

**Department of Health and Human Services  
Food and Drug Administration (FDA)  
Center for Biologics Evaluation and Research (CBER)  
Division of Epidemiology (DE)**

**PHARMACOVIGILANCE PLAN BLA MEMORANDUM**

**Date:** June 14, 2021

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**Subject:** Pharmacovigilance Plan Review

**Sponsor:** Merck Sharp & Dohme Corp.

**Product<sup>1</sup>:** Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein], (b) (4) ; VAXNEUVANCE

**Application Type/Number:** BLA 125741/0

**Proposed Indication:** 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

**Submission Date:** October 21, 2020

**Action Due Date:** July 18, 2021

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<sup>1</sup> The product was referred to as V114 in the clinical development program.

## 1. OBJECTIVE

The purpose of this memorandum is to assess the adequacy of the sponsor's proposed Pharmacovigilance Plan based on the known safety profile of VAXNEUVANCE (Pneumococcal 15 valent Conjugate Vaccine [CRM197 Protein], (b) (4) ), also referred to as V114 (the name used in the clinical development program).

## 2. PRODUCT INFORMATION

### 2.1. Product Description

VAXNEUVANCE (Pneumococcal 15 valent Conjugate Vaccine [CRM197 Protein], (b) (4) ) 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. CRM197 is a nontoxic mutant of diphtheria toxin (originating from *Corynebacterium diphtheriae* C7) expressed recombinantly in *Pseudomonas fluorescens*.

VAXNEUVANCE is an opalescent suspension for intramuscular injection supplied in a 0.5 mL single-dose prefilled syringe. Each 0.5 mL dose contains 2.0 mcg each of *S. pneumoniae* polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F, and 4.0 mcg of polysaccharide serotype 6B, 30 mcg of CRM197 carrier protein, 1.55 mg L-histidine, 1 mg of polysorbate 20, (b) (4) mg sodium chloride, and 125 mcg of aluminum as aluminum phosphate adjuvant. VAXNEUVANCE does not contain any preservatives.

### 2.2. Proposed Indication

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

## 3. PERTINENT REGULATORY HISTORY

The Sponsor submitted an Investigational New Drug application (IND 14977) for V114 on February 15, 2012. V114 was granted Breakthrough Therapy designation under the IND on May 10, 2019. The Sponsor submitted the final component of the rolling BLA for V114 on November 17, 2020. On January 11, 2021, the FDA classified the BLA as Priority Review.

## 4. WORLDWIDE POSTMARKETING DATA

Not applicable. This product is not marketed in any country worldwide.

## 5. KNOWN SAFETY INFORMATION FOR PNEUMOCOCCAL CONJUGATE VACCINES

Prevnar 13 (Pfizer) is the only licensed pneumococcal conjugate vaccine currently in use in the United States. Similar to V114, Pevnar 13 is composed of pneumococcal polysaccharides conjugated to carrier protein CRM197 with an aluminum phosphate adjuvant. Although only V114 contains serotypes 22F and 33F, both vaccines contain the following 13 serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

According to the Package Insert, the safety of Pevnar 13 in adults aged 18 and older was evaluated in seven clinical studies which included 91,593 adults (48,806 received Pevnar 13) ranging in age from 18 through 101 years. These clinical studies included adults with stable preexisting underlying diseases, prior 23-valent pneumococcal polysaccharide vaccination, and concomitant influenza vaccination. Overall, the most commonly reported solicited adverse reactions (>5%) in adults included pain at the injection site (>50%), fatigue (>30%), headache (>20%), muscle pain (>20%), joint pain (>10%), decreased appetite (>10%), injection site redness (>10%), injection site swelling (>10%), limitation of arm movement (>10%), vomiting (>5%), fever (>5%), chills (>5%), and rash (>5%). For the six studies that evaluated safety and immunogenicity, serious adverse events within one month of vaccination were rare after Pevnar 13 vaccination (0.2-1.4%). Twelve participants who received Pevnar 13 in these studies died. Two deaths were within 30 days of vaccination and both occurred in participants over 65 years of age (cardiac failure one month after Pevnar 13 and influenza vaccine, peritonitis 20 days after Pevnar 13).<sup>2</sup>

The safety profile described in the Pevnar 13 Package Insert is also reflected in postmarketing reporting. A query of the VAERS database on 4/28/21 found the ten most common MedDRA<sup>3</sup> Preferred Terms in Pevnar 13 VAERS reports were consistent with the solicited adverse reactions for adults and children as described in the Package Insert.

Table 1. Ten most common MedDRA Preferred Terms in Pevnar 13 VAERS reports

Rank	MedDRA Preferred Term	N
1	Pyrexia	8156
2	Injection site erythema	5391
3	Injection site swelling	3585
4	Erythema	3224
5	Injection site pain	2869
6	Rash	2798
7	Vomiting	2741
8	Crying	2569

<sup>2</sup> Package Insert - Pevnar 13. <https://www.fda.gov/media/107657/download>. Accessed June 1, 2021.

<sup>3</sup> Medical Dictionary for Regulatory Activities (MedDRA) is a standardized medical terminology used to facilitate sharing of regulatory information internationally for medical products used by humans. There are five levels of MedDRA hierarchy, with the Preferred Term (PT) level representing distinct medical concepts. (Source: <https://www.meddra.org/>).

9	Irritability	2542
10	Pain	2135

Abbreviations: Medical Dictionary for Regulatory Activities (MedDRA)

Data mining<sup>4</sup> also supports the safety of Prevnar 13, with no data mining signals (EB05>2.0) from US VAERS reports and data mining signals from World VAERS reports (Table 2) representing either confounding by indication, possible cases of vaccination failure, or non-specific injection site reactions.

Table 2. Data mining for Prevnar 13 – Worldwide reporting

Event	N	EB05
Allergy to metals	193	2.098
Heat oedema	7	2.064
Injection site abscess sterile	50	6.379
Meningitis pneumococcal	248	2.475
Pneumococcal bacteraemia	280	2.583
Pneumococcal infection	167	2.54
Reaction to excipient	103	2.408
Scratch	126	2.34
Serology positive	57	3.305
Skin wound	45	3.203
Streptococcus test positive	606	2.43
Vaccination site granuloma	115	2.179
Vaccination site pruritus	49	2.057
Wound	68	2.257

Several reviews of the published literature support the safety of pneumococcal conjugate vaccines in general. In 2019, Vadlamudi et al.<sup>5</sup> published a systematic review and meta-analysis on the immunogenicity and safety of 13-valent pneumococcal conjugate vaccine (PCV13) compared to 23-valent pneumococcal polysaccharide vaccine (PPSV23) in immunocompetent adults. The authors evaluated five randomized controlled trials, including 4561 participants ranging in age from 50 to 95 years. They concluded that overall local and systemic reactions were comparable for the two vaccines, although pneumococcal vaccine-naïve PCV13 participants were more likely to experience local reactions. Deaths were reported in three studies, but no deaths were

<sup>4</sup> Data mining performed on 4/27/21 using Empirica Signal (Signals tab for Prevnar 13, Main views, data lock point 4/23/21). The minimum standard analysis is the “All signals summary table” in the signal management application. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock date listed. The background database contains VAERS reports since 1990. Data mining results with EB05 > 2 are considered signals of disproportionate reporting. Data mining findings are subject to a number of potential limitations and are to be regarded as “hypothesis generating.” Data mining findings do not imply causality.

<sup>5</sup> Vadlamudi NK, Parhar K, Altre Malana KL, Kang A, Marra F. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine compared to 23-valent pneumococcal polysaccharide in immunocompetent adults: A systematic review and meta-analysis. *Vaccine*. 2019 Feb 14;37(8):1021-1029. doi: 10.1016/j.vaccine.2019.01.014. Epub 2019 Jan 23. PMID: 30685252.

attributed to vaccination and although pooled all-cause mortality was elevated (RR 3.13, 95% CI 0.45-21.70), this finding was not statistically significant. In 2008, DeStafano et al.<sup>6</sup> published a systematic review of pre- and post-licensure safety data for pneumococcal conjugate vaccines (PCV7 and PCV9). The authors evaluated 42 studies and concluded that “no major safety problems were identified” with a possible exception of respiratory adverse events, for which there was conflicting data, with one study showing a statistically significant increased risk of hospitalization for reactive airway disease (including asthma) that was not seen in another large trial. In addition, authors found that PCV7 resulted in more local reactions than comparator vaccines, although reactions were generally mild and self-limited. In 2016, Ciapponi et al.<sup>7</sup> published a systematic review and meta-analysis on the interchangeability between pneumococcal conjugate vaccines. The authors evaluated 46 studies to assess interchangeability with respect to efficacy, cost-effectiveness, immunogenicity, and safety. Five randomized controlled trials evaluating safety of PCV7, PCV10, and PCV11 were included for safety. Authors concluded that although there was no direct information available on interchangeability between pneumococcal conjugate vaccines, they had similar immunogenicity and safety. Lastly, in 2020, Chilson et al.<sup>8</sup> published a review of immunogenicity and safety of PCV13 in patients with immunocompromising conditions. The authors evaluated 30 studies including 2406 participants with immunocompromising conditions (e.g., asplenia, sickle cell disease, HIV infection, etc.). They concluded that PCV13 was immunogenic and “largely well tolerated” among immunocompromised participants, despite variable and generally lower antibody responses compared to healthy controls.

## **6. DESCRIPTION OF PRODUCT SAFETY DATABASE**

### **6.1. Clinical Studies**

#### *6.1.1. Study Designs*

The clinical development program to support licensure of V114 in adults includes safety data from seven completed clinical studies: one phase 2 study (V114-007) and six phase 3 studies (V114-016, V114-017, V114-018, V114-019, V114-020, V114-021) (Table A3). Each study was a multisite, randomized, double-blind, controlled study designed to evaluate safety, tolerability, and immunogenicity of V114. One study (V114-021), which evaluated concomitant administration of V114 with inactivated influenza

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<sup>6</sup> Destefano F, Pfeifer D, Nohynek H. Safety profile of pneumococcal conjugate vaccines: systematic review of pre- and post-licensure data. *Bull World Health Organ.* 2008 May;86(5):373-80. doi: 10.2471/blt.07.048025. PMID: 18545740; PMCID: PMC2647448.

<sup>7</sup> Ciapponi A, Lee A, Bardach A, Glujovsky D, Rey-Ares L, Luisa Cafferata M, Valanzasca P, García Martí S. Interchangeability between Pneumococcal Conjugate Vaccines: A Systematic Review and Meta-Analysis. *Value Health Reg Issues.* 2016 Dec;11:24-34. doi: 10.1016/j.vhri.2015.12.001. Epub 2016 Mar 17. PMID: 27986195.

<sup>8</sup> Chilson E, Scott DA, Schmoele-Thoma B, Watson W, Moran MM, Isturiz R. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine in patients with immunocompromising conditions: a review of available evidence. *Hum Vaccin Immunother.* 2020 Nov 1;16(11):2758-2772. doi: 10.1080/21645515.2020.1735224. Epub 2020 Jun 12. PMID: 32530360; PMCID: PMC7746253.

vaccine, was placebo-controlled. The other six studies were active-comparator controlled with Prevnar 13 (hereafter referred to as PCV13). The six active-comparator controlled studies evaluated a single dose of V114 or PCV13 either alone (V114-007, V114-019, V114-020) or as part of a sequential regimen with PPSV23 (V114-016, V114-017, V114-018). One of the active-comparator controlled studies (V114-020) was a lot consistency study.

### 6.1.2. Study Populations

The study populations in the seven clinical studies 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 (Table A3). One study evaluated V114 in healthy adults aged 65 years and older (V114-007). Three studies evaluated V114 in adults aged 50 years and older who were pneumococcal vaccine-naïve (V114-016, V114-019, and V114-020). One study evaluated V114 in adults aged 18-49 years who were pneumococcal vaccine-naïve, immunocompetent, with and without risk factors for pneumococcal disease (V114-017). One study evaluated V114 in immunocompromised adults aged 18 years and older who were infected with HIV (V114-018). One study evaluated concomitant administration of V114 with inactivated influenza vaccine in adults aged 50 years and older with or without prior 23-valent pneumococcal vaccination (PPSV23) (V114-021).

Overall, 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. The majority of participants (72.3%) were white; American Indian or Alaska Native, Asian, and Black or African American participants each made up 7% to 10% of the overall population. Approximately 20% of participants were of Hispanic or Latino ethnicity. The majority (54.6%) of participants were female. The majority of participants were immunocompetent (95.9%); one study (V114-018) included 302 immunocompromised adults who were infected with HIV (all with CD4+ T-cell count  $\geq$  50 cells/ $\mu$ L and HIV ribonucleic acid  $<$ 50,000 copies/mL at screening; four with CD4+ T-cell count less than 200 cells/ $\mu$ L at screening).

### 6.1.3. Exposure

Overall, 7438 participants enrolled across the seven clinical studies; 5630 participants received V114 and 1808 participants received Prevnar 13.

*Reviewer comment: V114 was studied in diverse populations and adequately reflects intended use of the vaccine in adults, with the exception of immunocompromised patients. Although Study V114-018 evaluated V114 in adults infected with HIV, patients with other forms of immunosuppression are not well represented in these studies (for example, other acquired or congenital immunodeficiency, functional or anatomic*

*asplenia, autoimmune disease, and those receiving immunosuppressive therapy or treatments associated with organ or bone marrow transplantation). This issue is discussed further in the section 8.3 Missing Information. Of note, pregnant/lactating women and children were excluded from V114 studies. However, V114 is not intended for use in these populations at this time.*

## **6.2. Safety Evaluation**

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 with the following information reported daily by participants:

- Day 1 through 5 postvaccination: solicited injection-site AEs (erythema, pain, swelling) and oral body temperature
- Day 1 through 14: 1) solicited systemic AEs (arthralgia, fatigue, headache, myalgia), 2) other unsolicited AEs (including injection-site AEs after Day 5), and 3) use of concomitant medications and vaccinations

For complaints reported on the VRC, the investigator reviewed the data with the participant 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 at least six months in all six of the Phase 3 studies and was 30 days in the phase 2 study (V114-007). Duration of follow up for nonserious AEs in all seven studies was 14 days.

For aggregate analysis of adverse events, the sponsor pooled safety data across the three phase 3 studies involving pneumococcal naïve adults aged 50 years and older (V114-016, V114-019, and V114-020) to create an “integrated population.” For the pooled analysis of the integrated population, the sponsor used a prespecified weighted approach and associated 95% confidence intervals to make between-group comparisons. The remaining four studies were analyzed separately (V114-007, V114-017, V114-018, and V114-021).

*Reviewer comment: Assessment of AEs was consistent across the seven clinical studies. Duration of follow up was adequate with all six Phase 3 studies having a follow up duration for SAEs of at least six months. Pooling of studies for the “integrated population” is appropriate given these studies had similar study designs and study populations. The sponsor appropriately applied weighting for the analysis of the integrated population and also presented unweighted and unpooled analyses for comparison, with no major discrepancies in findings identified by this reviewer.*

*During the review process, the clinical team noted that for some solicited adverse events, there was a difference in rates of AEs assessed by the investigator in the Case Report Form (eCRF) compared to those reported directly by the participant in the*

*Vaccine Report Card (VRC). The most notable differences were seen for myalgia and arthralgia, with concordance rates for the two methods of around 40-50% for some studies. The review team acknowledged that the investigator assessment may be more accurate in cases where participants inaccurately reported AEs in the VRC. For example, a participant who experienced pain at the injection site might incorrectly report this as “myalgia” in the VRC; the investigator would correct this to “injection site pain” during their assessment. Conversely, the review team expressed concern about the investigator assessment also potentially introducing recall bias, since VRC reviews by site investigators were conducted on Day 15 (telephone contact). For example, a participant may not accurately recall the details of the symptoms they reported on the VRC if the investigator asks a clarifying question several days later. The sponsor responded to these concerns (125741/0.22) by assuring that uniform processes for assessing cases were followed—as prespecified in the protocol—and argued in favor of using the investigator-assessed AE rates as the most unbiased representation of solicited AE data. After further consideration, the review team agreed to use the investigator-assessed AE rates for the Package Insert, with additional explanation on the method of assessment. Neither the clinical reviewer nor the sponsor felt these discrepancies would influence the overall safety profile of V114 in a clinically meaningful way. This reviewer’s assessment of solicited adverse events is based on the investigator-assessed AE rates, as presented in the clinical study reports. Causality assessments for AEs discussed in this review memo are based on this reviewer’s assessment of case narratives, not the investigator’s causality assessment.*

## **7. ADVERSE EVENTS**

### **7.1. Study V114-007**

#### Study description

V114-007 was a Phase 2 randomized controlled trial to evaluate safety, tolerability, and immunogenicity of V114 compared to PCV13 in 253 healthy adults aged 65 and older who were previously vaccinated with PPSV23.

#### Most common AEs

The most common AEs (experienced by more than 5% of participants) following PCV (V114 or PCV13) were the solicited injection-site and systemic AEs. Following V114, the most common AEs were injection site pain (57.5%), fatigue (18.1%), injection site swelling (15.7%), myalgia (15.7%), headache (13.4%), injection site erythema (9.4%), and arthralgia (5.5%).

#### Injection-site AEs

Overall injection-site AEs following PCV were more common following V114 than PCV13 (63.0% vs 50.8%). For specific injection-site AEs following PCV, V114 participants more often reported injection site pain (57.5% vs. 46.0%) and injection site swelling (15.7% vs. 6.3%) than PCV13 participants. Most solicited injection-site AEs

following PCV were mild or moderate in intensity with no notable differences in 'severe' injection-site AEs between V114 and PCV13 groups.

### Systemic AEs

Overall systemic AEs following PCV were comparable for V114 and PCV13 participants (39.4% vs. 40.5%). For specific systemic AEs following PCV, there were no notable differences between V114 and PCV13 groups. Most solicited systemic AEs following PCV were mild or moderate in intensity with no notable differences in 'severe' systemic AEs between V114 and PCV13 groups.

### Serious and fatal AEs

There were two SAEs in this study, both in the PCV13 group. Both SAEs were unlikely related to vaccination: 1) a 70-year-old male with coronary artery disease, hypercholesterolemia, and diabetes mellitus type 2 who experienced an acute myocardial infarction on Day 3 postvaccination, and 2) a 69-year-old female with a history of osteopenia, osteoarthritis, and scoliosis who fell after she underwent hip replacement and experienced a periprosthetic fracture on Day 35 postvaccination.

There were no deaths reported in this study.

*Reviewer comments: The overall safety profile for V114 is comparable to PCV13 in this study, although V114 participants experienced more overall injection site AEs (and specifically, injection site pain and injection site swelling). This study suggests V114 has an acceptable safety profile in adults aged 65 and older with prior PPSV23 vaccination. Important limitations of this Phase 2 study include the lack of invasive pneumococcal disease risk factors in this healthy study population and the short duration of follow up for AEs (30 days).*

## **7.2. Study V114-017**

### Study description

V114-017 was a Phase 3 randomized controlled trial to evaluate safety, tolerability, and immunogenicity of V114 (compared to PCV13) followed by PPSV23 six months later in 1515 adults aged 18-49 years who were pneumococcal vaccine-naïve, immunocompetent, with and without risk factors for pneumococcal disease (including chronic lung disease, tobacco use, diabetes mellitus, chronic liver disease, chronic heart disease, and alcohol consumption).

### Most common AEs

The most common AEs (experienced by more than 5% of participants) following PCV (V114 or PCV13) were the solicited injection-site and systemic AEs. Following V114, the most common AEs were injection site pain (76.3%), fatigue (34.3%), myalgia (28.8%), headache (26.5%), injection site swelling (22.1%), injection site erythema (15.3%), and arthralgia (12.7%).

The most common AEs (experienced by more than 5% of participants) following PPSV23 (V114 or PCV13 groups) were the solicited injection-site and systemic AEs. Following PPSV23 (for the V114 group), the most common AEs were injection site pain (68.9%), fatigue (30.1%), injection site swelling (29.4%), myalgia (24.1%), injection site erythema (22.7%), headache (21.2%), and arthralgia (12.0%).

#### Injection-site AEs

Overall injection-site AEs following PCV were more common following V114 than PCV13 (78.7% vs. 72.0%). For specific injection-site AEs following PCV, V114 participants more often reported injection site pain (76.3% vs. 68.8%) than PCV13 participants. Most solicited injection site AEs following PCV were mild or moderate in intensity with no notable differences in 'severe' injection-site AEs between V114 and PCV13 groups.

Overall injection-site AEs following PPSV23 were comparable for V114 and PCV13 participants (71.3% vs. 69.9%). For specific solicited injection-site AEs following PPSV23, there were no notable differences between V114 and PCV13 groups. Most solicited injection site AEs following PPSV23 were mild or moderate in intensity with no notable differences in 'severe' injection-site AEs between V114 and PCV13 groups.

#### Systemic AEs

Overall systemic AEs following PCV were comparable for V114 and PCV13 participants (62.3% vs. 63.0%). For specific systemic AEs, V114 participants more often reported complaints in the 'Gastrointestinal disorders' System Organ Class (SOC) than PCV13 participants (6.0% vs. 3.4%), and this difference appeared largely due to greater reporting of nausea following V114 than PCV13 (2.5% vs. 1.1%). Most solicited systemic AEs following PCV were mild or moderate in intensity with no notable differences in 'severe' systemic AEs (including nausea) between V114 and PCV13 groups.

Overall systemic AEs following PPSV23 were comparable for both V114 and PCV13 participants (51.0% and 51.9%). For specific systemic AEs following PPSV23, there were no notable differences between V114 and PCV13 groups. Most solicited systemic AEs following PPSV23 were mild or moderate in intensity with no notable differences in 'severe' systemic AEs between V114 and PCV13 groups.

#### Serious and fatal AEs

Overall serious AEs (SAEs) following PCV were comparable for V114 and PCV13 participants (4.3% vs. 3.2%). For specific SAEs following PCV, there were no notable differences between V114 and PCV13 groups. In the V114 group, there was insufficient information (no serotype reported) to assess whether a 21-year-old participant's case of streptococcal pneumonia on Day 52, Postvaccination 1 was due to vaccination failure (Participant # (b) (6)). All other SAEs following PCV were unlikely related to study vaccination.

Overall SAEs following PPSV23 were comparable for V114 and PCV13 participants (0.3% vs. 0.9%). For specific SAEs following PPSV23, there were no notable differences between V114 and PCV13 groups. In the PCV13 group, one SAE was possibly related to study vaccination: a 21-year-old man with epilepsy experienced a generalized tonic-clonic seizure on Day 2, Postvaccination 2 (Participant (b) (6) [REDACTED]). All other SAEs following PPSV23 were unlikely related to study vaccination.

Three participants died in the V114 group (0.3%) and two participants died in the PCV13 group (0.5%) during the study. One additional participant died in the V114 group after the study reporting period. In the V114 group, deaths included: 1) a 21-year-old man with a history of suicide attempt died from completed suicide on Day (b) (6), 2) a 49-year-old woman died after being hit by a vehicle on Day (b) (6), 3) a 46-year-old man with multiple comorbidities experienced pulmonary embolism on Day 183 and died from a cardiac arrest on Day (b) (6), and 4) a 49-year-old man with a history of alcoholic cirrhosis died from hepatic encephalopathy on Day (b) (6). In the PCV13 group, deaths included: 1) a 25-year-old man experienced pneumonia on Day 30, had a complicated hospital course, and died from cardiac failure on Day (b) (6), and 2) a 48-year-old man with history of mitral valve replacement on anticoagulation died from a hemorrhagic stroke on Day (b) (6). There was insufficient information (no organism or serotype reported) to assess whether the death of the 25-year-old man from pneumonia in the PCV13 group was due to vaccination failure. All other deaths were unlikely related to study vaccination.

*Reviewer comment: The overall safety for V114 is comparable to PCV13 in this study, although V114 participants experienced more overall injection site AEs (and specifically, injection site pain), and nausea than PCV13 participants. Tolerability of PPSV23 six months after PCV appeared comparable between V114 and PCV13 participants. This study suggests V114 (in sequence with PPSV23) has an acceptable safety profile in immunocompetent, pneumococcal vaccine-naïve adults aged 18-49 years with and without risk factors for pneumococcal disease. Strengths of this study include the large number of participants who received V114 (n = 1133), the high proportion of participants (39.2%) who were American Indian or Alaska Native (a population at high risk for invasive pneumococcal disease), and the high proportion of participants with at least one risk factor for invasive pneumococcal disease (74.8%). A limitation of this study is the exclusion of immunocompromised participants.*

### **7.3. Study V114-018**

#### Study description

V114-018 was a Phase 3 randomized controlled trial to evaluate safety, tolerability, and immunogenicity of V114 (compared to PCV13) followed by PPSV23 eight weeks later in 302 adults infected with HIV.

#### Most common AEs

The most common AEs (experienced by more than 5% of participants) following PCV (V114 or PCV13) were the solicited injection-site and systemic AEs (excluding arthralgia). Following V114, the most common AEs were injection site pain (57.9%), fatigue (20.4%), headache (13.2%), myalgia (12.5%), injection site swelling (11.8%), and injection site erythema (5.3%).

The most common AEs (experienced by more than 5% of participants) following PPSV23 (V114 or PCV13 groups) were the solicited injection-site and systemic AEs (excluding arthralgia). Following PPSV23 (for the V114 group), the most common AEs were injection site pain (53.3%), injection site swelling (20.0%), fatigue (12.7%), myalgia (11.3%), injection site erythema (10.0%), and headache (8.7%).

### Injection-site AEs

Overall injection-site AEs following PCV were more common following V114 than PCV13 (63.8% vs. 54.7%). For specific injection-site AEs following PCV, V114 participants more often reported injection site pain (57.9% vs. 52.0%) and injection site swelling (11.8% vs. 4.0%) than PCV13 participants. Most solicited injection-site AEs following PCV were mild or moderate in intensity with no notable differences in 'severe' injection-site AEs between V114 and PCV13 groups.

Overall injection-site AEs following PPSV23 were less common for V114 participants than PCV13 participants (55.3% vs. 65.5%). For specific injection-site AEs following PPSV23, V114 participants less often reported injection site erythema (10.0% vs 12.2%), injection site pain (53.3% vs. 62.2%), and injection site swelling (20.0% vs. 29.1%) than PCV13 participants. Most solicited injection site AEs following PPSV23 were mild or moderate in intensity with V114 participants less often reporting 'severe' solicited AEs than PCV13 participants (1.3% vs. 4.1%). For specific solicited injection site AEs following PPSV23, V114 participants less often reported 'severe' injection site pain than PCV13 participants (0.7% vs. 3.4%).

### Systemic AEs

Overall systemic AEs following PCV were more common following V114 than PCV13 (42.8% vs. 36.0%). For specific systemic AEs following PCV, V114 participants more often reported fatigue (20.4% vs. 13.3%), headache (13.2% vs. 9.3%), and myalgia (12.5% vs. 9.3%) than PCV13 participants. Most solicited systemic AEs following PCV were mild or moderate in intensity with no notable differences in 'severe' solicited systemic AEs between V114 and PCV13 groups.

Overall systemic AEs following PPSV23 were comparable for both V114 and PCV13 participants (32.7% vs. 34.5%). For specific systemic AEs following PPSV23, V114 participants more often reported fatigue (12.7% vs. 10.8%) and arthralgia (2.7% vs. 1.4%) than PCV13 participants. Conversely, V114 participants less often reported myalgia (11.3% vs. 12.2%) than PCV13 participants. Most solicited systemic AEs

following PPSV23 were mild or moderate in intensity with no notable differences in 'severe' solicited systemic AEs between V114 and PCV13 groups.

### Serious and fatal AEs

Overall serious AEs (SAEs) following PCV were more common following V114 (2.0%) than PCV13 (0%). All of these SAEs were unlikely related to study vaccination.

Overall SAEs following PPSV23 were less common for V114 participants (1.3%) than PCV13 participants (4.1%). All of these SAEs were unlikely related to study vaccination.

There were no deaths reported in this study.

### HIV-related laboratory parameters

Laboratory monitoring in this study included measurement of CD4+ T-cell count and plasma HIV RNA viral load at baseline, Day 30, and Week 12. No adverse events were associated with HIV laboratory parameters (CD4+ T-cell count or plasma HIV RNA viral load). Similarly, no clinically meaningful changes in HIV laboratory parameters were observed from baseline to postvaccination for either treatment group (V114 or PCV13). Lastly, the distribution of solicited adverse events across treatment groups was comparable for participants with CD4+ T-cell count from  $\geq 200$  to  $< 500$  cells/ $\mu\text{L}$  versus participants with CD4+ T-cell count  $\geq 500$  cells/ $\mu\text{L}$ .

*Reviewer comment: The overall safety for V114 is comparable to PCV13 in this study, although V114 participants experienced more overall injection site AEs (and specifically, injection site pain and injection site swelling), and overall systemic AEs (and specifically, fatigue, headache, and myalgia) following V114 than PCV13 participants. Tolerability of PPSV23 eight weeks after PCV appeared comparable between V114 and PCV13 participants, although overall systemic AEs following PPSV23 were more common in the PCV13 group and several imbalances in specific solicited systemic AEs were observed between V114 and PCV13 groups. Importantly for this specific study population, this study did not demonstrate any safety concerns regarding HIV laboratory parameters. This study suggests V114 (in sequence with PPSV23) has an acceptable safety profile in adults infected with HIV and CD4+ T-cell count of 200 cells/ $\mu\text{L}$  or greater (only four participants in this study had CD4+ T-cell count less than 200 cells/ $\mu\text{L}$  at baseline). Strengths of this study include the evaluation of V114 in adults infected with HIV—which is an important risk factor for invasive pneumococcal disease—and the monitoring of HIV laboratory parameters. However, a limitation is the small number of participants who received V114 ( $n = 152$ ). Lastly, although this study largely excluded adults with poorly controlled HIV, eligibility criteria are comparable to the study mentioned in the PCV13 Package Insert which included adults with CD4+ T-cell count  $\geq 200$  cells/ $\mu\text{L}$  and serum HIV RNA  $< 50\text{K}$  copies/mL. In addition, based on evidence that vaccination at lower CD4+ T-cell counts may result in reduced immunogenicity, some authors recommend delaying vaccination with PCV until immunological recovery (CD4+*

*T-cell count  $\geq 200$  cells/ $\mu$ L) for optimal immunogenicity.<sup>9</sup> CDC also provides further guidance on which vaccinations people living with HIV should discuss with their doctor based on their CD4+ T-cell count (above or below 200 cells/ $\mu$ L).<sup>10</sup>*

#### **7.4. Study V114-021**

##### Study description

V114-021 was a Phase 3 randomized controlled trial to evaluate safety, tolerability, and immunogenicity of V114 when administered concomitantly with inactivated influenza vaccine (compared to nonconcomitant administration) in 1200 healthy adults  $\geq 50$  years of age without a history of invasive pneumococcal disease or prior administration of any PCV, with or without prior PPSV23 vaccination.

##### Most common AEs

The most common AEs (experienced by more than 5% of participants) following any vaccination (concomitant or nonconcomitant groups) were the solicited injection-site and systemic AEs. For the concomitant group, the most common AEs were injection site pain (68.8%), fatigue (27.2%), myalgia (23.7%), headache (21.5%), injection site swelling (14.3%), injection site erythema (10.8%), and arthralgia (9.3%).

##### Injection-site AEs

Overall injection-site AEs were comparable for participants in the concomitant and nonconcomitant groups (71.7% vs. 73.8%). For specific injection-site AEs, participants in the concomitant group less often reported injection site bruising (1.2% vs. 2.7%) and more often reported injection site pruritis (2.0% vs. 0.8%) than participants in the nonconcomitant group. Most solicited injection-site AEs following vaccination were mild or moderate in intensity with 'severe' injection site pain (0.7% vs. 2.5%) reported less often in the concomitant group compared to the nonconcomitant group.

##### Systemic AEs

Overall systemic AEs were comparable for participants in the concomitant and nonconcomitant groups (56.8% vs. 57.9%). For specific systemic AEs, participants in the concomitant group more often reported AEs in the 'Cardiac disorders' System Organ Class (SOC) than participants in the nonconcomitant group (1.7% vs 0.2%). The Preferred Term with the largest difference between concomitant and nonconcomitant groups was cardiac failure congestive (n=4, 0.7% vs. none). Participants in the concomitant group also more often reported AEs in the 'Gastrointestinal disorders' SOC than participants in the nonconcomitant group (7.2% vs. 4.9%), with participants in the

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<sup>9</sup> Garrido HMG, Schnyder JL, Tanck MWT, Vollaard A, Spijker R, Grobusch MP, Goorhuis A. Immunogenicity of pneumococcal vaccination in HIV infected individuals: A systematic review and meta-analysis. *EClinicalMedicine*. 2020 Nov 23;29-30:100576. doi: 10.1016/j.eclinm.2020.100576. PMID: 33294820; PMCID: PMC7695973.

<sup>10</sup> HIV Infection and Adult Vaccination. <https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/hiv.html> Accessed April 29, 2021.

concomitant group more often reporting abdominal pain (1.0% vs. 0.2%), diarrhea (2.8% vs. 2.2%), and nausea (2.2% vs. 1.0%) than participants in the nonconcomitant group. Most solicited systemic AEs following vaccination were mild or moderate in intensity with 'severe' arthralgia (0.3% vs. 1.7%) and 'severe' fatigue (0.5% vs. 2.3%) reported less often in the concomitant group compared to the nonconcomitant group. Of note, there were no notable differences in severity for abdominal pain, diarrhea, or nausea.

### Serious and fatal AEs

Overall serious AEs (SAEs) were more common in the concomitant group (3.7%) than the nonconcomitant group (2.3%). All of these SAEs (including the four cases of cardiac failure congestive in the V114 group) were unlikely related to study vaccination.

One participant (0.2%) in the concomitant group died during the reporting period for the study compared to none in the nonconcomitant group. One additional participant died in the V114 group after the study reporting period. Both deaths were unlikely related to study vaccination: 1) an 81-year-old man with multiple cardiovascular risk factors (type 2 diabetes mellitus, hypertension, obesity, hyperlipidemia, and peripheral vascular disorder) presented to an emergency department in cardiac arrest (asystole) on Day (b) (6) after concomitant vaccination with V114 and influenza vaccine (Day (b) (6) after placebo). He was diagnosed with myocardial infarction as the cause of death, 2) a 72-year-old man with a history of hypertension was hospitalized for myocardial infarction on Day 182 postvaccination 1 (Day 142 postvaccination 2) and died on Day (b) (6) postvaccination 1. No further information regarding cause of death was provided but the participant's spouse reported the patient was also diagnosed with atrial fibrillation, autoimmune polyglandular syndrome, and "possibly had a stroke due to a blood clot."

*Reviewer comment: The overall safety for V114 concomitantly administered with influenza vaccine is comparable to V114 and influenza vaccine administered sequentially, although minor imbalances (<1-2%) were observed between groups for gastrointestinal symptoms (specifically, abdominal pain, diarrhea, and nausea) and two 'severe' systemic symptoms (arthralgia and fatigue). This reviewer suspects the imbalance in cardiac failure congestive is due to chance alone, since after review of the individual reports, each of the four cases in the V114 group appeared unlikely related to vaccination.*

## **7.5. Integrated Population (Studies V114-016, V114-019, and V114-020)**

### Description of pooled studies

The sponsor created an "integrated population" (n = 4186) by pooling safety data from three phase 3 studies in pneumococcal naïve adults aged 50 years and older (V114-016, V114-019, and V114-020). V114-016 included a dose of PPSV23 1 year after PCV administration; V114-019 and V114-020 evaluated single doses of PCV. For the integrated safety analysis, the sponsor performed both weighted (discussed here)

and unweighted analyses of the integrated population and separately reported safety results for each individual study.

### Most common AEs

The most common AEs (experienced by more than 5% of participants) following PCV (V114 or PCV13) were the solicited injection-site and systemic AEs. Following V114, the most common AEs were as follows: injection site pain (58.5%), myalgia (19.5%), fatigue (20.2%), headache (14.5%), injection site swelling (14.5%), injection site erythema (11.1%), and arthralgia (6.3%).

### Injection-site AEs

Overall injection-site AEs following PCV were more common following V114 than PCV13 (63.7% vs. 51.4%). For specific injection-site AEs following PCV, V114 participants more often reported injection site pain (58.5% vs. 45.9%) than PCV13 participants, a finding that was consistently seen across the three pooled studies. Most solicited injection-site AEs following PCV were mild or moderate in intensity with no notable differences in 'severe' injection-site AEs between V114 and PCV13 groups.

### Systemic AEs

Overall systemic AEs following PCV were more common following V114 than PCV13 (45.1% vs. 39.1%). For specific systemic AEs following PCV, V114 participants more often reported myalgia (19.5% vs. 14.8%) than PCV13 participants, a finding that was consistently seen across the three pooled studies. Most solicited systemic AEs following PCV were mild or moderate in intensity with no notable differences in 'severe' systemic AEs between V114 and PCV13 groups. Of note, 3 participants (0.2%) in the V114 group and 1 participant (0.1%) in the PCV13 group reported a maximum temperature  $\geq 105.8$  °F (41.0 °C). This finding is discussed further in the reviewer comment below.

### Serious and fatal AEs

Overall serious AEs (SAEs) following PCV were comparable for V114 and PCV13 participants (2.1% vs. 2.2%). For specific SAEs following PCV, there were no notable differences between V114 and PCV13 groups. In the V114 group, there was insufficient information (no organism or serotype reported) to assess whether three cases of pneumonia were due to vaccination failure (Participant (b) (6) [REDACTED]). In the PCV13 group, there was insufficient information (no organism or serotype reported) to assess whether one case of pneumonia was due to vaccination failure (Participant (b) (6) [REDACTED]). All other SAEs were unlikely related to study vaccination.

Four participants died in the V114 group (0.1%) and one participant died in the PCV13 group (0.1%). In the V114 group, deaths included: 1) a 74-year-old man with a history of hypothyroidism and atrial fibrillation died on Day (b) (6) [REDACTED] of unknown causes

(family refused to provide additional details), 2) a 69-year-old man with a history of diabetes mellitus type 2, hypertension, osteoarthritis, died on Day (b) (6) due to an unknown cause (attributed to pre-existing conditions), 3) a 66-year-old man with a history of hypertension, asthma, chronic obstructive pulmonary disease, died on Day (b) (6) due to chronic obstructive pulmonary disease, cardiac failure congestive, and acute respiratory failure, and 4) a 69-year-old man with a history of atrial fibrillation died on Day (b) (6) due to pancreatic carcinoma. In the PCV13 group, the one death was: an 82-year-old man with a history of bradycardia, palpitations, cardiac murmur, ventricular extrasystoles, and recent non-ST elevation myocardial infarction died on Day (b) (6) due to “probable arrhythmia” during sleep. All deaths were unlikely related to study vaccination.

*Reviewer comment: The overall safety profile for V114 is comparable to PCV13 in these studies that comprise the integrated population, although V114 participants experienced more overall injection site AEs (and specifically, injection site pain) and overall systemic AEs (and specifically, myalgia). The imbalances favoring PCV13 for injection site pain and myalgia were also seen across the three studies that comprise the integrated population when unpooled. These studies suggest that V114 has an acceptable safety profile in pneumococcal naïve adults aged 50 years and older. Strengths of this analysis include the large number of participants in the integrated population who received V114 (n = 3032) and the ability to assess AEs for both pooled and unpooled study populations.*

*Regarding the four participants who reported a maximum temperature  $\geq 105.8$  °F, the sponsor reported that these were likely erroneous entries, but provided very limited data. After receiving additional clinical information through an Information Request (125741/0.24), this reviewer agreed with the sponsor’s assessment that these temperature recordings are most likely erroneous. None of the participants experienced a serious adverse event and none reported adverse events consistent with an elevated temperature (e.g. feeling feverish). Although one of the participants only reported one post-vaccination temperature, for the remaining three participants all other temperature recordings for postvaccination Days 1-5 were less than 100.4 °F. In addition, the elevated temperatures appear to be reported randomly (Day 1, 2, 3, and 5, respectively for each participant) rather than follow a biological pattern (i.e. clustering closer to vaccination date). Because participants were responsible for measuring and entering their own temperatures, it seems most likely these elevated temperatures were due to measurement or entry error.*

## **7.6. Summary of Adverse Events**

Safety data from the seven clinical studies reviewed here demonstrates an acceptable safety profile for V114. The overall safety profile for V114 was comparable to PCV13 in the six active comparator studies, although V114 participants experienced more solicited adverse events than PCV13 participants.

In all six active comparator studies, participants who received V114 experienced more overall injection site AEs and specifically, injection site pain. However, the proportion of subjects with ‘severe’ solicited AEs (including injection site pain) was typically comparable across these studies. In addition, V114 participants also experienced other solicited AEs more than PCV13 participants in some but not all active comparator studies. For example, Study V114-018 and the integrated population studies (V114-016, V114-019, and V114-020) showed higher rates of overall systemic AEs, and specifically, fatigue, headache, and myalgia, compared to PCV13. Aside from differences in solicited AEs, there were no consistent trends in unsolicited AEs across these studies. Finally, for all seven clinical studies submitted in support of V114 licensure, there were no SAEs or deaths that this reviewer considered related to vaccination with V114.

## 8. REVIEW OF SPONSOR’S PROPOSED PHARMACOVIGILANCE PLAN

A summary of the sponsor’s pharmacovigilance plan (PVP) is provided in Table 3 below.

Table 3. Sponsor’s Proposed Pharmacovigilance Plan\*

Safety concern	Pharmacovigilance activities
<b>Important identified risks</b>	
None	Not applicable
<b>Important potential risks</b>	
None	Not applicable
<b>Missing information</b>	
Safety of more than one dose administered < 1 year apart to immunocompromised adults	Routine Pharmacovigilance  Additional pharmacovigilance: Study V114-022: Safety and Immunogenicity of V114 in Recipients of Allo-HSCT

Abbreviations: allogeneic hematopoietic stem cell transplant (allo-HSCT)

\*Adapted from Table 2, US Risk Management Plan Annex, Version 1.0 (125741/0.4)

The sponsor proposes routine pharmacovigilance (adverse reaction reporting and signal detection) for all AEs. To address the missing information “Safety of more than one dose administered < 1 year apart to immunocompromised adults,” the sponsor has initiated Study V114-022, a phase 3, multicenter, randomized, double-blind, active-comparator controlled clinical study to evaluate the safety, tolerability, and immunogenicity of V114 (compared to PCV13) in recipients of allogeneic hematopoietic stem cell transplant (allo-HSCT). PCV (V114 or PCV13) is administered to participants as a 3-dose regimen and eligible participants also receive a single dose of PPSV23 12 months after allo-HSCT. Participants who develop chronic graft versus host disease during the first year after allo-HSCT are considered ineligible to receive PPSV23 and instead receive a fourth dose of PCV (V114 or PCV13) 12 months after allo-HSCT.

Participants aged 3 years and older who have received allo-HSCT are eligible and the sponsor plans to enroll approximately 250 adult and 50 pediatric participants with an overall randomization ratio of 1:1 (V114:PCV13). The sponsor plans to submit the final clinical study report in the fourth quarter of 2022. Aside from this ongoing phase 3 clinical study, there are no additional planned or ongoing studies of V114 to address safety concerns identified in this pharmacovigilance plan.

### **8.1. Important Identified Risks**

The sponsor did not list any important identified risks for V114.

*Reviewer comment: This reviewer agrees with the sponsor's assessment regarding important identified risks.*

### **8.2. Important Potential Risks**

The sponsor did not list any important potential risks for V114.

*Reviewer comment: This reviewer considered whether the sponsor should add "Anaphylactic reactions (including anaphylaxis)" as an important potential risk. Although there were no SAEs for anaphylaxis attributed to V114 in the submitted clinical studies, anaphylaxis is a well-recognized risk associated with vaccines and clinical trials may not be adequately powered to detect such rare events. However, based on the reported incidence of anaphylaxis after other pneumococcal conjugate vaccines (PCV7 and PCV13),<sup>11</sup> this reviewer does not expect the incidence of anaphylaxis to be higher for V114 compared to other vaccines. In addition, the risk of anaphylaxis is addressed in the proposed Package Insert for V114 (Contraindications section). Therefore, this reviewer agrees with the sponsor not listing any important potential risks in the PVP.*

### **8.3. Missing Information**

The sponsor listed "Safety of more than one dose administered < 1 year apart to immunocompromised adults" as the only missing information category. The sponsor anticipates that off-label use of V114 in this population may occur. In addition, the sponsor cites clinical studies for Prevnar 13 in HIV infected adults<sup>12</sup> and adult HSCT<sup>13</sup>

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<sup>11</sup> McNeil MM, Weintraub ES, Duffy J, Sukumaran L, Jacobsen SJ, Klein NP, Hambidge SJ, Lee GM, Jackson LA, Irving SA, King JP, Kharbanda EO, Bednarczyk RA, DeStefano F. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol.* 2016 Mar;137(3):868-78. doi: 10.1016/j.jaci.2015.07.048. Epub 2015 Oct 6. PMID: 26452420; PMCID: PMC4783279.

<sup>12</sup> Borat AE, Madhi SA, Laudat F, Sundaraiyer V, Gurtman A, Jansen KU, Scott DA, Emini EA, Gruber WC, Schmoele-Thoma B. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine in HIV-infected individuals naive to pneumococcal vaccination. *AIDS.* 2015 Jul 17;29(11):1345-54. doi: 10.1097/QAD.0000000000000689. PMID: 25888646; PMCID: PMC4521829.

<sup>13</sup> Cordonnier C, Ljungman P, Juergens C, Maertens J, Selleslag D, Sundaraiyer V, Giardina PC, Clarke K, Gruber WC, Scott DA, Schmoele-Thoma B; 3003 Study Group. Immunogenicity, safety, and tolerability of 13-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine in recipients of allogeneic hematopoietic stem cell transplant aged ≥2 years: an open-label study. *Clin Infect Dis.* 2015 Aug 1;61(3):313-23. doi: 10.1093/cid/civ287. Epub 2015 Apr 13. PMID: 25870329; PMCID: PMC4503811.

recipients which suggest that the safety profile may differ when more than one dose is administered less than one year apart.

*Reviewer comment: This reviewer agrees with the sponsor's inclusion of "Safety of more than one dose administered < 1 year apart to immunocompromised adults" in the PVP as missing information for the following reasons: 1) each of the clinical studies excluded immunocompromised individuals, 2) none of the clinical studies evaluated repeated doses of V114, 3) off-label use is expected to occur in this population, and 4) limited evidence suggests the possibility of increased reactogenicity of PCV13 in allo-HSCT recipients who receive more than one dose less than one year apart.<sup>13</sup>*

*This reviewer considered whether other excluded or underrepresented populations—specifically, other immunocompromised individuals, pregnant/lactating women, or children—should be considered as missing information.*

*Although adults infected with HIV were studied in V114-018 and recipients of allo-HSCT are being studied in V114-022, all other types of immunocompromised individuals were excluded from these studies, including other acquired or congenital immunodeficiency, functional or anatomic asplenia, autoimmune disease, and those receiving immunosuppressive therapy. Although these populations are at risk for invasive pneumococcal disease and expected to receive V114, there is no reason to believe the safety profile of V114 would be different in these populations. A 2016 review of 2976 postmarketing reports to VAERS for PCV13 did not detect any unexpected AEs for immunocompromised individuals.<sup>14</sup> Similar to the Prevnar 13 Package Insert,<sup>15</sup> the sponsor's proposed Package Insert for V114 includes a warning about the potential for reduced immune response to V114 in immunocompromised individuals. Therefore, it is appropriate for the sponsor to not include other immunocompromised populations in missing information.*

*Pregnant women were excluded from all clinical studies and participants of childbearing potential were instructed to use effective birth control methods throughout the study period. Across the clinical studies, there were ten reported pregnancies among ten participants in the V114 group. Four of the ten participants were vaccinated with V114 within six weeks prior to conception. Pregnancy outcomes included eight live births, one spontaneous abortion, and one elective abortion. There were no congenital or other abnormalities reported among the known infant outcomes. On February 5, 2021, this reviewer submitted an information request to the sponsor requesting further explanation as to why they did not include pregnant/lactating women in missing information since pregnant women were excluded from clinical studies and some women who may be eligible for vaccination due to risk factors for invasive pneumococcal disease may also*

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<sup>14</sup> Haber P, Arana J, Pilishvili T, Lewis P, Moro PL, Cano M. Post-licensure surveillance of 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged  $\geq 19$  years old in the United States, Vaccine Adverse Event Reporting System (VAERS), June 1, 2012-December 31, 2015. *Vaccine*. 2016 Dec 7;34(50):6330-6334. doi: 10.1016/j.vaccine.2016.10.052. Epub 2016 Nov 9. PMID: 27836437.

<sup>15</sup> Prevnar 13 – Package Insert. <https://www.fda.gov/media/107657/download> Accessed May 4, 2021.

*be pregnant/lactating. The sponsor responded on February 11, 2021 (125741/0.9), stating that based on V114 preclinical animal studies and the experience with currently licensed pneumococcal vaccines, they do not expect the safety profile for V114 administered to pregnant/lactating women to differ from the known safety profile for V114 in nonpregnant/nonlactating adults, and they plan to monitor reports of V114 exposure in pregnant/lactating women via routine pharmacovigilance (with “targeted follow-up questionnaires specific to pregnancy/lactation per standard process”). This reviewer also notes that V114 is not specifically indicated for pregnant women and the Pregnancy section of the proposed Package Insert states that “Available data on VAXNEUVANCE administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.” For comparison to the other currently licensed pneumococcal vaccines, this reviewer also evaluated how this issue is addressed in the Package Insert and the Risk Management Plan for both Prevnar 13 and Pneumovax 23. The Package Inserts for both Prevnar 13 and Pneumovax 23 comment on the lack of adequate data regarding vaccine-associated risks in pregnancy. For the Risk Management Plans, the Prevnar 13 Risk Management Plan (version 6.1, 2015) includes “Vaccine exposure during pregnancy and lactation” as missing information but addresses this with routine pharmacovigilance only. The Pneumovax 23 Risk Management Plan (version 2, 2018) previously had “exposure during pregnancy” and “exposure during lactation” listed as missing information but they were “...removed in accordance with the revised guidance since patients who are pregnant or who are lactating are not in the indicated population.” Therefore, for the reasons stated, this reviewer agrees with the sponsor’s rationale for not including pregnant/lactating women in the missing information section of the PVP. In addition, the lack of a clear precedent for including pregnant/lactating women in the PVP for other pneumococcal vaccines further supports this decision.*

*Lastly, although each of the clinical studies enrolled adults only, this reviewer noted that the clinical development program includes ongoing studies in infants/children. Therefore, this reviewer also sought further clarification as to why infants/children were not included in missing information. The sponsor responded that they will update the PVP as needed based on final phase 3 clinical study results, but that use in infants and children is not anticipated at the time of the approval for this initial submission. This reviewer agrees with the sponsor’s rationale for not including infants/children as missing information in the PVP.*

## **9. DE ASSESSMENT**

The sponsor’s PVP adequately reflects the safety concerns based on the clinical trial experience. There are no important identified or potential risks in the sponsor’s proposed PVP. This risk assessment is consistent with the safety profile observed in the clinical trials, which showed that although V114 was more reactogenic than Prevnar 13 for certain solicited adverse events, there were no concerning differences in rates of SAEs and there were no SAEs or deaths that this reviewer attributed to vaccination with

V114. The safety concern listed under missing information (Safety of more than one dose administered < 1 year apart to immunocompromised adults) should be adequately addressed through completion of the ongoing study (V114-022). Other populations discussed (other immunocompromised, pregnancy/lactating, infants/children) do not warrant inclusion in the PVP at this time and the sponsor will update the PVP regarding infants/children as needed based on phase 3 clinical study results.

The reviewed 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 that is specifically designed to evaluate safety as a primary endpoint.

## **10. DE RECOMMENDATIONS**

No additional actions recommended prior to approval. The sponsor's proposed pharmacovigilance plan is adequate. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

## Appendix

Table A1. Materials reviewed in support of this assessment

Date received	Source	Document Type	Document(s) reviewed
21-Oct-2020	Sponsor, 125741/0.0	2.2 Introduction	Introduction
17-Nov-2020	Sponsor, 125741/0.1	1.14.1.3 Draft Labeling Text	US Package Insert
17-Nov-2020	Sponsor, 125741/0.1	5.3.5.3 Reports of Analyses of Data from More than One Study	Integrated Summary of Safety
17-Nov-2020	Sponsor, 125741/0.1	2.7.4 Summary of Clinical Safety	Summary of Clinical Safety
25-Nov-2020	Sponsor, 125741/0.3	1.16.1 Risk Management (Non-REMS)	Core Risk Management Plan (RMP), version 1.0, data lock point 16-Sept-2020, date finalized 2-Nov-2020
25-Jan-2021	Sponsor, 125741/0.4	1.16.1 Risk Management (Non-REMS)	US Risk Management Plan Annex, Version 1.0, date 02-Nov-2020
11-Feb-2021	Sponsor, 125741/0.9	1.11.3 Clinical Information Amendment	Response to FDA IR #5 Received 05FEB21
24-Mar-2021	Sponsor, 125741/0.22	1.11.3 Clinical Information Amendment	Response to FDA IR #12 Received 17MAR21†
2-Apr-2021	Sponsor, 125741/0.24	1.11.3 Clinical Information Amendment	Response to FDA IR #14 Received 26MAR21

\*Materials reviewed also includes pertinent safety data in the seven clinical studies submitted in support of V114 licensure (eCTD folder: 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

†Response to information request from clinical reviewers regarding solicited adverse events reported in Package Insert

Table A2. DE information requests

IR #	IR sent	Description of IR	Sponsor response received	Am #
1	23-Nov-2020	Request for PVP	25-Nov-2020	3
2	11-Jan-2021	Request to align indication in PVP with indication in the proposed Package Insert	25-Jan-2021	4

5	5-Feb-2021	Request for further explanation on PVP missing information (pregnant/lactating women, infants/children)	11-Feb-2021	9
14	26-Mar-2021	Request for additional information on participants reporting maximum temperature $\geq 105.8$ °F	2-Apr-2021	24

Abbreviations: Division of Epidemiology (DE), Information Request (IR), Amendment (Am), Pharmacovigilance Plan (PVP)

Table A3. Overview of Clinical Trials\*

Study Number	Design	Purpose	Population	Randomization / Exposure
V114-007	Phase 2 multicenter randomized double-blind active-comparator controlled	Safety, tolerability, and immunogenicity of V114 compared to PCV13	Healthy adults $\geq 65$ years of age previously vaccinated with PPSV23 $\geq 1$ year prior	Randomization ratio V114:PCV13 = 1:1 Number randomized/PCV vaccinated V114 (n = 127/127) PCV13 (n = 126/126)
V114-016	Phase 3 multicenter randomized double-blind active-comparator controlled	Safety, tolerability, and immunogenicity of V114 (or PCV13) followed by PPSV23 1 year later	Healthy adults $\geq 50$ years of age who were pneumococcal vaccine-naïve	Randomization ratio V114:PCV13 = 1:1 Number randomized/PCV vaccinated V114 (n = 327/326) PCV13 (n = 325/325)
V114-017	Phase 3 multicenter randomized double-blind active-comparator controlled	safety, tolerability, and immunogenicity of V114 (or PCV13) followed by PPSV23 6 months later	Adults 18-49 years of age who were pneumococcal vaccine-naïve, immunocompetent, with and without risk factors for pneumococcal disease†	Randomization ratio V114:PCV13 = 3:1 Number randomized/PCV vaccinated V114 (n = 1135/1133) PCV13 (n = 380/379)
V114-018	Phase 3 multicenter randomized double-blind active-comparator controlled	safety, tolerability, and immunogenicity of V114 followed by PPSV23 8 weeks later in adults with HIV	Immunocompromised adults $\geq 18$ years of age who were infected with HIV and pneumococcal vaccine-naïve‡	Randomization ratio V114:PCV13 = 1:1 Number randomized/PCV vaccinated V114 (n = 152/152) PCV13 (n = 150/150)

V114-019	Phase 3 multicenter randomized double-blind active-comparator controlled	safety, tolerability, and immunogenicity of V114 compared to PCV13	Adults ≥ 50 years of age who were pneumococcal vaccine-naïve	Randomization ratio V114:PCV13 = 1:1 Number randomized/PCV vaccinated V114 (n = 604/602) PCV13 (n = 601/600)
V114-020	Phase 3 multicenter randomized double-blind active-comparator controlled lot consistency study	safety, tolerability, and immunogenicity of V114 compared to PCV13	Adults ≥ 50 years of age who were pneumococcal vaccine-naïve	Randomization ratio V114 Lot 1:V114 Lot 2: V114 Lot 3:PCV13 = 3:3:3:1 Number randomized/ PCV vaccinated V114 Lot 1 (n = 702/698) V114 Lot 2 (n = 704/704) V114 Lot 3 (n = 701/700) PCV13 (n = 233/231)
V114-021	Phase 3 multicenter randomized double-blind placebo-controlled	safety, tolerability, and immunogenicity of V114 when administered concomitantly with inactivated influenza vaccine	Healthy adults ≥ 50 years of age with or without prior PPSV23 vaccination	Randomization ratio concomitant:nonconcomitant = 1:1 Number randomized/ PCV vaccinated concomitant (n = 600/599) nonconcomitant (n = 600/587)

Abbreviations: pneumococcal conjugate vaccine (PCV), 13-valent pneumococcal conjugate vaccine (PCV13), 23-valent pneumococcal polysaccharide vaccine (PPSV23), human immunodeficiency virus (HIV)

\*Adapted from: Table 2.7.4 Summary of Clinical Safety Studies with V114 (2.7.4 Summary of Clinical Safety) and Table of all Clinical Trials (5.2 Tabular Listing of All Clinical Trials).

†Risk factors for pneumococcal disease (V114-017) included “underlying comorbidities (i.e. diabetes mellitus, chronic liver disease, chronic lung disease including asthma, chronic heart disease) and behavioral factors (current smoker, increased alcohol use).”

‡Eligibility criteria included CD4+ T-cell count ≥ 50 cells/μL and plasma HIV ribonucleic acid (RNA) <50,000 copies/mL at screening.