HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VAXNEUVANCE safely and effectively. See full prescribing information for VAXNEUVANCE.

VAXNEUVANCE® (Pneumococcal 15-valent Conjugate Vaccine)
Suspension for Intramuscular Injection
Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------
VAXNEUVANCE® is a vaccine indicated for active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F in individuals 6 weeks of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------
For intramuscular injection only.
Each dose of VAXNEUVANCE is 0.5 mL. (2.1)
Children: Administer VAXNEUVANCE as a 4-dose series at 2, 4, 6 and 12 through 15 months of age. (2.3)
Adults: Administer VAXNEUVANCE as a single dose in adults 18 years of age and older. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
Suspension for injection (0.5 mL dose), supplied as a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------
Severe allergic reaction (e.g., anaphylaxis) to any component of VAXNEUVANCE or to diphtheria toxoid. (4)

---------- WARNINGS AND PRECAUTIONS----------
Apnea following intramuscular vaccination has been observed in some infants born prematurely. A decision about when to administer VAXNEUVANCE to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.3)

---------- ADVERSE REACTIONS ----------
The most commonly reported solicited adverse reactions:

- in children vaccinated with a 4-dose series at 2, 4, 6 and 12 through 15 months of age, provided as a range across the series, were: irritability (57.3% to 63.4%), somnolence (24.2% to 47.5%), injection-site pain (25.9% to 40.3%), fever ≥38.0°C (13.3% to 20.4%), decreased appetite (14.1% to 19.0%), injection-site induration (13.2% to 15.4%), injection-site erythema (13.7% to 21.4%) and injection-site swelling (11.3% to 13.4%). (6.1)
- in children and adolescents 2 through 17 years of age vaccinated with a single dose 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%) and injection-site induration (6.8%). (6.1)
- in adults 18 through 49 years of age were: injection-site pain (75.8%), fatigue (34.3%), myalgia (28.8%), headache (26.5%), injection-site swelling (21.7%), injection-site erythema (15.1%) and arthralgia (12.7%). (6.1)
- in adults 50 years of age and older were: injection-site pain (66.8%), myalgia (26.9%), fatigue (21.5%), headache (18.9%), injection-site swelling (15.4%), injection-site erythema (10.9%) and arthralgia (7.7%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov .

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage
Each dose of VAXNEUVANCE is 0.5 mL.

2.2 Administration
Hold the prefilled syringe horizontally and shake vigorously immediately prior to use to obtain an opalescent suspension. 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, whenever solution and container permit. Do not use if particulate matter or discoloration is observed.

2.3 Vaccination Schedule
Children
Administer VAXNEUVANCE as a 4-dose series at 2, 4, 6 and 12 through 15 months of age (and at least 2 months after the third dose). The first dose may be given as early as 6 weeks of age.

The 4-dose series initiated with a lower valency pneumococcal conjugate vaccine can be completed with VAXNEUVANCE *[see Clinical Studies (14.1)]*.

Adults
Administer VAXNEUVANCE as a single dose in adults 18 years of age and older.

2.4 Catch-Up Vaccination Schedule in Children and Adolescents
Children 7 months through 17 years of age who have never received a pneumococcal conjugate vaccine may receive VAXNEUVANCE according to the schedule in Table 1:

Table 1: Catch-Up Vaccination Schedule for Individuals Initiating Vaccination at 7 Months Through 17 Years of Age

Age at First Dose	Total Number of 0.5 mL Doses
7 through 11 months of age	3*
12 through 23 months of age	2†
2 years through 17 years of age	1

* The first 2 doses are given at least 4 weeks apart; third dose given after the one-year birthday, separated from the second dose by at least 2 months.
† Two doses at least 2 months apart.

Children and Adolescents Previously Vaccinated with a Pneumococcal Conjugate Vaccine
Administer a single dose of VAXNEUVANCE to children and adolescents 2 years through 17 years of age who have received an incomplete series of another pneumococcal conjugate vaccine. At least 2 months should elapse between receipt of the last dose of another pneumococcal conjugate vaccine and administration of VAXNEUVANCE.

3 DOSAGE FORMS AND STRENGTHS

VAXNEUVANCE is a suspension for intramuscular injection supplied in a 0.5 mL single-dose prefilled syringe.

4 CONTRAINDICATIONS

Do not administer VAXNEUVANCE to individuals with a severe allergic reaction (e.g., anaphylaxis) to any component of VAXNEUVANCE or to diphtheria toxoid. *[See Description (11).]*

5 WARNINGS AND PRECAUTIONS

5.1 Management of Allergic Reactions
Appropriate medical treatment to manage allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of VAXNEUVANCE.

5.2 Altered Immunocompetence
Some individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to VAXNEUVANCE. *[See Use in Specific Populations (8.6).]*

5.3 Apnea in Premature Infants
Apnea following intramuscular vaccination has been observed in some infants born prematurely. A decision about when to administer VAXNEUVANCE to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The most commonly reported solicited adverse reactions in children vaccinated with a 4-dose series at 2, 4, 6, and 12 through 15 months of age, provided as a range across the series, were: irritability (57.3% to 63.4%), somnolence (24.2% to 47.5%), injection-site pain (25.9% to 40.3%), fever ≥38.0°C (13.3% to 20.4%), decreased appetite (14.1% to 19.0%), injection-site induration (13.2% to 15.4%), injection-site erythema (13.7% to 21.4%) and injection-site swelling (11.3% to 13.4%).

The most commonly reported solicited adverse reactions in children and adolescents 2 through 17 years of age vaccinated with a single dose 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%) and injection-site induration (6.8%).

The most commonly reported solicited adverse reactions in adults 18 through 49 years of age were: injection-site pain (75.8%), fatigue (34.3%), myalgia (28.8%), headache (26.5%), injection-site swelling (21.7%), injection-site erythema (15.1%) and arthralgia (12.7%).

The most commonly reported solicited adverse reactions in adults 50 years of age and older were: injection-site pain (66.8%), myalgia (26.9%), fatigue (21.5%), headache (18.9%), injection-site swelling (15.4%), injection-site erythema (10.9%) and arthralgia (7.7%).

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

Safety Assessment in Children Receiving a 4-Dose Series

The safety of VAXNEUVANCE in healthy infants (6 weeks through 11 months of age) and children (12 months through 15 months of age) was assessed in 4 randomized, double-blind clinical studies (Studies 8-11 (NCT03893448, NCT03620162, NCT03692871 and NCT02987972)) conducted in the Americas, Europe, and Asia Pacific. These studies included 3,349 participants who received at least one dose of a 4-dose series of VAXNEUVANCE, 1,814 participants who received at least one dose of a 4-dose series of Prevnar 13 [Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)], and 538 participants who received VAXNEUVANCE to complete a 4-dose series of pneumococcal conjugate vaccine initiated with Prevnar 13. In the United States (including Puerto Rico), 2,827 participants received at least one dose of either VAXNEUVANCE or Prevnar 13 and 2,409 participants completed a 4-dose series of either vaccine. Overall, the median age of the participants was 9.0 weeks (6-12 weeks) and 48.6% were female. The racial distribution was as follows: 57.1% were White, 26.4% were Asian, 9.5% were Multi-racial, 4.7% were Black or African American, and 18.8% were of Hispanic or Latino ethnicity. There were no meaningful differences in demographic characteristics across the vaccination groups.

In Studies 8 and 9, Pentacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate [Tetanus Toxoid Conjugate] Vaccine) (DTaP-IPV-Hib vaccine) for US participants or a non-US-licensed DTaP-IPV-Hib vaccine for non-US participants was administered concomitantly with VAXNEUVANCE at 2, 4 and 6 months of age. RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent) and RECOMBIVAX HB (Hepatitis B Vaccine [Recombinant]) were also administered concomitantly at 2, 4, and 6 months of age. M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live), VAQTA (Hepatitis A Vaccine, Inactivated), VARIVAX (Varicella Virus Vaccine Live), and Hiberix (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate]) were administered concomitantly with VAXNEUVANCE at 12 through 15 months of age. Study 9 also evaluated the use of VAXNEUVANCE to complete a pneumococcal conjugate vaccine series initiated with Prevnar 13.

Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. Study investigators reviewed the VRC with the participant or participant's legal guardian 15 days postvaccination to ensure consistency with protocol definitions. The analyses presented in Tables 2-3 below reflect the information based on the final assessment by the study investigators. 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 via rectal or axillary measurement. Unsolicited adverse events were monitored using the VRC through 14 days postvaccination. The duration of the safety follow-up period for serious adverse events following the last study vaccination was 1 month in Study 11 and 6 months in Studies 8-10.

Solicited Adverse Reactions in Children Receiving a 4-Dose Series

Study 8 was a multicenter, double-blind, active comparator-controlled study that assessed the safety of VAXNEUVANCE when administered as a 4-dose series in children (N=858 received VAXNEUVANCE and N=855 received Prevnar 13). The percentage of US participants with solicited adverse reactions that occurred within 14 days following administration of VAXNEUVANCE or Prevnar 13 are shown in Tables 2-3. Solicited adverse reactions following administration of VAXNEUVANCE lasted a median of 1 day with 90.6% of reactions lasting ≤3 days.

Table 2: Percentage of US Participants with Solicited Local Adverse Reactions in Infants at 2, 4, 6 and 12 through 15 Months of Age After Vaccination (Study 8)*

Dose	Dose 1		Dose 2		Dose 3		Dose 4	
	VAXNEUVANCE (%) N=598	Prevnar 13 (%) N=600	VAXNEUVANCE (%) N=584	Prevnar 13 (%) N=570	VAXNEUVANCE (%) N=559	Prevnar 13 (%) N=540	VAXNEUVANCE (%) N=532	Prevnar 13 (%) N=507
Local Reactions†								
Pain‡								
Any	40.3	39.5	32.0	28.8	30.8	26.9	25.9	25.0
Mild	24.1	23.2	18.7	14.7	17.9	16.7	16.9	16.4
Moderate	14.7	15.2	12.5	13.3	12.3	10.0	8.8	8.7
Severe	1.5	1.2	0.9	0.7	0.5	0.2	0.2	0.0
Induration								
Any	14.0	12.7	13.2	16.1	15.4	16.3	13.7	14.6
≤2.5 cm	11.0	10.0	9.1	11.4	10.7	11.5	7.5	8.5
2.6-7.6 cm	2.8	5.4	4.1	4.7	4.7	4.8	6.2	6.1
>7.6 cm	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0
Erythema								
Any	13.7	14.7	16.4	22.5	20.4	23.9	21.4	24.1
≤2.5 cm	11.0	10.8	12.7	16.7	15.4	17.4	14.7	16.8
2.6-7.6 cm	2.3	3.5	3.8	5.6	4.8	6.5	6.8	7.1
>7.6 cm	0.3	0.2	0.0	0.2	0.2	0.0	0.0	0.2
Swelling								
Any	12.9	12.7	13.2	11.4	13.4	10.4	11.3	10.8
≤2.5 cm	9.5	7.2	8.2	6.5	8.6	5.7	5.8	7.3
2.6-7.6 cm	3.2	5.3	4.8	4.6	4.8	4.4	5.5	3.4
>7.6 cm	0.0	0.2	0.2	0.0	0.0	0.0	0.0	0.0

* Study 8 (NCT03893448) was a randomized, double-blind, active comparator-controlled clinical study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination following each dose. The table represents the final assessment by the study investigators upon review of the VRC 15 days postvaccination, to ensure consistency with protocol definitions.

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

‡ Mild: awareness of symptoms, but easily tolerated; moderate: definitely acting like something is wrong; severe: extremely distressed or unable to do usual activities.

N=Number of participants vaccinated, including those with missing solicited adverse event data. The percentage of participants with missing solicited adverse event data, provided as a range across the 4-dose series, was 0.8% to 3.9%.

Table 3: Percentage of US Participants with Solicited Systemic Adverse Reactions in Infants at 2, 4, 6 and 12 through 15 Months of Age After Vaccination (Study 8)*

Dose	Dose 1		Dose 2		Dose 3		Dose 4	
	VAXNEUVANCE (%) N=598	Prevnar 13 (%) N=600	VAXNEUVANCE (%) N=584	Prevnar 13 (%) N=570	VAXNEUVANCE (%) N=559	Prevnar 13 (%) N=540	VAXNEUVANCE (%) N=532	Prevnar 13 (%) N=507
Systemic Reactions†								
Irritability‡								
Any	63.4	67.3	57.4	58.1	59.0	55.4	57.3	56.6
Mild	27.3	29.3	23.6	21.9	30.2	28.9	28.0	26.6
Moderate	31.4	33.0	30.0	33.2	25.0	24.4	26.7	27.4
Severe	4.7	5.0	3.6	3.0	3.8	2.0	2.6	2.6
Somnolence‡								
Any	47.5	52.7	35.6	39.3	31.1	30.2	24.2	29.6
Mild	24.2	29.5	20.2	18.8	19.1	16.3	13.9	17.0
Moderate	21.6	21.8	14.6	19.6	11.4	12.8	10.0	11.8
Severe	1.7	1.3	0.9	0.9	0.5	1.1	0.4	0.8
Decreased appetite‡								
Any	18.2	19.0	19.0	16.0	14.1	17.8	17.5	16.4
Mild	11.0	11.2	12.0	8.2	7.5	11.1	9.2	10.7
Moderate	6.7	7.2	7.0	7.4	6.3	6.5	7.9	5.5
Severe	0.5	0.7	0.0	0.4	0.4	0.2	0.4	0.2
Urticaria‡								
Any	1.2	0.8	1.5	1.4	1.1	1.9	3.4	2.6
Mild	0.8	0.5	1.4	0.7	1.1	1.5	1.7	1.2
Moderate	0.2	0.2	0.2	0.7	0.0	0.2	1.5	1.2
Severe	0.2	0.2	0.0	0.0	0.0	0.2	0.2	0.2
Fever§, ¶								
≥38.0°C	18.4	16.4	20.4	21.7	20.0	20.0	13.3	14.0
≥38.0°C to <39.0°C	17.3	15.7	18.5	18.1	17.2	17.2	12.1	13.2
≥39.0°C to <40.0°C	1.0	0.7	1.6	3.4	2.4	2.5	0.8	0.8
≥40.0°C	0.0	0.0	0.4	0.2	0.4	0.2	0.4	0.0

* Study 8 (NCT03893448) was a randomized, double-blind, active comparator-controlled clinical study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination following each dose. The table represents the final assessment by the study investigators upon review of the VRC 15 days postvaccination, to ensure consistency with protocol definitions.
† Solicited on Day 1 through Day 14 postvaccination following each dose.
‡ Mild: awareness of symptoms, but easily tolerated; moderate: definitely acting like something is wrong; severe: extremely distressed or unable to do usual activities.
§ Solicited on Day 1 through Day 7 postvaccination following each dose.
¶ Percentages reflect the number of participants with temperature data.
Following Doses 1-3, rectal temperature measurements were provided for 76.7% to 77.6% of participants and axillary temperature measurements were provided for 22.4% to 23.3% of participants, provided as a range across the doses.
Following Dose 4, rectal temperature measurements were provided for 70.6% of participants and axillary temperature measurements were provided for 29.4% of participants.
N=Number of participants vaccinated, including those with missing solicited adverse event data. The percentage of participants with missing solicited adverse event data, provided as a range across the 4-dose series, was 0.8% to 3.9%.

Across Studies 8-10 (excluding participants in Study 9 who received VAXNEUVANCE to complete a pneumococcal conjugate vaccine series initiated with Prevnar 13), the percentage of participants with fever that occurred within 7 days following administration of VAXNEUVANCE or Prevnar 13 is shown in Table 4.

Table 4: Percentage of Participants with Fever in Infants at 2, 4, 6 and 12 through 15 Months of Age After Vaccination (Studies 8-10)*

Dose	Dose 1		Dose 2		Dose 3		Dose 4	
	VAXNEUVANCE (%) N=2,995	Prevnar 13 (%) N=1,458	VAXNEUVANCE (%) N=2,902	Prevnar 13 (%) N=1,394	VAXNEUVANCE (%) N=2,865	Prevnar 13 (%) N=1,344	VAXNEUVANCE (%) N=2,772	Prevnar 13 (%) N=1,287
Fever†								
≥38.0°C	15.2	12.6	19.2	18.3	17.1	16.4	15.2	13.0
≥38.0°C to <39.0°C	14.4	11.7	17.1	15.8	14.6	14.7	12.7	11.4
≥39.0°C to <40.0°C	0.7	0.9	2.0	2.2	2.3	1.6	1.9	1.4
≥40.0°C	0.0	0.0	0.1	0.3	0.2	0.1	0.5	0.2

* Studies 8-10 (NCT03893448, NCT03620162 and NCT03692871) were randomized, double-blind, active comparator-controlled clinical studies. Licensed pediatric vaccines were administered concomitantly according to the study design or local recommended schedule.

† Solicited on Day 1 through Day 7 postvaccination following each dose.

Following Doses 1-3, rectal temperature measurements were provided for 53.2% to 54.9% of participants and axillary temperature measurements were provided for 45.1% to 46.8% of participants, provided as a range across the doses.

Following Dose 4, rectal temperature measurements were provided for 47.0% of participants and axillary temperature measurements were provided for 53.0% of participants.

N=Number of participants with temperature data.

Unsolicited Adverse Reactions in Children Receiving a 4-Dose Series

Across Studies 8-11 (excluding participants in Study 9 who received VAXNEUVANCE to complete a pneumococcal conjugate vaccine series initiated with Prevnar 13), injection-site urticaria within 14 days following each dose of VAXNEUVANCE occurred in up to 0.6% of children. Participants in these studies may have received either US-licensed or non-US licensed concomitant vaccines according to the local recommended schedule.

Serious Adverse Events in Children Receiving a 4-Dose Series

Among children who received VAXNEUVANCE (N=3,349) or Prevnar 13 (N=1,814) across Studies 8-11 (excluding participants in Study 9 who received VAXNEUVANCE to complete a pneumococcal conjugate vaccine series initiated with Prevnar 13), serious adverse events up to 6 months following vaccination with the 4-dose series were reported by 9.6% of VAXNEUVANCE recipients and by 8.9% of Prevnar 13 recipients. Participants in these studies may have received either US-licensed or non-US licensed concomitant vaccines according to the local recommended schedule.

Up to 30 days following completion of Doses 1 through 3, serious adverse events were reported by 4.8% of VAXNEUVANCE recipients and by 5.0% of Prevnar 13 recipients. An adverse reaction of febrile seizure was reported in a 9 week old female (Study 11) one day after receiving VAXNEUVANCE (Dose 1) and recommended infant vaccines. Up to 30 days following Dose 4, serious adverse events were reported by 1.0% of VAXNEUVANCE recipients and by 0.7% of Prevnar 13 recipients.

There were no notable patterns or numerical imbalances between vaccination groups for specific categories of serious adverse events that would suggest a causal relationship to VAXNEUVANCE.

Safety of VAXNEUVANCE When Used to Complete a 4-Dose Pneumococcal Conjugate Vaccine Series Initiated with Prevnar 13

The safety profile observed when VAXNEUVANCE was used to complete a 4-dose pneumococcal conjugate vaccine series initiated with Prevnar 13 was similar to the safety profile following a complete 4-dose regimen of either VAXNEUVANCE or Prevnar 13 *[see Clinical Studies (14.1)]*.

Safety Assessment in Infants and Children Receiving Catch-Up Vaccination

The safety of VAXNEUVANCE in healthy infants and children 7 months through 17 years of age was assessed in a double-blind, multi-regional, clinical study (Study 12, NCT03885934). Participants were randomized to receive 1 to 3 doses of VAXNEUVANCE (N=303) or Prevnar 13 (N=303), depending on age at enrollment. All infants and children less than 2 years of age were pneumococcal vaccine-naïve. Among 352 children 2 through 17 years of age, 42.9% had a history of previous vaccination with a lower valency

pneumococcal conjugate vaccine. Among participants 7 through 11 months of age, the median age was 8.0 months, 48.4% were female, 82.8% were Asian, 17.2% were White and none were of Hispanic or Latino ethnicity. Among participants 12 through 23 months of age, the median age was 18.0 months, 54.0% were female, 83.3% were Asian, 16.7% were White and 0.8% were of Hispanic or Latino ethnicity. Among participants 2 through 17 years of age, the median age was 4.0 years, 47.7% were female, 66.8% were White, 33.0% were Asian, and none were of Hispanic or Latino ethnicity. The safety assessment was consistent with that used in Studies 8-11, as described above with the exception that in children 3 years of age and older, oral or axillary temperature measurements were obtained. The duration of the safety follow-up period for serious adverse events following the last dose of vaccine within each age cohort was 6 months.

Solicited Adverse Reactions in Children Receiving Catch-Up Vaccination
Among participants 7 through 11 months of age who received 3 doses of VAXNEUVANCE (N=64) or Prevnar 13 (N=64), the percentage of participants reporting solicited local and systemic adverse reactions that occurred within 14 days following any dose (VAXNEUVANCE participants vs. Prevnar 13 participants) were: fever ≥38.0°C (21.9% vs. 14.1%), irritability (32.8% vs. 43.8%), injection-site erythema (28.1% vs. 34.4%), somnolence (21.9% vs. 15.6%), injection-site swelling (18.8% vs. 15.6%), injection-site pain (18.8% vs. 7.8%), injection-site induration (17.2% vs. 14.1%), decreased appetite (15.6% vs. 18.8%) and urticaria (1.6% vs. 4.7%).

Among participants 12 through 23 months of age who received 2 doses of VAXNEUVANCE (N=62) or Prevnar 13 (N=64), the percentage of participants reporting solicited local and systemic adverse reactions that occurred within 14 days following any dose (VAXNEUVANCE participants vs. Prevnar 13 participants) were: fever ≥38.0°C (11.3% vs. 9.4%), irritability (35.5% vs. 21.9%), injection-site pain (33.9% vs. 23.4%), somnolence (24.2% vs. 17.2%), decreased appetite (22.6% vs. 18.8%), injection-site erythema (21.0% vs. 21.9%), injection-site swelling (14.5% vs. 12.5%) and injection-site induration (8.1% vs. 9.4%).

In children 2 through 17 years of age, the percentage of participants with solicited adverse reactions that occurred within 14 days following administration of a single dose of VAXNEUVANCE or Prevnar 13 is shown in Table 5.

Table 5: Percentage of Participants with Solicited Local and Systemic Adverse Reactions in Children and Adolescents 2 Years Through 17 Years of Age Using a Catch Up Vaccination Schedule (Study 12)*

	VAXNEUVANCE (%) N=177	Prevnar 13 (%) N=175
Local Reactions[†]		
Pain[‡]		
Any	54.8	56.6
Moderate	27.7	22.9
Severe	4.5	1.7
Swelling		
Any	20.9	24.0
2.6-7.6 cm	10.2	12.0
>7.6 cm	0.0	0.6
Erythema		
Any	19.2	21.1
2.6-7.6 cm	6.2	7.4
>7.6 cm	1.1	0.6
Induration		
Any	6.8	14.9
2.6-7.6 cm	3.4	5.7
>7.6 cm	0.0	0.0
Systemic Reactions[†, ‡]		
Myalgia[§]		
Any	23.7	16.6
Moderate	14.7	6.9
Severe	0.6	0.6
Fatigue[§]		
Any	15.8	17.1
Moderate	6.2	5.7

	VAXNEUVANCE (%) N=177	Prevnar 13 (%) N=175
Severe	2.8	0.6
Headache[§]		
Any	11.9	13.7
Moderate	6.2	8.6
Severe	0.6	0.6
Somnolence[§]		
Any	2.8	2.9
Moderate	1.7	1.1
Severe	0.0	0.6
Irritability[§]		
Any	2.8	4.0
Moderate	0.6	0.6
Severe	0.0	0.0
Decreased appetite[§]		
Any	2.3	2.9
Moderate	0.6	1.7
Severe	0.0	0.0
Urticaria[§]		
Any	1.1	1.1
Moderate	0.0	0.0
Severe	0.0	0.0
Fever[¶, #]		
≥38.0°C	4.0	1.7
≥38.0°C to <39.0°C	2.8	1.7
≥39.0°C to <40.0°C	1.1	0.0
≥40.0°C	0.0	0.0

* Study 12 (NCT03885934) was a randomized, double-blind, active comparator-controlled clinical study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination following each dose. The table represents the final assessment by the study investigators upon review of the VRC 15 days postvaccination, to ensure consistency with protocol definitions.

† 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, Prevnar 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, arthralgia and urticaria were solicited from Day 1 through Day 14 following vaccination; no events of arthralgia were reported in VAXNEUVANCE recipients.

§ Moderate: definitely acting like something is wrong; severe: extremely distressed or unable to do usual activities.

¶ Solicited on Day 1 through Day 7 postvaccination following each dose.

Percentages reflect the number of participants with temperature data.

The percentage of participants 2 to <3 years of age with rectal temperature measurements was 5.0% and with axillary temperature measurements was 95.0%.

The percentage of participants ≥3 to 17 years of age with oral temperature measurements was 65.4% and with axillary temperature measurements was 34.6%.

N=Number of participants vaccinated.

Clinical Trials Experience in Adults

Safety Assessment in Clinical Studies

The safety of VAXNEUVANCE was assessed in 7 randomized, double-blind clinical studies conducted in the Americas, Europe and Asia Pacific, in which 5,630 adults 18 years of age and older received VAXNEUVANCE and 1,808 adults received Prevnar 13. In Studies 1-3 (NCT03950622, NCT03950856, and NCT03480763), a total of 3,032 adults 50 years of age and older with no history of pneumococcal vaccination received VAXNEUVANCE and 1,154 participants received Prevnar 13. In Study 4 (NCT03547167), adults 18 through 49 years of age with no history of pneumococcal vaccination, including individuals with increased risk of developing pneumococcal disease, received VAXNEUVANCE (N=1,134) or Prevnar 13 (N=378), followed by PNEUMOVAX 23 six months later. In Study 5 (NCT02573181), adults 65 years of age and older previously vaccinated with PNEUMOVAX 23 (at least 1 year prior to study entry) received VAXNEUVANCE (N=127) or Prevnar 13 (N=126). In Study 6 (NCT03615482), adults 50 years of age and older received VAXNEUVANCE concomitantly with a seasonal inactivated quadrivalent influenza vaccine (Fluarix Quadrivalent; QIV) (Group 1, N=600) or nonconcomitantly 30 days after QIV (Group 2, N=585). In this study population, 20.9% of individuals had a history of prior vaccination with PNEUMOVAX 23. In Study 7 (NCT03480802), HIV-infected adults 18 years of age and older received VAXNEUVANCE (N=152) or Prevnar 13 (N=150), followed by PNEUMOVAX 23 two months later.

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. Overall, the mean age of the participants was 58 years and 54.6% were female. The racial distribution was as follows: 72.3% were White, 9.9% were Asian, 8.1% were American Indian or Alaska Native, 7.4% were Black or African American, and 18.1% were of Hispanic or Latino ethnicity.

In all studies, safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. Study investigators reviewed the VRC with the participants 15 days postvaccination to ensure consistency with protocol definitions. The analyses presented in Tables 1-3 below reflect the information based on the final assessment by the study investigators. Oral body temperature and injection-site adverse reactions were solicited on Day 1 through Day 5 postvaccination. Systemic adverse reactions 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 for serious adverse events postvaccination with VAXNEUVANCE was 1 month in Study 5; 2 months in Study 7; 6 months in Studies 1, 2, 4 and 6; and 12 months in Study 3.

Solicited Adverse Reactions

The percentage of participants with solicited adverse reactions that occurred within 5 or 14 days following administration of VAXNEUVANCE or Prevnar 13 in 3 studies are shown in Tables 6-8. The majority of solicited adverse reactions lasted ≤3 days.

Table 6: Percentage of Participants with Solicited Local and Systemic Adverse Reactions in Pneumococcal Vaccine-Naïve Adults 50 Years of Age and Older (Study 2)*

	VAXNEUVANCE (%) N=2,103	Prevnar 13 (%) N=230
Local Reactions†		
Pain		
Any	66.8	52.2
Grade 3‡	0.9	0.0
Erythema		
Any	10.9	9.6
>10 cm	0.6	0.4
Swelling		
Any	15.4	14.3
>10 cm	0.2	0.0
Systemic Reactions§		
Fatigue		
Any	21.5	22.2
Grade 3‡	0.7	0.9
Headache		
Any	18.9	18.7
Grade 3‡	0.8	0.0
Myalgia		
Any	26.9	21.7
Grade 3‡	0.4	0.0
Arthralgia		
Any	7.7	5.7
Grade 3‡	0.2	0.0
Fever†, ¶		
≥38.0°C and <38.5°C	0.6	0.4
≥38.5°C and <39.0°C	0.1	0.0
≥39.0°C	0.0	0.0

* Study 2 (NCT03950856) was a randomized (9:1), double-blind, active comparator-controlled, lot to lot consistency study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. The table represents the final assessment by the study investigators upon review of the VRC 15 days postvaccination, to ensure consistency with protocol definitions.
† Solicited on Day 1 through Day 5 postvaccination.
‡ Any use of narcotic pain reliever or prevents daily activity.
§ 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 7: Percentage of Participants with Solicited Local and Systemic Adverse Reactions in Pneumococcal Vaccine-Naïve Adults 18 to 49 Years of Age With or Without Risk Factors for Pneumococcal Disease (Study 4)*

	VAXNEUVANCE (%) N=1,134	Prevnar 13 (%) N=378
Local Reactions†		
Pain		
Any	75.8	68.8
Grade 3‡	1.1	1.6
Erythema		
Any	15.1	14.0
>10 cm	0.5	0.3
Swelling		
Any	21.7	22.2
>10 cm	0.4	0.5
Systemic Reactions§		
Fatigue		
Any	34.3	36.8
Grade 3‡	1.0	0.8
Headache		
Any	26.5	24.9
Grade 3‡	0.8	0.5
Myalgia		
Any	28.8	26.5
Grade 3‡	0.3	0.5
Arthralgia		
Any	12.7	11.6
Grade 3‡	0.4	0.0
Fever†, ¶		
≥38.0°C and <38.5°C	1.0	0.3
≥38.5°C and <39.0°C	0.3	0.0
≥39.0°C	0.2	0.0

* Study 4 (NCT03547167) was a randomized (3:1), double-blind, descriptive study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. The table represents the final assessment by the study investigators upon review of the VRC 15 days postvaccination, to ensure consistency with protocol definitions.
† Solicited on Day 1 through Day 5 postvaccination.
‡ Any use of narcotic pain reliever or prevents daily activity.
§ 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 8: Percentage of Participants with Solicited Local and Systemic Adverse Reactions in Adults 65 Years of Age and Older with Previous Pneumococcal Vaccination (Study 5)*

	VAXNEUVANCE (%) N=127	Prevnar 13 (%) N=126
Local Reactions†		
Pain		
Any	55.1	44.4
Grade 3‡	0.8	0.0
Erythema		
Any	7.9	7.1
>10 cm	0.8	0.0
Swelling		
Any	14.2	6.3
>10 cm	0.0	0.0
Systemic Reactions§		
Fatigue		
Any	18.1	19.0
Grade 3‡	0.0	0.0
Headache		
Any	13.4	15.9
Grade 3‡	0.0	0.0
Myalgia		
Any	15.7	11.1
Grade 3‡	0.8	0.0
Arthralgia		
Any	5.5	8.7
Grade 3‡	0.0	0.0
Fever†, ¶		
≥38.0°C and <38.5°C	1.6	0.0
≥38.5°C and <39.0°C	0.0	0.0
≥39.0°C	0.0	0.0

* Study 5 (NCT02573181) was a randomized, double-blind, descriptive study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. The table represents the final assessment by the study investigators upon review of the VRC 15 days postvaccination, to ensure consistency with protocol definitions.
† Solicited on Day 1 through Day 5 postvaccination.
‡ Any use of narcotic pain reliever or prevents daily activity.
§ 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
Across all studies, injection-site pruritus was reported to occur in up to 2.8% of adults vaccinated with VAXNEUVANCE.

Serious Adverse Events
Across all studies, among participants 18 years of age and older who received VAXNEUVANCE (excluding those who received QIV concomitantly; N=5,030) or Prevnar 13 (N=1,808), serious adverse events within 30 days postvaccination were reported by 0.4% of VAXNEUVANCE recipients and by 0.7% of Prevnar 13 recipients. In a subset of these studies, among those who received VAXNEUVANCE (N=4,751) and Prevnar 13 (N=1,532), serious adverse events within 6 months postvaccination were reported by 2.5% of VAXNEUVANCE recipients and by 2.4% of Prevnar 13 recipients.

There were no notable patterns or numerical imbalances between vaccination groups for specific categories of serious adverse events that would suggest a causal relationship to VAXNEUVANCE.

Safety with Concomitant Influenza Vaccine Administration
The safety profile was similar when VAXNEUVANCE was administered with or without inactivated quadrivalent influenza vaccine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

There are no adequate and well-controlled studies of VAXNEUVANCE in pregnant women. Available data on VAXNEUVANCE administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

Developmental toxicity studies have been performed in female rats administered a human dose of VAXNEUVANCE on four occasions; twice prior to mating, once during gestation and once during lactation. These studies revealed no evidence of harm to the fetus due to VAXNEUVANCE *[see Animal Data below]*.

Data

Animal Data

Developmental toxicity studies have been performed in female rats. In these studies, female rats received a human dose of VAXNEUVANCE by intramuscular injection on day 28 and day 7 prior to mating, and on gestation day 6 and on lactation day 7. No vaccine related fetal malformations or variations were observed. No adverse effect on pup weight up to post-natal day 21 was noted.

8.2 Lactation

Risk Summary

Human data are not available to assess the impact of VAXNEUVANCE on milk production, its presence in breast milk, or its effects on the breastfed child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VAXNEUVANCE and any potential adverse effects on the breastfed child from VAXNEUVANCE or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

The safety and effectiveness of VAXNEUVANCE have been established in individuals 6 weeks through 17 years of age *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. The safety and effectiveness of VAXNEUVANCE in individuals younger than 6 weeks of age have not been established.

8.5 Geriatric Use

Of the 4,389 individuals aged 50 years and older who received VAXNEUVANCE, 2,478 (56.5%) were 65 years and older, and 479 (10.9%) were 75 years and older *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. Overall, there were no clinically meaningful differences in the safety profile or immune responses observed in older individuals (65 to 74 years and 75 years of age and older) when compared to younger individuals.

8.6 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) who were randomized to receive a complete 4-dose series of either VAXNEUVANCE (N=142) or Prevnar 13 (N=144) within Study 8, Study 9, and Study 10. Participants in these studies may have received either US-licensed or non-US licensed concomitant vaccines according to the local recommended schedule. In descriptive analyses, serotype-specific immunoglobulin G (IgG) and opsonophagocytic activity (OPA) responses at 30 days postdose 3, predose 4 and at 30 days postdose 4 were numerically similar between vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes. The safety profile of VAXNEUVANCE was similar to the safety profile of Prevnar 13. In addition, the immune responses and safety profile in preterm infants receiving a 4-dose series of VAXNEUVANCE were similar to those observed in term infants in these studies. The effectiveness of VAXNEUVANCE in infants born prematurely has not been established.

Children with Sickle Cell Disease

In a double-blind, descriptive study (Study 13, NCT03731182), the safety and immunogenicity of VAXNEUVANCE were evaluated in children 5 through 17 years of age with sickle cell disease. Participants were randomized 2:1 to receive a single dose of VAXNEUVANCE (N=70) or Prevnar 13 (N=34). Immune responses were assessed by serotype-specific IgG GMCs and OPA GMTs at 30 days postvaccination for all 15 serotypes contained in VAXNEUVANCE. For all vaccine serotypes included in VAXNEUVANCE, serotype-specific IgG GMCs and OPA GMTs were higher following vaccination compared to pre-vaccination. IgG GMCs and OPA GMTs were numerically similar between the two vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for serotypes 22F and 33F. The safety profile of VAXNEUVANCE was similar to the safety profile of Prevnar 13. The effectiveness of VAXNEUVANCE in children with sickle cell disease has not been established.

Individuals with HIV Infection

Children with HIV Infection

In a double-blind, descriptive study (Study 14, NCT03921424), the safety and immunogenicity of VAXNEUVANCE were evaluated in HIV-infected children 6 through 17 years of age, with CD4+ T-cell count ≥200 cells per microliter and plasma HIV RNA value <50,000 copies/mL. Participants were randomized to receive a single dose of VAXNEUVANCE (N=203) or Prevnar 13 (N=204), followed by PNEUMOVAX 23 two months later. For all vaccine serotypes included in VAXNEUVANCE, serotype-specific IgG GMCs and OPA GMTs were higher following vaccination compared to pre-vaccination. Serotype-specific IgG GMCs and OPA GMTs were numerically similar for the 13 shared serotypes and higher for the 2 unique serotypes (22F and 33F) at 30 days following vaccination with VAXNEUVANCE or Prevnar 13 and were numerically similar for all 15 serotypes contained in VAXNEUVANCE at 30 days following subsequent vaccination with PNEUMOVAX 23. The safety profile of VAXNEUVANCE was similar to the safety profile of Prevnar 13. The effectiveness of VAXNEUVANCE in HIV-infected children has not been established.

Adults with HIV Infection

In a double-blind, descriptive study (Study 7), the safety and immunogenicity of VAXNEUVANCE were evaluated in pneumococcal vaccine-naïve HIV-infected adults 18 years of age and older, with CD4+ T-cell count ≥50 cells per microliter and plasma HIV RNA value <50,000 copies/mL. Participants were randomized to receive VAXNEUVANCE (N=152) or Prevnar 13 (N=150), followed by PNEUMOVAX 23 two months later *[see Adverse Reactions (6.1)]*. Anti-pneumococcal opsonophagocytic activity (OPA) geometric mean antibody titers (GMTs) were higher after administration of VAXNEUVANCE, compared to pre-vaccination, for the 15 serotypes contained in VAXNEUVANCE. After sequential administration with PNEUMOVAX 23, OPA GMTs observed at 30 days after PNEUMOVAX 23 vaccination were numerically similar between the two vaccination groups for all 15 serotypes contained in VAXNEUVANCE. The safety profile of VAXNEUVANCE was similar to the safety profile of Prevnar 13. The effectiveness of VAXNEUVANCE in HIV-infected adults has not been established.

Individuals with Hematopoietic Stem Cell Transplant

In a double-blind, descriptive study (Study 15, NCT03565900), the safety and immunogenicity of VAXNEUVANCE compared to Prevnar 13 were evaluated in participants who had received an allogeneic hematopoietic stem cell transplant (allo-HSCT) 3 to 6 months prior to enrollment. All participants had a history of stable engraftment and none had severe graft-versus-host disease. In this study, participants were randomized to receive 3 doses of VAXNEUVANCE (N=139) or Prevnar 13 (N=138), administered one month apart. Among those participants 3 through 17 years of age, 8 participants received VAXNEUVANCE and 6 participants received Prevnar 13. The remaining participants were 18 through 74 years of age. Twelve months after allo-HSCT, participants without chronic graft-versus-host disease (cGVHD) received a single dose of PNEUMOVAX 23 (N=164) and those with cGVHD received a fourth consecutive dose of VAXNEUVANCE (N=29) or Prevnar 13 (N=37). IgG GMCs and OPA GMTs were higher after administration of 3 doses of VAXNEUVANCE, compared to pre-vaccination, for the 15 serotypes contained in VAXNEUVANCE. Serotype-specific IgG GMCs and OPA GMTs were numerically similar between the two vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the two unique serotypes (22F and 33F). Similarly, in participants who received VAXNEUVANCE or Prevnar 13 twelve months after allo-HSCT, IgG GMCs and OPA GMTs at 30 days following vaccination were numerically similar between the two vaccination groups for the 13 shared

serotypes and higher in VAXNEUVANCE for the two unique serotypes (22F and 33F). In participants who received PNEUMOVAX 23 twelve months after allo-HSCT, IgG GMCs and OPA GMTs at 30 days following vaccination were numerically similar between those who had received either 3 doses of VAXNEUVANCE or Prevnar 13 for all 15 serotypes contained in VAXNEUVANCE. The safety profile of VAXNEUVANCE was similar to the safety profile of Prevnar 13. The effectiveness of VAXNEUVANCE in recipients of allo-HSCT has not been established.

11 DESCRIPTION

VAXNEUVANCE (Pneumococcal 15-valent Conjugate Vaccine) is a sterile suspension of purified capsular polysaccharides from *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM_{197}. Each pneumococcal capsular polysaccharide is activated via sodium metaperiodate oxidation and then individually conjugated to CRM_{197} carrier protein via reductive amination. CRM_{197} is a non-toxic variant of diphtheria toxin (originating from *Corynebacterium diphtheriae* C7) expressed recombinantly in *Pseudomonas fluorescens*.

Each of the fifteen serotypes is manufactured independently using the same manufacturing steps with slight variations to accommodate for differences in strains, polysaccharides and process stream properties. Each *S. pneumoniae* serotype is grown in media containing yeast extract, dextrose, salts and soy peptone. Each polysaccharide is purified by a series of chemical and physical methods. Then each polysaccharide is chemically activated and conjugated to the carrier protein CRM_{197} to form each glycoconjugate. CRM_{197} is isolated from cultures grown in a glycerol-based, chemically-defined, salt medium and purified by chromatography and ultrafiltration. The final vaccine is prepared by blending the fifteen glycoconjugates with aluminum phosphate adjuvant in a final buffer containing histidine, polysorbate 20 and sodium chloride.

Each 0.5 mL dose contains 2.0 mcg each of *S. pneumoniae* 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, 30 mcg of CRM_{197} carrier protein, 1.55 mg L-histidine, 1 mg of polysorbate 20, 4.50 mg sodium chloride, and 125 mcg of aluminum as aluminum phosphate adjuvant. VAXNEUVANCE does not contain any preservatives.

The tip cap and plunger stopper of the prefilled syringe are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Protection against invasive disease is conferred mainly by antibodies (Immunoglobulin G [IgG] directed against capsular polysaccharides) and opsonophagocytic activity (OPA) against *S. pneumoniae*. VAXNEUVANCE induces IgG antibodies and OPA against the serotypes contained in the vaccine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

VAXNEUVANCE has not been evaluated for carcinogenic or mutagenic potential or for impairment of male fertility in animals. VAXNEUVANCE administered to female rats had no effect on fertility *[see Use in Specific Populations (8.1)]*.

14 CLINICAL STUDIES

Immune responses elicited by VAXNEUVANCE and Prevnar 13 in children were measured by a pneumococcal electrochemiluminescence (Pn ECL) assay for total IgG and a multiplexed opsonophagocytic assay (MOPA) for opsonophagocytic killing for the 15 pneumococcal serotypes contained in VAXNEUVANCE postdose 3, predose 4 and postdose 4. In children, a serotype-specific Immunoglobulin G (IgG) antibody level corresponding to ≥0.35 mcg/mL using the WHO enzyme linked immunosorbent assay (ELISA) has been used as the threshold value for the clinical evaluation of pneumococcal conjugate vaccines. Immune responses elicited by VAXNEUVANCE and Prevnar 13 in adults were measured by MOPA and Pn ECL assays for the 15 pneumococcal serotypes contained in VAXNEUVANCE pre- and post-vaccination.

14.1 Clinical Trials in Children

Children Receiving a 4-Dose Series

In a double-blind, active comparator-controlled study (Study 8), participants were randomized to receive VAXNEUVANCE (N=860) or Prevnar 13 (N=860) in a 4-dose series; the first 3 doses were administered to infants at 2, 4, and 6 months of age and the fourth dose was administered to children 12 through 15 months of age. Pentacel (US participants) or a non-US-licensed DTaP-IPV-Hib vaccine (non-US participants), RECOMBIVAX HB, and RotaTeq were administered concomitantly with each of the 3 infant doses. VAQTA, M-M-R II, VARIVAX, and Hiberix were administered concomitantly with the fourth dose. *[See Adverse Reactions (6.1) and Clinical Studies (14.3).]*

Study 8 assessed serotype-specific IgG response rates, IgG geometric mean concentrations (GMCs), and opsonophagocytic activity (OPA) geometric mean titers (GMTs), for all 15 serotypes contained in VAXNEUVANCE. At 30 days postdose 3, VAXNEUVANCE was noninferior to Prevnar 13 for the 13 shared serotypes, as assessed by the proportion of participants meeting the serotype-specific IgG threshold value of ≥0.35 mcg/mL (response rate). VAXNEUVANCE was noninferior for the 2 unique vaccine serotypes, as assessed by the IgG response rates for serotypes 22F and 33F compared with the response rate for serotype 6B (the lowest response rate for any of the shared serotypes in Prevnar 13 among US participants, excluding serotype 3) at 30 days postdose 3 (Table 9).

Table 9: Proportions of US Participants with IgG Response Rates ≥0.35 mcg/mL at 30 Days Following Dose 3 in Infants Administered VAXNEUVANCE at 2, 4 and 6 Months of Age (Study 8)

Pneumococcal Serotype	VAXNEUVANCE (n=452-455)	Prevnar 13 (n=426-430)	Percentage Point Difference (VAXNEUVANCE – Prevnar 13) (95% CI)*, †
	Observed Response Percentage	Observed Response Percentage	
Serotype			
1	93.8	98.6	-4.8 (-7.5, -2.4)
3	93.1	74.0	19.1 (14.4, 24.0)
4	94.7	98.1	-3.4 (-6.1, -1.0)
5	93.4	96.0	-2.6 (-5.7, 0.3)
6A	92.7	99.3	-6.6 (-9.4, -4.2)
6B	86.7	89.9	-3.2 (-7.5, 1.1)
7F	98.7	100.0	-1.3 (-2.9, -0.4)
9V	96.7	97.2	-0.5 (-2.9, 1.9)
14	97.8	98.1	-0.3 (-2.4, 1.7)
18C	96.2	98.1	-1.9 (-4.3, 0.3)
19A	97.4	99.8	-2.4 (-4.3, -1.0)
19F	98.5	100.0	-1.5 (-3.2, -0.6)
23F	89.8	91.4	-1.5 (-5.4, 2.4)
Additional Serotypes			
22F	98.0	‡	8.1 (5.1, 11.5)
33F	84.8	‡	-5.1 (-9.5, -0.7)

* CIs are based on the Miettinen & Nurminen method.

† A conclusion of non-inferiority of VAXNEUVANCE to Prevnar 13 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 non-inferiority of VAXNEUVANCE to Prevnar 13 is based on the comparison of the response rate for the 2 additional serotypes to the lowest responding Prevnar 13 serotype (serotype 6B), excluding serotype 3.

n=Number of participants contributing to the analysis.

CI=Confidence interval; IgG=Immunoglobulin G.

At 30 days postdose 3, serotype-specific IgG GMCs in the VAXNEUVANCE group were noninferior to Prevnar 13 for 12 of the 13 shared serotypes, except for serotype 6A. The IgG response to serotype 6A missed the prespecified noninferiority criterion 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). VAXNEUVANCE was noninferior to Prevnar 13 for the 2 unique serotypes, as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F compared with the IgG GMCs for serotype 4 (the lowest IgG GMC for any of the shared serotypes in Prevnar 13 among US participants, excluding serotype 3) (Table 10).

Table 10: Serotype-Specific IgG GMCs at 30 Days Following Dose 3 in US Infants Administered VAXNEUVANCE at 2, 4 and 6 Months of Age (Study 8)

Pneumococcal Serotype	VAXNEUVANCE (n=452-455)	Prevnar 13 (n=426-430)	GMC Ratio* (VAXNEUVANCE/Prevnar 13) (95% CI)*, †
	GMC	GMC	
Serotype			
1	1.02	1.54	0.66 (0.61, 0.73)
3	0.96	0.56	1.70 (1.54, 1.86)
4	1.07	1.11	0.97 (0.89, 1.06)
5	1.29	1.69	0.76 (0.68, 0.85)
6A	1.33	2.48	0.53 (0.48, 0.60)
6B	1.42	1.58	0.90 (0.76, 1.06)
7F	2.17	2.83	0.77 (0.70, 0.84)
9V	1.47	1.48	1.00 (0.90, 1.10)
14	4.17	5.57	0.75 (0.66, 0.85)
18C	1.29	1.55	0.83 (0.76, 0.91)
19A	1.39	1.88	0.74 (0.67, 0.82)
19F	1.82	2.33	0.78 (0.72, 0.85)
23F	1.09	1.23	0.89 (0.79, 1.01)
Additional Serotypes			
22F	4.01	‡	3.63 (3.26, 4.04)
33F	1.38	‡	1.25 (1.09, 1.44)

* 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 of VAXNEUVANCE to Prevnar 13 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 non-inferiority of VAXNEUVANCE to Prevnar 13 is based on the comparison of the GMC for the 2 additional serotypes to the lowest responding Prevnar 13 serotype (serotype 4), excluding serotype 3.

n=Number of participants contributing to the analysis.

CI=Confidence interval; GMC=Geometric mean concentration (mcg/mL); IgG=Immunoglobulin G.

At 30 days postdose 4, serotype-specific IgG GMCs for VAXNEUVANCE were noninferior to Prevnar 13 for all 13 shared serotypes (the lower bound of the 2-sided 95% CI for the GMC ratio [VAXNEUVANCE/Prevnar 13] being >0.5) and for the 2 unique serotypes 22F and 33F as assessed by the IgG GMCs for serotypes 22F and 33F compared with the IgG GMCs for serotype 4 (the lowest IgG GMC for any of the shared serotypes in Prevnar 13 among US participants, excluding serotype 3) (Table 11).

Table 11: Serotype-Specific IgG GMCs at 30 Days Following Dose 4 in US Infants Administered VAXNEUVANCE at 2, 4, 6 and 12 to 15 Months of Age (Study 8)

Pneumococcal Serotype	VAXNEUVANCE (n=466-470)	Prevnar 13 (n=443-447)	GMC Ratio* (VAXNEUVANCE/Prevnar 13) (95% CI)*, †
	GMC	GMC	
Serotype			
1	1.21	1.82	0.66 (0.60, 0.73)
3	0.91	0.63	1.43 (1.30, 1.57)
4	1.07	1.42	0.76 (0.68, 0.84)
5	2.21	3.47	0.64 (0.57, 0.71)
6A	3.56	5.93	0.60 (0.54, 0.67)
6B	4.70	6.07	0.77 (0.69, 0.87)
7F	3.22	4.65	0.69 (0.62, 0.77)
9V	2.18	2.86	0.76 (0.69, 0.84)
14	5.09	6.21	0.82 (0.72, 0.93)
18C	2.37	2.59	0.92 (0.82, 1.02)
19A	3.86	4.93	0.78 (0.71, 0.86)
19F	3.32	4.02	0.83 (0.75, 0.91)
23F	1.85	2.88	0.64 (0.57, 0.72)
Additional Serotypes			
22F	6.76	‡	4.77 (4.28, 5.32)
33F	3.80	‡	2.68 (2.40, 3.00)

* GMC ratios and CIs 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 of VAXNEUVANCE to Prevnar 13 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 non-inferiority of VAXNEUVANCE to Prevnar 13 is based on the comparison of the GMC for the 2 additional serotypes to the lowest responding Prevnar 13 serotype (serotype 4), excluding serotype 3.

n=Number of participants contributing to the analysis.

CI=Confidence interval; GMC=Geometric mean concentration (mcg/mL); IgG=Immunoglobulin G.

Additionally, IgG response rates and IgG GMCs at 30 days postdose 3 and IgG GMCs at 30 days postdose 4 were statistically significantly greater for VAXNEUVANCE compared to Prevnar 13 for serotype 3 and the 2 unique serotypes (22F, 33F).

Serotype-specific OPA GMTs and response rates at 30 days postdose 3 and OPA GMTs at 30 days postdose 4 were descriptively evaluated in a subset of participants in Study 8. Serotype-specific OPA GMTs and response rates were numerically similar across groups for the 13 shared serotypes and higher in the VAXNEUVANCE group for the 2 unique serotypes.

Children Receiving VAXNEUVANCE to Complete a 4-Dose Series Initiated with Prevnar 13

In a double-blind, active comparator-controlled, descriptive study (Study 9), participants were randomized in a 1:1:1:1:1 ratio to one of five vaccination groups. Two vaccination groups received a 4-dose series composed entirely of either VAXNEUVANCE (N=180) or Prevnar 13 (N=179). The remaining 3 study groups received either 1, 2, or 3 doses of Prevnar 13 followed by VAXNEUVANCE to complete the 4-dose series (N=180, 180, and 181, respectively). Participants also received other pediatric vaccines concomitantly *[see Adverse Reactions (6.1) and Clinical Studies (14.3)]*. Serotype-specific IgG GMCs for the 13 shared serotypes at 30 days postdose 4 were numerically similar for participants completing the vaccination series with VAXNEUVANCE compared to participants who received a complete series with Prevnar 13.

Children and Adolescents Receiving Catch-Up Vaccination

In a double-blind, active comparator-controlled, descriptive study (Study 12), participants were enrolled in three age cohorts (7 through 11 months of age, 12 through 23 months of age, and 2 through 17 years of age) and randomized to receive VAXNEUVANCE (N=303) or Prevnar 13 (N=303). Children in the two

youngest age cohorts were pneumococcal vaccine-naïve at enrollment. Children in the oldest age cohort (2 through 17 years of age) were either pneumococcal vaccine-naïve, not fully vaccinated, or had completed a dosing regimen with a lower valency pneumococcal conjugate vaccine (excluding Prevnar 13). Participants who were pneumococcal vaccine-naïve at enrollment received 1 to 3 doses of VAXNEUVANCE or Prevnar 13, depending on age at enrollment and according to the schedule shown in Table 1. All participants 2 through 17 years of age received one dose of VAXNEUVANCE. Catch-up vaccination with VAXNEUVANCE elicited immune responses, as assessed by serotype-specific IgG GMCs at 30 days following the last dose of vaccine, in children 7 months through 17 years of age that were numerically similar 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 numerically similar between the vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes.

14.2 Clinical Trials in Pneumococcal Vaccine-Naïve Adults

Study 1

Study 1 assessed serotype-specific opsonophagocytic activity (OPA) responses for each of the 15 serotypes contained in VAXNEUVANCE at 30 days postvaccination in a double-blind, active comparator-controlled study that enrolled pneumococcal vaccine-naïve participants 50 years of age and older. Participants were randomized to receive either VAXNEUVANCE (N=604) or Prevnar 13 (N=601) at sites in USA, Canada, Spain, Taiwan, and Japan. The mean age of participants was 66 years and 57.3% were female. The racial distribution was as follows: 67.7% were White, 25.1% were Asian, 6.1% were Black or African American and 22.0% were of Hispanic or Latino ethnicity.

Table 12 summarizes the OPA geometric mean antibody titers (GMTs) at 30 days postvaccination for the 15 serotypes contained in VAXNEUVANCE. The study demonstrated that VAXNEUVANCE is noninferior to Prevnar 13 for the 13 shared serotypes and induces statistically significantly greater OPA GMTs compared to Prevnar 13 for shared serotype 3 and for the 2 unique serotypes (22F, 33F).

Table 12: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults 50 Years of Age and Older (Study 1)

Pneumococcal Serotype	VAXNEUVANCE (N = 602)		Prevnar 13 (N = 600)		GMT Ratio* (VAXNEUVANCE/Prevnar 13) (95% CI)*
	n	GMT*	n	GMT*	
Serotype†					
1	598	257	598	321	0.80 (0.66, 0.97)
3‡	598	215	598	133	1.62 (1.40, 1.87)
4	598	1109	598	1633	0.68 (0.57, 0.80)
5	598	445	598	560	0.79 (0.64, 0.98)
6A	596	5371	596	5276	1.02 (0.85, 1.22)
6B	598	3984	598	3179	1.25 (1.04, 1.51)
7F	596	4575	596	5830	0.78 (0.68, 0.90)
9V	598	1809	597	2193	0.83 (0.71, 0.96)
14	598	1976	598	2619	0.75 (0.64, 0.89)
18C	598	2749	598	2552	1.08 (0.91, 1.27)
19A	598	3177	597	3921	0.81 (0.70, 0.94)
19F	598	1688	598	1884	0.90 (0.77, 1.04)
23F	598	2029	598	1723	1.18 (0.96, 1.44)
Additional Serotypes§					
22F	594	2381	585	73	32.52 (25.87, 40.88)
33F	598	8010	597	1114	7.19 (6.13, 8.43)

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

† Non-inferiority for the 13 shared serotypes was met if the lower bound of the 95% CI for the GMT ratio (VAXNEUVANCE/Prevnar 13) was > 0.5.

‡ Statistically significantly greater OPA GMT for serotype 3 was based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE/Prevnar 13) > 1.2.

§ Statistically significantly greater OPA GMTs for serotypes 22F and 33F was based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE/Prevnar 13) > 2.0.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis that had at least one pre-dose OPA measurement (VAXNEUVANCE, n=537-597; Prevnar 13, n=545-595) or post-dose OPA measurement (VAXNEUVANCE, n=568-580; Prevnar 13, n=528-574).

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titer; OPA=opsonophagocytic activity.

Study 3

In a double-blind, active comparator-controlled, descriptive study (Study 3), pneumococcal vaccine-naïve adults 50 years of age and older were randomized to receive either VAXNEUVANCE (N=327) or Prevnar 13 (N=325), followed by PNEUMOVAX 23 one year later.

Following vaccination with PNEUMOVAX 23, OPA GMTs were numerically similar between the two vaccination groups for the 15 serotypes in VAXNEUVANCE.

Study 4

In a double-blind, descriptive study (Study 4), adults 18 through 49 years of age, including individuals with increased risk of developing pneumococcal disease, were randomized to receive VAXNEUVANCE (N=1,135) or Prevnar 13 (N=380), followed by PNEUMOVAX 23 six months later *[see Adverse Reactions (6.1)]*. Among those who received VAXNEUVANCE, 620 participants had one risk factor and 228 participants had two or more risk factors for pneumococcal disease.

Table 13 presents OPA GMTs in the overall study population for each of the 15 serotypes 30 days following vaccination with VAXNEUVANCE or Prevnar 13.

Table 13: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults 18 through 49 Years of Age With or Without Risk Factors for Pneumococcal Disease (Study 4)

Pneumococcal Serotype	VAXNEUVANCE (N = 1,133)			Prevnar 13 (N = 379)		
	n	Observed GMT	95% CI*	n	Observed GMT	95% CI*
Serotype						
1	1004	267	(242, 295)	337	267	(220, 324)
3	990	198	(184, 214)	336	150	(129, 173)
4	1001	1401	(1294, 1517)	338	2568	(2268, 2908)
5	1003	560	(508, 618)	339	731	(613, 873)
6A	994	12763	(11772, 13838)	333	11313	(9739, 13141)
6B	999	10164	(9486, 10891)	338	6958	(5987, 8086)
7F	1004	5725	(5382, 6090)	338	7583	(6762, 8503)
9V	1000	3353	(3132, 3590)	339	3969	(3541, 4449)
14	1001	5245	(4860, 5660)	339	5863	(5191, 6623)
18C	999	5695	(5314, 6103)	339	3050	(2685, 3465)
19A	1001	5335	(4985, 5710)	339	5884	(5221, 6632)
19F	1003	3253	(3051, 3468)	339	3272	(2949, 3631)
23F	1001	4828	(4443, 5247)	337	3876	(3323, 4521)
Additional Serotypes						
22F	991	3939	(3654, 4246)	317	291	(221, 383)
33F	999	11734	(10917, 12612)	334	2181	(1826, 2606)

* 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; OPA=opsonophagocytic activity.

Following vaccination with PNEUMOVAX 23, the OPA GMTs for the 15 serotypes in VAXNEUVANCE were numerically similar among participants who had received VAXNEUVANCE or Prevnar 13 for the first vaccination.

14.3 Concomitant Vaccination

Children

In Study 8, the concomitant administration of Pentacel with each of the 3 infant doses of either VAXNEUVANCE (N=598) or Prevnar 13 (N=601) was evaluated 30 days following the third dose; concomitant administration of single doses of VAQTA, M-M-R II, VARIVAX and Hiberix with the fourth dose of either VAXNEUVANCE or Prevnar 13 was evaluated 30 days following vaccination. There was no evidence that VAXNEUVANCE, as compared to Prevnar 13, interfered with the immune responses to these concomitantly administered vaccines. The immune responses to the antigens in Pentacel following completion of the 4-dose series were not evaluated.

In Study 9, the concomitant administration of RECOMBIVAX HB with either VAXNEUVANCE (N=124) or Prevnar 13 (N=266) was evaluated 30 days following the third dose of pneumococcal conjugate vaccine. Most infants (97.2%) received a birth dose of hepatitis B vaccine, followed by two doses of RECOMBIVAX HB administered concomitantly with VAXNEUVANCE or Prevnar 13. There was no evidence that VAXNEUVANCE, as compared to Prevnar 13, interfered with the immune response to RECOMBIVAX HB.

Adults

In a double-blind, randomized study (Study 6), adults 50 years of age and older were randomized to receive VAXNEUVANCE concomitantly administered with a seasonal inactivated quadrivalent influenza vaccine (Fluarix Quadrivalent; QIV) (Group 1, N=600) or VAXNEUVANCE 30 days after receiving QIV (Group 2, N=600) *[see Adverse Reactions (6.1)]*. Pneumococcal vaccine serotype OPA GMTs were evaluated 30 days after VAXNEUVANCE and influenza vaccine strain hemagglutinin inhibition assay (HAI) GMTs were evaluated 30 days after QIV. The noninferiority criteria for the comparisons of GMTs [lower limit of the

2-sided 95% confidence interval (CI) of the GMT ratio (Group 1/Group 2) >0.5] were met for the 15 pneumococcal serotypes in VAXNEUVANCE and for the 4 influenza vaccine strains tested.

16 HOW SUPPLIED/STORAGE AND HANDLING

VAXNEUVANCE is supplied as follows:
Carton of one 0.5 mL single-dose prefilled Luer Lock syringes with tip caps. NDC 0006-4329-02
Carton of ten 0.5 mL single-dose prefilled Luer Lock syringes with tip caps. NDC 0006-4329-03

Store refrigerated at 2°C to 8°C (36°F to 46°F).
Do not freeze. Protect from light.

The tip cap and plunger stopper of the prefilled syringe are not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patient, parent or guardian to read the FDA-approved patient labeling (Patient Information).

Discuss the following with the patient, parent or guardian:

- Provide the required vaccine information to the patient, parent or guardian.
- Inform the patient, parent or guardian of the benefits and risks associated with vaccination.
- Inform the patient, parent or guardian that vaccination with VAXNEUVANCE may not protect all vaccine recipients.
- Discuss the importance of completing the vaccination series unless contraindicated.
- Instruct the patient, parent or guardian to report any serious adverse reactions to their healthcare provider who in turn should report such events to the vaccine manufacturer or the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967, or report online at www.vaers.hhs.gov .

Manufactured by: Merck Sharp & Dohme LLC
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U.S. license number 0002

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uspi-v114-i-2405r004