Summary Basis for Regulatory Action

Date:	July 16, 2021
From:	Qun Wang, PhD Review Committee Chair Division of Vaccines and Related Products Applications Office of Vaccines Research and Review
BLA STN:	125741/0
Applicant:	Merck Sharp and Dohme Corp.
Submission Receipt Date:	Rolling Submission: October 21, 2020 & November 17, 2020
Action Due Date:	July 16, 2021
Proper Name:	Pneumococcal 15-Valent Conjugate Vaccine
Proprietary Name:	VAXNEUVANCE
Indication:	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 adults 18 years of age and older

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OVRR/DBPAP) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	 Mustafa Akkoyunlu, MD, PhD John Cipollo, PhD James Erich Keller, PhD Gregory Price Marie Anderson, PhD M. Nahid Parvin, PhD Claire Wernly, PhD Emnet Yitbarek, PhD
Clinical • Clinical (OVRR/DVRPA) • Postmarketing safety epidemiological review (OBE/DE) • BIMO	 Anuja Rastogi, MD, MHS Nick Geagan, DO Brendan Day, MD, MPH Malcolm Nasirah, PharmD, MS, BCGP
Statistical • Clinical data (OBE/DB) • Non-clinical data	 Zhong Gao, PhD Xinyu Tang, PhD
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office)	 Ching-Long (Joe) Sun, PhD
Labeling • Promotional (OCBQ/APLB) • PNR (OCBQ/APLB) • Container/Carton (OVRR/DVRPA)	 Michael Brony, PharmD Oluchi Elekwachi, PharmD, MPH Daphne Stewart
Other Reviews not captured above categories, for example: • Consults	 Brenda Baldwin, PhD Elizabeth Teeple, PhD

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1. Introduction

Merck Sharp and Dohme Corp. submitted the Biologics License Application (BLA) STN125741 for licensure of their Pneumococcal 15-Valent Conjugate Vaccine with the proprietary name VAXNEUVANCE. VAXNEUVANCE is indicated 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 adults 18 years of age and older.

VAXNEUVANCE is a suspension of 15 distinct pneumococcal capsular polysaccharides individually conjugated to a non-toxic diphtheria CRM_{197} protein originating from *Corynebacterium diphtheriae* C7. VAXNEUVANCE is supplied as a 0.5 mL dose in 1.5 mL single-dose prefilled syringes for intramuscular injection. Each 0.5 mL dose contains 2.0 µg each of *S. pneumoniae* polysaccharides (except for serotype 6B, formulated at 4 µg/dose), 30 µg of CRM_{197} carrier protein, 1.55 mg mM L-histidine, 1 mg of polysorbate 20, 4.50 mg sodium chloride, and 125 µg of aluminum as aluminum phosphate adjuvant. VAXNEUVANCE does not contain preservatives. The shelf life for the final drug product is 18 months from the date of manufacture when stored at 2°C to 8°C.

The clinical development program conducted to support use in adults includes one Phase 2 study and six Phase 3 studies conducted across the Americas, Europe, and Asia Pacific. Over 5,600 adults received VAXNEUVANCE in these studies, including those with and without prior pneumococcal vaccination. The immunogenicity and safety results presented in the application support the use of VAXNEUVANCE for active immunization for the prevention of invasive disease caused by the *S. pneumoniae* serotypes contained in the vaccine in adults 18 years of age and older.

2. Background

S. pneumoniae is a gram-positive bacterium which is a major cause of otitis media, community-acquired pneumonia, sepsis, and meningitis, resulting in considerable morbidity and mortality.[1] Invasive pneumococcal disease (IPD) occurs as a result of the spread of *S. pneumoniae* to normally sterile body sites, such as the blood and spinal fluid. Infants, elderly, and immunocompromised individuals are at an increased risk for developing IPD. As of 2017, in the United States (US), more than 31,000 cases and more than 3,500 deaths from IPD (bacteremia and meningitis) have occurred in adults.[2] Mortality rates for IPD range from 11% to 30% in adults, with higher rates in adults ≥ 65 years of age. Worldwide, it is estimated that *S. pneumoniae* is responsible for 15 cases of IPD per 100,000 persons per year, and over a million deaths annually.[3]

There are over 90 immunologically and structurally distinct capsule polysaccharide serotypes of pneumococci, among which a relatively small subset is commonly found to cause carriage and disease. At the time of this BLA submission, three licensed pneumococcal vaccines are available for prevention of pneumococcal disease in US. Pneumovax 23 (PPV23), a 23-valent pneumococcal polysaccharide vaccine, is approved for use in persons ≥50 years of age and persons ≥2 years of age who are at increased risk of pneumococcal disease. PPV23 is composed of purified pneumococcal capsular polysaccharide from 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) without any adjuvant. A single 0.5 mL

dose of PPV23 is administered intramuscularly or subcutaneously. Prevnar 13 (PCV13), a 13-valent pneumococcal conjugate vaccine and a successor of Prevnar (PCV7), is approved for use in children ages 6 weeks through 5 years as a four-dose immunization series, children 6 through 17 years of age as a single dose, and adults 18 years and older as a single dose. PCV13 is composed of 13 serotypes of *S. pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) individually conjugated to a nontoxic variant of diphtheria toxin CRM_{197} protein. PCV13 contains aluminum phosphate as an adjuvant and is administered intramuscularly. In June 2021, the FDA approved Prevnar 20 (PCV20), which is composed of capsular polysaccharide serotypes contained in PCV13 and 7 additional pneumococcal serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) individually conjugated to CRM_{197}. PCV20 is indicated for active immunization of adults 18 years of age and older for the prevention of pneumonia and invasive disease caused by the 20 vaccine serotypes. The main mechanism of action of these licensed pneumococcal vaccines is by induction of serotype-specific, anti-capsular antibodies with opsonophagocytic killing activity against *S. pneumoniae*.

Pneumococcal vaccines have demonstrated efficacy and effectiveness against invasive disease in adults caused by the serotypes contained in those vaccines.[4, 5] Following the introduction of PCV7 in 2000, the incidence of antibiotic-resistant invasive disease declined among young children and adults due to reductions in infections caused by serotypes included in the vaccine. The introduction of PCV13 in 2010 led to further reductions in antibiotic resistant IPD rates.[6] However, pneumococcal disease remains a substantial cause of morbidity and mortality in adults partially due to the increasing numbers of cases of invasive disease caused by non-vaccine serotypes.

Merck Sharp and Dohme Corp. (the Applicant) initiated 15-valent pneumococcal conjugate vaccine development for adult indication in 2011 under IND. Over the course of VAXNEUVANCE development, CBER held several consultations with the Applicant. **Table 1** provides a list of key regulatory activities associated with this BLA submission.

Table 1. Regulatory History

Regulatory Event / Milestone	**Date**
1. Pre-IND meeting for adult Indication	06/15/2011
2. IND submission	02/15/2012
3. End of Phase 2 meeting	02/23/2018
4. Breakthrough Therapy designation granted	05/10/2019
5. Pre-BLA meeting	10/05/2020
6. BLA 125741/0 submissions (rolling submission)	10/21/2020 & 11/17/2020
7. BLA filed	01/11/2021
8. Mid-Cycle communication	03/17/2021
9. Late-Cycle meeting	05/12/2021
10. Action due date	07/16/2021

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Product Composition

VAXNEUVANCE is a sterile suspension of purified capsular polysaccharides from *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 22F, 23F, and 33F, individually conjugated to CRM_{197}, a non-toxic variant of diphtheria toxin that is purified from *Pseudomonas fluorescens*. Each 0.5 mL dose contains 2.0 µg each of *S. pneumoniae* polysaccharide serotypes (except for serotype 6B, which is formulated at 4.0 µg/dose), 30 µg of CRM_{197}, 1.55 mg L-histidine, 1 mg of polysorbate 20, 4.50 mg sodium chloride, and 125 µg of aluminum as aluminum phosphate adjuvant without any preservatives.

Manufacturing Overview

The polysaccharides are produced at the (b) (4) manufacturing site. The CRM_{197} carrier protein is produced at (b) (4) . The monovalent bulk conjugates are produced at the (b) (4) . The drug product (DP) is formulated and filled at the (b) (4) .

The principles of quality-by-design detailed in ICH Q8 (R2) and the Failure Mode Effects Analysis (FMEA) in ICH Q9 were used to evaluate the process parameters and establish the in-process attributes and parameter ranges for establishment of specifications. Critical process parameters and critical quality attributes were established throughout the manufacturing process for intermediates, drug substance (DS) and DP manufacture. In-process controls were established where appropriate. Key process attributes and key operating parameters were also established.

Release and in-process tests were developed and validated as appropriate for all intermediates, DSs, and DP. Hold-times have been established and are supported by validation data. Release and in-process testing panels adequately measure quality and safety attributes throughout the manufacturing processes. Key tests, used in these panels, are also incorporated into the stability program of the respective intermediates, DS and DP. In these cases, the release tests serve as a baseline to track quality and safety attributes that are further assayed in the respective stability testing programs.

Drug Substances

VAXNEUVANCE DS components are composed of 15 pneumococcal polysaccharide serotypes individually conjugated to CRM_{197} carrier protein. Each purified conjugate bulk is a distinct DS referred to as the serotype-specific monovalent bulk conjugate (MBC).

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

Drug Product

Manufacturing Process

The DP is composed of a mixture of the 15 MBCs in a sterile liquid suspension filled into a 1.5 mL glass syringe barrel assembly and closed with a plunger stopper for intramuscular injection. The DP manufacture consists of (b) (4) main processes: (b) (4) . Sodium chloride buffer (b) (4) aluminum phosphate adjuvant (APA). The resulting APA (b) (4) histidine buffer, polysorbate 20 (b) (4) prefilled syringes are received from the DP manufacturing facility for assembly with the plunger rod to form the final combination product.

Process Validation and Evaluation

The DP PPQ was performed using (b) (4) manufacturing batches. Critical process parameters and in-process controls were demonstrated to conform within their established limits. Samples taken from the PPQ batches met the pre-determined acceptance criteria for all the tests. All batches met the release specifications. (b) (4) validation on the product contact (b) (4) used during DP production at (b) (4) was successfully completed. The integrity of the (b) (4) used in the process, as well as the (b) (4) were verified. All excipients, including histidine, sodium chloride, and phosphate, were tested to comply with the reference quality standard, (b) (4) as applicable. The PPQ for the formulation and fill of the DP is satisfactory. CBER considers the DP manufacturing process consistent and validated.

DP Specifications

VAXNEUVANCE DP specifications for release and stability are included in **Table 2**.

Table 2. VAXNEUVANCE Drug Product Final Fill Specifications

Attribute	Test Method	Acceptance Criteria
Appearance	(b) (4)	Opalescent (b) (4)
Identity by (b) (4)	(b) (4)	(b) (4)
Saccharide Content by (b) (4))	(b) (4)	(b) (4)

Attribute	Test Method	Acceptance Criteria
Conjugated Saccharide Content by (b) (4)	(b) (4)	Criteria: (R, S) Serotype 3: (b) (4) Serotypes 1, 4, 5, 9V, 19A: (b) (4) Serotypes 6A, 7F, 14, 18C, 19F, 22F, 23F, 33F: (b) (4) Serotype 6B: (b) (4)
(b) (4)	(b) (4)	(b) (4)
Aluminum Content (mg/mL)	(b) (4)	(b) (4)
Polysorbate-20	(b) (4)	(b) (4)
(b) (4) (b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4) .
(b) (4)	(b) (4)	(b) (4)
Container Closure Integrity	(b) (4)	No Leaks detected (S)[a]
Endotoxin (EU/mL)	(b) (4)	(b) (4)
Sterility	(b) (4)	No growth[b]

[1] **R**=used for release, **S**=used for stability
[a] Result will be reported as conforms for a passing result
[b] Release Sterility sample tested on (b) (4))
(b) (4)

The release and stability acceptance criteria for the DP have been established as per ICH Q6B, (b) (4) the World Health Organization technical report on pneumococcal conjugate vaccines and previous clinical and commercial-scale manufacturing experience.

Stability

(b) (4) clinical Phase 3 DP batch and (b) (4) DP batches (hereafter, the formal stability studies (FSS) and PPQ batches), including (b) (4) DP batches, were enrolled in the primary stability study. The stability batches were held at the recommended storage condition of (b) (4) (2 to 8 °C). The stability data support a proposed shelf life of 18 months for DP when stored at 2 to 8 °C as a suspension in prefilled syringes.

Analytical methods used in the stability program are a subset of those used on release with the addition of conjugated saccharide content. The tests include appearance, saccharide content (b) (4) conjugated saccharide content, (b) (4)

(b) (4), container closure integrity, endotoxin and sterility. (b) (4) saccharide data, which were calculated based on the (b) (4) tests, were also provided.

The Applicant committed to develop (b) (4) protein and (b) (4) protein tests as part of the stability protocol under IND. Both tests have been qualified and introduced as a stability characterization method for ongoing stability studies for the commercial-scale FSS and PPQ batches and the (b) (4) stability batch in 2021. The Applicant committed to assess the data from the completed FSS and PPQ batches (FSS (b) (4)-month time point in Mar 2022 and PPQ (b) (4)-month time point in Nov 2022), as well as any in-progress stability batches. The Applicant's commitment and timeline to continue stability studies of the FSS and PPQ batches are appropriate.

Comparability Protocols

There are no comparability protocols.

b. Testing Specifications

The analytical methods and their validations and/or qualifications for the VAXNEUVANCE vaccine drug substance and drug product were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of VAXNEUVANCE are listed in **Table 3** below. The activities performed and inspectional histories are noted in the **Table 3** below.

Table 3: Facilities involved in manufacturing, packaging, and release testing of VAXNEUVANCE

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification/ Results
(b) (4) **Drug Substance (MBC[1])**: manufacture, release testing; (b) (4) testing (chemical) **Drug Product**: release testing (chemical)	(b) (4)	N/A	Records request in lieu of on-site inspection	Requested documents reviewed and found acceptable Mutual Reliance Inspection (b) (4) **VAI[3]**
(b) (4)	(b) (4)	(b) (4)	Waived	CDER November (b) (4), **VAI**

(b) (4) **Drug Substance (CRM197):** manufacture, release testing				
Merck Sharp & Dohme Corp. (b) (4) **Drug Substance** (b) (4)**:** manufacture, release testing **Drug Product:** pre-filled syringe device assembly and labelling, release testing	(b) (4)	(b) (4)	Waived	Team Bio and OVRR (b) (4), **VAI**
(b) (4) **Drug Product:** formulation, fill and inspection, APA manufacture and testing (Microbiological), release testing (Microbiological)	(b) (4)	(b) (4)	Waived	Team Bio (b) (4) **VAI**

[1] Monovalent bulk conjugates
[2] Aluminum phosphate adjuvant
[3] Voluntary action indicated
[4] Pneumococcal polysaccharides

The most recent inspection of (b) (4) This was a compliance Mutual Reliance Inspection (based on CDER's product) performed by the (b) (4) The 2018 inspection was reviewed by the FDA/CDER and classified as voluntary action indicated (VAI). Due to the COVID-19 public health emergency, CBER used its authority under Section 704(a)(4) to request manufacturing site records from (b) (4). The records request was conducted in lieu of performing an on-site inspection. The requested manufacturing site records appeared acceptable.

CDER conducted a pre-license inspection of (b) (4) All 483 issues were resolved, and the inspection was classified as VAI.

Team Biologics conducted a surveillance inspection of Merck (b) (4) in (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

Team Biologics conducted a surveillance inspection of Merck (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The drug product is filled in a 1.5 mL single-dose glass syringe (b) (4) with a Luer-Lok adapter. The rigid tip cap is polypropylene, and the plunger stopper is bromobutyl with a (b) (4). All parts of the syringe are supplied by (b) (4) and

follow (b) (4) testing. Container closure integrity of syringes filled at (b) (4) were tested using (b) (4)) performed by (b) (4) respectively. All testing passed acceptance criteria.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical intramuscular immunogenicity studies were performed in (b) (4) rabbits and infant rhesus monkeys. All serotypes included in the vaccine were immunogenic in all three (b) (4) rabbit and two infant rhesus monkey studies.

Four repeat-dose toxicity studies were performed in rats to evaluate the preclinical safety of VAXNEUVANCE. These were two 85-day intramuscular repeat-dose toxicity studies with a 28-day recovery period, one intramuscular embryo-fetal developmental and preweaning toxicity study, and one intramuscular postnatal development toxicity study. All studies were conducted under Good Laboratory Practice regulations. For specifics regarding study design and outcomes, reference is made to the toxicology review documents.

In repeat-dose toxicity studies, vaccine administration resulted in local muscle and subcutis inflammation at the injection sites. No treatment-related mortality or toxicologically relevant changes (clinical signs, body weight, relative food consumption, ophthalmoscopic parameters, gross anatomy, or organ weight) were found. An expected immunogenic finding of lymphoid hyperplasia or histiocytic infiltrate in the draining lymph nodes was noted. The symptoms were completely or partially resolved 28 days post dose. No other adverse effects were observed.

In embryo-fetal developmental studies, female rats received a human dose of VAXNEUVANCE by intramuscular injection on day 28 and day 7 prior to mating, on gestation day 6, and on lactation day 7. The vaccine administration did not have any effects on female reproductivity and fetal/embryonal development. No impact on fertility parameters, ovarian and uterine examination and litter parameters, or natural delivery parameters were observed. In postnatal studies, there were no fetal external, soft tissue, coronal or skeletal abnormalities, and body weight changes attributed to vaccine administration.

Overall, VAXNEUVANCE administration as repeated doses in rats did not induce systemic toxicity. VAXNEUVANCE induced vaccine-specific serologic antibody response in the test animals. Under the conditions of the nonclinical studies, the vaccine formulations were well tolerated.

5. Clinical Pharmacology

VAXNEUVANCE induces a serotype-specific immunoglobulin G (IgG) and opsonophagocytic activity (OPA) responses. Protection against invasive disease is thought to be conferred mainly by opsonophagocytic killing of *S. pneumoniae* serotypes contained within the vaccine. The relative contributions of cell-mediated immunity to protection from *S. pneumoniae* are unknown.

6. Clinical/Statistical

a. Clinical Program

Adults (N=5,630) were enrolled and received a single dose of VAXNEUVANCE in one Phase 2 and six Phase 3 studies, all of which were conducted under IND and under the investigational product name of V114. The median age of participants in the seven clinical studies was 62 years (range 18-98 years), with approximately 45% of participants aged 65 years and older. The majority of participants were from North America (62.3%) with remaining participants in Europe, Asia, Australia, and South America. Participants enrolled at more than 260 clinical sites in 18 countries.

For all studies, immunogenicity endpoints were used to demonstrate VAXNEUVANCE effectiveness for prevention of IPD when comparing the OPA immune responses to PCV13. The effectiveness of PCV13 for the prevention of invasive disease by vaccine serotypes has been previously demonstrated in adults.[7,8] Although there is no established immune correlate of protection for prevention of IPD in adults, CBER accepts a demonstration of statistical non-inferiority of OPA titers to support traditional approval of new higher valency pneumococcal conjugate vaccines for the prevention of IPD caused by vaccine serotypes.

This SBRA will focus on the four Phase 3 studies that provided the principal immunogenicity and safety data (V114-019, V114-016, V114-017, V114-020) in vaccine-naïve adults 18 years and older. Safety and supportive immunogenicity data generated from two other Phase 3 studies (V114-018, V114-021) and from the Phase 2 study (V114-007) are briefly discussed.

Clinical Serology Assay

Vaccine-induced antibody binding to capsular polysaccharides and antibody-mediated opsonophagocytic killing of encapsulated *S. pneumoniae* is the main mechanism involved in the protection from pneumococcal disease. Therefore, an OPA assay was used to assess the effectiveness of VAXNEUVANCE. In addition to OPA, serotype-specific IgG antibody responses for all 15 serotypes were measured using a pneumococcal electrochemiluminescence (Pn ECL) assay.

A multiplexed OPA (MOPA) was used to evaluate the clinical endpoints for all Phase 3 studies and a qualified MOPA (MOPA-4) was used to evaluate the Phase 2 study V114-007. Each MOPA assay run includes an (b) (4) test (b) (4) The Applicant indicated that while the (b) (4) positivity rate was within the expected range for studies V114-021 and V114-018, the positivity rate is markedly higher (up to 18% postvaccination) in studies V114-016, V114-017, V114-019,

and V114-20 following a change to a critical reagent. Given the low proportion of participants reporting (<5%) systemic antibiotic use around the time of blood draws, (b) (4) As a result, the OPA data presented in the Clinical Study Reports (CSRs) for Studies V114-016, V114-017, V114-019, and V114-20 do not exclude samples that tested (b) (4) positive. CBER recommended that only (b) (4) negative serum samples should be included in MOPA analyses because the presence of bactericidal substances in serum could potentially inflate OPA titers. The Applicant re-tested the samples that were previously (b) (4) -positive with a modified (b) (4) test and provided a statistical report for OPA testing results that excluded (b) (4) -positive serum samples for the primary and key secondary OPA analyses. The (b) (4) -negative OPA testing results were submitted to the application and are presented in the Table 4 & 5 of the VAXNEUVANCE US prescribing information and this SBRA (Table 5).

The MOPA used to evaluate Phase 3 study samples was validated at (b) (4) and the clinical samples were tested at (b) (4) The Phase 2 study V114-007 samples were evaluated in a qualified MOPA (MOPA-4) at (b) (4) The MOPA-4 was qualified at the (b) (4) . The (b) (4) used in the quantification of serotype specific IgG antibodies in Phase 3 study samples was validated and bridged to World Health Organization's (b) (4) . A qualified version of this (b) (4) was used to measure serum IgG antibodies in the Phase 2 study V114-007. Qualification of (b) (4) and the testing of study V114-007 samples were done by (b) (4) . The review prompted several information requests related to the standard operating procedure, validation, and assay quality control performance. Merck addressed these comments in several amendments. Overall, the MOPA used in the evaluation of clinical endpoints for the Phase 3 studies, the MOPA-4 for the evaluation of Phase 2 study V114-007, and the (b) (4) assay used for the evaluation serum IgG antibody responses were adequate for their intended uses.

Phase 3 Studies in Vaccine Naïve Adult Subjects

The Applicant conducted four Phase 3 studies which provided the principal data to support the safety and immunogenicity of VAXNEUVANCE for the intended indication, as well as data to support clinical lot consistency (**Table 4**). These four studies enrolled participants ≥18 years of age without prior history of pneumococcal vaccination at over 180 sites in 14 countries, including the US. The primary objective of these studies was to compare the serotype specific OPA geometric mean titers (GMTs) at 30 days postvaccination with VAXNEUVANCE versus PCV13.

Table 4: Summary of Phase 3 Studies in Pneumococcal Vaccine-Naïve Adults

Study Number	Region	Description	Population	Study Groups: # Enrolled
V114-019 (NCT03950622)	Canada Japan Spain Taiwan USA	Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Adults ≥50 Years	Healthy pneumococcal vaccine-naïve adults ≥50 years of age	V114*: 604 PCV13: 601
V114-020	Australia Chile	Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-	Healthy pneumococcal	V114 Lot 1: 667 V114 Lot 2: 667

Study Number	Region	Description	Population	Study Groups: # Enrolled
(NCT03950856)	Denmark Finland Great Britain USA	controlled, Lot-to-Lot Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Adults ≥50 Years	vaccine-naïve adults ≥50 years of age	V114 Lot 3: 667 PCV13: 220
V114-016 (NCT03480763)	Spain South Korea Taiwan USA	Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PPV23 One Year Later in Healthy Adults ≥50 Years	Healthy pneumococcal vaccine-naïve adults ≥50 years of age	V114+PPV23: 300 PCV13+PPV23: 300
V114-017 (NCT03547167)	Australia New Zealand Canada Chile Poland Russia USA	Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PPV23 Six Months Later in Immunocompetent Adults Between 18 and 49 Years of Age at Increased Risk for Pneumococcal Disease	Adults 18 to 49 years of age, includes adults with medical conditions for which ACIP pneumococcal vaccination is recommended	V114+PPV23: 1125 PCV13+PPV23: 375

*Product name under IND

Study V114-019 sought to demonstrate the immunogenicity and safety of VAXNEUVANCE in adults ≥50 years of age without prior history of pneumococcal conjugate vaccination. The primary objectives evaluated the immunologic non-inferiority of VAXNEUVANCE to PCV13 for the 13 shared serotypes and the statistical superiority of VAXNEUVANCE to PCV13 for the two unique serotypes in VAXNEUVANCE at 30-day postvaccination. Non-inferiority and statistical superiority were assessed by serotype specific OPA GMTs at 30 days postvaccination based on the following pre-specified statistical criteria:

1. Statistical non-inferiority: the lower bounds of the 2-sided 95% confidence intervals (CIs) of the OPA GMT ratios (VAXNEUVANCE/PCV13) are greater than 0.5 for the shared serotypes.
2. Statistical superiority: the lower bounds of the 2-sided 95% CIs of the OPA GMT ratios are greater than 2.0 for the 2 unique serotypes (22F and 33F), and greater than 1.2 for Serotype 3, which is included in both vaccines.

The results of serotype specific OPA GMTs are shown in **Table 5**. Study V114-019 demonstrated noninferior immunogenicity for the 13 shared serotypes in VAXNEUVANCE and PCV13, and statistically superior immunogenicity for serotypes 22F, 33F and 3 in VAXNEUVANCE compared to those in PCV13.

Table 5: Study V114-019 Serotype-Specific OPA GMTs, PPAS

Pneumococcal Serotype	VAXNEUVANCE (N=515-598) GMTs	PCV13 (N=488-598) GMTs	GMT Ratio (VAXNEUVANCE/PCV13) [95% CI]
1	257	321	0.80 [**0.66**,0.97]
3	215	133	1.62 [**1.40**,1.87]

Pneumococcal Serotype	VAXNEUVANCE (N=515-598) GMTs	PCV13 (N=488-598) GMTs	GMT Ratio (VAXNEUVANCE/PCV13) [95% CI]
4	1109	1633	0.68 [**0.57**,0.80]
5	445	560	0.79 [**0.64**,0.98]
6A	5371	5276	1.02 [**0.85**,1.22]
6B	3984	3179	1.25 [**1.04**,1.51]
7F	4575	5830	0.78 [**0.68**,0.90]
9V	1809	2193	0.83 [**0.71**,0.96]
14	1976	2619	0.75 [**0.64**,0.89]
18C	2749	2552	1.08 [**0.91**,1.27]
19A	3177	3921	0.81 [**0.70**,0.94]
19F	1688	1884	0.90 [**0.77**,1.04]
23F	2029	1723	1.18 [**0.96**,1.44]
22F	2381	73	32.52 [**25.87**,40.88]
33F	8010	1114	7.19 [**6.13**,8.43]

Source: Adapted from STN 125741.0, module 5.3.5.4 IK Statistical Report, Table 7 and Table 14
PPAS: Per Protocol Analyses Set; **N**: # participants in PPAS; **GMTs**: Geometric Mean Titers; **GMTR**: GMT ratios: estimated from cLDA model). Bold numbers indicate lower limits of 95% CI for which statistical testing was performed for the respective test and respective serotypes.

Study V114-020 was a lot-to-lot consistency study in which a total of 2,220 pneumococcal vaccine-naïve adults ≥50 years of age were randomized 3:3:3:1 to one of three VAXNEUVANCE clinical lots. The primary objectives were to evaluate the safety and tolerability of VAXNEUVANCE and to compare serotype specific OPA GMTs at 30 days post-vaccination across 3 different lots of VAXNEUVANCE. The 3 lots were considered equivalent if for each pairwise comparison of VAXNEUVANCE vaccine lots, the 2-sided 95% CI of the ratio of GMTs was contained within pre-specified equivalence margin [95% CI: 0.5, 2.0] for each of the 15 VAXNEUVANCE serotypes. The non-inferiority criteria were met for all serotypes in VAXNEUVANCE in the three clinical lots, demonstrating lot-to-lot equivalency.

Study V114-017 descriptively evaluated the immunogenicity of VAXNEUVANCE in pneumococcal vaccine-naïve, immunocompetent adults 18 to 49 years of age who are at increased risk for pneumococcal disease due to an underlying medical condition (e.g., diabetes mellitus, chronic heart disease, chronic liver disease, chronic lung disease including asthma), behavioral risk factor (e.g., smoking, increased alcohol use), and/or a Native American living at or near a tribal reservation, a community with increased risk of pneumococcal disease transmission. The OPA GMTs following VAXNEUVANCE at the 30 days postvaccination for most shared serotypes were similar to those observed following PCV13 vaccination, except for serotypes 4 and 7F which had lower OPA GMTs following VAXNEUVANCE compared to PCV13. However, following the sequential administration of PPV23 six month after VAXNEUVANCE, OPA GMTs were similar across study groups for all shared serotypes, including 4 and 7F.

Study V114-016 evaluated sequential administration of PPV23 12 months after VAXNEUVANCE administration in pneumococcal vaccine-naïve adults ≥50 years of age. Study V114-016 demonstrated comparable OPA GMTs for the 13 shared serotypes in VAXNEUVANCE and PCV13 when each vaccine was following by administration of PPV23 twelve months later. Similarly, for the 14 shared serotypes in VAXNEUVANCE and PPV23, comparable OPA GMTs were observed in participants who received VAXNEUVANCE followed by PPV23 as in those who received PCV13 followed by

PPV23. For the unique serotype 22F, OPA GMTs were higher in the VAXNEUVANCE group compared to the PCV13 group at one month after PPV23 and were comparable across groups for the unique serotype 33F.

In summary, in healthy immunocompetent adults 18 years of age and older without prior history of pneumococcal vaccination, the OPA immune responses elicited in VAXNEUVANCE recipients are non-inferior for shared serotypes and statistically superior for unique serotypes (22F, 33F) when compared to PCV13.

Supportive Clinical Studies

The Applicant submitted two additional Phase 3 studies (V114-018 and V114-021) and a Phase 2 study (V114-007) to support licensure.

Study V114-021 (NCT03615482) was a Phase 3 randomized, double-blind, placebo-controlled, multi-center study to evaluate the safety and immunogenicity of VAXNEUVANCE and a quadrivalent influenza vaccine (Fluarix Quadrivalent, GlaxoSmithKline Biologicals) [QIV] administered concomitantly, compared to sequential administration of QIV followed by VAXNEUVANCE one month later (non-concomitant study group). A total of 1,200 healthy adults ≥50 years of age were randomized 1:1 to the concomitant group or the non-concomitant group. Study V114-021 demonstrated immunologic noninferiority for all 15 serotypes based on OPA GMTs at one-month post VAXNEUVANCE vaccination when VAXNEUVANCE was administered concomitantly with QIV compared to when VAXNEUVANCE was administered one month after QIV. In addition, noninferior immune responses were demonstrated for all 4 influenza strains based on influenza strain-specific hemagglutination inhibition GMTs at one-month post QIV vaccination when QIV was administered concomitantly with VAXNEUVANCE compared to when QIV was administered one month prior to VAXNEUVANCE.

Study V114-018 (NCT03480802) was a descriptive study (without hypothesis testing) to evaluate the safety and immunogenicity of VAXNEUVANCE compared to PCV13 in HIV-infected adults ≥18 years of age. A total of 300 HIV-infected adults were randomized (1:1) to receive either VAXNEUVANCE or PCV13. Participants received PPV23 eight weeks after pneumococcal conjugate vaccination, as recommended by the ACIP for HIV+ individuals over the age of 2 years. VAXNEUVANCE elicited an immune response in adults infected with HIV as assessed by OPA GMTs for all 15 serotypes contained in the vaccine at 30 days postvaccination compared to pre-vaccination. Following PPV23 administration, OPA GMTs were numerically similar between the two vaccination groups for all 15 serotypes contained in VAXNEUVANCE. The effectiveness of VAXNEUVANCE in HIV-infected individuals has not been evaluated.

Study V114-007 (NCT02573181) was a Phase 2 descriptive study to evaluate the impact of prior receipt of PPV23 on the immunogenicity of a single dose of VAXNEUVANCE compared to PCV13. Adult ≥65 years of age previously vaccinated with PPV23 (at least 1 year prior to study entry) received VAXNEUVANCE (N=127) or PCV13 (N=126). In general, the OPA data 30 days postvaccination from this Phase 2 study align with the immunogenicity data from the larger Phase 3 studies described previously.

Postmarketing

No safety signals have been identified to date that would justify a postmarketing study. For pediatric studies required by Pediatric Research Equity Act PREA (21 U.S.C. 355c), reference is made to the pediatric section of this document.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspections were issued for three clinical study sites that participated in the conduct of study Protocol 019-00. The inspections did not reveal substantive issues that impact the data submitted in this BLA.

c. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. Under PREA, the submission of this original BLA required a Pediatric Study Plan for the claimed indications.

The review team presented the Applicant's Pediatric Study Plan to the FDA Pediatric Review Committee on May 4, 2021. The committee agreed with the Applicant's request for a partial waiver of the pediatric study requirement for infants 0 to <6 weeks of age because VAXNEUVANCE does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group (section 505B(a)(4)(B)(iii) of the Act). The committee agreed with the Applicant's request for a deferral of studies in children 6 weeks through 17 years of age for this application because the product is ready for approval for use in adults and the pediatric studies have not been completed (505B(a)(3)(A)(i) of the Act).

7. Safety and Pharmacovigilance

Safety Results

The safety database consists of 7,438 participants ≥18 years of age who enrolled in the seven clinical studies described in the previous section. A total of 5,630 participants received one dose of VAXNEUVANCE and 1,808 participants received PCV13. The study populations included adults from diverse populations with respect to age, race/ethnicity, health status (healthy, risk factors for pneumococcal disease, or immunocompromised), prior pneumococcal vaccination status, and concomitant influenza vaccination. The majority of participants were immunocompetent (95.9%); one study (V114-018) included 302 adults who were infected with HIV.

Safety evaluation methods were consistent across all seven studies in the clinical development program. After administration of the study vaccine, all participants were observed for at least 30 minutes for any immediate reactions. Postvaccination safety

evaluations were reported on Vaccination Report Cards (VRCs) with the following information reported daily by participants:

- Day 1 through 5 postvaccination: solicited injection-site adverse reactions (erythema, pain, swelling) and oral body temperature

- Day 1 through 14 postvaccination:
    1. solicited systemic Adverse Events (AE) (fever, arthralgia, fatigue, headache, myalgia)
    2. other unsolicited AEs (including injection-site AEs after Day 5)
    3. use of concomitant medications and vaccinations

For complaints reported on the VRC, the investigator reviewed the data with the participant on Day 15 and reported events meeting the AE definition in the clinical database. Investigators also assessed intensity, toxicity, and seriousness of AEs according to protocol-specified criteria. Duration of follow up for serious AEs (SAEs) was 30 days in Study V114- 007; 2 months in Study V114-018, and at least six months postvaccination in the rest of the Phase 3 studies. Duration of follow up for nonserious AEs in all seven studies was 14 days.

No safety concerns were identified when a dose of VAXNEUVANCE was administered to adults ≥18 years of age, with or without prior pneumococcal vaccine exposure. The most frequently reported solicited adverse reactions included injection site pain, fatigue, and myalgia. Across all studies, there were 8 VAXNEUVANCE recipients and 3 PCV13 recipients who died during the safety follow-up (≥40 days post-vaccination). None of the deaths were considered related to study vaccinations. The rates of reported SAEs among studies were from 1.6% to 4.3% and the types of SAEs across groups were similar and included clinical events that are often reported in the populations evaluated. None of the reported SAEs were assessed by CBER clinical reviewers as related to study vaccinations.

The available safety data do not substantiate a need for safety-related postmarketing studies.

Pharmacovigilance Plan

The Applicant submitted a Risk Management Plan that includes a Pharmacovigilance Plan (PVP) for VAXNEUVANCE to address “Important Identified Risks”, “Important Potential Risks”, and “Missing Information”. There are no important identified or potential risks for VAXNEUVANCE. The following safety concern is considered missing information: “Safety of more than one dose administered <1 year apart to immunocompromised adults.” To address this safety concern, the Applicant plans to complete an ongoing Phase 3, randomized, double-blind, active comparator-controlled, parallel-group, multicenter, clinical study to describe the safety, tolerability, and immunogenicity of VAXNEUVANCE and PCV13 when administered as a 3-dose regimen in recipients of allogeneic hematopoietic stem cell transplant. Aside from this ongoing clinical study, there are no additional pharmacovigilance activities beyond routine pharmacovigilance (adverse reactions reporting and signal detection) in the PVP.

The PVP for VAXNEUVANCE is adequate for the labeled indication. The available data do not indicate a safety signal which would require either a Risk Evaluation and Mitigation Strategy (REMS), or a postmarketing commitment (PMC) or postmarketing requirement (PMR) study.

8. Labeling

The proposed proprietary name, VAXNEUVANCE was reviewed by the Advertising and Promotional Labeling Branch (APLB) on January 5, 2021 and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on January 15, 2021.

APLB reviewed the proposed prescribing information (PI), patient labeling, and package/container labels on April 21, 2021 and found them acceptable from a promotional and comprehension perspective. All labeling issues regarding the PI, patient labeling, and the carton and container labels were resolved following the exchange of information and discussions with the Applicant.

9. Advisory Committee Meeting

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting because FDA review of this submission did not identify concerns or issues which would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

The FDA granted priority review designation for this BLA on January 11, 2021 on the basis that the proposed indication meets the criteria as a drug that treats or prevents a serious condition and, if approved, would provide a significant improvement in effectiveness in treatment or prevention of a serious condition. FDA's decision to grant priority review was based on the perceived burden of pneumococcal disease in adults attributable to the unique serotypes (22F and 33F) in VAXNEUVANCE.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Review Committee recommends approval of VAXNEUVANCE for the labeled indication and usage based on the review of the clinical, pre-clinical, and product-related data submitted in the original BLA.

b. Benefit/Risk Assessment

The Applicant has submitted data to support the safety and effectiveness of VAXNEUVANCE. The Review Committee agrees that the risk/benefit balance for VAXNEUVANCE is favorable and supports approval for use in adults 18 years of age and older.

c. Recommendation for Postmarketing Activities

The Applicant has committed to conduct the following postmarketing activities, which are specified in the approval letter.

PEDIATRIC REQUIREMENTS

1. Deferred pediatric study under PREA (Study V114-029) to evaluate the safety and immunogenicity of VAXNEUVANCE in healthy infants 6 through 12 weeks of age as a 4-dose schedule (2, 4, 6, and 12 to15 months of age).

   Final Protocol Submission: February 22, 2019
   Study Completion Date: December 31, 2021
   Final Report Submission: April 30, 2022

2. Deferred pediatric study under PREA (Study V114-024) to evaluate the safety and immunogenicity of VAXNEUVANCE when given as catch-up vaccination in healthy children 7 months through 17 years of age.

   Final Protocol Submission: December 5, 2019
   Study Completion Date: September 30, 2021
   Final Report Submission: December 31, 2021

3. Deferred pediatric study under PREA (Study V114-027) to evaluate the safety and immunogenicity of four-dose schedules of VAXNEUVANCE and Prevnar 13 with doses administered at 2, 4, 6 and 12 to 15 months of age, as compared to mixed schedules which begin with Prevnar 13 and change to VAXNEUVANCE at doses 2, 3 or 4.

   Final Protocol Submission: August 16, 2018
   Study Completion Date: April 30, 2021
   Final Report Submission: July 31, 2021

4. Deferred pediatric study under PREA (Study V114-030) to evaluate the safety and immunogenicity of VAXNEUVANCE in HIV-infected children 6 through 17 years of age.

   Final Protocol Submission: December 5, 2019
   Study Completion Date: August 31, 2022
   Final Report Submission: December 31, 2022

12. References

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8. Based on the efficacy confirmed in the Pfizer's PCV13 Study 6115A1-3006: Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA)