

VAXNEUVANCE® Suspension for Injection
(Pneumococcal 15-valent Conjugate Vaccine)

1. INDICATIONS AND USAGE

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

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

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

2. DOSAGE AND ADMINISTRATION

2.1 General

The vaccination schedule for VAXNEUVANCE should be based on official recommendations. The national immunization practice recommendations/guidelines should also be considered.

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.

2.2 Pediatrics

Routine Vaccination Schedule for Infants and Toddlers

4-Dose Regimen (Three-Dose Primary Series Followed by a Toddler Dose)

The recommended vaccination regimen consists of 4 doses of VAXNEUVANCE, with the first dose given as early as 6 to 12 weeks of age, with an interval of 4 to 8 weeks between doses in the primary series. The fourth dose should be administered at approximately 11 through 15 months of age and at least 2 months after the third dose.

3-Dose Regimen (Two-Dose Primary Series Followed by a Toddler Dose)

The alternative vaccination regimen consists of 3 doses of VAXNEUVANCE, with the first dose given as early as 6 weeks of age, and a second dose administered 8 weeks later. The third dose should be administered at approximately 11 through 15 months of age.

Preterm Infants

Preterm infants (<37 weeks gestation at birth) should receive a 4-dose regimen (three-dose primary series followed by a toddler dose) of VAXNEUVANCE, with the first dose given as early as 6 to 12 weeks of age, with an interval of 4 to 8 weeks between doses in the primary series. The fourth dose should be administered at approximately 11 through 15 months of age and at least 2 months after the third dose. *[See Warnings and Precautions (5) and Use in Specific Populations (7.5).]*

Prior Vaccination with Another Pneumococcal Conjugate Vaccine

The vaccination regimen can be completed with VAXNEUVANCE if initiated with another pneumococcal conjugate vaccine *[see Clinical Studies (10)]*.

Catch-Up Vaccination Schedule for Children 7 Months Through 17 Years of Age

For children 7 months through 17 years of age who are pneumococcal vaccine-naïve or not fully vaccinated or completed a dosing regimen with lower-valency pneumococcal conjugate vaccines, the following catch-up schedule should be considered:

Infants 7 Through 11 months of age

Three doses, with the first two doses given at least 4 weeks apart. The third dose is given after 12 months of age, separated from the second dose by at least 2 months.

Children 12 Through 23 months of age

Two doses, with an interval of 2 months between doses.

Children and adolescents 2 Through 17 years of age

One single dose.

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

2.3 Adults

One single dose.

2.4 Special Populations

The dosing schedule in special populations should be guided by official recommendations and may include more than one dose of VAXNEUVANCE *[see Use in Specific Populations (7.5)]*.

3. INSTRUCTIONS FOR USE

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

When VAXNEUVANCE is administered at the same time as another injectable vaccine(s), the vaccines should always be given at different injection sites *[see Drug Interactions and Other Forms of Interactions (6.1)]*.

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.

4. 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 Pharmaceutical Particulars (15.2).]*

5. WARNINGS AND PRECAUTIONS

Individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to VAXNEUVANCE. *[See Drug Interactions and Other Forms of Interactions (6.2) and Use in Specific Populations (7.5).]*

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 all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine. The administration of the vaccine should be postponed in subjects suffering from acute severe febrile illness or acute infection.

As with other intramuscular injections, the vaccine should be given with caution to individuals receiving anticoagulant therapy, or to those with thrombocytopenia or any coagulation disorder such as hemophilia. Bleeding or bruising may occur following an intramuscular administration in these individuals.

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

VAXNEUVANCE has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 8. Adverse Reactions may temporarily affect the ability to drive or use machines.

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

6. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

6.1 Use with Other Vaccines

Infants and Children Less Than 2 Years of Age

VAXNEUVANCE can be administered concomitantly with other routine pediatric vaccines [see *Adverse Reactions (8) and Clinical Studies (10)*].

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 Adverse Reactions (8) and Clinical Studies (10)*]. There are no data on the concomitant administration of VAXNEUVANCE with other vaccines.

6.2 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 Warnings and Precautions (5)*].

7. USE IN SPECIFIC POPULATIONS

7.1 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.

7.2 Nursing Mothers

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

7.3 Pediatric Use

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

7.4 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 Adverse Reactions (8) and Clinical Studies (10)*].

7.5 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 Prevnar 13 [Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein)]], Protocol 029 and Protocol 031). In these studies, 354 participants were randomized to receive VAXNEUVANCE or Prevnar 13 as a 4-dose regimen with the first dose administered at 2 months of age, followed by 2 additional doses at least 4 weeks apart and a fourth dose at 11 through 15 months of age. Serotype-specific immunoglobulin G (IgG) and opsonophagocytic activity (OPA) responses at 30 days following the primary series, prior to the toddler dose and at 30 days following the toddler dose were generally comparable between vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the two unique serotypes (22F and 33F). The safety profile and immune responses in preterm infants receiving 4 doses of VAXNEUVANCE were generally consistent with those observed in the overall healthy infant population in these studies (including preterm and term infants) [*see Adverse Reactions (8) and Clinical Studies (10)*].

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 Prevnar 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 Adverse Reactions (8)*].

Individuals Living with HIV

Children Living with HIV

In a double-blind, descriptive study (Protocol 030), the safety and immunogenicity of VAXNEUVANCE were evaluated in children 6 to 17 years of age living with HIV, with CD4+ T-cell count ≥ 200 cells per microliter and plasma HIV RNA value $< 50,000$ copies/mL. In this study, 407 participants were randomized to receive a single dose of either VAXNEUVANCE or Prevnar 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 Adverse Reactions (8)*].

Adults Living with HIV

In a double-blind, descriptive study (Protocol 018), the safety and immunogenicity of VAXNEUVANCE were evaluated in pneumococcal vaccine-naïve adults ≥ 18 years of age living with HIV, with CD4+ T-cell count ≥ 50 cells per microliter and plasma HIV RNA value $< 50,000$ copies/mL. In this study, 302 participants were randomized to receive either VAXNEUVANCE or Prevnar 13, followed by PNEUMOVAX 23 two months later.

VAXNEUVANCE was immunogenic as assessed by OPA GMTs 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 Adverse Reactions (8)*].

Individuals with Hematopoietic Stem Cell Transplant

In a double-blind, descriptive study (Protocol 022), the safety and immunogenicity of VAXNEUVANCE were evaluated in children (≥ 3 years of age) and adults who 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 uncontrolled graft-versus-host disease. In this study, 277 participants were randomized to receive 3 doses of VAXNEUVANCE or Prevnar 13, administered one month apart. Twelve months after allo-HSCT, participants without chronic graft-versus-host disease (cGVHD) received a single dose of PNEUMOVAX 23 and those with cGVHD received a fourth dose of either VAXNEUVANCE or Prevnar 13. VAXNEUVANCE was immunogenic in recipients of allo-HSCT, as assessed by IgG GMCs and OPA GMTs at 30 days following the third dose of VAXNEUVANCE for all 15 serotypes contained in the vaccine. 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). Similarly, in participants who received either VAXNEUVANCE or Prevnar 13 twelve months after allo-HSCT, IgG GMCs and OPA GMTs at 30 days following vaccination 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). In participants who received PNEUMOVAX 23 twelve months after allo-HSCT, IgG GMCs and OPA GMTs at 30 days following vaccination were generally comparable between the two vaccination groups for all 15 serotypes contained in VAXNEUVANCE. The safety profile of VAXNEUVANCE in recipients of allo-HSCT was generally consistent with the known safety profile of VAXNEUVANCE.

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 Prevnar 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 *Clinical Studies (10)*]. 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 *Adverse Reactions (8)*].

8. ADVERSE REACTIONS

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 *Clinical Studies (10)*]. 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 Prevnar 13. Additionally, four of these studies evaluated safety in preterm infants (<37 weeks gestation at birth) [see *Use in Specific Populations (7.5)*]. Across all 5 studies, 4,286 participants received a complete regimen of VAXNEUVANCE, 2,405 participants received a complete regimen of Prevnar 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 Prevnar 13 based on pooled data from four studies (excluding mixed 4-dose regimens) are shown in Tables 1 and 2. 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 $\leq 1.3\%$ of infants and toddlers following each dose, with the exception of irritability, which occurred in $\leq 5.2\%$ of the participants.

Table 1: 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 |
|------|--------|--------|--------|
|------|--------|--------|--------|

| | VAXNEUVAN CE (%) N=3,589 | Prevnar 13 (%) N=2,058 | VAXNEUVAN CE (%) N=3,521 | Prevnar 13 (%) N=1,998 | VAXNEUVAN CE (%) N=2,925 | Prevnar 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 2: 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 | Prevnar 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 Prevnar 13 [see *Clinical Studies (10)*].

Safety of a Mixed Dose Regimen of Different Pneumococcal Conjugate Vaccines

The safety profiles of mixed 4-dose regimens of VAXNEUVANCE and Prevnar 13 were generally comparable to those of complete 4-dose regimens of either VAXNEUVANCE or Prevnar 13 [see *Clinical Studies (10)*].

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 Prevnar 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 Prevnar 13 within each age cohort are shown in Tables 3, 4 and 5. 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 $\leq 1.6\%$ of infants and children 7 months through 23 months of age following each dose, and $\leq 4.5\%$ of children and adolescents 2 through 17 years of age.

Table 3: 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 | |
| | VAXNEUVAN CE (%) N=64 | Prevnar 13 (%) N=64 | VAXNEUVAN CE (%) N=63 | Prevnar 13 (%) N=64 | VAXNEUVAN CE (%) N=63 | Prevnar 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 4: 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 | Prevnar 13 (%) N=64 | VAXNEUVANCE (%) N=62 | Prevnar 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 5: 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 | Prevnar 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, 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, 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 Prevnar 13 (PCV13). A descriptive study (Protocol 017) evaluated the safety of VAXNEUVANCE in pneumococcal vaccine-naïve adults 18 to 49 years of age.

The safety of VAXNEUVANCE in adults 65 years of age and older who were previously vaccinated with PNEUMOVAX 23 (at least 1 year prior to study entry) was evaluated in an additional descriptive study (Protocol 007).

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

Safety was evaluated using a Vaccination Report Card for up to 14 days postvaccination. Oral body temperature and injection-site adverse events were solicited on Day 1 through Day 5 postvaccination. Systemic adverse events were solicited on Day 1 through Day 14 postvaccination. Unsolicited adverse events were reported on Day 1 through Day 14

postvaccination. The duration of the safety follow-up period postvaccination with VAXNEUVANCE was 1 month in Protocol 007, 6 months in Protocol 019, Protocol 020, Protocol 017 and Protocol 021 and 12 months in Protocol 016.

Solicited Adverse Reactions

The percentage of participants with solicited adverse reactions that occurred within 5 or 14 days following administration of VAXNEUVANCE or Pevnar 13 in 5 studies are shown in Tables 6 and 7. All solicited adverse reactions occurred in $\geq 5\%$ 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 $\leq 1.5\%$ of adults.

Table 6: 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 | |
| | <u>VAXNEUVA</u> <u>NCE (%)</u> N=602 | <u>PCV</u> <u>13</u> <u>(%)</u> N=600 | <u>VAXNEUVA</u> <u>NCE (%)</u> N=2,103 | <u>PCV</u> <u>13</u> <u>(%)</u> N=230 | <u>VAXNEUVA</u> <u>NCE (%)</u> N=327 | <u>PCV</u> <u>13</u> <u>(%)</u> N=324 | <u>VAXNEUVA</u> <u>NCE (%)</u> N=1,134 | <u>PCV</u> <u>13</u> <u>(%)</u> 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 7: 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.

9. OVERDOSAGE

There are no data with regard to overdose.

10. CLINICAL STUDIES

BURDEN OF DISEASE

Pneumococcal disease is associated with significant morbidity and mortality in both children and adults worldwide. Although all age groups may be affected by pneumococcal disease, the highest rates of disease occur in young children <5 years of age and adults ≥65 years of age. Among children, the incidence of invasive pneumococcal disease (IPD) and mortality associated with IPD is highest among infants <1 year of age. In addition, mortality rates are elevated in older adults, adults with comorbid conditions (e.g., diabetes mellitus, chronic lung disease, chronic liver disease), and especially in immunocompromised individuals (e.g., HIV infection, cancer, transplant, immunosuppressive therapies). Adults with 2 or more comorbid conditions may have a risk of pneumococcal disease that is comparable to that of immunocompromised individuals.

Clinical syndromes include both invasive pneumococcal disease (i.e. sepsis, meningitis, and bacteremic pneumonia) and noninvasive disease (e.g., non-bacteremic pneumonia and acute otitis media). Bacteremic pneumococcal pneumonia represents approximately 80-90% of IPD cases in adults. Community acquired pneumonia (CAP) remains one of the most important causes of death from infection in many countries, with *S. pneumoniae* being one of the most commonly identified bacterial pathogens. Acute otitis media, a middle ear infection frequently caused by *S. pneumoniae*, is one of the most common infectious diseases of childhood and is a major cause of morbidity and antibiotic usage.

CLINICAL STUDIES

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

Six double-blind, clinical studies (Protocol 008, Protocol 024, Protocol 025, Protocol 026, 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 Prevnar 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 Prevnar 13 recipients. At 30 days following the toddler dose, VAXNEUVANCE is non-inferior to Prevnar 13 for the 13 shared serotypes and superior for the 2 unique serotypes, as assessed by the proportion of participants meeting the serotype-specific IgG threshold value of ≥ 0.35 mcg/mL (response rate) (Table 8). Serotype-specific IgG GMCs are non-inferior to Prevnar 13 for the 13 shared serotypes and superior to Prevnar 13 for the 2 unique serotypes at 30 days following the toddler dose (Table 9).

Table 8: Proportions of Participants with IgG Response Rates ≥ 0.35 mcg/mL in Toddlers Administered a 3-Dose Regimen (Protocol 025)

| Pneumococcal Serotype | VAXNEUVANCE (N=588) | Prevnar 13 (N=591) | Percentage Point Difference* |
|-----------------------|---------------------|--------------------|------------------------------|
|-----------------------|---------------------|--------------------|------------------------------|

| | Observed Response Percentage (m/n) | Observed Response Percentage (m/n) | (VAXNEUVANCE – Pprevnar 13) (95% CI)* |
|------------------------------------|---|---|---|
| 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 – Pprevnar 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 – Pprevnar 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 9: Serotype-Specific IgG GMCs in Toddlers Administered a 3-Dose Regimen
(Protocol 025)**

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

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

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

‡ A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevnam 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 Prevnam 13 for the 13 shared serotypes. OPA GMTs for both 22F and 33F were higher in VAXNEUVANCE recipients compared to Prevnam 13 recipients.

In another double-blind, active comparator-controlled study (Protocol 026), 1,191 participants were randomized to receive VAXNEUVANCE or Prevnam 13 as a 3-dose regimen. The primary series was administered to infants at 3 and 5 months of age followed by the toddler dose at 12 months of age. Participants also received other pediatric vaccines concomitantly, including VAXELIS (Diphtheria, tetanus, pertussis [acellular, component], hepatitis B, poliovirus [inactivated], and Haemophilus type b conjugate vaccine) with all 3 doses, and M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) and VARIVAX (Varicella Virus Vaccine Live) 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 toddler dose, VAXNEUVANCE is non-inferior to Prevnam 13 for the 13 shared serotypes (the lower bound of the 2-sided 95% CI for the difference in the serotype-specific IgG response rates [VAXNEUVANCE - Prevnam 13] was greater than -10 percentage points). VAXNEUVANCE is superior to Prevnam 13 for the 2 unique serotypes, 22F and 33F (the lower bound of the 2-sided 95% CI for the difference in the serotype-specific IgG response rates [VAXNEUVANCE - Prevnam 13] was greater than 10 percentage points). Similarly, VAXNEUVANCE is non-inferior to Prevnam 13 for the 13 shared serotypes (the lower bound of the 2-sided 95% CI for the serotype-specific IgG GMC ratio [VAXNEUVANCE/Prevnam 13] was greater than 0.5). VAXNEUVANCE is superior to Prevnam 13 for the 2 unique serotypes (the

lower bound of the 2-sided 95% CI for the serotype-specific IgG GMC ratio [VAXNEUVANCE/Prevnam 13] was greater than 2.0).

Additionally, VAXNEUVANCE elicits functional antibodies, as assessed by serotype-specific OPA GMTs at 30 days following the toddler dose, that are generally comparable to Prevnam 13 for the 13 shared serotypes and higher for the two unique serotypes (22F and 33F).

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 Prevnam 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 - Prevnam 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 Prevnam 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 Prevnam 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 a pentavalent combination vaccine (Pentacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate [Tetanus Toxoid Conjugate] Vaccine) or Pentavac (Diphtheria, Tetanus, Pertussis [acellular, component], Poliomyelitis [inactivated] and *Haemophilus influenzae* type b Conjugate Vaccine [adsorbed])) 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 Prevnar 13 for the 13 shared serotypes, as assessed by IgG response rates (Table 10). VAXNEUVANCE is non-inferior for the 2 unique serotypes, as assessed by the IgG response rates for serotypes 22F and 33F in recipients of VAXNEUVANCE compared with the response rate for serotype 23F in recipients of Prevnar 13 (the lowest response rate for any of the shared serotypes, excluding serotype 3), with percentage point differences of 6.7% (95% CI: 4.6, 9.2) and -4.5% (95% CI: -7.8, -1.3), respectively.

Additionally, VAXNEUVANCE is superior to Prevnar 13 for the 2 unique serotypes and for shared serotype 3 as assessed by IgG response rates at 30 days following the primary series (Table 10).

Table 10: Proportions of Participants with IgG Response Rates ≥ 0.35 mcg/mL in Infants Administered a 3-Dose Primary Series (Protocol 029)

| Pneumococcal Serotype | VAXNEUVANCE (N=858) | Prevnar 13 (N=856) | Percentage Point Difference* (VAXNEUVANCE – Prevnar 13) (95% CI)* |
|-----------------------|---|---|---|
| | Observed Response Percentage (m/n) | Observed Response Percentage (m/n) | |
| 13 Shared Serotypes† | | | |
| 1 | 95.7 (672/702) | 99.1 (659/665) | -3.4 (-5.2, -1.8) |
| 3‡ | 94.7 (662/699) | 79.2 (524/662) | 15.6 (12.1, 19.2) |
| 4 | 96.4 (674/699) | 98.6 (654/663) | -2.2 (-4.0, -0.6) |

| | | | |
|--|----------------|-----------------|-------------------|
| 5 | 95.3 (669/702) | 97.4 (647/664) | -2.1 (-4.2, -0.2) |
| 6A | 93.7 (658/702) | 98.6 (654/663) | -4.9 (-7.1, -3.0) |
| 6B | 88.6 (619/699) | 92.0 (609/662) | -3.4 (-6.6, -0.3) |
| 7F | 99.0 (694/701) | 99.8 (664/665) | -0.8 (-1.9, -0.1) |
| 9V | 97.1 (680/700) | 98.2 (649/661) | -1.0 (-2.8, 0.6) |
| 14 | 97.9 (685/700) | 97.9 (647/661) | -0.0 (-1.6, 1.6) |
| 18C | 97.4 (682/700) | 98.3 (651/662) | -0.9 (-2.6, 0.7) |
| 19A | 97.9 (687/702) | 99.7 (663/665) | -1.8 (-3.2, -0.8) |
| 19F | 99.0 (693/700) | 100.0 (663/663) | -1.0 (-2.1, -0.4) |
| 23F | 91.5 (639/698) | 91.8 (607/661) | -0.3 (-3.2, 2.7) |
| 2 Serotypes Unique to VAXNEUVANCE [§] | | | |
| 22F | 98.6 (691/701) | 3.5 (23/660) | 95.1 (93.1, 96.5) |
| 33F | 87.3 (613/702) | 2.1 (14/664) | 85.2 (82.3, 87.7) |

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

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

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

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

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

CI=confidence interval; IgG=immunoglobulin G.

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

compared with the IgG GMC for serotype 4 in recipients of Prevnar 13 (the lowest IgG GMC for any of the shared serotypes, excluding serotype 3) with a GMC ratio of 3.64 (95% CI: 3.33, 3.98) and 1.24 (95% CI: 1.10, 1.39), respectively.

VAXNEUVANCE is also superior to Prevnar 13 for the 2 unique serotypes and for shared serotype 3 as assessed by IgG GMCs at 30 days following the primary series (Table 11).

Table 11: Serotype-Specific IgG GMCs in Infants Administered a 3-Dose Primary Series (Protocol 029)

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

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

† A conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevnam 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/Prevnam 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/Prevnam 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 Prevnam 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 Prevnam 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 12).

VAXNEUVANCE is superior to Prevnam 13 for the 2 unique serotypes and for shared serotype 3, as assessed by IgG GMCs at 30 days following the toddler dose (Table 12).

**Table 12: Serotype-Specific IgG GMCs in Toddlers Administered a 4-Dose Regimen
(Protocol 029)**

| Pneumococcal Serotype | VAXNEUVANCE (N=858) | | Prevnam 13 (N=856) | | GMC Ratio* (VAXNEUVANCE/Prevnam 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/Prevnam 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/Prevnam 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/Prevnam 13) being >2.0.

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

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

VAXNEUVANCE elicits functional antibodies, as assessed by serotype-specific OPA GMTs at 30 days following the primary series and following the toddler dose, that are generally

comparable to Prevnar 13 for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes.

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

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

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

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

unique serotypes 22F and 33F. Within each age cohort, serotype-specific IgG GMCs at 30 days following the last dose of vaccine were generally comparable between the vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes.

Clinical Trials Experience in Adults 18 Years of Age and Older

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

In each study, immunogenicity was assessed by serotype-specific opsonophagocytic activity (OPA) and immunoglobulin G (IgG) responses at 30 days postvaccination. Study endpoints included OPA geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs). The pivotal study (Protocol 019) was designed to show non-inferiority of the OPA GMTs compared to Prevnar 13 for the 13 shared serotypes (in common between VAXNEUVANCE and Prevnar 13) and superiority for the 2 serotypes unique to VAXNEUVANCE (22F and 33F) and for shared serotype 3. Superiority assessment was based on the between-group comparisons of OPA GMTs and proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA titers from prevaccination to 30 days postvaccination.

Clinical Trials Conducted in Pneumococcal Vaccine-Naïve Adults

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

Serotype-specific IgG GMCs were generally consistent with the results observed for the OPA GMTs.

Table 13: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults ≥50 Years of Age (Protocol 019)

| Pneumococcal Serotype | VAXNEUVANCE (N=602) | | Prevnam 13 (N=600) | | GMT Ratio* (VAXNEUVANCE/Prevnam 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/Prevnam 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/Prevnam 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/Prevnam 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 Prevnam 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 Prevnam 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 Prevnam 13, followed by PNEUMOVAX 23 six months later. VAXNEUVANCE elicited immune responses to all 15 serotypes as assessed by OPA GMTs (Table 14) 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 14: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults 18-49 Years of Age With or Without Risk Factors for Pneumococcal Disease (Protocol 017)

| Pneumococcal Serotype | VAXNEUVANCE (N=1,133) | | | Prevnar 13 (N=379) | | |
|-----------------------|--------------------------|--------------|--------------------|-----------------------|--------------|-------------------|
| | n | Observed GMT | 95% CI* | n | Observed GMT | 95% CI* |
| 13 Shared Serotypes | | | | | | |
| 1 | 1019 | 268.6 | (243.7, 296.0) | 341 | 267.2 | (220.4, 323.9) |
| 3 | 1004 | 199.3 | (184.6, 215.2) | 340 | 150.6 | (130.6, 173.8) |
| 4 | 1016 | 1416.0 | (1308.9, 1531.8) | 342 | 2576.1 | (2278.0, 2913.2) |
| 5 | 1018 | 564.8 | (512.7, 622.2) | 343 | 731.1 | (613.6, 871.0) |
| 6A | 1006 | 12928.8 | (11923.4, 14019.0) | 335 | 11282.4 | (9718.8, 13097.5) |
| 6B | 1014 | 10336.9 | (9649.4, 11073.4) | 342 | 6995.7 | (6024.7, 8123.2) |
| 7F | 1019 | 5756.4 | (5410.4, 6124.6) | 342 | 7588.9 | (6775.3, 8500.2) |
| 9V | 1015 | 3355.1 | (3135.4, 3590.1) | 343 | 3983.7 | (3557.8, 4460.7) |
| 14 | 1016 | 5228.9 | (4847.6, 5640.2) | 343 | 5889.8 | (5218.2, 6647.8) |
| 18C | 1014 | 5709.0 | (5331.1, 6113.6) | 343 | 3063.2 | (2699.8, 3475.5) |
| 19A | 1015 | 5369.9 | (5017.7, 5746.8) | 343 | 5888.0 | (5228.2, 6631.0) |
| 19F | 1018 | 3266.3 | (3064.4, 3481.4) | 343 | 3272.7 | (2948.2, 3632.9) |
| 23F | 1016 | 4853.5 | (4469.8, 5237.2) | 340 | 3887.3 | (3335.8, 4438.8) |

| | | | | | | |
|-----------------------------------|------|---------|-----------------------|-----|--------|---------------------|
| | | | 5270.2) | | | 4530.0) |
| 2 Serotypes Unique to VAXNEUVANCE | | | | | | |
| 22F | 1005 | 3926.5 | (3645.9, 4228.7) | 320 | 291.6 | (221.8, 383.6) |
| 33F | 1014 | 11627.8 | (10824.6, 12490.7) | 338 | 2180.6 | (1828.7, 2600.2) |

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

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

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

Sequential Administration of Pneumococcal Vaccines in Adults

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

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

The sequential administration of VAXNEUVANCE followed by PNEUMOVAX 23 was evaluated with an interval of 2 months in immunocompromised individuals (Protocol 018) and an interval of 6 months in immunocompetent individuals with or without risk factors for pneumococcal disease (Protocol 017). *[See Use in Specific Populations (7.5).]*

Clinical Trials Conducted in Adults with Prior Pneumococcal Vaccination

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

Concomitant Vaccination

Infants and Toddlers

The immunogenicity of routine infant vaccines administered concomitantly with VAXNEUVANCE was evaluated within 4 double-blind, active comparator-controlled studies (Protocol 025, Protocol 026, 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 Prevnar 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 026, approximately 1,100 participants received VAXELIS administered concomitantly with all 3 doses of VAXNEUVANCE or Prevnar 13. At 30 days following the toddler dose, immune responses to the vaccine-specific antigens for VAXELIS met non-inferiority criteria when administered concomitantly with VAXNEUVANCE.

In Protocol 029, approximately 1,700 participants received a pentavalent combination vaccine (Pentacel n=1,199 and Pentavac n=515) administered concomitantly with the infant primary series of VAXNEUVANCE or Prevnar 13. Approximately 1,500 participants received VAQTA, HIBERIX, M-M-R II and VARIVAX, administered concomitantly with the toddler dose of VAXNEUVANCE or Prevnar 13. At 30 days following completion of the primary series, immune responses to the antigens contained in Pentacel and Pentavac 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 Prevnar 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 non-inferior to VAXNEUVANCE administered nonconcomitantly with QIV (based on a 2-fold non-inferiority 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 non-inferior to QIV administered nonconcomitantly (based on a 2-fold non-inferiority margin) as assessed by

influenza strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV for all 4 influenza strains.

11. CLINICAL PHARMACOLOGY

11.1 Therapeutic Class

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

11.2 Mechanism of Action

VAXNEUVANCE contains serotype-specific pneumococcal capsular polysaccharides, each of which is conjugated to a carrier protein (CRM₁₉₇), and elicits antibodies that enhance opsonization, phagocytosis, and killing of pneumococci to protect against pneumococcal disease. VAXNEUVANCE elicits a T-cell dependent immune response. Carrier protein-specific helper T-cells support specificity, functionality and maturation of serotype-specific B cells.

Immune responses following natural exposure to *S. pneumoniae* or following pneumococcal vaccination can be determined through the measurements of OPA and IgG responses. OPA represents functional antibodies capable of opsonizing pneumococcal capsular polysaccharides for presentation to phagocytic cells for engulfment and subsequent killing and are considered an important immunologic surrogate measure of protection against pneumococcal disease in adults. OPA titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%. Serotype-specific immune responses (OPA and IgG) for the 15 serotypes contained in VAXNEUVANCE were measured using a validated multiplexed opsonophagocytic assay (MOPA) and a validated pneumococcal electrochemiluminescence (Pn ECL) assay, bridged to the WHO reference enzyme linked immunosorbent assay (ELISA). In children, a serotype-specific IgG antibody level corresponding to ≥ 0.35 mcg/mL using the WHO ELISA has been used as the threshold value for the clinical evaluation of pneumococcal conjugate vaccines.

12. PHARMACEUTICAL FORM

VAXNEUVANCE is a suspension for injection available in 0.5 mL single-dose prefilled syringes. The vaccine is an opalescent suspension.

13. PHARMACEUTICAL PARTICULARS

13.1 Chemistry

VAXNEUVANCE (Pneumococcal 15-valent Conjugate Vaccine [CRM₁₉₇ Protein], adsorbed) 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 CRM₁₉₇. Each pneumococcal capsular polysaccharide is activated via sodium metaperiodate oxidation and then individually conjugated to CRM₁₉₇ carrier protein via reductive amination. CRM₁₉₇ is a nontoxic mutant of diphtheria toxin (originating from *Corynebacterium diphtheriae* C7) expressed recombinantly in *Pseudomonas fluorescens*.

Each of the fifteen serotypes is manufactured independently using a common manufacturing platform with slight variations to accommodate for differences in strains, polysaccharides and process stream properties. The process consists of the fermentation steps to produce the inactivated pneumococcal bacteria and the purification process which consists of clarification, ultrafiltration, polishing and recovery to produce purified polysaccharides. Each activated polysaccharide is conjugated to lysine groups on the CRM₁₉₇ carrier protein using reductive amination. The pneumococcal polysaccharide powder is dissolved, size reduced to a target molecular mass, chemically activated, and buffer-exchanged by ultrafiltration. The CRM₁₉₇ protein carrier is then conjugated to the activated pneumococcal polysaccharide. The final vaccine is prepared by blending the fifteen conjugates with aluminum phosphate adjuvant in a final buffer containing histidine, polysorbate 20 and sodium chloride.

13.2 Composition

Active Ingredient

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 CRM₁₉₇ carrier protein.

Inactive Ingredients (List of excipients)

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).

13.3 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.

13.4 Shelf Life

Refer to outer carton.

13.5 Nature and contents of container

0.5 mL suspension in pre-filled syringe (Type I glass) with a plunger stopper (latex-free bromobutyl rubber) and tip cap (latex-free styrene-butadiene rubber).

13.6 Availability

VAXNEUVANCE is supplied as follows:

- 1 single-dose prefilled syringe with 2 separate needles

Product Owner:

Merck Sharp & Dohme LLC
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P.O. Box 2000
Rahway, New Jersey 07065
USA

Date of Revision: February 2024



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