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

1. THERAPEUTIC CLASS

VAXNEUVANCE is a conjugated polysaccharide vaccine that protects against invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae*.

2. ACTIVE INGREDIENTS

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

3. INACTIVE INGREDIENTS

Each 0.5 mL dose contains 1.55 mg L-histidine, 1 mg of polysorbate 20, 4.50 mg sodium chloride, water for injection and 125 mcg of aluminum (as aluminum phosphate adjuvant).

4. PHARMACOLOGY

MECHANISM OF ACTION

VAXNEUVANCE contains 15 purified pneumococcal capsular polysaccharides from *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, with the additional serotypes 22F and 33F), each conjugated to a carrier protein (CRM_{197}). VAXNEUVANCE elicits a T-cell dependent immune response to induce antibodies that enhance opsonization, phagocytosis, and killing of pneumococci to protect against pneumococcal disease.

Immune responses following natural exposure to *Streptococcus pneumoniae* or following pneumococcal vaccination can be determined by measuring opsonophagocytic activity (OPA) and immunoglobulin G (IgG) responses. OPA represents functional antibodies and is considered an important immunologic surrogate measure of protection against pneumococcal disease in adults. In children, a serotype-specific IgG antibody level corresponding to ≥0.35 µg/mL using the WHO enzyme linked immunosorbent assay (ELISA) has been used as the threshold value for the clinical evaluation of pneumococcal conjugate vaccines.

CLINICAL STUDIES

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 Prevenar 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 pediatric 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 Prevenar 13 recipients. At 30 days following the toddler dose, VAXNEUVANCE is non-inferior to Prevenar 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 1). Serotype-specific IgG GMCs are non-inferior to Prevenar 13 for the 13 shared serotypes and superior to Prevenar 13 for the 2 unique serotypes at 30 days following the toddler dose (Table 2).

Table 1: 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)	Prevenar 13 (N=591)	Percentage Point Difference* (VAXNEUVANCE - Prevenar 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 – Prevenar 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 – Prevenar 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 2: Serotype-Specific IgG GMCs in Toddlers Administered a 3-Dose Regimen (Protocol 025)

Pneumococcal Serotype	VAXNEUVANCE (N=588)		Prevenar 13 (N=591)		GMC Ratio* (VAXNEUVANCE/Prevenar 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	71.79 (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/Prevenar 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/Prevenar 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 Prevenar 13 for the 13 shared serotypes. OPA GMTs for both 22F and 33F were higher in VAXNEUVANCE recipients compared to Prevenar 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 Prevenar 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 - Prevenar 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 Prevenar 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 Prevenar 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), VARIVAX (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 Prevenar 13 for the 13 shared serotypes, as assessed by IgG response rates (Table 3). 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 Prevenar 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 Prevenar 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 3).

Table 3: 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)	Prevenar 13 (N=856)	Percentage Point Difference* (VAXNEUVANCE – Prevenar 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 – Prevenar 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 – Prevenar 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 – Prevenar 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 Prevenar 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/Prevenar 13] being 0.48 versus >0.5) (Table 4). VAXNEUVANCE is non-inferior to Prevenar 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 Prevenar 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 Prevenar 13 for the 2 unique serotypes and for shared serotype 3 as assessed by IgG GMCs at 30 days following the primary series (Table 4).

Table 4: Serotype-Specific IgG GMCs in Infants Administered a 3-Dose Primary Series (Protocol 029)

Pneumococcal Serotype	VAXNEUVANCE (N=858)		Prevenar 13 (N=856)		GMC Ratio* (VAXNEUVANCE/Prevenar 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/Prevenar 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/Prevenar 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/Prevenar 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 Prevenar 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 Prevenar 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 5).

VAXNEUVANCE is superior to Prevenar 13 for the 2 unique serotypes and for shared serotype 3, as assessed by IgG GMCs at 30 days following the toddler dose (Table 5).

Table 5: Serotype-Specific IgG GMCs in Toddlers Administered a 4-Dose Regimen (Protocol 029)

Pneumococcal Serotype	VAXNEUVANCE (N=858)		Prevenar 13 (N=856)		GMC Ratio* (VAXNEUVANCE/Prevenar 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/Prevenar 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/Prevenar 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/Prevenar 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 Prevenar 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 Prevenar 13. In the three other vaccination groups, the vaccination series was initiated with Prevenar 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 Prevenar 13 and for participants administered a complete dosing regimen of Prevenar 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 Prevenar 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 Prevenar 13 respectively, according to an age-appropriate schedule *[see 7. DOSAGE AND ADMINISTRATION, 7.2 Posology]*. 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 Prevenar 13 for the shared serotypes and higher than Prevenar 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 Prevenar 13 [Pneumococcal 13 valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)] (PCV13) for the 13 shared serotypes (in common between VAXNEUVANCE and Prevenar 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 Prevenar 13. The study demonstrated that VAXNEUVANCE is noninferior to Prevenar 13 for the 13 shared serotypes and superior for the 2 unique serotypes and for shared serotype 3. Table 6 summarizes the OPA GMTs at 30 days postvaccination. Serotype-specific IgG GMCs were generally consistent with the results observed for the OPA GMTs.

Table 6: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults ≥50 Years of Age (Protocol 019)

Pneumococcal Serotype	VAXNEUVANCE (N = 602)		Prevenar 13 (N = 600)		GMT Ratio* (VAXNEUVANCE/Prevenar 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/Prevenar 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/Prevenar 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/Prevenar 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 Prevenar 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 Prevenar 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 Prevenar 13, followed by PNEUMOVAX 23 [pneumococcal vaccine polyvalent] six months later. VAXNEUVANCE elicited immune responses to all 15 serotypes as assessed by OPA GMTs (Table 7) 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 7: 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)			Prevenar 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 Prevenar 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). *[See 11. USE IN SPECIAL POPULATIONS, 11.5 Individuals at Increased Risk for Pneumococcal Disease.]*

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 Prevenar 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.

Concomitant Vaccination

Infants and Toddlers
The immunogenicity of routine infant vaccines administered concomitantly with VAXNEUVANCE was evaluated within 3 double-blind, active comparator-controlled studies (Protocol 025, Protocol 029 and Protocol 027). In Protocol 025, approximately 1,200 participants received Rotarix concomitantly with the infant primary series and INFANRIX hexa concomitantly with the infant primary series and toddler dose of VAXNEUVANCE or Prevenar 13. Immune responses to Rotarix administered concomitantly with VAXNEUVANCE met non-inferiority criteria, as assessed by anti-rotavirus immunoglobulin A GMTs at 30 days following completion of the primary series. Similarly, immune responses to INFANRIX hexa administered concomitantly with VAXNEUVANCE met non-inferiority criteria, as assessed by the antigen-specific response rate to each antigen in INFANRIX hexa at 30 days following the toddler dose.

In Protocol 029, approximately 1,700 participants received Pentacel administered concomitantly with the infant primary series of VAXNEUVANCE or Prevenar 13. Approximately 1,500 participants received VAQTA, HIBERIX, M-M-R II and VARIVAX, administered concomitantly with the toddler dose of VAXNEUVANCE or Prevenar 13. At 30 days following completion of the primary series, immune responses to all antigens contained in Pentacel met non-inferiority criteria when administered concomitantly with VAXNEUVANCE. At 30 days following the toddler dose, immune responses to vaccine-specific antigens for VAQTA, HIBERIX, M-M-R II and VARIVAX met non-inferiority criteria when administered concomitantly with VAXNEUVANCE.

In Protocol 027, approximately 900 participants received RECOMBIVAX HB and RotaTeq concomitantly with VAXNEUVANCE or Prevenar 13 in the infant primary series. At 30 days following the primary series, immune responses to vaccine-specific antigens for RECOMBIVAX HB and RotaTeq met non-inferiority criteria when administered concomitantly with VAXNEUVANCE.

These studies support the concomitant administration of VAXNEUVANCE with any of the following vaccine antigens: diphtheria, tetanus, pertussis, poliomyelitis (serotypes 1, 2 and 3), hepatitis A, hepatitis B, *Haemophilus influenzae* type b, measles, mumps, rubella, varicella and rotavirus vaccine, either as monovalent or combination vaccines.

Adults
In a double-blind, randomized study (Protocol 021), 1,200 adults 50 years of age and older, with or without a history of prior PNEUMOVAX 23 vaccination, were randomized to receive VAXNEUVANCE concomitantly or nonconcomitantly with seasonal inactivated quadrivalent influenza vaccine (QIV). One vaccination group received VAXNEUVANCE and QIV concomitantly, followed by placebo 30 days later. A second vaccination group received QIV and placebo concomitantly, followed by VAXNEUVANCE 30 days later.

VAXNEUVANCE administered concomitantly with QIV is noninferior to VAXNEUVANCE administered nonconcomitantly with QIV (based on a 2-fold noninferiority margin), as assessed by pneumococcal OPA GMTs at 30 days postvaccination with VAXNEUVANCE for all 15 serotypes contained in the vaccine. OPA GMTs were slightly lower for some serotypes when VAXNEUVANCE was administered concomitantly with QIV compared to VAXNEUVANCE administered alone. QIV administered concomitantly with VAXNEUVANCE is noninferior to QIV administered nonconcomitantly (based on a 2-fold noninferiority margin) as assessed by influenza strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV for all 4 influenza strains.

5. ANIMAL TOXICOLOGY

Repeat Dose Toxicity and Local Tolerance
Repeat-dose toxicity studies in rats at doses up to 17 times the infant human dose and 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. INDICATION

VAXNEUVANCE is indicated 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 in infants, children and adolescents from 6 weeks to less than 18 years of age.

VAXNEUVANCE is indicated 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 in individuals 18 years of age and older.

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

The use of this vaccine should be in accordance with official recommendations.

7. DOSAGE AND ADMINISTRATION

7.1 General

Dosage
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.

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 10. DRUG INTERACTIONS, 10.1 Use with Other Vaccines]*.

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.

7.2 Posology

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 immunization 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 immunization 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 immunization 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 9. PRECAUTIONS and 11. USE IN SPECIAL POPULATIONS, 11.5 Individuals at Increased Risk for Pneumococcal Disease*].
Prior vaccination with another pneumococcal conjugate vaccine	Infants and children who have begun immunization with another pneumococcal conjugate vaccine may switch to VAXNEUVANCE at any point in the schedule [*see 4. PHARMACOLOGY*].
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.

8. 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 2. ACTIVE INGREDIENTS and 3. INACTIVE INGREDIENTS.]*

9. PRECAUTIONS

Individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to VAXNEUVANCE. *[See 10. DRUG INTERACTIONS, 10.2 Use with Immunosuppressive Therapies and 11. USE IN SPECIAL POPULATIONS, 11.5 Individuals at Increased Risk for Pneumococcal Disease]*

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.

10. DRUG INTERACTIONS

10.1 Use with Other Vaccines

Infants and Children Less Than 2 Years of Age
VAXNEUVANCE can be administered concomitantly with other routine pediatric vaccines *[see 12. ADVERSE REACTIONS and 4. PHARMACOLOGY, Clinical Studies]*.

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 12. ADVERSE REACTIONS, 12.1 Clinical Trials Experience and 4. PHARMACOLOGY, Clinical Studies]*. There are no data on the concomitant administration of VAXNEUVANCE with other vaccines.

10.2 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 9. PRECAUTIONS]*.

11. USE IN SPECIAL POPULATIONS

11.1 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 embryofetal lethality or fetal 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.

11.2 Nursing Mothers

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

11.3 Pediatric Use

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

11.4 Geriatric Use

Of the 4,344 individuals aged 50 years and older who received VAXNEUVANCE, 2,470 (56.9%) were 65 years and older, and 479 (11.0%) were 75 years and older *[see 12. ADVERSE REACTIONS, 12.1 Clinical Trials Experience and 4. PHARMACOLOGY, Clinical Studies]*.

11.5 Individuals 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 Prevenar 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 Prevenar 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 12. ADVERSE REACTION, 12.1 Clinical Trials Experience and 4. PHARMACOLOGY, Clinical Studies]*.

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 Prevenar 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 12. ADVERSE REACTIONS, 12.1 Clinical Trials Experience]*.

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 Prevenar 13, 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 12. ADVERSE REACTIONS, 12.1 Clinical Trials Experience]*.

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 Prevenar 13, followed by PNEUMOVAX 23 two months later. VAXNEUVANCE was immunogenic as assessed by OPAGMTs and IgG 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 12. ADVERSE REACTIONS, 12.1 Clinical Trials Experience]*.

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 Prevenar 13, followed by PNEUMOVAX 23 six months later. Of those who received 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 *[see 4. PHARMACOLOGY, Clinical Studies]*. 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 12. ADVERSE REACTIONS, 12.1 Clinical Trials Experience]*.

12. ADVERSE REACTIONS

12.1 Clinical Trials Experience

Children 6 Weeks Through 17 Years of Age

Infants and Toddlers Receiving a Routine Vaccination Schedule

The safety of VAXNEUVANCE in healthy infants (from 6 weeks of age at first vaccination) and toddlers (11 months through 15 months of age) was assessed in 5 randomized, double-blind, active comparator-controlled clinical studies (Protocol 008, Protocol 025, Protocol 027, Protocol 029 and Protocol 031) of 7,229 participants conducted across the Americas, Europe, and Asia Pacific. In four of these studies (Protocol 008, Protocol 027, Protocol 029 and Protocol 031), the safety of VAXNEUVANCE was evaluated when administered as a 4-dose regimen given at 2, 4, 6 and 12 through 15 months of age. A fifth study (Protocol 025) evaluated the safety of VAXNEUVANCE when administered as a 3-dose regimen given at 2, 4 and 11 through 15 months of age. All 5 studies evaluated the safety of VAXNEUVANCE when administered concomitantly with other routine pediatric vaccinations *[see 4. PHARMACOLOGY, Clinical Studies]*. Protocol 027 also evaluated the safety of mixed 4-dose regimens in participants who completed the regimen with VAXNEUVANCE after receiving one or more doses of Prevenar 13. Additionally, four of these studies evaluated safety in preterm infants (<37 weeks gestation at birth) *[see 11. USE IN SPECIAL POPULATIONS, 11.5 Individuals at Increased Risk for Pneumococcal Disease]*. Across all 5 studies, 4,286 participants received a complete regimen of VAXNEUVANCE, 2,405 participants received a complete regimen of Prevenar 13 and 538 participants received a mixed regimen.

Safety was evaluated using a Vaccination Report Card for up to 14 days postvaccination. Injection-site adverse events and systemic adverse events were solicited on Day 1 through Day 14 postvaccination. Body temperature was solicited on Day 1 through Day 7 postvaccination. Unsolicited adverse events were reported on Day 1 through Day 14 postvaccination. The duration of the safety follow-up period following the last vaccination with VAXNEUVANCE was 1 month in Protocol 008 and 6 months in Protocol 025, Protocol 027, Protocol 029 and Protocol 031.

Solicited Adverse Reactions in Infants and Toddlers Receiving a Routine Vaccination Schedule

The percentage of infants (preterm and term) and toddlers with solicited adverse reactions that occurred within 14 days following administration of VAXNEUVANCE or Prevenar 13 based on pooled data from four studies (excluding mixed 4-dose regimens) are shown in Tables 8 and 9. 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 >7.6 cm) occurred in ≤1.3% of infants and toddlers following each dose, with the exception of irritability, which occurred in ≤5.2% of the participants.

Table 8: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 14 Days Postvaccination in Infants Receiving a Primary Series (Protocols 025*, 027, 029 and 031)

Dose	**Dose 1**		**Dose 2**		**Dose 3**	
	VAXNEUVANCE (%) N=3,589	**Prevenar 13 (%) N=2,058**	**VAXNEUVANCE (%) N=3,521**	**Prevenar 13 (%) N=1,998**	**VAXNEUVANCE (%) N=2,925**	**Prevenar 13 (%) N=1,409**
Local Reactions[†]						
Pain	27.1	24.1	19.8	18.0	19.1	18.8
Erythema	17.1	14.1	20.0	20.8	17.0	19.1
Swelling	13.7	11.6	11.6	10.7	9.9	9.3
Induration	12.6	13.5	12.6	15.9	11.4	13.1
Systemic Reactions[†]						
Decreased Appetite	17.0	15.9	15.4	14.0	13.9	14.3
Irritability	55.1	53.2	50.7	47.3	47.0	43.7
Somnolence	40.7	41.3	27.5	27.8	22.8	24.1
Urticaria	1.1	1.5	1.4	1.6	1.6	1.8
Elevated Body Temperature[‡,§]						
≥38.0°C and <39.0°C	43.4	42.0	39.3	39.6	35.7	37.4
≥39.0°C and <40.0°C	2.2	2.6	3.4	4.6	3.5	3.1
≥40.0°C	0.2	0.0	0.3	0.4	0.5	0.2

* Full term infants in Protocol 025 received Dose 1 and Dose 2 as part of a 2-dose primary series. Preterm infants in Protocol 025 received Dose 1, Dose 2 and Dose 3 as part of a 3-dose primary series.

[†] Solicited on Day 1 through Day 14 postvaccination following each dose.

[‡] Solicited on Day 1 through Day 7 postvaccination following each dose.

[§] Percentages reflect the number of participants with temperature data based on a rectal equivalent temperature.

N=Number of participants vaccinated.

Table 9: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 14 Days Postvaccination in Toddlers (Protocols 025, 027, 029 and 031)

Dose	Toddler Dose	
	VAXNEUVANCE (%) N=3,373	Prevenar 13 (%) N=1,886
Local Reactions*		
Pain	21.0	18.6
Erythema	21.6	22.0
Swelling	12.6	11.6
Induration	13.1	14.8
Systemic Reactions*		
Decreased Appetite	19.4	17.1
Irritability	45.7	42.5
Somnolence	21.8	21.5
Urticaria	2.6	2.5
Elevated Body Temperature†,‡		
≥38.0°C and <39.0°C	34.4	35.3
≥39.0°C and <40.0°C	4.3	4.4
≥40.0°C	0.8	0.5

* Solicited on Day 1 through Day 14 postvaccination following each dose.
† Solicited on Day 1 through Day 7 postvaccination following each dose.
‡ Percentages reflect the number of participants with temperature data based on a rectal equivalent temperature.
N=Number of participants vaccinated.

Unsolicited Adverse Reactions in Infants and Toddlers Receiving a Routine Vaccination Schedule
Injection-site urticaria occurred in up to 0.3% of infants and toddlers following each dose of VAXNEUVANCE.

Safety with Concomitant Administration in Infants and Toddlers
The safety profile was similar when other routine pediatric vaccines were administered concomitantly with VAXNEUVANCE or Prevenar 13 *[see 4. PHARMACOLOGY, Clinical Studies]*.

Safety of a Mixed Dose Regimen of Different Pneumococcal Conjugate Vaccines
The safety profiles of mixed 4-dose regimens of VAXNEUVANCE and Prevenar 13 were generally comparable to those of complete 4-dose regimens of either VAXNEUVANCE or Prevenar 13 *[see 4. PHARMACOLOGY, Clinical Studies]*.

Infants, Children and Adolescents Receiving a Catch-Up Vaccination Schedule
The safety of VAXNEUVANCE in healthy infants, children and adolescents from 7 months through 17 years of age was assessed in a double-blind, active comparator-controlled clinical study (Protocol 024) in which 606 participants were randomized to receive 1 to 3 doses of VAXNEUVANCE or Prevenar 13, depending on age at enrollment. All infants and children less than 2 years of age were pneumococcal vaccine-naïve. Among children and adolescents from 2 through 17 years of age (N=352), 42.9% had a history of previous vaccination with a lower-valency pneumococcal conjugate vaccine. The safety assessment

was consistent with that used in the studies evaluating a routine vaccination schedule. The duration of the safety follow-up period following the last study vaccination within each age cohort was 6 months.

Solicited Adverse Reactions in Infants, Children and Adolescents Receiving a Catch-Up Vaccination Schedule

The percentage of participants with solicited adverse reactions that occurred within 14 days following administration of VAXNEUVANCE or Prevenar 13 within each age cohort are shown in Tables 10, 11 and 12. 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 >7.6 cm) occurred in ≤1.6% of infants and children 7 months through 23 months of age following each dose, and ≤4.5% of children and adolescents 2 through 17 years of age.

Table 10: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 14 Days Postvaccination in Infants Receiving a Catch-Up Vaccination Schedule (Protocol 024)

Age	**7 Months Through 11 Months of Age**					
Dose	**Dose 1**		**Dose 2**		**Dose 3**	
	VAXNEUVANCE (%) N=64	**Prevenar 13 (%) N=64**	**VAXNEUVANCE (%) N=63**	**Prevenar 13 (%) N=64**	**VAXNEUVANCE (%) N=63**	**Prevenar 13 (%) N=64**
Local Reactions*						
Pain	7.8	6.3	14.3	1.6	7.9	1.6
Erythema	20.3	31.3	12.7	14.1	11.1	9.4
Swelling	9.4	14.1	14.3	6.3	12.7	6.3
Induration	14.1	7.8	6.3	9.4	7.9	7.8
Systemic Reactions*						
Decreased Appetite	6.3	12.5	9.5	7.8	4.8	4.7
Irritability	21.9	26.6	17.5	18.8	14.3	14.1
Somnolence	12.5	12.5	7.9	7.8	11.1	1.6
Urticaria	1.6	0.0	0.0	1.6	0.0	3.1
Elevated Body Temperature†,‡						
≥38.0°C and <39.0°C	46.9	39.1	44.4	46.9	50.8	39.1
≥39.0°C and <40.0°C	3.1	4.7	7.9	3.1	1.6	1.6
≥40.0°C	1.6	1.6	1.6	0.0	3.2	0.0

* Solicited on Day 1 through Day 14 postvaccination following each dose.
† Solicited on Day 1 through Day 7 postvaccination following each dose.
‡ Percentages reflect the number of participants with temperature data based on rectal equivalent temperature.
N=Number of participants vaccinated.

Table 11: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 14 Days Postvaccination in Toddlers Receiving a Catch-Up Vaccination Schedule (Protocol 024)

Age	**12 Months Through 23 Months of Age**			
Dose	**Dose 1**		**Dose 2**	
	VAXNEUVANCE (%) N=62	**Prevenar 13 (%) N=64**	**VAXNEUVANCE (%) N=62**	**Prevenar 13 (%) N=64**
Local Reactions*				
Pain	17.7	12.5	24.2	14.1
Erythema	11.3	15.6	11.3	9.4
Swelling	11.3	9.4	6.5	3.1
Induration	6.5	9.4	4.8	3.1
Systemic Reactions*				
Decreased Appetite	16.1	14.1	9.7	9.4
Irritability	29.0	14.1	16.1	14.1
Somnolence	21.0	12.5	16.1	4.7
Elevated Body Temperature†,‡				
≥38.0°C and <39.0°C	32.3	35.9	29.0	26.6
≥39.0°C and <40.0°C	8.1	6.3	3.2	3.1
≥40.0°C	1.6	0.0	1.6	0.0

* For all participants, reactions were solicited on Day 1 through Day 14 postvaccination following each dose.
† Solicited on Day 1 through Day 7 postvaccination following each dose.
‡ Percentages reflect the number of participants with temperature data based on equivalent rectal temperature.
N=Number of participants vaccinated.

Table 12: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 14 Days Postvaccination in Children and Adolescents Receiving a Catch-Up Vaccination Schedule (Protocol 024)

Age	**2 Years Through 17 Years of Age**	
Dose	**Dose 1**	
	VAXNEUVANCE (%) N=177	**Prevenar 13 (%) N=175**
Local Reactions*		
Pain	54.8	56.6
Erythema	19.2	21.1
Swelling	20.9	24.0
Induration	6.8	14.9
Systemic Reactions*,†		
Decreased Appetite	2.3	2.9
Irritability	2.8	4.0
Somnolence	2.8	2.9
Urticaria	1.1	1.1
Fatigue	15.8	17.1
Headache	11.9	13.7
Myalgia	23.7	16.6
Elevated Body Temperature‡,§		
≥38.0°C and <39.0°C	4.0	4.6
≥39.0°C and <40.0°C	1.7	0.0
≥40.0°C	0.0	0.0

* For all participants, reactions were solicited on Day 1 through Day 14 postvaccination following each dose.
† Different systemic adverse events were solicited for participants 2 to <3 years of age, than for participants ≥3 to 17 years of age. For participants <3 years of age (VAXNEUVANCE N=32, Prevenar 13 N=28), decreased appetite, irritability, somnolence, and urticaria were solicited from Day 1 through Day 14 following vaccination. For participants ≥3 to 17 years of age, fatigue, headache, myalgia, and urticaria were solicited from Day 1 through Day 14 following vaccination.
‡ Solicited on Day 1 through Day 7 postvaccination following each dose.
§ Percentages reflect the number of participants with temperature data based on equivalent oral temperature.
N=Number of participants vaccinated.

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 Prevenar 13 (PCV 13). 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.

Solicited Adverse Reactions

The percentage of participants with solicited adverse reactions that occurred within 5 or 14 days following administration of VAXNEUVANCE or Prevenar 13 in 5 studies are shown in Tables 13 and 14. All solicited adverse reactions occurred in ≥5% of participants with VAXNEUVANCE; older adults reported fewer solicited adverse reactions than younger adults, regardless of vaccination group. 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 >10 cm) occurred in ≤1.5% of adults.

Table 13: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 5 or 14 Days Postvaccination in Pneumococcal Vaccine-Naïve Adults

	Protocol 019		Protocol 020		Protocol 016		Protocol 017	
Age in Years	≥50						18-49	
	VAXNEUVANCE (%) N=602	**PCV13 (%) N=600**	**VAXNEUVANCE (%) N=2103**	**PCV13 (%) N=230**	**VAXNEUVANCE (%) N=327**	**PCV13 (%) N=324**	**VAXNEUVANCE (%) N=1134**	**PCV13 (%) N=378**
Local Reactions*								
Pain	54.0	42.3	66.8	52.2	55.0	41.4	75.8	68.8
Erythema	9.0	11.3	10.9	9.6	9.8	5.6	15.1	14.0
Swelling	12.5	11.2	15.4	14.3	16.2	11.4	21.7	22.2
Systemic Reactions†								
Fatigue	17.4	17.3	21.5	22.2	23.5	13.9	34.3	36.8
Headache	11.6	13.0	18.9	18.7	14.1	12.7	26.5	24.9
Myalgia	15.4	12.0	26.9	21.7	17.7	11.1	28.8	26.5
Arthralgia	5.3	5.5	7.7	5.7	6.4	5.2	12.7	11.6
Elevated Body Temperature*‡								
≥38.0°C and <39.0°C	0.3	1.3	0.7	0.4	0.6	0.6	1.3	0.3
≥39.0°C	0.2	0.0	0.0	0.0	0.6	0.6	0.2	0.0

* Solicited on Day 1 through Day 5 postvaccination

† Solicited on Day 1 through Day 14 postvaccination

‡ Percentages are based on the number of participants with temperature data

N=Number of participants vaccinated

Table 14: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 5 or 14 Days Postvaccination in Adults with Previous Pneumococcal Vaccination

	Protocol 007	
Age in Years	**≥65**	
	VAXNEUVANCE (%) N=127	**PCV13 (%) N=126**
Local Reactions*		
Pain	55.1	44.4
Erythema	7.9	7.1
Swelling	14.2	6.3
Systemic Reactions†		
Fatigue	18.1	19.0
Headache	13.4	15.9
Myalgia	15.7	11.1
Arthralgia	5.5	8.7
Elevated Body Temperature*‡		
≥38.0°C and <39.0°C	1.6	0.0
≥39.0°C	0.0	0.0

* Solicited on Day 1 through Day 5 postvaccination
† Solicited on Day 1 through Day 14 postvaccination
‡ Percentages are based on the number of participants with temperature data
N=Number of participants vaccinated

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.

13. OVERDOSAGE

There are no data with regards to overdose.

14. STORAGE

Special Precautions for Storage
Store refrigerated at 2°C to 8°C (36°F to 46°F).
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.

15. SHELF LIFE

Please refer to the expiry date on the outer carton.

16. APPEARANCE AND AVAILABILITY

Sterile, opalescent, liquid suspension.
Packed in 0.5mL single dose prefilled syringes (1s and 10s).

17. MANUFACTURER

MSD International GmbH T/A MSD Ireland (Carlow)
Dublin Road, Carlow,
Co. Carlow, Ireland

18. PACKER AND RELEASER

Merck Sharp & Dohme B.V.
Waarderweg 39, Haarlem
2031 BN, Netherlands

19. PRODUCT REGISTRATION HOLDER

MERCK SHARP & DOHME (MALAYSIA) SDN. BHD.
Lot No. B-22-1 & B-22-2, Level 22
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Date of revision: 6th September 2023