



**Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)**

POSTMARKETING REAL WORLD EVIDENCE REVIEW MEMORANDUM

Date: June 3, 2024

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Subject: Real-World Evidence Review of “A Test-Negative Case-Control Study to Evaluate the Effectiveness of V116 Against Pneumococcal Pneumonia in Older Adults” Study Protocol

Sponsor: Merck Sharp & Dohme LLC

Product: CAPVAXIVE (V116)

Application Type/Number: STN 125814/0

Proposed Use: Active immunization for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older.
Active immunization for the prevention of pneumonia by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older.

Submission Date: October 18, 2023

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1 OBJECTIVE

The purpose of this review is to assess the adequacy of the proposed postmarketing, real-world evidence (RWE) study titled “A Test-Negative Case-Control Study to Evaluate the Effectiveness of V116 Against Pneumococcal Pneumonia in Older Adults” designed to evaluate vaccine effectiveness (VE) of V116 against pneumococcal pneumonia caused by serotypes contained in V116.

2 MATERIALS REVIEWED

Table 1. Amendments and Documents Reviewed

Date and Amendment	Relevant Documents/Documents Reviewed
STN 125814/0 October 18, 2023	<ul style="list-style-type: none">Study protocol titled “Test-Negative Case-Control Study to Evaluate the Effectiveness of V116 Against Pneumococcal Pneumonia in Older Adults (version 1.0)”.Request for accelerated approval.
STN 125814/0.8 January 2, 2024	<ul style="list-style-type: none">Response to IR#6 sent on December 22, 2023, regarding timeline and specifics of real-world study.
STN 125814/0.11 February 9, 2024	<ul style="list-style-type: none">Response to IR#9 comment #1 sent on February 7, 2024, regarding study milestones.
STN 125814/0.12 February 14, 2024	<ul style="list-style-type: none">Response to IR#9 comments #2-3 sent on February 7, 2024, regarding inclusion of enrollment targets and inclusion of protocol identifier.Revised study protocol titled “A Test-Negative Case-Control Study to Evaluate the Effectiveness of V116 Against Pneumococcal Pneumonia in Older Adults (V116-011-00-v2)”.
STN 125814/0.13 February 15, 2024	<ul style="list-style-type: none">Response to IR#8 sent on February 1, 2024, regarding cross-reactive serotypes and assays.
STN 125814/0.14 March 8, 2024	<ul style="list-style-type: none">Updated response to IR#8 sent on February 1, 2024, regarding cross-reactive serotypes and assays.
STN 125814/0.17 March 28, 2024	<ul style="list-style-type: none">Response to IR#12 sent on March 15, 2024, regarding study milestones and data analysis.
STN 125814/0.29 May 8, 2024	<ul style="list-style-type: none">Response to IR#24 sent on May 3, 2024, regarding developmental data submitted to support the specificity of V116 SSUAD assay for serotype 15C
STN 125814/0.33 May 30, 2024	<ul style="list-style-type: none">Response to IR#29 sent on May 29, 2024, regarding study milestones dates for SSUAD and PAD assays validation protocol and report.

3 SUMMARY OF STUDY DOCUMENTS AND RWE REVIEW COMMENTS

A. Background

The sponsor, Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc, is developing a pneumococcal 21-valent conjugate vaccine (V116) intended to support the indication for (a) active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older, and (b) active immunization for the prevention of pneumonia by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older.

The sponsor is seeking accelerated approval to support the indication for the prevention of pneumonia caused by vaccine-type serotypes. The sponsor plans to conduct a post-licensure confirmatory study using a test-negative case-control design to verify the effectiveness of V116 against pneumococcal pneumonia caused by vaccine-type serotypes.

B. Real-World Evidence (RWE) Study Rationale

The sponsor proposes to conduct a post-licensure real-world study using a test negative design (TND) due to significant challenges associated with conducting a randomized clinical trial to demonstrate the efficacy of V116 against pneumococcal pneumonia. The sponsor stated that the feasibility of conducting a randomized, active-controlled efficacy trial of V116 compared to a currently licensed pneumococcal vaccine is limited due to the sample size requirements. Similarly, a placebo-controlled trial is also constrained by sample size requirements and offering a placebo further presents an ethical challenge in United States (US) and countries where pneumococcal vaccination is routinely recommended for adults ≥ 65 years of age and adults ≥ 19 years of age with chronic medical conditions that confer an increased risk of pneumococcal disease. Additionally, routine pneumococcal recommendation for adults in the US results in relatively high vaccine uptake, and the vaccine naïve population willing to enroll in a randomized study may be small and not representative of the larger vaccinated population.

C. Real-World Data (RWD) Source

This real-world study uses both primary and secondary data collection and will enroll patients hospitalized for community acquired pneumonia (CAP). The study will be conducted across different countries, including the US.

Specific details on the data sources used for ascertaining exposure, outcomes and covariates are included in Section 3.F.

D. Study Milestones

Study milestones and enrollment targets are presented in Table 2.

Table 2 Study Milestones and Enrollment Targets

Milestones	Planned Date
Final protocol submission	May 30, 2025
Final study implementation readiness verification submission	June 16, 2025
Study initiation	June 30, 2025
Enrollment targets projected:	
25% (3,750)	First half 2027 Progress Report
50% (7,500)	Second half 2027 Progress Report
75% (11,250)	First half 2028 Progress Report
100% (15,000)	Second half 2028 Progress Report
Study completion	June 29, 2029
Final study report submission	December 31, 2029

Source: STN 125814/0.12, Study Protocol V116-011-00-v2, p 4.

- *Reviewers' comments: The timely availability of results is a critical consideration for postmarketing RWE studies conducted to provide confirmatory evidence in support of accelerated approval. Further, study progress reports are required to be submitted no less frequently than every 180 days and should include progress towards enrollment targets. The sponsor provided the study milestones in a response to IR#9 (submitted to: STN125814/0.11) and indicated that the study will be completed by June 2029, which is reasonable since that would be within 5 years from the anticipated approval date. The final report will be submitted 6 months thereafter. Further, as requested in IR#9, the revised protocol (submitted to: 125814/0.12) included enrollment targets that would allow monitoring of the progress of their study actual enrollment against the protocol-specified target enrollment. This would allow the sponsor to include additional sites in a timely manner to fulfill the enrollment targets. To ensure timely*

implementation of the study, the sponsor also indicated in their response to IR#9 (submitted to: STN125814/0.11) and IR#12 (submitted to 125814/0.17), that they will submit the study implementation readiness verification for the U.S. sites in June 2025, according to the milestone listed in Table 2, as enrollment in the U.S. is anticipated to start first based on expected dates of licensure and uptake of V116. Thereafter, the sponsor will plan for the submission of the implementation readiness verification for the non-US sites after site selection is finalized. The sponsor also stated in their response to IR#12 that enrollment from all study sites will be closely monitored to allow for completion of the study by June 29, 2029.

E. Key Study/Research Question(s)

i. Primary Objectives

- To assess the effectiveness of V116 in preventing hospitalized, confirmed CAP (invasive and non-invasive) caused by *S. pneumoniae* serotypes contained in V116 among patients who received no other pneumococcal vaccines than V116 in the previous 5 years.

ii. Secondary Objectives

- To assess the effectiveness of V116 in preventing hospitalized, confirmed non bacteremic pneumococcal pneumonia (NBPP; confirmed CAP with absence of *S. pneumoniae* in blood culture or culture from other sterile sites) caused by *S. pneumoniae* serotypes contained in V116 among patients who received no other pneumococcal vaccines than V116 in the previous 5 years.

iii. Exploratory Objectives

- To assess the effectiveness of V116 in preventing hospitalized, confirmed CAP (invasive and non-invasive) caused by *S. pneumoniae* serotypes contained in V116, irrespective of prior pneumococcal vaccines received.

The sponsor also anticipates conducting additional exploratory and sensitivity analyses, including by vaccine type, number of and time since prior pneumococcal vaccines, and inclusion of cross-reactive serotypes, depending on available patient numbers.

F. Methods

i. Study Design and Setting:

This study uses a test-negative case-control design and will be conducted in hospitals across different countries, including the US. A feasibility study conducted in 2023 identified three other countries (i.e., Denmark, Spain and Netherlands) besides US that the sponsor deemed as strong candidates primarily due to access to vaccination data and high recruitment potential and capabilities for laboratory sample management. Other potential candidate countries under consideration included Canada, Germany and United Kingdom. The sponsor also plans to conduct a pilot study and the final selection of study sites and countries will be determined after the pilot. The pilot phase is also intended to help evaluate planned study operations and procedures, refine study methods, including choice and definition of covariates, sample size and analysis plan, and to determine the best source(s) from which to collect required study data elements.

- *Reviewers' comments: The sponsor has shortlisted a list of potential countries where the test-negative real-world study can be conducted, but the final list will be determined after the pilot study is completed. Results from the pilot study are important for determining the data sources from which study elements will be collected. In the response to our IR (submitted to 125814/0.8),*

the sponsor indicated that qualified sites from the countries of interest will meet requirements such as access to a sufficiently large eligible population of CAP patients, ability to access complete vaccination history records for enrolled patients, capabilities to conduct required sample collection and data collection, adequate uptake of V116 (e.g., vaccination coverage >20%), and ability to provide individual patient record level data to comply with submission requirements. Further, the sponsor indicated that the pilot phase of the study is planned to conclude in Q2 2025, an interim report is expected to be available by Q4 2024 and a final report available in Q2 2025. Review of the pilot study results, especially the final list of countries and sites, and the data sources used to determine vaccination status, will be conducted when the pilot study results reports are available.

ii. Study Population/Eligibility Criteria:

Patients ≥ 65 years of age presenting to participating hospitals or urgent care centers with suspected CAP will be considered for enrollment into the study. Patients with confirmed CAP by clinical signs and symptoms and radiography will be the source population for cases and controls identification.

Inclusion Criteria:

1. Male or female, ≥ 65 years of age, at the time of signing informed consent.
2. Subject (or legally acceptable representative) has provided documented informed consent for the study.
3. Assessed in hospital or referred to hospital from urgent care setting with clinical suspicion of CAP (Note: Patients referred from assisted living care/centers will be eligible)
4. Has ≥ 2 of the following 10 clinical signs or symptoms: fever (oral temperature $>38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ or tympanic temperature $>38.5^{\circ}\text{C}/101.2^{\circ}\text{F}$), hypothermia ($<35.5^{\circ}\text{C}/95.9^{\circ}\text{F}$ measured by a healthcare provider), chills or rigors, pleuritic chest pain, new or worsening cough, sputum production, dyspnea (shortness of breath), tachypnea (respiratory rate $>20/\text{min}$), malaise, or abnormal auscultatory findings suggestive of pneumonia (rales or evidence of pulmonary consolidation including dullness on percussion, bronchial breath sounds, or egophony).
5. Radiographic findings consistent with pneumonia (e.g., pleural effusion, increased pulmonary density, alveolar infiltrates [multi-lobar, lobar, or segmental] containing air bronchograms).

Exclusion Criteria:

Patients with any of the following criteria will be excluded from the study:

1. Transfer from other hospitals, skilled nursing care, or acute rehabilitation.
2. Aspiration pneumonia, hospital-acquired bacterial pneumonia (if a patient develops signs or symptoms 48 hours after being hospitalized), or ventilator-associated bacterial pneumonia.
3. Patients hospitalized for pneumonia or respiratory infection within the last 30 days.
4. Patients with known bronchial obstruction or a history of post-obstructive pneumonia (Note: this criterion does not exclude patients who have chronic obstructive pulmonary disease [COPD]).
5. Patients with primary or metastatic lung cancer.
6. Patients with cystic fibrosis, known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis.
7. Patients who do not/ are not able to provide a urine sample (e.g., anuric) and a blood sample.
8. V116 administration within 30 days prior to diagnosis date of CAP.
9. Patients who have incomplete or unavailable vaccination data according to criteria that will be established for each study site and region.

Further, patients who received pneumococcal vaccines other than V116 within 5 years prior to the date of CAP hospitalization will be excluded from the analyses of the primary and secondary objectives.

iii. Exposure of Interest/Ascertainment:

The exposure of interest is V116 vaccination. Patients are considered vaccinated if they have received V116 at least one month prior to the index date. The index date for both cases and controls will be defined as the date of hospitalization of confirmed CAP (see next section for details on outcome ascertainment). Exposure to other pneumococcal vaccination in the 5 years prior to index date will also be captured to determine inclusion or exclusion in the analyses of the primary and secondary objectives.

To ascertain V116 and other pneumococcal vaccination status, multiple sources may be queried, as available, which may include patients' vaccination cards, patients' primary care provider's other treating physician's records, electronic health records (EHR), state or local vaccine registries, and claims for reimbursement and billing databases. Vaccination records will be considered as evidence of vaccination if there is at least a partial date (month and year).

Completeness of vaccination records will also be determined based on consideration of factors as applicable to each study site and region, such as duration of membership within the healthcare network, duration of health insurance coverage, duration of residence in state or region covered by a vaccination registry, and/or active patient status with a physician(s) practice. The sponsor plans to exclude CAP patients with unknown or incomplete vaccination information from the primary analysis.

- Reviewers' comments: *While multiple different sources such as vaccination cards, EHR, vaccine registries, claims and billing databases may be used to ascertain vaccination history, there still exists a potential for misclassification of vaccine exposure, especially with misclassifying vaccinated individuals as unvaccinated, thereby biasing the VE toward the null. The sponsor indicated that to minimize the effect of misclassified pneumococcal vaccination status, they plan to assess completeness of vaccination records, and participants with unknown and incomplete vaccination records will be excluded from the primary analysis. Further, the completeness of vaccination histories and suitability of different sources of vaccination data will also be assessed in their pilot study. Further review of the pilot study results, particularly with respect to the final list of data sources used for ascertaining vaccine exposure in each country, is needed once the pilot study results reports are available in Q4 2024 and Q2 2025.*

iv. Outcome of Interest/Ascertainment:

The primary outcome of interest is hospitalized, confirmed CAP caused by vaccine-type serotypes i.e., vaccine-type CAP (VT-CAP). Both cases and controls will have hospitalized, confirmed CAP, where a diagnosis of CAP will be made at study entry based on examination of radiologic imaging including chest X-ray, CT scan or MRI, and clinical judgement of attending physician. Additionally, CAP diagnosis will be adjudicated by an adjudication committee including one or more radiologists to confirm the diagnosis of pneumonia.

Determination of cases versus controls for the primary and secondary objectives are as follow:

Table 3 Determination of Cases and Controls

	Cases	Controls
Primary Objective	<ul style="list-style-type: none"> Confirmed CAP (invasive and noninvasive) who test positive for at least one <i>S</i>. 	<ul style="list-style-type: none"> Confirmed CAP (invasive and noninvasive) for whom V116 serotypes are not identified by any method

	<p><i>pneumoniae</i> serotype included in V116 (VT-CAP).</p> <ul style="list-style-type: none"> • VT-CAP will be identified by positive SSUAD or by serotyping or other routine culture (e.g., blood or sputum culture) for vaccine-type <i>S. pneumoniae</i>. 	
Secondary Objective	<ul style="list-style-type: none"> • Confirmed non-bacteremic CAP caused by serotypes included in V116 (vaccine-type non-bacteremic pneumococcal pneumonia; VT-NBPP). • VT-NBPP will be identified by a positive SSUAD or by serotyping of other routine culture (e.g., sputum culture) for vaccine-type <i>S. pneumoniae</i>, and further requires an absence of <i>S. pneumoniae</i> in blood culture or other routine culture from a sterile site. 	<ul style="list-style-type: none"> • Confirmed non-bacteremic CAP for whom V116 serotypes are not identified by any method

Abbreviations: VT-CAP=vaccine-type community acquired pneumonia; VT-NBPP=vaccine-type non bacteremic pneumococcal pneumonia; SSUAD= serotype specific urinary antigen detection.

Source: Developed by reviewer based on STN 125814/0.12, Study Protocol V116-011-00-v2, p 22

Both cases and controls will have confirmed CAP. The index date for both cases and controls will be defined as the date of hospitalization for confirmed CAP. Detection of serotypes is based on laboratory assessments, as described below.

- *Reviewers' comments: Ideally, the controls should be as similar to the cases as possible with regards to the underlying risk profile for pneumococcal CAP. The controls in this study comprised individuals with radiologically confirmed CAP for whom V116 serotypes are not identified i.e., a mix of both non-V116 serotypes of pneumococcal etiology and non-pneumococcal etiology. In earlier communications (CRMTS#14116, WRO sent on August 30, 2022), we stated that the controls should be limited to radiologically confirmed CAP caused by non-V116 serotypes of pneumococcal etiology but if that is not feasible, then the sponsor should conduct a sensitivity analysis where non-pneumococcal CAP are excluded from the controls. In responses submitted to IND 19316.106 and IND 19316.137, the sponsor indicated that restricting controls to only non-V116 pneumococcal CAP would be challenging given the low number expected. However, the sponsor agreed to conduct a sensitivity analysis where controls are restricted to non-V116 serotype pneumococcal CAP (i.e., CAP of non-pneumococcal origins will be excluded), and added it to the revised protocol (submitted to: 125814/0.12) indicating that the analysis will be performed if numbers allow, if not, a descriptive summary will be provided.*

Laboratory Procedures/Assessments

- **Urine Sample:** A urine sample will be collected from each enrolled participant at the time of enrollment, within 48 hours of hospital presentation. The urine sample will be analyzed with the serotype specific urinary antigen detection (SSUAD), and with (b) (4) pneumococcal urinary antigen. Both assessments will support detection of pneumococcal serotypes contained in V116.
 - The sponsor's V116 SSUAD is currently being developed to detect and understand serotype distribution and disease burden caused by V116 vaccine types. The SSUAD is a multiplex technique to detect pneumococcal serotype specific capsular antigen polysaccharide in urine. The V116 SSUAD will support detection of the following pneumococcal serotypes contained in the vaccine: 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A,

15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B. The V114 SSUAD covering serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F, will also be run such that a total of 30 serotypes can be detected across the V114 and V116 panels. The V116 SSUAD will be qualified and validated prior to any testing. The sponsor also indicated that the SSUAD targeting serotype 6A uses antibodies raised against 6A polysaccharide and detects both 6A and 6C polysaccharides, and the SSUAD targeting serotype 15C uses antibodies raised against de-O-acetylated 15B polysaccharides is expected to detect both 15B and 15C. However, in a response to our (submitted to 125814/0.13), the sponsor indicated that the SSUAD and PAD assays have the specificity to detect serotype 15C.

- **Blood Sample:** Blood samples will be collected from all enrolled subjects to assess bacteremia, and if *S. pneumoniae* is identified, to determine serotype. Research personnel will obtain one set of blood cultures (one aerobic and one anaerobic bottle). Blood cultures drawn as standard of care may be used. Blood cultures will be collected on enrolled subjects within 48 hours of hospital presentation. Positive *S. pneumoniae* results will be documented. Research personnel will obtain isolates from cultures positive for *S. pneumoniae* and ship them to a central laboratory selected by the sponsor for serotyping via PAD. The initial version of the protocol submitted to the BLA (125814/0) included (b) (4) assay, but this was removed in the revised protocol submitted to 125814/0.12 (V116-011-00-v2).
- **Other samples:** The following laboratory tests will be available for some but not all enrolled subjects according to standard of care: sputum culture, pleural fluid culture, bronchoalveolar lavage culture, endotracheal aspirate culture, CSF culture, If isolates from cultures positive for *S. pneumoniae* are identified from other sites, the isolate will be shipped to a central laboratory selected by the Sponsor for serotyping via PAD.

➤ *Reviewers' comments: IR#6 and IR#8 were sent regarding the laboratory assessments. Specifically, the reviewers wanted to know when the SSUAD validation results will be available for review and raised concerns regarding the cross-reactivity between 6A and 6C, and 15B and 15C, which will likely lead to misidentification of 6C and 15B as vaccine serotypes 6A and 15C in the SSUAD and PAD assays. The sponsor provided responses to these IRs in 125814/0.8, 125814/0.13 and 125814/0.14. IR#24 was sent to follow-up on the developmental data submitted to support the specificity of V116 SSUAD assay for serotype 15C (submitted to: 125814/0.14), and to request for the protocol used to obtain the developmental data. Responses were provided in 125718/0.29. IR#29 was sent on May 29, 2024, indicating that we intend to include a milestone date of July 31, 2024, for the submission of the validation protocol and a milestone date of December 31, 2024, for the submission of the final validation report for the SSUAD and PAD assays. IR#29 also indicated that the sponsor should not start the evaluation of clinical samples in the SSUAD and PAD assays before the Agency reviews and finds the assays adequate for their intended use. The Sponsor responded in 125814/0.33 that given the complexity of the 21-valent assays, the previously proposed timeline for assay validation (i.e., submitting validation packages by 2Q2025) is necessary to ensure a thorough validation and thus, they commit to submitting the validation package by May 30, 2025, before the final study implementation readiness verification submission date of June 16, 2025. The validation protocols will be submitted by November 1, 2024. Both assays will follow the precedent of the 15-valent V114 assay validation packages and prior Agency feedback will be incorporated into the validation protocols. The sponsor also agreed to not to evaluate study samples in SSUAD and PAD assays until the Agency review deems the assays adequate for their intended use. We defer to the serology reviewers on these serology-related issues and if the responses to IRs are adequate. The serology reviewers plan to*

communicate further with the sponsor post-licensure regarding details of the submitted developmental data and the methodology used.

v. Covariates/Variables:

Potential confounders will be included in the study analysis. These may include age, lifestyle (e.g., living in nursing home, smoking), immunocompromising conditions or treatments, some chronic conditions (e.g., diabetes mellitus), certain comorbid conditions (e.g., asplenia, COPD, and asthma), study site, calendar time, gender, recent CAP history, antibiotic use, vaccination against respiratory diseases (e.g., influenza and SARS-CoV-2), healthcare utilization, and other health seeking behavior markers.

The patient pneumonia infection risk level is also expected to be considered as a potential confounder and used to describe the study population. The risk levels will be modeled after CDC's classification and will include low risk (i.e., immunocompetent without known chronic disease), at-risk (i.e., immunocompetent but with certain chronic diseases present) and high-risk (i.e., immunocompromised).

The pilot phase of the study will evaluate the availability of confounder information at the study sites and identify the list of potential confounders to include in the study analysis.

vi. Study Size:

A total of approximately 15,000 enrolled subjects yielding an expected 5,230 evaluable subjects is required to assess the primary objective of the study using the base-case assumptions below:

- Evaluability rate of 35% as approximately 65% of screened subjects are expected to be excluded from analyses of the primary objective due to the following: declining to participate, <65 years of age, no vaccination records, prior pneumococcal vaccination (other than V116) within five years, CAP not radiographically confirmed, or SSUAD or blood culture testing not available/complete.
- 1: 15 case to control ratio
- 95% power
- VE of 60%
- 1-sided type I error (α) = 2.5%
- V116 uptake = 20%

These sample size assumptions are expected to allow meeting the primary study objective and declaring VE if the minimum observed VE in this study is 43%. The corresponding 2-sided 95% CI for the VE of (21% to 59%) excludes the planned 20% lower bound of the 95% CI for VE.

The study enrollment is contingent upon licensure and recommendation of the vaccine following regulatory approval and requires reasonable uptake ($\geq 20\%$) in the catchment area of the hospitals where the study will be conducted. The sponsor indicated that they would monitor the vaccine uptake in the catchment area, percentage of CAP cases that are caused by V116-type serotypes (while blinded to V116 exposure status), and percentage with prior pneumococcal vaccination other than V116, as well as other sample size assumptions.

- *Reviewers' comments: Ongoing monitoring of the enrollment progress is critical to ensure timely completion of the study. Please refer to Section D (study milestones) for details regarding sponsor's enrollment targets. Given that real-world studies may be susceptible to confounding potential biases, we suggested in IR#6 for the sponsor to increase the planned lower bound (LB) of the 2-sided 95% CI for the VE to be significantly greater than 20%.*

In their response (submitted to: 125814/0.8), the sponsor proposes to maintain the original plan of setting the LB to be >20% because they will implement several measures to mitigate potential confounding and bias and stated that this threshold enables them to balance the study sample size effectively and preserve high statistical power, and importantly, ensure timely conduct of this study and reporting of results. Upon review of the measures to address potential confounding, including the addition of a negative control exposures analysis based on our feedback from CRMTS #14116 and IR#6 (see subsection ix on potential bias/control for confounding for further details), this response is reasonable given the need to balance sample size, study feasibility and timeliness of results.

vii. Study Procedure and Data Collection

The table below details the study procedures and timing.

Table 4 Study Procedures

Screening Procedures				
	Within 48 hours	2 days to 1 month	Within 6 months	Notes
Informed Consent	X			Consent must be obtained before any study procedures are performed.
Assignment of Study ID	X			
Collection of urine sample	X			
Collection of blood sample	X			Blood must be collected prior to administration of antibiotics.
Routine collection of other samples, as appropriate	X			Sputum/respiratory and pleural fluid cultures (when appropriate) may be collected as a part of standard medical care.
Medical record review and patient interview for inclusion/exclusion criteria	X			
Inclusion/Exclusion criteria (including confirmation of CAP)		X		
Post-enrollment Procedures				
Adjudication of CAP diagnosis			X	
Vaccination record review including V116 vaccination status			X	A period of up to approximately six months may be required to obtain access to health records external to the enrolling study site. No follow-up visits after the qualifying hospitalization for CAP are planned.
Collection of comorbidities			X	A period of up to approximately six months may be required to obtain access to health records external to the enrolling study site. No follow-up visits after the qualifying hospitalization for CAP are planned.
Routine testing of blood culture	X			Pneumococcal isolate to be collected for future PAD testing
Testing in (b) (4)	X			
Testing in SSUAD			X	

Testing in PAD			X	To be performed on <i>S. pneumoniae</i> isolated from cultures
Classification of cases & controls			X	Team assessing case/control status blinded to vaccination information

Source: STN 125814/0.12, Study Protocol V116-011-00-v2, Table 1, p 26.

Data collection will be broken into 5 components: 1) data collected from sites and/or patients at the time of enrollment, 2) imaging and other diagnostic workups for confirmation of CAP, 3) sample collection (urine sample and blood cultures), 4) clinical chart review and EHR data extraction; 5) comprehensive collection of vaccination data from available sources.

viii. Data Analyses/Statistical Methods:

Descriptive statistics will be calculated for cases and controls.

Primary Objective

Using logistic regression, odds ratios (OR) with 95% confidence intervals will be estimated adjusting for potential confounders. The vaccine effectiveness (VE) will be expressed as a percentage and estimated as 1 minus the adjusted OR multiplied by 100. The analytical population will comprise patients with confirmed CAP meeting the inclusion and exclusion criteria, and further excluding CAP patients with unknown or incomplete vaccination information and those who received a non-V116 pneumococcal vaccine in the 5 years prior to their CAP hospitalization index date.

The OR will be the odds of vaccination with V116 among the cases (i.e., VT-CAP) relative to the odds of vaccination with V116 among the controls (i.e., confirmed CAP cases for whom V116 serotypes are not identified). Both crude and adjusted ORs will be presented. A pre-specified set of potential confounders will be included to and likely include enrolling site, calendar time (e.g., month and year of enrollment), age, pneumococcal risk level, influenza vaccination status and SARS-CoV-2 vaccination status. As mentioned in subsection F.v (covariates), the list of confounders will be finalized after the pilot phase.

Secondary Objective

The analysis for the secondary analysis will be similar as that for the primary objective, but the analytical population will be further restricted to NBPP patients.

The OR for this objective will be the odds of vaccination with V116 among the cases (i.e., confirmed VT-NBPP) relative to the odds of vaccination with V116 among the controls (i.e., confirmed non-bacteremic CAP cases for whom V116 serotypes are not identified). VE against confirmed VT-NBPP will also be expressed in percent and estimated as 1 minus the OR multiplied by 100. A similar set of potential confounders as those identified for the primary objective will be pre-specified to estimate the adjusted VE against NBPP.

Exploratory Objective

The analysis for the exploratory objective will be similar to the primary analysis, except that the analytical population will not exclude CAP patients based on prior pneumococcal vaccines received.

Sensitivity Analysis

Stratified analyses will be performed for the primary objective according to the following factors dependent on available numbers within strata:

- Sex (male, female),
- Age (categories),
- Risk level for pneumococcal disease including immunocompromise status (Low Risk, At Risk, High Risk)
- Country,
- Receipt of influenza vaccine

Further, a sensitivity analysis of the primary effectiveness endpoint will be conducted in which the definition of cases remains the same, but controls are restricted to only those with non-V116 serotype

pneumococcal CAP i.e., CAP of non-pneumococcal origins will be excluded. This analysis will only be conducted if there is an adequate number of controls, and if not, a descriptive summary will be provided.

- *Reviewers' comments: In IR#6, we recommended including a sensitivity analysis based on receipt of influenza vaccination to further examine if results may differ by preventative health-seeking behavior. We also noted that due to residual bias, the finding of consistent results between countries or health systems would provide additional reassurance. In the response (submitted to: 125814/0.8), the sponsor agreed to include the suggested sensitivity analyses by receipt of influenza vaccination and by country. These were included in the revised protocol submitted to 125814/0.12. In IR#12, we also recommended a subgroup analysis for people 80 years of age and older and the sponsor responded (submitted to: 125814/0.17) that an age category subgroup of 80 years of age and older will be included. They also stated that, should the numbers in this age group be too small to allow for estimation of VE within this strata, descriptive results would be provided instead.*

ix. Potential Bias/Control for Confounding:

To minimize the effect of misclassified pneumococcal vaccination status, the sponsor plans to assess the completeness of vaccination histories for all participants according to established criteria at each participating site. The completeness of vaccination histories and suitability of different sources of vaccination data, including EHR, vaccination registries, claims for vaccination and vaccination cards, will be evaluated in a pilot study, prior to study start.

While the test-negative design minimizes bias due to health-seeking behavior, residual unmeasured confounding could remain. The sponsor plans to address this by exploring the association of selected negative control exposures with the outcome of confirmed CAP. For example, Herpes zoster/shingles vaccine, which would not be expected to have any association with CAP and is also specifically recommended for disease prevention in adults, will be assessed as a negative control exposure. The sponsor also indicated that influenza, RSV, or COVID-19 vaccines will be explored as potential negative control exposures, though it is less clear whether they would have any potential association with V116 vaccine-type CAP (case status) over non-V116 VT CAP (control status). The inclusion of other potential negative control exposures as indicators of health-seeking behavior, such as breast cancer screening in females or prostate cancer screening in males, will be explored if complete source of data such as integrated electronic health record from all healthcare settings is available for all or a subset of study participants.

- *Reviewers' comments: While reviewing the first version of the study protocol, we provided feedback (CRMTS#14116) that while the use of a well-designed test-negative approach can decrease bias due to health seeking behavior, residual bias may still be present and therefore, the sponsor should consider the use of negative endpoints in their analysis to examine the impact of residual bias. In responses to CRMTS#14116 (submitted to: IND 19316.106), the sponsor agreed with the suggestion and further indicated in a response to IR#6 (submitted to: 125814/0.8) that they would include multiple potential negative control exposures rather than negative control outcomes, given the study's test-negative case-control design. The sponsor indicated that other vaccinations may serve as negative control exposures, reflecting healthcare-seeking behavior, and could include herpes zoster/shingles vaccine, influenza, RSV and COVID-19 vaccines. In the revised protocol submitted to 125814/0.12, details on the negative exposure analysis were included as described in subsection ix. In IR#12, we noted that the use of influenza, RSV and COVID-19 vaccinations as negative exposures should be restricted to exploratory analyses given*

that complications of these diseases may include pneumonia outcomes. We also suggested that the sponsor explore use of other preventative healthcare services as negative control exposures. In the sponsor's response (submitted to: 125814/0.14), the sponsor agreed with the comments and noted that the revised protocol (V116-011-00-v2) indicated that breast cancer screening in females and prostate cancer screening in males will be explored as negative control exposures if sufficiently complete data on these services can be obtained for all or a substantial subset of study participants.

In general, the use of a well-designed, test-negative case-control study provides some advantages with regards to control for health-seeking bias and confounding. Besides the negative control exposure analysis, other aspects of the study design and analysis will also help minimize residual bias. First, in the primary analysis, all participants will be naïve to pneumococcal vaccines other than V116. Second, a sensitivity analysis based on receipt of influenza vaccination is added which allows further examination of results by preventative health-seeking behavior. As pointed out by the sponsor in their responses to CRMTS#14116 (submitted to: IND 19316.106), the capture of hospitalization for CAP in the older adult population ≥ 65 years (as opposed to medical office visits) is likely to be more uniform due to the severity of the condition, and less likely the result of individual health-seeking behavior to seek medical care. With the planned systematic testing for serotypes implemented as a study procedure for all patients, there should be no significant concern for bias related to the choice to obtain a test result for pneumococcal disease.

4 REVIEWER’S CONCLUSIONS

The proposed design of the RWE study is adequate and, if implemented as proposed, would provide evidence to verify the effectiveness of V116 against vaccine-type CAP. Throughout the review process, recommendations regarding addressing bias have been provided to the sponsor, and these were addressed by additional sensitivity analyses and negative control exposure analyses. The use of a test-negative design, together with the sensitivity and negative control exposure analyses, attenuates unmeasured health-seeking behavior bias, which is a concern for RWE vaccine effectiveness studies. Upon completion of the pilot phase of the study, the sponsor will provide the finalized list of study sites and data sources to be used for collection of study elements, for further evaluation. It is expected that the sponsor will work with due diligence to ensure that this RWE study is performed according to the agreed-upon protocol and careful monitoring of the study progress will be conducted to ensure that the study phases can be completed according to the expected timelines and study milestones.