SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

VAXNEUVANCE™ (Pneumococcal 15-valent Conjugate Vaccine [CRM_{197} Protein], adsorbed)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mL dose contains 32 µg of total pneumococcal polysaccharide (2.0 µg each of polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F, and 4.0 µg of polysaccharide serotype 6B) conjugated to 30 µg of CRM_{197} carrier protein, and 125 µg of aluminum (as aluminum phosphate adjuvant).

For the full list of excipients, see *section 6.1*.

3 PHARMACEUTICAL FORM

VAXNEUVANCE™ is a suspension for injection available in 0.5 mL single-dose prefilled syringes.

The vaccine is an opalescent suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VAXNEUVANCE is a vaccine indicated in infants, children and adolescents from 6 weeks through 17 years of age (prior to the 18th birthday) for active immunization for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F.

VAXNEUVANCE™ is indicated in adults 18 years of age and older for active immunization for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F).

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

4.2 Posology and method of administration

General

The vaccination schedule for VAXNEUVANCE should be based on official recommendations.

Posology

Administer a 0.5 mL dose of VAXNEUVANCE intramuscularly.

Method of administration

For intramuscular use only. Do not inject intravascularly.

The preferred site for injection is the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in children and adults. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

Routine vaccination schedule in infants and children aged 6 weeks to less than 2 years	
Two-dose primary series followed by a booster dose	The recommended immunisation regimen consists of 3 doses of Vaxneuvance, each of 0.5 ml. The first dose is given as early as 6 weeks of age, with a second dose administered 8 weeks later. The third (booster) dose is recommended between 11 through 15 months of age.
Three-dose primary series followed by a booster dose	An immunisation regimen consisting of 4 doses of Vaxneuvance, each of 0.5 mL, may be given. This primary series consists of 3 doses, with the first dose given as early as 6 weeks of age, with an interval of 4 to 8 weeks between doses in the primary series. The fourth (booster) dose is recommended between 11 through 15 months of age and at least 2 months after the third dose.
Preterm infants (<37 weeks gestation at birth)	The recommended immunisation regimen consists of a three-dose primary series of Vaxneuvance followed by a fourth (booster) dose, each of 0.5 mL, as per three-dose primary series followed by a booster dose posology (see sections 4.4 and 5.1).
Prior vaccination with another pneumococcal conjugate vaccine	Infants and children who have begun immunisation with another pneumococcal conjugate vaccine may switch to Vaxneuvance at any point in the schedule (see section 5.1).
Catch-up vaccination schedule for children 7 months to less than 18 years of age	
Unvaccinated infants 7 to less than 12 months of age	3 doses, each of 0.5 mL, with the first two doses given at least 4 weeks apart. A third (booster) dose is

	recommended after 12 months of age, separated from the second dose by at least 2 months.
Unvaccinated children 12 months to less than 2 years of age	2 doses, each of 0.5 mL, with an interval of 2 months between doses.
Unvaccinated or not fully vaccinated children and adolescents 2 to less than 18 years of age	1 dose (0.5 mL). If a previous pneumococcal conjugate vaccine was administered, at least 2 months should elapse before administering Vaxneuvance.
Vaccination schedule for individuals 18 years of age and older	
Individuals 18 years of age and older	1 dose (0.5 mL). The need for revaccination with a subsequent dose of Vaxneuvance has not been established.

If a previous pneumococcal conjugate vaccine was administered, at least 2 months should elapse before receiving VAXNEUVANCE.

Instructions for use

VAXNEUVANCE™ should not be diluted or mixed with other vaccines. The full recommended dose of the vaccine should be used.

When VAXNEUVANCE™ is administered at the same time as another injectable vaccine(s), the vaccines should always be given at different injection sites (see *section 4.5*).

Because this product is a suspension containing an adjuvant, hold horizontally and shake vigorously immediately prior to use to obtain an opalescent suspension in the vaccine container. Do not use the vaccine if it cannot be resuspended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. This product should not be used if particulate matter or discoloration is found.

The prefilled syringe is for single use only and should not be used for more than one individual. Attach a needle by twisting in a clockwise direction until the needle fits securely on the syringe. Inject the entire contents of the syringe. Exercise caution to avoid harm from an accidental needle stick.

Special populations

Elderly (≥ 65 years of age)

Of the 4 344 individuals aged 50 years and older who received, 2 470 (56.9 %) were 65 years and older, and 479 (11.0 %) were 75 years and older (*see sections 4.8 and 5.1)*.

Paediatric use

The safety and effectiveness of VAXNEUVANCE™ in children younger than 6 weeks of age have not yet been established.

Individuals at Increased Risk for Pneumococcal Disease

One dose of VAXNEUVANCE™ should be given to individuals who have one or more underlying conditions predisposing them to an increased risk of pneumococcal disease (i.e. adults living with human immunodeficiency virus (HIV) or immunocompetent adults 18 to 49 years of age with risk factors for pneumococcal disease; *see section 5.1*).

4.3 Contraindications

VAXNEUVANCE™ is contraindicated in individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or any diphtheria toxoid-containing vaccine. See *section 6.1*.

4.4 Special warnings and precautions for use

Individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to VAXNEUVANCE (See *sections 4.5 and 5.1*).

The potential risk of apnea should be considered when administering any intramuscular vaccine to infants born prematurely. As the benefit of vaccination is high in this group of infants, vaccination generally should not be withheld or delayed.

As with any vaccine, VAXNEUVANCE may not protect all vaccine recipients.

This medicinal product contains less than 1 mmol sodium (23 milligrams) per dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Use with Other Vaccines

Infants and Children Less Than 2 Years of Age

VAXNEUVANCE can be administered concomitantly with other routine paediatric vaccines (See *sections 4.5 and 5.1*).

Children and Adolescents 2 Through 17 Years of Age

There are no data on the concomitant administration of VAXNEUVANCE with other vaccines.

Adults

VAXNEUVANCE can be administered concomitantly with inactivated influenza vaccine (see *sections 4.8 and 5.1*). There are no data on the concomitant administration of VAXNEUVANCE with other vaccines.

Use with Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, corticosteroids, therapeutic proteins and targeted immunomodulators may reduce the immune responses to vaccines (*see section 4.4)*.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal Data

Developmental and reproductive toxicity studies have been performed in female rats at a dose approximately 200 times the adult human dose on a mcg/kg basis. In these studies, female rats received VAXNEUVANCE (32 mcg/rat/dose) by intramuscular injection 28 days and 7 days prior to mating, on gestation day 6 and on lactation day 7. There was no evidence of embryofoetal lethality or foetal malformations and variations and no adverse effects on pre-weaning development were observed. Antibodies to all 15 serotypes contained in VAXNEUVANCE were detected in offspring, attributable to the acquisition of maternal antibodies via placental transfer during gestation and possibly via lactation.

Human Data

There are no adequate and well-controlled studies of VAXNEUVANCE in pregnant women, and human data available from clinical trials with VAXNEUVANCE have not established the presence or absence of vaccine-associated risk during pregnancy. The decision to vaccinate a woman who is pregnant should consider the woman's risk of pneumococcal disease; VAXNEUVANCE should be administered only if clearly needed.

Breastfeeding

It is not known whether this vaccine is excreted in human milk.

Fertility

No human data on the effect of VAXNEUVANCE on fertility are available. Animal studies in female rats do not indicate harmful effects (*see section 5.3*).

4.7 Effects on ability to drive and use machines

VAXNEUVANCE has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Clinical Trials Experience

Paediatric population

Infants and children aged 6 weeks to less than 2 years

The safety of Vaxneuvance in healthy infants, including preterm infants (from 6 weeks of age at first vaccination) and children (11 through 15 months of age) was assessed as a 3 dose or 4 dose regimen in 5 clinical studies with a total of 7,229 participants.

All 5 studies evaluated the safety of Vaxneuvance when administered concomitantly with other routine paediatric vaccines. In these studies, 4,286 participants received a complete regimen of Vaxneuvance, 2,405 participants received a complete regimen of the 13-valent pneumococcal conjugate vaccine (PCV) and 538 participants received Vaxneuvance when used to complete a regimen initiated with the 13-valent PCV (mixed dose regimen).

The most frequent adverse reactions were pyrexia ≥38 °C (75.2 %), irritability (74.5 %), somnolence (55.0 %), injection-site pain (44.4 %), injection-site erythema (41.7 %), decreased appetite (38.2 %), injection-site induration (28.3 %) and injection-site swelling (28.2 %) based on results in 3,589 participants (Table 1), excluding participants who received a mixed dose regimen. The majority of solicited adverse reactions were mild to moderate (based on intensity or size) and of short duration (≤3 days). Severe reactions (defined as being extremely distressed or unable to do usual activities or size of injection site reaction >7.6 cm) occurred in ≤3.5 % of infants and children following any dose, with the exception of irritability which occurred in 11.4 % of participants.

Children and adolescents 2 to less than 18 years of age

The safety of Vaxneuvance in healthy children and adolescents was assessed in a study that included 352 participants 2 to less than 18 years of age, of whom 177 received a single dose of Vaxneuvance.

In this age cohort, 42.9 % of all participants had a history of previous vaccination with a lower valency pneumococcal conjugate vaccine.

The most frequent adverse reactions were injection-site pain (54.8 %), myalgia (23.7 %), injection-site swelling (20.9 %), injection-site erythema (19.2 %), fatigue (15.8 %), headache (11.9 %), injection-site induration (6.8 %), and pyrexia ≥38 °C (5.6 %) (Table 1). The majority of solicited adverse reactions were mild to moderate (based on intensity or size) and of short duration (≤3 days);

severe reactions (defined as being extremely distressed or unable to do usual activities or size of injection site reaction >7.6 cm) occurred in ≤4.5 % of children and adolescents.

Adults 18 years of age and older

The safety of VAXNEUVANCE in healthy and immunocompetent adults was assessed in 6 randomized, double-blind clinical studies (Protocol 007, Protocol 016, Protocol 017, Protocol 019, Protocol 020 and Protocol 021) conducted across the Americas, Europe and Asia Pacific, which included 7 136 adults ranging in age from 18 to 98 years. Each study enrolled adults with stable underlying medical conditions and/or risk factors that are known to increase the risk of pneumococcal disease.

VAXNEUVANCE was administered to 5 478 adults; 1,134 were 18 to 49 years of age, 1 874 were 50 to 64 years of age, and 2 470 were 65 years of age and older. Of those who received VAXNEUVANCE, 5,101 adults were pneumococcal vaccine-naïve and 377 adults were previously vaccinated with PNEUMOVAX 23 at least 1 year prior to enrollment.

The safety of VAXNEUVANCE in pneumococcal vaccine-naïve adults 50 years of age and older was evaluated in 3 active comparator-controlled clinical studies (Protocol 016, Protocol 019 and Protocol 020) in which 3 032 participants received VAXNEUVANCE and 1 154 participants received Pneumococcal 13-valent Conjugate Vaccine (PCV13). A descriptive study (Protocol 017) evaluated the safety of VAXNEUVANCE in pneumococcal vaccine-naïve adults 18 to 49 years of age.
The safety of VAXNEUVANCE in adults 65 years of age and older who were previously vaccinated with PNEUMOVAX 23 (at least 1 year prior to study entry) was evaluated in an additional descriptive study (Protocol 007).

The safety of concomitant administration of VAXNEUVANCE with seasonal inactivated influenza vaccine was evaluated in 1,196 adults 50 years of age and older, including those with or without a history of prior vaccination with PNEUMOVAX 23 (Protocol 021).

Safety was evaluated using a Vaccination Report Card for up to 14 days postvaccination. Oral body temperature and injection-site adverse events were solicited on Day 1 through Day 5 postvaccination. Systemic adverse events were solicited on Day 1 through Day 14 postvaccination. Unsolicited adverse events were reported on Day 1 through Day 14 postvaccination. The duration of the safety follow-up period postvaccination with VAXNEUVANCE was 1 month in Protocol 007,

6 months in Protocol 019, Protocol 020, Protocol 017 and Protocol 021 and 12 months in Protocol 016.

The most frequently reported adverse reactions following vaccination with Vaxneuvance were solicited. In the pooled analysis of the 7 studies, the most frequent adverse reactions were injection site pain (64.6%), fatigue (23.4%), myalgia (20.7%), headache (17.3%), injection-site swelling (16.1%), injection-site erythema (11.3%) and arthralgia (7.9%) (Table 1). The majority of solicited adverse reactions were mild (based on intensity or size) and of short duration (≤3 days); severe reactions (defined as an event that prevents normal daily activity or size of injection site reaction >10 cm) occurred in ≤1.5% of adults across the clinical programme.

Older adults reported fewer adverse reactions than younger adults.

Tabulated list of adverse reactions

In clinical studies of adults, local and systemic adverse reactions were solicited daily after vaccination for 5 and 14 days, respectively and in infants, children and adolescents up to 14 days after vaccination.

In all populations, unsolicited adverse reactions were reported for 14 days after vaccination.

Adverse reactions reported for all age groups are listed in this section per system organ class, in decreasing order of frequency and seriousness. The frequency is defined as follows:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions

System Organ Class	Adverse Reactions	Frequency		
		Infants/Children/Adolescents		Adults
		6W to <2Y	2 to <18Y§	
Metabolism and nutrition disorders	Decreased appetite	Very common	Common	-
Psychiatric disorders	Irritability	Very common	Common	-
Immune system	Hypersensitivity	-	-	Rare

disorders	reaction including tongue oedema, flushing, and throat tightness			
Nervous system disorders	Somnolence	Very common	Common	-
	Headache -	-	Very common	Very common
	Dizziness - -	-	-	Uncommon †
Skin and subcutaneous tissue disorders	Urticaria	Common	Common	Rare
	Rash	Common	Not known ‡	Uncommon
Gastrointestinal disorders	Nausea	-	- Common	Uncommon †
	Vomiting	Common	Uncommon	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	-	Very common	Very common
	Arthralgia	-	-	Common*
General disorders and administration site conditions	Pyrexia☐	Very common	Common	Uncommon †
	≥39°C	Very common	-	-
	≥40 °C	Common	-	-
	Injection-site pain	Very common	Very common	Very common
	Injection-site erythema	Very common	Very common	Very common
	Injection-site swelling	Very common	Very common	Very common
	Injection-site induration	Very common	Common	-
	Injection-site urticaria	Uncommon	-	-
	Fatigue	-	Very common	Very common
	Injection-site pruritus	-	-	Common

	Injection-site warmth	-	-	Uncommon
	Injection-site bruising/haematoma	Common	Common	Uncommon
	Chills	-	-	Uncommon †

§Different systemic adverse events were solicited for participants 2 to <3 years of age, than for participants ≥3 to less than 18 years of age.
For participants <3 years of age (Vaxneuvance N=32, 13-valent PCV N=28), decreased appetite, irritability, somnolence and urticaria were solicited from Day 1 through Day 14 following vaccination. For participants ≥3 to less than 18 years of age, fatigue, headache, myalgia, and urticaria were solicited from Day 1 through Day 14 following vaccination.

† common in adults 18 to 49 years of age

‡ In clinical trials, no events were observed following Vaxneuvance in healthy children and adolescents and two events were observed in special populations (sickle cell disease and HIV).

*very common in adults 18 to 49 years of age

☐defined as temperature ≥38 °C

Unsolicited Adverse Reactions

Injection-site pruritus occurred in 1.0 % to 2.8 % of pneumococcal vaccine-naïve adults vaccinated with VAXNEUVANCE™.

Safety with Concomitant Influenza Vaccine Administration

The safety profile of VAXNEUVANCE™ when administered concomitantly with inactivated influenza vaccine was generally consistent with the safety profile of VAXNEUVANCE™.

Additional information in special populations

Populations at increased risk for pneumococcal disease

Adults 18 to 49 years of age with chronic conditions and other risk factors

The safety profile of VAXNEUVANCE in adults 18 to 49 years of age with 1 risk factor or 2 or more risk factors for pneumococcal disease was generally consistent with the safety profile in the overall study population (*see section 5.1).*

Adults living with HIV

The safety profile of VAXNEUVANCE in individuals living with HIV was generally consistent with the safety profile in immunocompetent pneumococcal vaccine-naïve adults (*see section 5.1)*.

Safety with Concomitant Influenza Vaccine Administration

The safety profile of VAXNEUVANCE when administered concomitantly with inactivated influenza vaccine was generally consistent with the safety profile of VAXNEUVANCE.

Post-marketing Experience

Not applicable.

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 "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There are no data with regard to overdose.

5 PHARMACOLOGICAL PROPERTIES

A30.1 Biologicals – Antigens

5.1 Pharmacodynamic properties

VAXNEUVANCE™ is a conjugated polysaccharide vaccine that protects against invasive disease and pneumonia caused by *Streptococcus pneumoniae*.

Mechanism of action

VAXNEUVANCE™ contains serotype-specific pneumococcal capsular polysaccharides, each of which is conjugated to a carrier protein (CRM_{197}), and elicits antibodies that enhance opsonization, phagocytosis, and killing of pneumococci to protect against pneumococcal disease. VAXNEUVANCE™ elicits a T-cell dependent immune response. Carrier protein-specific helper T-cells support specificity, functionality and maturation of serotype-specific B cells.

Immune responses following natural exposure to *S. pneumoniae* or following pneumococcal vaccination can be determined through the measurements of OPA and IgG responses. OPA represents functional antibodies capable of opsonizing pneumococcal capsular polysaccharides for presentation to phagocytic cells for engulfment and subsequent killing and are considered an important immunologic surrogate measure of protection against pneumococcal disease in adults. OPA titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50 %. Serotype-specific immune responses (OPA and IgG) for the 15 serotypes contained in VAXNEUVANCE were measured using a validated multiplexed opsonophagocytic assay (MOPA) and

a validated pneumococcal electrochemiluminescence (Pn ECL) assay, bridged to the WHO reference enzyme linked immunosorbent assay (ELISA). In children, a serotype-specific IgG antibody level corresponding to ≥0.35 mcg/mL using the WHO ELISA has been used as the threshold value for the clinical evaluation of pneumococcal conjugate vaccines.

Clinical Trials Experience

Clinical Trials Experience in Children 6 Weeks Through 17 Years of Age

Five double-blind, clinical studies (Protocol 008, Protocol 024, Protocol 025, Protocol 027, and Protocol 029) conducted across the Americas, Europe and Asia Pacific evaluated the immunogenicity of VAXNEUVANCE in healthy infants, children and adolescents. In each study, immunogenicity was assessed by serotype-specific immunoglobulin G (IgG) response rates (the proportion of participants meeting the serotype-specific IgG threshold value of ≥0.35 mcg/mL) and IgG geometric mean concentrations (GMCs) at 30 days following the primary series and/or following the toddler dose. In a subset of participants, opsonophagocytic activity (OPA) geometric mean titers (GMTs) were also measured at 30 days following the primary series and/or following the toddler dose.

Infants and Toddlers Receiving a Routine Vaccination Schedule

3-Dose Regimen

In a pivotal, double-blind, active comparator-controlled study (Protocol 025), 1,184 participants were randomized to receive VAXNEUVANCE or PCV 13 as a 3-dose regimen. The primary series was administered to infants at 2 and 4 months of age and the toddler dose was administered at 11 through 15 months of age. Participants also received other paediatric vaccines concomitantly, including Rotarix [rotavirus vaccine, live] with the infant primary series and INFANRIX hexa [diphtheria, tetanus, pertussis (acellular), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed)] with all 3 doses in the complete regimen *[see Concomitant Vaccination]*. VAXNEUVANCE elicits immune responses, as assessed by IgG response rates, IgG GMCs and OPA GMTs, for all 15 serotypes contained in the vaccine. At 30 days following the primary series, serotype-specific IgG response rates and IgG GMCs were generally comparable for the 13 shared serotypes and higher for the 2 unique serotypes (22F and 33F) in VAXNEUVANCE recipients, compared to Prevnar 13 recipients. At 30 days following the toddler dose, VAXNEUVANCE is non-inferior to Prevnar 13 for the 13 shared serotypes and superior for the 2 unique serotypes, as assessed by the proportion of participants meeting the serotype-specific IgG threshold value of ≥0.35 mcg/mL (response rate) (Table 2). Serotype-specific IgG GMCs are non-inferior to Prevnar 13

for the 13 shared serotypes and superior to Prevnar 13 for the 2 unique serotypes at 30 days following the toddler dose (Table 3).

Table 2: Proportions of Participants with IgG Response Rates ≥0.35 mcg/mL in Toddlers Administered a 3-Dose Regimen (Protocol 025)

Pneumococcal Serotype	VAXNEUVANCE (N=588)	Prevnar 13 (N=591)	Percentage Point Difference* (VAXNEUVANCE - Prevnar 13) (95% CI)*
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	
13 Shared Serotypes†			
1	96.7 (521/539)	99.4 (534/537)	-2.8 (-4.7, -1.3)
3	92.0 (496/539)	83.8 (450/537)	8.2 (4.4, 12.2)
4	95.7 (516/539)	97.9 (524/535)	-2.2 (-4.5, -0.1)
5	99.1 (534/539)	100.0 (535/535)	-0.9 (-2.2, -0.2)
6A	98.5 (531/539)	98.9 (529/535)	-0.4 (-1.9, 1.1)
6B	97.4 (525/539)	99.1 (530/535)	-1.7 (-3.5, -0.1)
7F	99.8 (538/539)	99.8 (535/536)	0.0 (-0.9, 0.9)
9V	98.9 (533/539)	100.0 (537/537)	-1.1 (-2.4, -0.4)
14	99.8 (538/539)	100.0 (537/537)	-0.2 (-1.0, 0.5)
18C	98.9 (533/539)	99.3 (532/536)	-0.4 (-1.8, 0.9)
19A	99.1 (534/539)	100.0 (535/535)	-0.9 (-2.2, -0.2)
19F	99.6 (537/539)	100.0 (537/537)	-0.4 (-1.3, 0.3)
23F	96.8 (521/538)	97.4 (521/535)	-0.5 (-2.7, 1.5)
2 Serotypes Unique to VAXNEUVANCE‡			
22F	99.6 (537/539)	5.8 (31/535)	93.8 (91.5, 95.6)
33F	99.1 (534/539)	4.2 (22/530)	94.9 (92.7, 96.5)

* Estimated difference and CI are based on the Miettinen & Nurminen method.
† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI for the difference in percentages (VAXNEUVANCE – Prevnar 13) being >-10 percentage points.
‡ A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 95% CI for the difference in percentages (VAXNEUVANCE – Prevnar 13) being >10 percentage points.
N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.
CI=confidence interval; IgG=immunoglobulin G.

Table 3: Serotype-Specific IgG GMCs in Toddlers Administered a 3-Dose Regimen (Protocol 025)

Pneumococcal Serotype	VAXNEUVANCE (N=588)		Prevnar 13 (N=591)		GMC Ratio* (VAXNEUVANCE/Prevnar 13) (95% CI)*
	n	GMC	n	GMC	
13 Shared Serotypes†					
1	539	1.29	537	2.08	0.62 (0.57, 0.68)
3	539	0.84	537	0.66	1.28 (1.17, 1.39)
4	539	1.29	535	1.73	0.75 (0.68, 0.82)
5	539	1.97	535	3.06	0.64 (0.59, 0.70)
6A	539	3.10	535	4.57	0.68 (0.61, 0.76)
6B	539	4.17	535	4.37	0.95 (0.85, 1.07)
7F	539	3.09	536	3.93	0.79 (0.72, 0.85)
9V	539	2.14	537	2.99	0.72 (0.66, 0.78)
14	539	5.26	537	7.04	0.75 (0.67, 0.83)
18C	539	1.94	536	2.22	0.88 (0.80, 0.95)
19A	539	4.68	535	5.65	0.83 (0.75, 0.91)
19F	539	4.09	537	4.63	0.88 (0.80, 0.97)
23F	538	1.52	535	1.75	0.87 (0.79, 0.97)
2 Serotypes Unique to VAXNEUVANCE†,‡					
22F	539	5.98	535	0.08	71.19 (65.16, 79.10)
33F	539	3.41	530	0.07	46.58 (42.19, 51.42)

* GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilizing the natural log-transformed antibody concentrations as the response and a single term for vaccination group.

† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevnar 13) being >0.5.

‡ A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevnar 13) being >2.0.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
CI=confidence interval; GMC=geometric mean concentration (mcg/mL); IgG=immunoglobulin G.

Additionally, VAXNEUVANCE elicits functional antibodies, as assessed by serotype-specific OPA GMTs at 30 days following the toddler dose, that are generally comparable to Prevnar 13 for the 13 shared serotypes. OPA GMTs for both 22F and 33F were higher in VAXNEUVANCE recipients compared to Prevnar 13 recipients.

4-Dose Regimen

In a double-blind, active comparator-controlled study (Protocol 008), 1,051 participants were randomized in a 1:1:1 ratio to receive one of two lots of VAXNEUVANCE or Prevnar 13 as a 4-dose regimen. The primary series was administered to infants at 2, 4 and 6 months of age and the toddler dose was administered at 12 through 15 months of age. VAXNEUVANCE met non-inferiority criteria (the lower bound of the 2-sided 95% CI of the differences in the response rates [VAXNEUVANCE - Prevnar 13] was greater than -15 percentage points) for the 13 shared serotypes as assessed by the serotype-specific IgG response rates at 30 days after the primary series. Serotype-specific IgG GMCs at 30 days following the primary series and 30 days following the toddler

dose were generally comparable across both lots of VAXNEUVANCE and Prevnar 13 for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes (22F and 33F).

In a pivotal, double-blind, active comparator-controlled study (Protocol 029), 1,720 participants were randomized to receive VAXNEUVANCE or Prevnar 13 as a 4-dose regimen. The primary series was administered to infants at 2, 4, and 6 months of age and the toddler dose was administered at 12 through 15 months of age. Participants also received other pediatric vaccines concomitantly, including RECOMBIVAX HB (Hepatitis B Vaccine [Recombinant]), RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent) and Pentacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate [Tetanus Toxoid Conjugate] Vaccine) in the infant primary series. HIBERIX (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate]), M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live), ONVARA (Varicella Virus Vaccine Live) and VAQTA (Hepatitis A Vaccine, Inactivated) were administered concomitantly with the toddler dose *[see Concomitant Vaccination]*.

VAXNEUVANCE elicits immune responses, as assessed by IgG response rates, IgG GMCs and OPA GMTs for all 15 serotypes contained in the vaccine. At 30 days following the primary series, VAXNEUVANCE is non-inferior to Prevnar 13 for the 13 shared serotypes, as assessed by IgG response rates (Table 4). VAXNEUVANCE is non-inferior for the 2 unique serotypes, as assessed by the IgG response rates for serotypes 22F and 33F in recipients of VAXNEUVANCE compared with the response rate for serotype 23F in recipients of Prevnar 13 (the lowest response rate for any of the shared serotypes, excluding serotype 3), with percentage point differences of 6.7% (95% CI: 4.6, 9.2) and -4.5% (95% CI: -7.8, -1.3), respectively.

Additionally, VAXNEUVANCE is superior to Prevnar 13 for the 2 unique serotypes and for shared serotype 3 as assessed by IgG response rates at 30 days following the primary series (Table 4).

Table 4: Proportions of Participants with IgG Response Rates ≥0.35 mcg/mL in Infants Administered a 3-Dose Primary Series (Protocol 029)

Pneumococcal Serotype	VAXNEUVANCE (N=858)	Prevnar 13 (N=856)	Percentage Point Difference* (VAXNEUVANCE – Prevnar 13) (95% CI)*
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	
13 Shared Serotypes†			
1	95.7 (672/702)	99.1 (659/665)	-3.4 (-5.2, -1.8)
3‡	94.7 (662/699)	79.2 (524/662)	15.6 (12.1, 19.2)
4	96.4 (674/699)	98.6 (654/663)	-2.2 (-4.0, -0.6)
5	95.3 (669/702)	97.4 (647/664)	-2.1 (-4.2, -0.2)
6A	93.7 (658/702)	98.6 (654/663)	-4.9 (-7.1, -3.0)
6B	88.6 (619/699)	92.0 (609/662)	-3.4 (-6.6, -0.3)
7F	99.0 (694/701)	99.8 (664/665)	-0.8 (-1.9, -0.1)
9V	97.1 (680/700)	98.2 (649/661)	-1.0 (-2.8, 0.6)
14	97.9 (685/700)	97.9 (647/661)	-0.0 (-1.6, 1.6)
18C	97.4 (682/700)	98.3 (651/662)	-0.9 (-2.6, 0.7)
19A	97.9 (687/702)	99.7 (663/665)	-1.8 (-3.2, -0.8)
19F	99.0 (693/700)	100.0 (663/663)	-1.0 (-2.1, -0.4)
23F	91.5 (639/698)	91.8 (607/661)	-0.3 (-3.2, 2.7)
2 Serotypes Unique to VAXNEUVANCE†,§			
22F	98.6 (691/701)	3.5 (23/660)	95.1 (93.1, 96.5)
33F	87.3 (613/702)	2.1 (14/664)	85.2 (82.3, 87.7)

* Estimated difference and CI are based on the Miettinen & Nurminen method.

† A conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI for the difference in percentages (VAXNEUVANCE – Prevnar 13) being >-10 percentage points.

‡ A conclusion of superiority for serotype 3 is based on the lower bound of the 2-sided 95% CI for the difference in percentages (VAXNEUVANCE – Prevnar 13) being >0 percentage points.

§ A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 2-sided 95% CI for the difference in percentages (VAXNEUVANCE – Prevnar 13) being >10 percentage points.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.

CI=confidence interval; IgG=immunoglobulin G.

At 30 days following the primary series, serotype-specific IgG GMCs are non-inferior to Prevnar 13 for 12 of the 13 shared serotypes. The IgG response to serotype 6A narrowly missed the prespecified non-inferiority criteria by a small margin (the lower bound of the 2-sided 95% CI for the GMC ratio [VAXNEUVANCE/Prevnar 13] being 0.48 versus >0.5) (Table 11). VAXNEUVANCE is non-inferior to Prevnar 13 for the 2 unique serotypes, as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F in recipients of VAXNEUVANCE compared with the IgG GMC for serotype 4 in recipients of Prevnar 13 (the lowest IgG GMC for any of the shared serotypes, excluding serotype 3) with a GMC ratio of 3.64 (95% CI: 3.33, 3.98) and 1.24 (95% CI: 1.10, 1.39), respectively.

VAXNEUVANCE is also superior to Prevnar 13 for the 2 unique serotypes and for shared serotype 3 as assessed by IgG GMCs at 30 days following the primary series (Table 5).

Table 5: Serotype-Specific IgG GMCs in Infants Administered a 3-Dose Primary Series (Protocol 029)

Pneumococcal Serotype	VAXNEUVANCE (N=858)		Prevnar 13 (N=856)		GMC Ratio* (VAXNEUVANCE/Prevnar 13) (95% CI)*
	n	GMC	n	GMC	
13 Shared Serotypes†					
1	702	1.21	665	1.89	0.64 (0.59, 0.69)
3‡	699	1.08	662	0.62	1.73 (1.61, 1.87)
4	699	1.29	663	1.35	0.95 (0.88, 1.03)
5	702	1.63	664	2.25	0.72 (0.66, 0.80)
6A	702	1.55	663	2.95	0.52 (0.48, 0.58)
6B	699	1.60	662	1.97	0.81 (0.71, 0.93)
7F	701	2.48	665	3.23	0.77 (0.71, 0.83)
9V	700	1.73	661	1.89	0.91 (0.84, 1.00)
14	700	4.78	661	6.80	0.70 (0.63, 0.78)
18C	700	1.53	662	2.00	0.76 (0.70, 0.83)
19A	702	1.63	665	2.29	0.71 (0.65, 0.77)
19F	700	2.01	663	2.72	0.74 (0.69, 0.79)
23F	698	1.31	661	1.47	0.89 (0.80, 0.99)
2 Serotypes Unique to VAXNEUVANCE†,§					
22F	701	4.91	660	0.05	92.03 (83.47, 101.47)
33F	702	1.67	664	0.06	29.50 (26.16, 33.26)

* GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilizing the natural log-transformed antibody concentrations as the response and a single term for vaccination group.

† A conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevnar 13) being >0.5.

‡ A conclusion of superiority for serotype 3 is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevnar 13) being >1.2

§ A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevnar 13) being >2.0.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

CI=confidence interval; GMC=geometric mean concentration (mcg/mL); IgG=immunoglobulin G.

At 30 days following the toddler dose, serotype-specific IgG GMCs for VAXNEUVANCE are non-inferior to Prevnar 13 for all 13 shared serotypes and for the 2 unique serotypes as assessed by the IgG GMCs for serotypes 22F and 33F in VAXNEUVANCE recipients compared with the IgG GMC for serotype 4 in Prevnar 13 recipients (the lowest IgG GMC for any of the shared serotypes, excluding serotype 3) with a GMC ratio of 4.69 (95% CI: 4.30, 5.11) and 2.59 (95% CI: 2.36, 2.83), respectively (Table 6).

VAXNEUVANCE is superior to Prevnar 13 for the 2 unique serotypes and for shared serotype 3, as assessed by IgG GMCs at 30 days following the toddler dose (Table 6).

Table 6: Serotype-Specific IgG GMCs in Toddlers Administered a 4-Dose Regimen (Protocol 029)

Pneumococcal Serotype	VAXNEUVANCE (N=858)		Prevnar 13 (N=856)		GMC Ratio* (VAXNEUVANCE/Prevnar 13) (95% CI)*
	n	GMC	n	GMC	
13 Shared Serotypes†					
1	715	1.35	685	2.03	0.66 (0.62, 0.72)
3‡	712	0.96	686	0.71	1.35 (1.25, 1.46)
4	713	1.23	682	1.60	0.77 (0.71, 0.84)
5	713	2.49	682	3.95	0.63 (0.58, 0.69)
6A	713	3.70	682	6.21	0.60 (0.54, 0.65)
6B	712	4.76	682	6.43	0.74 (0.67, 0.81)
7F	714	3.42	686	4.85	0.70 (0.65, 0.77)
9V	716	2.40	686	3.29	0.73 (0.67, 0.80)
14	716	5.61	685	6.95	0.81 (0.73, 0.89)
18C	713	2.62	684	3.08	0.85 (0.78, 0.93)
19A	715	4.10	685	5.53	0.74 (0.68, 0.80)
19F	715	3.55	685	4.47	0.79 (0.74, 0.86)
23F	713	2.04	683	3.32	0.61 (0.56, 0.68)
2 Serotypes Unique to VAXNEUVANCE†,§					
22F	714	7.52	682	0.11	68.80 (63.10, 75.02)
33F	714	4.15	677	0.09	44.91 (41.04, 49.14)

* GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilizing the natural log-transformed antibody concentrations as the response and a single term for vaccination group.

† A conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevnar 13) being >0.5.

‡ A conclusion of superiority for serotype 3 is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevnar 13) being >1.2

§ A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevnar 13) being >2.0.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

CI=confidence interval; GMC=geometric mean concentration (mcg/mL); IgG=immunoglobulin G.

VAXNEUVANCE elicits functional antibodies, as assessed by serotype-specific OPA GMTs at 30 days following the primary series and following the toddler dose, that are generally comparable to Prevnar 13 for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes.

Infants and Toddlers Receiving a Mixed Dose Regimen of Different Pneumococcal Conjugate Vaccines

In a double-blind, active comparator-controlled, descriptive study (Protocol 027), 900 participants were randomized in a 1:1:1:1:1 ratio to one of five vaccination groups to receive a complete or mixed dosing regimen of pneumococcal conjugate vaccines. In two vaccination groups, participants received a 4-dose regimen of either VAXNEUVANCE or Prevnar 13. In the three other vaccination groups, the vaccination series was initiated with Prevnar 13 and changed to VAXNEUVANCE at Dose 2, Dose 3 or Dose 4. Participants also received other pediatric vaccines concomitantly, including RECOMBIVAX HB (Hepatitis B Vaccine [Recombinant]) and RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent) *[see Concomitant Vaccination]*. Serotype-specific IgG GMCs at 30 days following the toddler dose were generally comparable for participants administered mixed regimens of

VAXNEUVANCE and Prevnar 13 and for participants administered a complete dosing regimen of Prevnar 13 for the 13 shared serotypes, as assessed by IgG GMC ratios.

Infants, Children and Adolescents Receiving a Catch-Up Vaccination Schedule

In a double-blind, active comparator-controlled, descriptive study (Protocol 024), 606 participants were randomized to receive 1 to 3 doses of VAXNEUVANCE or Prevnar 13, depending on age at enrollment. Children who were either pneumococcal vaccine-naïve or not fully vaccinated or completed a dosing regimen with lower-valency pneumococcal conjugate vaccines were randomized into three different age cohorts (7 through 11 months of age, 12 through 23 months of age and 2 through 17 years of age), to receive 3, 2 or 1 dose of VAXNEUVANCE or Prevnar 13 respectively, according to an age-appropriate schedule *[see Dosage and Administration (2.2)]*. VAXNEUVANCE elicited serotype-specific immune responses, as assessed by IgG GMCs at 30 days following the last dose of vaccine within each age cohort, for all 15 serotypes contained in the vaccine. Catch-up vaccination with VAXNEUVANCE elicited immune responses in children 7 months through 17 years of age that are comparable to Prevnar 13 for the shared serotypes and higher than Prevnar 13 for the unique serotypes 22F and 33F. Within each age cohort, serotype-specific IgG GMCs at 30 days following the last dose of vaccine were generally comparable between the vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes.

Clinical Trials Experience in Adults 18 Years of Age and Older

Six double-blind, clinical studies (Protocol 007, Protocol 016, Protocol 017, Protocol 019, Protocol 020 and Protocol 021) conducted across the Americas, Europe and Asia Pacific evaluated the immunogenicity of VAXNEUVANCE™ in healthy and immunocompetent adults across different age groups including individuals with or without previous pneumococcal vaccination. The clinical studies included adults with stable underlying medical conditions (e.g., diabetes mellitus, renal disorders, chronic heart disease, chronic liver disease, chronic lung disease including asthma) and/or behavioral risk factors (e.g., smoking, increased alcohol use) that are known to increase the risk of pneumococcal disease.

In each study, immunogenicity was assessed by serotype-specific opsonophagocytic activity (OPA) and immunoglobulin G (IgG) responses at 30 days postvaccination. Study endpoints included OPA geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs). The pivotal study (Protocol 19) was designed to show noninferiority of the OPA GMTs compared to Prevnar 13 for the 13 shared serotypes (in common between VAXNEUVANCE™ and Prevnar 13) and superiority for the 2 serotypes unique to VAXNEUVANCE™ (22F and 33F) and for shared serotype 3. Superiority

assessment was based on the between-group comparisons of OPA GMTs and proportions of participants with a ≥4-fold rise in serotype-specific OPA titers from prevaccination to 30 days postvaccination.

Clinical Trials Conducted in Pneumococcal Vaccine-Naïve Adults

In the pivotal, double-blind, active comparator-controlled study (Protocol 019), 1 205 pneumococcal vaccine-naïve adults aged 50 years or older were randomized to receive either VAXNEUVANCE™ or Prevnar 13. The study demonstrated that VAXNEUVANCE™ is noninferior to Prevnar 13 for the 13 shared serotypes and superior for the 2 unique serotypes and for shared serotype 3. Table 7 summarizes the OPA GMTs at 30 days postvaccination. Serotype-specific IgG GMCs were generally consistent with the results observed for the OPA GMTs.

Table 7: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults ≥50 Years of Age (Protocol 019)

Pneumococcal Serotype	VAXNEUVANCE™ (N = 602)		Prevnar 13 (N = 600)		GMT Ratio* (VAXNEUVANCE™ /Prevnar 13) (95% CI)*
	n	GMT*	n	GMT*	
13 Shared Serotypes†					
1	598	256.3	598	322.6	0.79 (0.66, 0.96)
3‡	598	216.2	598	135.1	1.60 (1.38, 1.85)
4	598	1125.6	598	1661.6	0.68 (0.57, 0.80)
5	598	447.3	598	563.5	0.79 (0.64, 0.98)
6A	596	5407.2	598	5424.5	1.00 (0.84, 1.19)
6B	598	4011.7	598	3258.2	1.23 (1.02, 1.48)
7F	597	4617.3	598	5880.6	0.79 (0.68, 0.90)
9V	598	1817.3	597	2232.9	0.81 (0.70, 0.94)
14	598	1999.3	598	2656.7	0.75 (0.64, 0.89)
18C	598	2757.7	598	2583.7	1.07 (0.91, 1.26)
19A	598	3194.3	598	3979.8	0.80 (0.70, 0.93)
19F	598	1695.1	598	1917.8	0.88 (0.76, 1.02)
23F	598	2045.4	598	1740.4	1.18 (0.96, 1.44)
2 Serotypes Unique to VAXNEUVANCE™§					
22F	594	2375.2	586	74.6	31.83 (25.35, 39.97)
33F	598	7994.7	597	1124.9	7.11 (6.07, 8.32)

* GMTs, GMT ratio, and 95% CI are estimated from a cLDA model.

† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE™/Prevnar 13) being > 0.5.

‡ A conclusion of superiority for serotype 3 is based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE™/Prevnar 13) being > 1.2.

§ A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE™/Prevnar 13) being > 2.0.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titer (1/dil);

OPA=opsonophagocytic activity

In a double-blind, lot consistency study (Protocol 020), 2 340 pneumococcal vaccine-naïve adults 50 years of age and older were randomized in a 3:3:3:1 ratio to receive 1 of 3 lots of VAXNEUVANCE™ or Prevnar 13. The study demonstrated that all 3 lots are equivalent as the lower and upper limits of the 95 % CI of the serotype-specific OPA GMT ratios between any 2 lots were within the equivalence margin (0.5 to 2.0) for all 15 serotypes. Immune responses following vaccination with VAXNEUVANCE™ were comparable to Prevnar 13 for the shared serotypes.

In a double-blind, descriptive study (Protocol 017), 1 515 immunocompetent adults 18 to 49 years of age with or without risk factors for pneumococcal disease were randomized 3:1 to receive either

VAXNEUVANCE™ or Prevnar 13, followed by PNEUMOVAX 23 six months later. VAXNEUVANCE™ elicited immune responses to all 15 serotypes as assessed by OPA GMTs (Table 8) and IgG GMCs. OPA GMTs and IgG GMCs were generally comparable between the two vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE™ for the 2 unique serotypes. Following vaccination with PNEUMOVAX 23, OPA GMTs and IgG GMCs were generally comparable between the two vaccination groups for all 15 serotypes in VAXNEUVANCE™.

Immune responses in adults with no risk factors (n=285; 25.2 %) who received VAXNEUVANCE™ were generally consistent with those observed in the overall study population.

Table 8: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults 18-49 Years of Age With or Without Risk Factors for Pneumococcal Disease (Protocol 017)

Pneumococcal Serotype	VAXNEUVANCE™ (N = 1 133)			Prevnar 13 (N = 379)		
	n	Observed GMT	95% CI*	n	Observed GMT	95% CI*
13 Shared Serotypes						
1	1019	268.6	(243.7, 296.0)	341	267.2	(220.4, 323.9)
3	1004	199.3	(184.6, 215.2)	340	150.6	(130.6, 173.8)
4	1016	1416.0	(1308.9, 1531.8)	342	2576.1	(2278.0, 2913.2)
5	1018	564.8	(512.7, 622.2)	343	731.1	(613.6, 871.0)
6A	1006	12928.8	(11923.4, 14019.0)	335	11282.4	(9718.8, 13097.5)
6B	1014	10336.9	(9649.4, 11073.4)	342	6995.7	(6024.7, 8123.2)
7F	1019	5756.4	(5410.4, 6124.6)	342	7588.9	(6775.3, 8500.2)
9V	1015	3355.1	(3135.4, 3590.1)	343	3983.7	(3557.8, 4460.7)
14	1016	5228.9	(4847.6, 5640.2)	343	5889.8	(5218.2, 6647.8)
18C	1014	5709.0	(5331.1, 6113.6)	343	3063.2	(2699.8, 3475.5)
19A	1015	5369.9	(5017.7, 5746.8)	343	5888.0	(5228.2, 6631.0)
19F	1018	3266.3	(3064.4, 3481.4)	343	3272.7	(2948.2, 3632.9)
23F	1016	4853.5	(4469.8, 5270.2)	340	3887.3	(3335.8, 4530.0)
2 Serotypes Unique to VAXNEUVANCE™						
22F	1005	3926.5	(3645.9, 4228.7)	320	291.6	(221.8, 383.6)
33F	1014	11627.8	(10824.6, 12490.7)	338	2180.6	(1828.7, 2600.2)

* The within-group 95 % CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity.

Sequential Administration of Pneumococcal Vaccines in Adults

In a double-blind, active comparator-controlled study (Protocol 016), 652 pneumococcal vaccine-naïve adults 50 years of age and older were randomized to receive either VAXNEUVANCE™ or Prevnar 13, followed by PNEUMOVAX 23 one year later. Following vaccination with PNEUMOVAX 23, OPA GMTs and IgG GMCs were comparable between the two vaccination groups for all 15 serotypes in VAXNEUVANCE™.

Immune responses elicited by VAXNEUVANCE™ persisted up to 12 months postvaccination as assessed by OPA GMTs and IgG GMCs. Immune responses at 30 days and 12 months postvaccination were comparable between the two vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE™ for the 2 unique serotypes.

The sequential administration of VAXNEUVANCE™ followed by PNEUMOVAX 23 was evaluated with an interval of 2 months in immunocompromised individuals (Protocol 018) and an interval of 6 months in immunocompetent individuals with or without risk factors for pneumococcal disease (Protocol 017).

Clinical Trials Conducted in Adults with Prior Pneumococcal Vaccination

In a double-blind, descriptive study (Protocol 007), 253 adults 65 years of age and older who were previously vaccinated with PNEUMOVAX 23 at least 1 year prior to study entry were randomized to receive either VAXNEUVANCE™ or Prevnar 13. IgG GMCs and OPA GMTs were generally comparable between the vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE™ for the 2 unique serotypes.

Clinical immunogenicity in special populations

Populations at increased risk for pneumococcal disease

Infants Born Prematurely

The safety and immunogenicity of VAXNEUVANCE were evaluated in preterm infants (<37 weeks gestation at birth) enrolled within 4 double-blind, active comparator-controlled studies (Protocol 025, Protocol 027 [groups receiving a complete 4-dose regimen of either VAXNEUVANCE or PCV 13 [Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)]], Protocol 029 and Protocol 031). In these studies, 354 participants were randomized to receive VAXNEUVANCE or Prevnar 13 as a 4-dose regimen with the first dose administered at 2 months of age, followed by 2 additional doses at least 4 weeks apart and a fourth dose at 11 through 15 months of age. Serotype-specific immunoglobulin G (IgG) and opsonophagocytic activity (OPA) responses at 30 days following the primary series, prior to the toddler dose and at 30 days following the toddler dose were generally comparable between vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the two unique serotypes (22F and 33F). The safety profile and immune responses in preterm infants receiving 4 doses of VAXNEUVANCE were generally consistent with those observed in the overall healthy infant population in these studies (including preterm and term infants) *(see section 4.8).*

Children with Sickle Cell Disease

In a double-blind, descriptive study (Protocol 023), the safety and immunogenicity of VAXNEUVANCE were evaluated in children 5 to 17 years of age with sickle cell disease. In this study, 104 participants were randomized 2:1 to receive a single dose of either VAXNEUVANCE or PCV 13. VAXNEUVANCE was immunogenic as assessed by serotype-specific IgG GMCs and OPA GMTs at 30 days postvaccination for all 15 serotypes contained in VAXNEUVANCE. Serotype-specific IgG GMCs and OPA GMTs were generally comparable between the two vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the two unique serotypes (22F and 33F). The safety profile of VAXNEUVANCE in children with sickle cell disease was generally consistent with the safety profile in healthy children (see section 4.8).

Individuals Living with HIV

Children Living with HIV

In a double-blind, descriptive study (Protocol 030), the safety and immunogenicity of VAXNEUVANCE were evaluated in children 6 to 17 years of age living with HIV, with CD4+ T-cell count ≥200 cells per microliter and plasma HIV RNA value <50,000 copies/mL. In this study, 407 participants were randomized to receive a single dose of either VAXNEUVANCE or Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (PCV13), followed by PNEUMOVAX 23 [pneumococcal vaccine polyvalent] two months later. VAXNEUVANCE was immunogenic as assessed by serotype-specific IgG GMCs and OPA GMTs at 30 days postvaccination for all 15 serotypes contained in VAXNEUVANCE. Serotype-specific IgG GMCs and OPA GMTs were generally comparable for the 13 shared serotypes and higher for the 2 unique serotypes (22F and 33F). After sequential administration with PNEUMOVAX 23, IgG GMCs and OPA GMTs were generally comparable at 30 days postvaccination between the two vaccination groups for all 15 serotypes contained in VAXNEUVANCE. The safety profile of VAXNEUVANCE in children living with HIV was generally consistent with the safety profile in healthy children (see section 4.8).

Adults Living with HIV

In a double-blind, descriptive study (Protocol 018), the safety and immunogenicity of VAXNEUVANCE™ were evaluated in pneumococcal vaccine-naïve adults ≥18 years of age living with HIV, with CD4+ T-cell count ≥50 cells per microliter and plasma HIV RNA value <50,000 copies/mL. In this study, 302 participants were randomized to receive either VAXNEUVANCE™ or Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (PCV13), followed by PNEUMOVAX 23 [pneumococcal vaccine polyvalent] two months later. VAXNEUVANCE™ was immunogenic as

assessed by geometric mean concentrations (GMCs) at 30 days postvaccination for all 15 serotypes contained in VAXNEUVANCE™. After sequential administration with PNEUMOVAX 23, OPA GMTs and IgG GMCs were generally comparable at 30 days postvaccination between the two vaccination groups for all 15 serotypes contained in VAXNEUVANCE™. The safety profile of VAXNEUVANCE™ in adults living with HIV was generally consistent with the safety profile in immunocompetent pneumococcal vaccine-naïve adults (*see section 4.8)*.

Individuals 18 to 49 Years of Age with Chronic Conditions and Other Risk Factors

In a double-blind, descriptive study (Protocol 017), the safety and immunogenicity of VAXNEUVANCE™ were evaluated in immunocompetent adults 18 to 49 years of age, including individuals with one or more of the following risk factors for pneumococcal disease: diabetes mellitus, chronic heart disease including heart failure, chronic liver disease with compensated cirrhosis, chronic lung disease including persistent asthma and chronic obstructive pulmonary disease (COPD), current tobacco use and increased alcohol consumption. Participants were randomized 3:1 to receive either VAXNEUVANCE™ or Pneumococcal 13-valent Conjugate Vaccine (PCV13), followed by PNEUMOVAX 23 six months later. Of those who received T VAXNEUVANCE™, 54.7 % (n=620) had 1 risk factor and 20.1 % (n=228) had 2 or more risk factors. In both of these risk factor subgroups, VAXNEUVANCE™ elicited immune responses to all 15 serotypes contained in the vaccine as assessed by OPA GMTs and IgG GMCs at 30 days postvaccination, which were generally consistent with those observed in the overall study population. Sequential administration of VAXNEUVANCE™ followed by PNEUMOVAX 23 was also immunogenic for all 15 serotypes. The safety profile of VAXNEUVANCE™ in both of these risk factor subgroups was generally consistent with the safety profile in the overall study population (*see section 4.8).*

5.2 Pharmacokinetic Properties

Not applicable

5.3 Preclinical safety data

Repeat Dose Toxicity and Local Tolerance

Repeat-dose toxicity studies in rats at doses up to 200 times the adult human dose on a mcg/kg basis, which included an evaluation of single-dose toxicity and local tolerance, revealed no hazards to humans.

Carcinogenesis

VAXNEUVANCE™ has not been evaluated for the potential to cause carcinogenicity.

Mutagenesis

VAXNEUVANCE™ has not been evaluated for the potential to cause genotoxicity.

Reproduction

VAXNEUVANCE™ administered to female rats at a dose approximately 200 times the adult human dose on a mcg/kg basis had no effects on mating performance, fertility or embryonic/fetal survival.

Development

VAXNEUVANCE™ administered to female rats at a dose approximately 200 times the adult human dose on a mcg/kg basis had no adverse effects on pre-weaning development. Antibodies to all 15 serotypes contained in VAXNEUVANCE™ were detected in offspring, attributable to the acquisition of maternal antibodies via placental transfer during gestation and possibly via lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

List of excipients

Sodium chloride (NaCl)

L-histidine

Polysorbate 20

Water for injections

For adjuvant, see section 2

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store refrigerated at 2 °C to 8 °C.

Do not freeze. Protect from light.

VAXNEUVANCE™ should be administered as soon as possible after being removed from the refrigerator.

In the event of temporary temperature excursions, stability data indicate that VAXNEUVANCE is stable at temperatures up to 25°C for 48 hours.

Keep out of reach of children.

6.5 Nature and contents of container

0,5 ml type I glass syringe with a plastic rigid tip cap and a bromobutyl plunger stopper.
The syringes are packaged in a tray and placed into cartons of 1 or 10, along with a leaflet.

6.6 Special precautions for disposal and other handling

- The vaccine should be used directly as supplied; no dilution or reconstitution is necessary.
- Hold horizontally and shake vigorously immediately prior to use to obtain an opalescent suspension. Do not use the vaccine if it cannot be resuspended.
- Inspect the suspension visually for particulate matter and discolouration prior to administration. Discard the vaccine if particulates are present and/or if it appears discoloured.
- Attach a needle with Luer lock connection by twisting in a clockwise direction until the needle fits securely on the syringe.
- Inject immediately using the intramuscular (IM) route, preferably in the deltoid area of the upper arm.
- Exercise care to avoid harm from an accidental needle stick.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd
117 16th Road
Halfway House
1685
South Africa

8 REGISTRATION NUMBER

56/30.1/0535

9 DATE OF FIRST AUTHORISATION

30 January 2024

10 DATE OF REVISION OF THE TEXT

13 September 2024