants 65 Years of Age and Older With Prior Pneumococcal Vaccination (Study 1006)[a,b,c,d]

	Prior PPSV23 only		Prior Prevenar 13 only		Prior Prevenar 13 and PPSV23	
	Before vaccination (N = 208 – 247)	After vaccination (N = 216 – 246)	Before vaccination (N = 210 - 243)	After vaccination (N = 201 – 243)	Before vaccination (N = 106 – 121)	After vaccination (N = 102 - 121)
	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]	GMT (95 % CI)[e]
15B	140 (104, 189)	647 (491, 853)	74 (56, 98)	1480 (1 093, 2 003)	190 (124, 291)	1067 (721, 1 578)
22F	167 (122, 230)	1773 (1 355, 2 320)	60 (45, 82)	4157 (3 244, 5 326)	286 (180, 456)	2718 (1 978, 3 733)
33F	1 129 (936, 1 362)	2 026 (1 684, 2 437)	606 (507, 723)	3 175 (2 579, 3 908)	1 353 (1 037, 1 765)	2 183 (1 639, 2 908)

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N = number of participants; OPA = opsonophagocytic activity; PPSV23 = pneumococcal polysaccharide vaccine (23-valent).

a. Study 1006 was conducted in the United States and in Sweden.

b. Assay results below the LLOQ were set to 0,5 × LLOQ in the analysis.

c. Evaluable immunogenicity population.

d. Open-label administration of Pneumococcal polysaccharide conjugate vaccine (20-valent)

e. 2-sided CIs based on the Student t distribution.

Concomitant vaccine administration

Paediatric population

In Study 1012, the concomitant administration of Infanrix hexa (containing DTaP, HBV, IPV, and Hib antigens) with all 3 doses of Pneumococcal polysaccharide conjugate vaccine (20-valent) or Prevenar 13 and single doses of a vaccine containing MMR antigens and Varilrix (varicella antigens) were also administered with the third dose and evaluated 1 month after the third (toddler) dose of Pneumococcal polysaccharide conjugate vaccine (20-valent) or Prevenar 13. Noninferiority was demonstrated for immune responses to diphtheria, tetanus, acellular pertussis, hepatitis B, poliovirus, Hib, MMR, and varicella vaccine antigens co-administered with Pneumococcal polysaccharide conjugate vaccine (20-valent) compared with Prevenar 13. The results from Study 1012 support co-administration of Pneumococcal polysaccharide conjugate vaccine (20-valent) with routine paediatric vaccines. No safety concerns were identified in this study.

In Study 1011, the concomitant administration of a vaccine containing DTaP, HBV, IPV antigens and Hiberix (Hib antigen) with each of the 3 infant doses of either Pneumococcal polysaccharide conjugate vaccine (20-valent) or Prevenar 13 were evaluated 1 month after the third dose. Concomitant administration of single doses of M-M-R II (MMR antigens) and Varivax (varicella antigens) with the fourth dose of either Pneumococcal polysaccharide conjugate vaccine (20-valent) or Prevenar 13 were evaluated 1 month following vaccination. Noninferiority was demonstrated for immune responses to the co-administered diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Hib vaccine antigens 1 month after 3 infant doses and coadministered MMR, and varicella virus vaccine antigens after the fourth (toddler) dose of Pneumococcal polysaccharide conjugate vaccine (20-valent) compared with Prevenar 13. The results from Study 1011 support co-administration of Pneumococcal polysaccharide conjugate vaccine (20-valent) with routine paediatric vaccines. No safety concerns were identified in this study.

Influenza and rotavirus vaccines were permitted to be administered concomitantly at any time during these studies according to local or national recommendations.

Adults

Clinical trial in adults to assess Pneumococcal polysaccharide conjugate vaccine (20-valent) given with influenza vaccine, adjuvanted (Fluad Quadrivalent, [QIV])

In a double-blind, randomised study B7471004 (Study 1004), adults 65 years of age and older were randomised in a 1:1 ratio to receive Pneumococcal polysaccharide conjugate vaccine (20-valent) concomitantly administered with an influenza vaccine, adjuvanted (Fluad Quadrivalent, [QIV]) (Group 1, N = 898) or Pneumococcal polysaccharide conjugate vaccine (20-valent) administered 1 month after receiving QIV (Group 2, N = 898). Pneumococcal serotype-specific OPA GMTs were evaluated 1 month after Pneumococcal polysaccharide conjugate vaccine (20-valent) and influenza vaccine strain hemagglutinin inhibition assay (HAI) GMTs were evaluated 1 month after QIV. The noninferiority criteria for the comparisons of OPA GMTs (lower limit of the 2-sided 95 % CI of the GMT ratio [Group 1/Group 2] > 0,5; 2-fold noninferiority criterion) were met for all 20 pneumococcal serotypes in Pneumococcal polysaccharide conjugate vaccine (20-valent). OPA GMTs were slightly lower for some serotypes when Pneumococcal polysaccharide conjugate vaccine (20-valent) was administered concomitantly with QIV compared to Pneumococcal polysaccharide conjugate vaccine (20-valent) administered alone. The noninferiority criteria for the comparisons of HAI GMTs (lower limit of the 2-sided 95 % CI for the GMT ratio [Group 1/Group 2] >0,67; 1,5-fold noninferiority criterion) were also met for all 4 influenza vaccine strains.

Clinical trial in adults to assess Pneumococcal polysaccharide conjugate vaccine (20-valent) given with a third (booster) dose of COVID-19 mRNA vaccine (Comirnaty [tozinameran])

In a double-blind, randomised descriptive study B7471026 (Study 1026), adults 65 years of age and older who had received 2 doses of COVID-19 mRNA vaccine (Comirnaty [tozinameran]) at least 6 months earlier, were randomised in a 1:1:1 ratio to receive Pneumococcal polysaccharide conjugate vaccine (20-valent) concomitantly administered with a third (booster) dose of COVID-19 mRNA vaccine (Comirnaty [tozinameran]) (N = 190), Pneumococcal polysaccharide conjugate vaccine (20-valent) administered alone (N = 191), or a third (booster) dose of COVID-19 mRNA vaccine (Comirnaty [tozinameran]) administered alone (N = 189).

Immune responses to both vaccines were observed after co-administration of Pneumococcal polysaccharide conjugate vaccine (20-valent) and COVID-19 mRNA vaccine (Comirnaty [tozinameran]). OPA GMTs for the 20 pneumococcal serotypes were similar to Pneumococcal polysaccharide conjugate vaccine (20-valent) administered alone and IgG GMCs for the full-length S-binding protein were similar to COVID-19 mRNA vaccine (Comirnaty [tozinameran]) administered alone. A post-hoc analysis found the immune responses to all 20 serotypes elicited by Pneumococcal polysaccharide conjugate vaccine (20-valent) when co-administered with COVID-19 mRNA vaccine (Comirnaty [tozinameran]) would have met conventional 2-fold noninferiority criteria compared to Pneumococcal polysaccharide conjugate vaccine (20-valent) alone, and the full-length S-binding IgG GMC elicited by COVID-19 mRNA vaccine (Comirnaty [tozinameran]) would have met conventional 1,5-fold noninferiority compared to COVID-19 mRNA vaccine (Comirnaty [tozinameran]) alone.

Prevenar 13 Immune responses in special populations

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

Studies in SCD, HIV and haematopoietic stem cell transplant (HSCT) participants have not been conducted with Pneumococcal polysaccharide conjugate vaccine (20-valent); however, safety and immunogenicity of Prevenar 13 are relevant to Pneumococcal polysaccharide conjugate vaccine (20-valent), since the vaccines are manufactured similarly and contain 13 of the same polysaccharide conjugates.

Sickle cell disease (SCD)

An open label single arm study 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 one or more doses of 23vPPV at least 6 months prior to enrolment. 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.

OPA GMTs in subjects with SCD, before and after each dose are presented in Table 14 for the evaluable immunogenicity population. In general, antibodies increased in response to dose 1, declined over the 6 months between doses 1 and 2, but remained higher than before dose 1 levels for all serotypes. OPA GMTs then increased in response to dose 2. The OPA GMTs after dose 2 were similar to or higher than those after dose 1 for subjects in the evaluable immunogenicity population for all serotypes.

Table 14. Pneumococcal OPA GMTs at Dose 1 and Dose 2–Evaluable Immunogenicity Population

Sero type	Pre-Dose 1 N[a]=95-131		Post-Dose 1 N[a]=89-123		Post-Dose 2 N[a]=89-118	
	GMT[b]	(95 % CI[c])	GMT[b]	(95 % CI[c])	GMT[b]	(95 % CI[c])
1	7	(5,7; 8,8)	56	(41,0; 77,4)	78	(59,5; 101,2)
3	13	(10,1; 17,5)	115	(93,0; 142,1)	105	(87,2; 127,2)
4	215	(129,6; 357,2)	2670	(2 128,1; 3 351,1)	3051	(2 536,7; 3 670,3)
5	10	(7,8; 13,9)	277	(198,4; 385,8)	273	(213,9; 349,2)
6A	246	(149,0; 404,8)	7845	(6 581,6; 9 349,9)	7633	(6 439,6; 9 048,6)
6B	626	(377,5; 1 037,4)	7535	(6 320,5; 8 983,5)	7601	(6 392,6; 9 038,6)
7F	344	(220,5; 537,9)	3348	(2 881,9; 3 888,5)	3723	(3 276,2; 4 230,1)
9V	234	(137,6; 398,7)	2312	(1 684,0; 3 172,8)	3467	(2 784,0; 4 317,6)
14	628	(425,8; 925,7)	2288	(1 906,6; 2 745,0)	2081	(1 770,5; 2 446,0)
18C	426	(235,7; 771,4)	4326	(3 250,3; 5 756,8)	5271	(4 267,8; 6 510,1)

19A	137	(100,0; 187,4)	1449	(1 164,2; 1 804,3)	1314	(1 084,4; 1 592,6)
19F	94	(55,0; 160,7)	1429	(1043,5; 1 957,3)	1507	(1 139,9; 1 992,2)
23F	34	(21,5; 54,8)	1607	(1 227,4; 2 102,7)	2330	(1 880,4; 2 887,0)

a. N = Number of subjects with a determinate OPA antibody titre to the given serotype.

b. Geometric mean titres (GMTs) were calculated using all subjects with available data for the specified blood draw.

c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titres.

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

The immunogenicity of Prevenar has been investigated in an open-label, multicentre 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 23vPPV at the age of 15 - 18 months. After primary immunisation, 95,6 % of the subjects had antibody levels of at least 0,35 ug/mL for all seven serotypes found in Prevenar (7-valent). 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.

HIV infection

Children and adults not previously vaccinated with a pneumococcal vaccine

In Study 6115A1-3002 (B1851021), 151 HIV infected participants 6 to < 18 years of age and 152 participants ≥ 18 years of age (CD4 ≥ 200 cells/µL, viral load < 50,000 copies/mL and free of active acquired immunodeficiency syndrome [AIDS]-related illness) not previously vaccinated with a pneumococcal vaccine

received 3 doses of Prevenar 13. As per general recommendations, a single dose of 23vPPV was subsequently administered. Vaccines were administered at 1-month intervals. Immune responses were assessed in 128 to 133 evaluable participants 6 to < 18 years of age and in 131 to 137 evaluable participants ≥ 18 years of age 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 to or higher than those after the first dose.

Adults previously vaccinated with PPSV23

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 23vPPV administered at least 6 months prior to enrolment. Participants received 3 doses of Prevenar 13: at enrolment, 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 significantly higher when compared to levels prior to vaccination. After the second and third dose of Prevenar 13, immune responses were comparable to or higher than those after the first dose. Participants who received 2 or more previous doses of 23vPPV showed a similar immune response compared with participants who received a single previous dose. The immune responses to Prevenar 13 observed in HIV infected adults were lower than the immune responses reported for healthy adults.

Haematopoietic stem cell transplant (HSCT)

In Study 6115A1-3003 (B1851022), 61 participants 2 to < 18 years of age and 190 participants ≥ 18 years of age with an allogeneic HSCT 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 23vPPV was administered 1 month after the fourth dose of Prevenar 13. Immune responses as measured by IgG GMCs, were assessed in 41 to 52 evaluable participants 2 to < 18 years of age and in 130 to 159 evaluable participants ≥ 18 years of age approximately 1 month after vaccination. Prevenar 13

elicited increased antibody levels after each dose. Immune responses after the fourth dose of Prevenar 13 were significantly increased for all serotypes compared with after the third dose with the exception of serotype 3 in the 2 to < 18 years age group. Overall, participants 2 to < 18 years of age had generally higher serotype-specific immune responses compared with those ≥ 18 years of age.

This study demonstrated that 4 doses of Prevenar 13 elicited serum IgG concentrations similar to those induced by a single dose in healthy participants of the same age group.

Paediatric population

Prevenar efficacy and Prevenar 13 effectiveness in children

Invasive pneumococcal disease (IPD)

The information captured in this section comes from published literature.

The impact of Prevenar 13 on the rates of IPD in the United States was measured using an active population-based and laboratory-based surveillance system: the Active Bacterial Core surveillance (ABCs). In 2000, Prevenar (7-valent) was introduced into the routine infant immunisation programme in the USA, with a 3 dose primary series and a booster dose in the second year of life. In 2010, Prevenar 13 replaced Prevenar.

For the 2012 - 2013 period, there were statistically significant declines in the incidence of IPD for the Prevenar-13 unique serotypes (i.e. “Prevenar 13 minus Prevenar” serotypes. The disease reductions were calculated using a model of observed versus expected (if Prevenar 13 had not replaced Prevenar) IPD cases with 95 % Interval Estimates (IEs) and are shown in Table 15.

Table 15. United States: IPD due to Prevenar-13 unique serotypes (Observed vs Expected)

Age Group, Years	Percent Change in Rate (95 % IE)	Percent Change in Rate (95 % IE)	Percent Change in Rate (95 % IE)

Table 15. United States: IPD due to Prevenar-13 unique serotypes (Observed vs Expected)

	2010 - 2011	2011 - 2012	2012 - 2013
<5	-66 (-61, -70)	-88 (-86, -89)	-93 (-91, -94)
5-17	-33 (-21, -45)	-59 (-48, -66)	-75 (-67, -80)
18-49	-33 (-26, -38)	-64 (-60, -68)	-72 (-69, -75)
50-64	-23 (-18, -28)	-54 (-50, -57)	-62 (-59, -65)
≥65	-23 (-13,-31)	-46 (-39, -52)	-58 (-52, -64)

In all age groups, these reductions were driven principally by declines in IPD caused by serotypes 19A and 7F. There was no significant increase in disease caused by non-Prevenar 13 serotypes among children younger than 5 years and most adult age groups, except for adults 50 – 64 years old where a 26 % increase (95 % IE 13–44) was detected in non-Prevenar 13 type IPD during 2012–13 compared to expected incidence, although no non-Prevenar 13 serotype predominated. However, serotype replacement may not be expected within 2 years after introduction of Prevenar 13.

The prevalence of at least one risk factor increased among children and adults with IPD after the introduction of Prevenar 13. The proportions of cases resulting in hospital admission were also higher in the period after the introduction of Prevenar 13 in both children and adults, but case-fatality rates did not change.

After the introduction of Prevenar 13, a reduction in the incidence of antibiotic-resistant IPD (vaccine serotype or non-vaccine serotype IPD) was also identified. Penicillin-non-susceptible IPD, erythromycin-non-susceptible IPD and multiply-non-susceptible IPD decreased by 78 – 96 % among children younger than 5 years. Among adults, reductions in the incidence of penicillin-non-susceptible IPD and multiply-non-susceptible IPD were also seen. The reductions in antibiotic non-susceptible IPD were largely attributable

to reductions in IPD caused by serotype 19A, the serotype associated with increased antibiotic non-susceptibility before the introduction of Prevenar 13.

In England and Wales, 23vPPV was in use for risk subjects > 2 years of age from 1992. This vaccine was also recommended for adults ≥ 80 years, ≥ 75 years and ≥ 65 years of age from 2003, 2004 and 2005, respectively. Prevenar (7-valent) was first recommended for risk children <2 years of age in 2002 and from 2005 for “risk children” <5 years. From 2006, Prevenar (7-valent) was introduced into the Routine Childhood Immunisation Programme with a catch-up campaign for children up to two years of age. As of April 2010, the Prevenar (7-valent) was replaced by Prevenar 13 and it simply replaced Prevenar (7-valent) at the point in the schedule that any child had reached. There was no catch-up program.

Four years after the introduction of Prevenar (7-valent) 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 Prevenar (7-valent) vaccine serotypes was reported in children under 2 years, in England and Wales. However, reductions were accompanied by an increase in IPD from non-vaccine serotypes, such as 7F, 19A and 22F, thus diminishing the effect of Prevenar (7-valent) on overall IPD incidence.

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 % (95 % CI 7; 94) in children less than 2 years of age to 91 % (95 % CI 33; 99) 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 % (95 % CI 6; 89) (serotype 3) to 100 % (95 % CI 62; 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). Overall, the reductions observed were attenuated by the increase in non-PCV13 IPD, both in adults ≥ 65 years and in children younger < 5 years - the two groups with the highest incidence of pneumococcal-attributable disease.

Table 16. Serotype specific number of cases and incidence reductions (%) of IPD in 2013/14 compared to 2008-2010 by age in England and Wales§#

	< 5 years of age			5 to 64 years of age			≥6 5 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	5	91 % (68 %; 98 %)**	458	77	83 % (74 %; 88 %)**	102	13	87 % (72 %; 94 %)**
3	26	8	68 % (6 %; 89 %)	178	73	59 % (38 %; 72 %)**	256	143	44 % (27 %; 57 %)**
6A	10	0	100 % (62 % ; 100 %;)**	53	5	90 % (56 %; 97 %)**	94	5	95 % (81 %; 99 %)**
7F	90	8	91 % (74 %; 97 %)**	430	160	63 % (50 %; 71%)**	173	75	56 % (37 %; 70 %)**
19A	85	7	91 % (75 %; 97 %)**	225	104	54 % (32 %; 65 %)**	279	97	65 % (53 %; 75 %)**
NVT	94	136	-34 % (-133 %, 23 %)	878	1068	- 8 % (31 %, 10,1 %)	867	1144	-13 % (-36 %, 0,6 %)

§ 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

No cases of serotype 5 IPD were identified

NVT Non-PCV13 serotypes

Otitis media (OM)

Information captured in this section has been taken from published literature.

A study was conducted one year following the introduction of Prevenar 13 in the USA. It utilised an insurance claims database of a large, nationwide managed health care plan. Enrolled children aged 6 years or younger and those with OM visits were identified (5,51 million child-years). There was a significant drop in OM visit rates that coincided with the introduction of Prevenar 13 in 2010 and the observed OM visit rates in 2010 and 2011 were lower than the projected rates based on the 2005 - 2009 trend (p<0,001).

In a multicentre surveillance study of *Streptococcus pneumoniae* isolates from spontaneous drainage, PE tube placement, myringotomy or mastoid surgical cultures from 8 children's hospitals in the USA were obtained. In 2011, 74 of 149 (50 %) isolates were Prevenar 13 plus a related serotype; in 2012 and 2013, these serotypes accounted for 47 of 116 (40,5 %) and 34 of 118 (29 %) of isolates, respectively.Overall, there was a reduction in the proportion of isolates included in Prevenar 13 over the 3 years following the introduction of that vaccine, including antibiotic resistant strains. Serotype 19A was the most common serotype isolated in each year. The number of serotype 19A isolates in 2013 (n = 12, 10,2 % of total) decreased 76 % compared with 2011 (n = 50, 33,6 % of total).

In a published study performed prospectively in Israel between 2004 and 2013, the impact on OM of introduction of a 2-dose primary series of Prevenar 13 plus booster dose in the second year of life was recorded in a population-based active-surveillance system including culture results of middle ear fluid obtained by tympanocentesis. The decision to perform tympanocentesis in the presence of OM was

independent of the study protocol. Overall, 6,122 OM episodes with middle ear fluid cultures were recorded in children less than 2 years of age. Declines in incidence were recorded from 2.1 to 0.1 cases per 1 000 children (96 %) for the Prevenar serotypes plus serotype 6A and a decline in incidence from 0,9 to 0,1 cases per 1 000 children (85 %) for the additional serotypes 1, 3, 5, 7F, and 19A in Prevenar 13. The annual overall pneumococcal incidence of OM declined from 9,6 to 2,1 cases per 1 000 children (77 %) between July 2004 (prior to the introduction of Prevenar) and June 2013 (post Prevenar 13 introduction). However, the true reduction of overall OM incidences could not be studied, as simple OM can be subclinical, subject to over- and under diagnosis and, above all, not subjected to middle ear fluid culture.

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

Information captured in this section has been taken from published literature.

The effect of Prevenar 13 on admissions to hospital in the USA 2 years after its introduction in 2010 was assessed using data from a private inpatient discharge record database covering approximately 20 % of inpatients in the USA. A multiple regression model was used to estimate change in admissions to hospital for all-cause pneumonia, invasive pneumococcal disease, non-invasive pneumococcal pneumonia, and empyema, and for negative controls, urinary tract infection and hospital admission for any reason. Direct cause and effect cannot be inferred from analyses of this type.

Reduction in hospital admission for all-cause pneumonia of 21 % [95 % CI 14 – 28] was reported for children aged less than 2 years and 17 % [95 % CI 7 – 27]. for those aged 2 – 4 years: For empyema the reduction was 50 % [95 % CI 22 – 68] for children age < 2 years, 46 % [95 % CI 21 – 64] for children 2 – 4 years, and 37 % [95 % CI 13 – 54] for those aged 5 – 17 years. All-cause pneumonia was reduced in adults 18 – 39

years (12 % (95 % CI 6 – 17) but not for other adult age groups. Non-invasive pneumococcal or lobar pneumonia fell for all age groups except toddlers aged 2 – 4 years.

In a multicentre observational study in France between June 2009 and May 2012 comparing the periods before and after the switch from Prevenar (7-valent) 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< 0,002) 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 Prevenar (7-valent) 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 61; 73) in outpatient visits and 32 % (95 % CI 22; 39) in hospitalisations for alveolar CAP (a dense opacity that may be a fluffy consolidation of a portion, whole of a lobe or of the entire lung, often containing air bronchogram and sometimes associated with pleural effusion) following the introduction of Prevenar 13 when compared to the period before the introduction of Prevenar (7-valent) was introduced.

Carriage

The information captured in this section has been taken from published literature.

A study of nasopharyngeal carriage of *Streptococcus pneumoniae* in predominantly black children 6 – 59 months of age presenting to a children's hospital emergency department in Atlanta, USA between 1 July 2010 and 30 June 2013 showed a significant reduction in carriage of Prevenar 13 serotypes and antibiotic-resistant strains after the introduction of Prevenar 13. The overall proportion of children with *Streptococcus pneumoniae* carriage ranged from 28 % to 35,4 % and did not significantly change through the study period. Carriage of Prevenar 13 serotypes decreased significantly from 29 % (36/124) to 3 % (3/99; p < 0,0001),

primarily due to a significant decrease in serotype 19A carriage from 25,8 % (32/124) to 3 % (3/99; P < 0,0001). The proportion of carriage isolates with nonsusceptibility to ceftriaxone declined from 22,6 % to 3 % and nonsusceptibility to penicillin also declined from 24 % to 3 %.

The proportion of pneumococcal carriage accounted for by non-PCV13 serotypes (excluding 6C) increased from 68,4 % (78/114) to 96,9 % (95/98; P < 0,0001). Non-PCV13 serotypes 35B, 15B/C, 11A, 21, 23B and 15A were the most commonly carried serotypes during the last 2 study periods. Carriage of serotype 35B increased during the 6 study periods from 8,9 % (11/124) to 25,3 % (25/99). Serotype 35B demonstrated moderate non-susceptibility to selected antibiotics.

Reduction of Antimicrobial Resistance (AMR)

The information captured in this section has been taken from published literature.

Following the introduction of Prevenar (7-valent) 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 medicines.

A post-hoc analysis of a double–blind, randomised, controlled study enrolling 1866 subjects in Israel conducted between February 2008 and September 2009, compared Prevenar (7-valent) and Prevenar 13. The reported reduction of new acquisitions of *S. pneumoniae,* serotypes 19A, 19F, and 6A not susceptible to either penicillin, erythromycin, clindamycin, penicillin plus erythromycin, or multiple medicines (≥3 antibiotics) ranged between 34 % and 62 % depending on serotype and antibiotic.

Data from 10 surveillance sites of the United States Centers for Disease Control and Prevention covering 31 million individuals show that from 2009 to 2013, rates of antibiotic-nonsusceptible IPD caused by serotypes included in Prevenar 13 but not in Prevenar (7-valent) decreased from 6,5 to 0,5 per 100 000 in children aged <5 years and from 4,4 to 1,4 per 100 000 in adults aged ≥ 65 years. Antibiotic-non-susceptible

IPD caused by non- Prevenar 13 serotypes increased from 41,8 % (n = 1995) to 65,0 % (n = 2397) (P < 0,001). Among antibiotic-non-susceptible IPD caused by non-Prevenar 13 serotypes, increases from 2009 to 2013 among children aged < 5 years (from 2,5 to 3, 1 per 100 000) and among adults aged ≥ 65 years (from 6,4 to 7,3 per 100 000) were observed. In 2013, the most frequent non-vaccine serotypes among cases with antibiotic-non-susceptible IPD were 35B (16,2 %), 33F (15,5 %), 22F (12,3 %), and 15A (11,7 %). Among multidrug-non-susceptible IPD, the most frequent non-vaccine serotypes were 35B (59,9 %), 15A (17,8 %), 6C (5,6 %), and 15C (5,6 %).

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

The efficacy of Prevenar (7-valent) was evaluated in two major trials – the Northern California Kaiser Permanente (NCKP) trial and the Finnish Otitis Media trial (FinOM). Both trials were randomised, double-blind, active-control trials in which infants were randomised to receive either Prevenar (7-valent) or control vaccine (NCKP, meningococcal serogroup C CRM-conjugate [MnCC] vaccine; FinOM, hepatitis B vaccine) in a four-dose series at 2, 4, 6, and 12 - 15 months of age. The various efficacy results from these trials (for invasive pneumococcal disease, pneumonia, and acute otitis media) are presented below (Table 17).

Table 17. Summary of efficacy of Prevenar (7-valent)

Test	Study	N	VE*	95 % CI
Invasive Pneumococcal Disease (IPD)				
Per-protocol	NCKP	30 258	97 %	85, 100
Intent-to-treat		37 866	94 %	81, 99
Pneumonia (Per-protocol)				
With vaccine serotype bacteraemia			87,5 %	7, 99
Clinical pneumonia with abnormal chest X-ray regardless of etiologic confirmation			35 %	4, 56
Acute Otitis Media (AOM)				
Per-protocol (reduction of)	NCKP	37 868		
Total episodes			7 %	4, 10
Recurrent AOM (3 episodes in 6 mo. or 4 episodes in 1 yr.)			9 %	3, 15
Recurrent AOM (5 episodes in 6 mo. or 6 episodes in 1 yr.)			23 %	7, 36
Tympanostomy tube placement			20 %	2, 35
Per-protocol (reduction of)	FinOM	1662		
Total episodes			6 %	-4, 16
All pneumococcal AOM			34 %	21, 45
Vaccine-serotype AOM			57 %	44, 67
Intent-to-treat				
Vaccine-serotype AOM			54 %	41, 64

*Vaccine efficacy

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Genotoxicity

PREVENAR 20 has not been tested for genotoxic potential

Carcinogenicity

PREVENAR 20 has not been tested for carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium phosphate

Sodium chloride

Succinic acid

Polysorbate 80

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other medicines.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

Pre-filled syringes should be stored in the refrigerator horizontally to minimise the resuspension time.

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

From a microbiological point of view, once removed from the refrigerator, the vaccine should be used immediately.

Stability data indicate that the vaccine is stable for 96 hours when stored at temperatures from 8 °C to 25 °C, or 72 hours when stored at temperatures from 0 °C to 2 °C. At the end of these time periods PREVENAR 20 should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

6.5 Nature and contents of container

0,5 mL suspension for injection in pre-filled syringe (Type I glass) with a tip cap (synthetic isoprene/bromobutyl blend rubber) and a grey plunger stopper (chlorobutyl rubber).

Pack sizes of 1, 10, and 50 pre-filled syringes, with or without needles [25G x 5/8" (0,5 x 16 mm) needle or 25G x 1″ (0,5 x 25 mm) needle]

Not all pack sizes may be marketed.

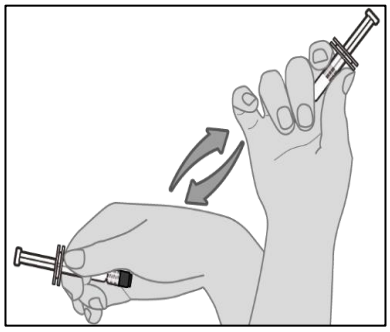
6.6 Special precautions for disposal and other handling

During storage, a white deposit and clear supernatant may be observed in the pre-filled syringe containing the suspension.

Preparation for administration

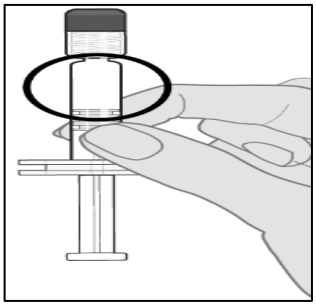
Step 1. Vaccine resuspension

Hold the pre-filled syringe horizontally between the thumb and the forefinger and shake vigorously until the contents of the syringe are a homogeneous white suspension. Do not use the vaccine if it cannot be resuspended.



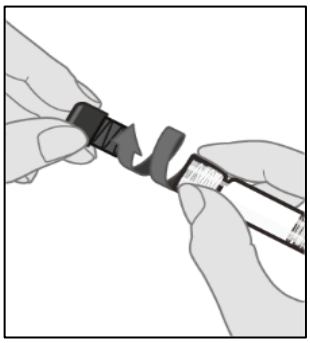
Step 2. Visual inspection

Visually inspect the vaccine for large particulate matter and discolouration prior to administration. Do not use if large particulate matter or discolouration is found. If the vaccine is not a homogeneous white suspension, repeat steps 1 and 2.



Step 3. Remove syringe cap

Remove the syringe cap from the Luer lock adapter by slowly turning the cap counterclockwise while holding the Luer lock adapter.



Note: Care should be taken to ensure that the extended plunger rod is not depressed while removing the syringe cap.

Step 4. Attach a sterile needle

Attach a 25G x 5/8" (0,5 x 16 mm) needle or 25G x 1″ (0,5 x 25 mm) needle appropriate for intramuscular administration to the pre-filled syringe by holding the Luer lock adapter and turning the needle clockwise.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

Building 2, 1st Floor

Maxwell Office Park

Magwa Crescent

Waterfall City, Midrand, 1685

South Africa

Tel: +27(0) 11 320 6000 / 0860 734 937 (Toll-free South Africa)

Manufacturer:

Pfizer Ireland Pharmaceuticals, Grange Castle Business Park, Clondalkin, Dublin 22 Ireland

8. REGISTRATION NUMBER

59/30.2/0853

9. DATE OF FIRST AUTHORISATION

22 July 2025

10. DATE OF REVISION OF THE TEXT