Official Protocol Title:	A Phase 3 Randomized, Double-blind, Placebo-Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 When Administered Concomitantly with Influenza Vaccine in Adults 50 Years of Age or Older
NCT number:	NCT05526716
Document Date:	09-Jun-2023

TITLE PAGE

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 3 Randomized, Double-blind, Placebo-Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 When Administered Concomitantly with Influenza Vaccine in Adults 50 Years of Age or Older

Protocol Number: 005-01

Compound Number: V116

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	NCT05526716
EU CT	Not Applicable
EudraCT	Not Applicable
JRCT	Not Applicable
WHO	Not Applicable
UTN	Not Applicable
IND	19316
Not Applicable	Not Applicable

Approval Date: 09 June 2023

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 1	09-JUN-2023	The primary reason for this amendment is to update the noninferiority margin for HAI analysis.
Original Protocol	18-MAY-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendment:

The primary reason for this amendment is to update the noninferiority margin for HAI analysis.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 9.6.1, Statistical Methods for Immunogenicity Analyses	For hypothesis 2 (H2), the statistical noninferiority criterion for HAI was revised from 0.50 to 0.67. The power calculations were updated accordingly.	This change was made to address an agency request. The statistical criteria for noninferiority of HAI immune responses was updated for consistency with the current standard of evaluation for influenza vaccines.

Section Number and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Throughout document	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other relevant changes and their primary reasons are included for completeness.
Section 1.1, Synopsis	For hypothesis 2 (H2), the statistical noninferiority criterion for HAI was revised from 0.50 to 0.67.	This change was made to address an agency request. The statistical criteria for noninferiority of HAI immune responses was updated for consistency with the current standard of evaluation for influenza vaccines.
Section 2.2.1, Pharmaceutical and Therapeutic Background	Clarified that serotype 20A is called serotype 20 throughout the protocol.	To clarify serotype identity.
Section 3, Hypotheses, Objectives, and Endpoints	For hypothesis 2 (H2), the statistical noninferiority criterion for HAI was revised from 0.50 to 0.67.	Refer to Section 1.1 rationale.
Section 6.1, Study Intervention(s) Administration	Terminology in the Dose Formulation column of Table 1 (Study Interventions) was revised. “Sterile Solution (Prefilled Syringe)” was revised to “Injection, Solution” and “Sterile Suspension (Prefilled Syringe)” was revised to “Injection, Suspension”.	To align with ISO standards.
Section 9.1, Statistical Analysis Plan Summary	For hypothesis 2 (H2), the statistical noninferiority criterion for HAI was revised from 0.50 to 0.67.	Refer to Section 1.1 rationale.

Section Number and Name	Description of Change	Brief Rationale
Section 9.9.1, Sample Size and Power for Immunogenicity Analyses	Updated the power calculations.	Refer to Section 1.1 rationale.
Section 10.1.6, Compliance with Study Registration and Results Posting Requirements	Updated references to EU regulations.	To comply with EU CTR requirements.
Section 10.6, Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Updated reference from Section 8.8 to Section 8.9 under scope of future biomedical research.	To correct section reference.
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the protocol.	To ensure clarity and accurate interpretation of the intent of the protocol, including alignment of terms with MedDRA preferred terminology.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Double-blind, Placebo-Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 When Administered Concomitantly with Influenza Vaccine in Adults 50 Years of Age or Older

Short Title: Safety and immunogenicity of V116 administered with influenza vaccine

Acronym: STRIDE-5

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Objectives and endpoints will be evaluated in adults ≥50 years of age who are administered V116 concomitantly with QIV or V116 administered sequentially with QIV.

Primary Objective	Primary Endpoint
• To evaluate the safety and tolerability of V116 when administered concomitantly with quadrivalent influenza vaccine (QIV) compared with V116 administered sequentially with QIV as assessed by the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs from Day 1 through Day 5 postvaccination • Solicited systemic AEs from Day 1 through Day 5 postvaccination • Vaccine-related Serious Adverse Events (SAEs) from Day 1 through the duration of participation in the study
• To compare the serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV. • **Hypothesis (H1):** V116 administered concomitantly with QIV is noninferior to V116 administered sequentially with QIV as assessed by serotype-specific OPA GMTs at 30 days postvaccination with V116.	• Serotype-specific OPA responses

• (The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% confidence interval [CI] of the OPA GMT ratio [concomitant group/sequential group] to be >0.50).	
• To compare the strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV administered concomitantly with V116 compared with QIV administered sequentially with V116. • **Hypothesis (H2):** QIV administered concomitantly with V116 is noninferior to QIV administered sequentially with V116 as assessed by strain-specific HAI GMTs at 30 days postvaccination with QIV. (The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% CI of the HAI GMT ratio [concomitant group/sequential group] to be greater than 0.67)	• Strain-specific HAI responses
Secondary Objectives	**Secondary Endpoints**
• To evaluate serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV.	• Serotype-specific IgG responses

• Within each vaccination group, to evaluate the serotype-specific Geometric Mean Fold Rises (GMFRs) and the proportion of participants who achieve a serotype-specific ≥4-fold rise from baseline to 30 days postvaccination with V116 for both OPA and IgG responses for participants administered V116 concomitantly with QIV and participants administered V116 sequentially with QIV.	• Serotype-specific OPA and IgG responses
• Within each vaccination group, to evaluate the strain-specific (1) GMFRs from baseline to 30 days postvaccination with QIV, (2) proportions of participants with an HAI titer ≥1:40 at 30 days postvaccination with QIV, and (3) proportions of participants that seroconvert at 30 days postvaccination with QIV for participants administered QIV concomitantly with V116 and participants administered QIV sequentially with V116.	• Strain-specific HAI responses

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Pneumococcal infection
Population	Adults ≥50 years of age
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 9 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last

Number of Participants:

Approximately 1000 participants will be randomized, with approximately 500 participants in each intervention group.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Concomitant Group	Pneumococcal 21-valent conjugate vaccine	4 µg of each PnPs antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B)	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Test Product
Concomitant Group	Quadrivalent influenza vaccine	Refer to product labeling	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Test Product
Concomitant Group	Placebo (sterile saline)	N/A	0.5 mL	IM	Single dose at Visit 3 (Day 30)	Placebo
Sequential Group	Quadrivalent influenza vaccine	Refer to product labeling	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Test Product
Sequential Group	Placebo (sterile saline)	N/A	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Placebo
Sequential Group	Pneumococcal 21-valent conjugate vaccine	4 µg of each PnPs antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B)	0.5 mL	IM	Single dose at Visit 3 (Day 30)	Test Product

Admin=administration; IM=intramuscular; NA=not applicable; PnPs=pneumococcal polysaccharide; QIV=quadrivalent influenza vaccine; V116=Pneumococcal 21-valent conjugate vaccine

Other current or former name(s) or alias(es) for study intervention(s) are as follows: V116, polyvalent pneumococcal conjugate vaccine (pPCV).

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study for approximately 7 months from the time the participant provides documented informed consent through the final contact.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

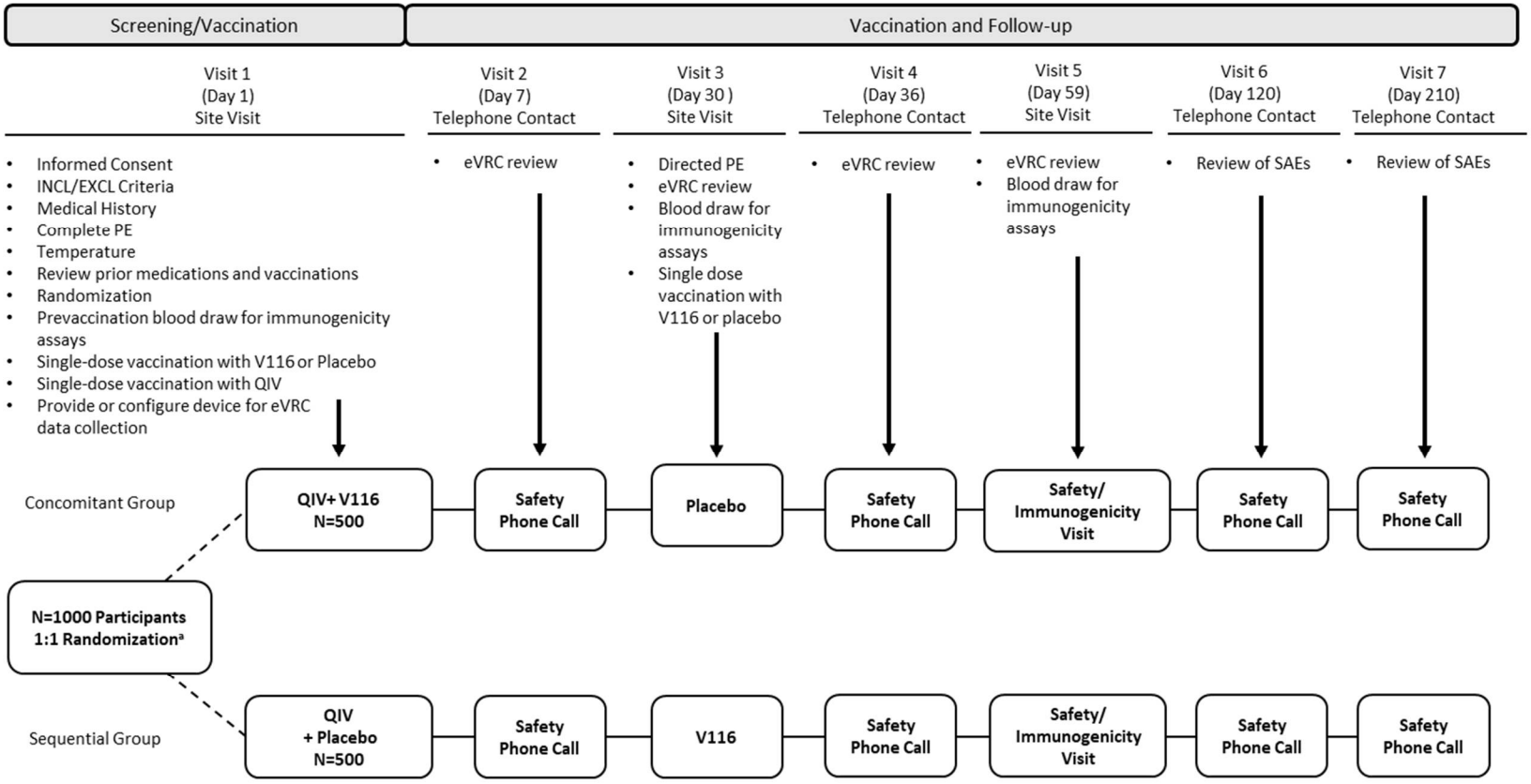
Study Accepts Healthy Participants: Yes

A list of abbreviations is in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 V116-005 Study Design



eVRC=electronic Vaccination Report Card; INCL/EXCL=Inclusion/exclusion; PE=physical examination; QIV=quadrivalent influenza vaccine; SAE=serious adverse event

[a] Randomization will be stratified by age (50 to 64, 65 to 74, 75 to 84, and ≥85 year of age), and prior pneumococcal vaccination status (PCV13 and PPSV23 naïve; prior PCV13 only; prior PPSV23 only; or prior PCV13 and PPSV23).

1.3 Schedule of Activities

Study Period:	**Intervention and Follow-up**							**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Visit Type	**Site Visit**	**Telephone Contact**	**Site Visit**	**Telephone Contact**	**Site Visit**	**Telephone Contact**	**Telephone Contact**	
Study Day:	**Day 1**	**Day 7**	**Day 30**	**Day 36**	**Day 59**	**Day 120**	**Day 210**	
Visit Window:		Day 7 to Day 10 after Visit 1	Day 30 to Day 44 after Visit 1	Day 7 to Day 10 After Visit 3	Day 30 to Day 44 After Visit 3	Day 76 to Day 104 After Visit 3	Day 166 to Day 194 After Visit 3	
Administrative Procedures								
Screening Procedures								
Informed Consent	X							Must be obtained before any study procedures are conducted.
Informed Consent for Optional Assay Development Blood Samples	X							Must be obtained before any sample collection.
Informed Consent for FBR	X							Must be obtained before any sample collection.
Assignment of Screening Number	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Postrandomization Procedures								
Assignment of Randomization Number	X							
Participant Identification Card	X							
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X	X	X			
QIV Administration (Open-label) (Right Arm)	X							
V116 or Placebo Administration (blinded) (Left Arm)	X		X					
Provide Electronic Device or Configure Participant's Own Electronic Device for eVRC Data Collection	X							

Study Period:	**Intervention and Follow-up**							**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Visit Type	**Site Visit**	**Telephone Contact**	**Site Visit**	**Telephone Contact**	**Site Visit**	**Telephone Contact**	**Telephone Contact**	
Study Day:	**Day 1**	**Day 7**	**Day 30**	**Day 36**	**Day 59**	**Day 120**	**Day 210**	
Visit Window:		Day 7 to Day 10 after Visit 1	Day 30 to Day 44 after Visit 1	Day 7 to Day 10 After Visit 3	Day 30 to Day 44 After Visit 3	Day 76 to Day 104 After Visit 3	Day 166 to Day 194 After Visit 3	
Review eVRC Data With Participant		X	X	X	X			
Collect Electronic Device From Participants Who Received an Electronic Device					X			
Complete Telephone Contact Questionnaire						X	X	
Safety Procedures								
Complete Physical Examination	X							Performed by investigator or medically qualified designee at screening and before vaccination.
Directed Physical Examination			X					Performed by investigator or medically qualified designee before vaccination.
Pregnancy Test (if applicable)	X		X					Females of reproductive potential must have a negative urine or serum test (consistent with local requirements and sensitive to ≤25 IU hCG) result before vaccination.
Body Temperature Measurement	X		X					Measured before vaccination. Participants with febrile illness within 72 hours before vaccination must be rescheduled.
Postvaccination Observation Period	X		X					Observed by blinded study-site personnel for at least 30 minutes postvaccination.
AE Monitoring	X	X	X	X	X	X	X	Nonserious AEs collected through Day 30 postvaccination. SAEs and deaths collected through duration of study participation.

Study Period:	**Intervention and Follow-up**							**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Visit Type	**Site Visit**	**Telephone Contact**	**Site Visit**	**Telephone Contact**	**Site Visit**	**Telephone Contact**	**Telephone Contact**	
Study Day:	**Day 1**	**Day 7**	**Day 30**	**Day 36**	**Day 59**	**Day 120**	**Day 210**	
Visit Window:		Day 7 to Day 10 after Visit 1	Day 30 to Day 44 after Visit 1	Day 7 to Day 10 After Visit 3	Day 30 to Day 44 After Visit 3	Day 76 to Day 104 After Visit 3	Day 166 to Day 194 After Visit 3	
Immunogenicity Procedures								
Serum for Pneumococcal Immunogenicity Assays	X		X		X			Visit 1 and Visit 3 samples should be collected before vaccination.
Serum for Influenza Immunogenicity Assays	X		X					Visit 1 and Visit 3 samples should be collected before vaccination.
Future Biomedical Research								
Blood (DNA) for Future Biomedical Research	X							For participants who provided FBR consent. Should be collected before vaccination at Visit 1, or at a later date as long as FBR consent is obtained prior to collection.
Assay Development Samples								
Serum for Optional Assay Development	X		X		X			For participants who provided consent for optional assay development. Visit 1 and Visit 3 samples should be collected before vaccination.

AE=adverse event; DNA=deoxyribonucleic acid; eVRC=electronic vaccination report card; hCG=human chorionic gonadotropin; FBR=future biomedical research; ID=identification; IU=international units; QIV=quadrivalent influenza vaccine; SAE=serious adverse event.

2 INTRODUCTION

The Sponsor is developing an investigational polyvalent pneumococcal 21-valent conjugate vaccine (V116) for the prevention of pneumococcal disease caused by the serotypes in the vaccine.

2.1 Study Rationale

Streptococcus pneumoniae is a major cause of vaccine-preventable disease worldwide. It is associated with considerable morbidity and mortality, with the highest burden seen in children <5 years and adults >70 years of age [Troeger, C., et al 2018]. PCV vaccination has reduced the incidence of disease caused by vaccine serotypes in the age groups being vaccinated (primarily children <5 years of age in most countries) and has had an indirect effect in other age groups.

However, an unmet medical need exists as increases in IPD due to serotypes not included in licensed PCVs have been observed in several countries, especially in adults.

V116 is an investigational PCV designed to address this unmet medical need and includes *S pneumoniae* serotypes not included in licensed PCVs, which account for the majority of IPD in adults.

Pneumococcal pneumonia is a frequent complication of influenza, and simultaneous vaccination against both in at-risk individuals has been shown to reduce rates of hospitalization and mortality [Dominguez, A., et al 2013] [Zhang, Y. Y., et al 2016]. Concomitant administration of PCV13, PCV15, and influenza vaccine results in robust immune responses for both pneumococcal and influenza antigens and can be a strategy to increase vaccination rates [Gilchrist, S. A., et al 2012] [Frenck, R. W. Jr., et al 2012] [Schwarz, T. F., et al 2011] [Schwarz, T. F. 2013] [Kobayashi, M., et al 2022].

In the US, ACIP guidelines recommend that immunocompetent at-risk individuals and high-risk individuals 19 to 64 years of age, as well as adults ≥65 years of age receive PCV15 followed by PPSV23, or PCV20 alone [Kobayashi, M., et al 2022]. PCV13 is approved for adults 18 years of age and older for the prevention of pneumococcal pneumonia and invasive disease caused by the 13 pneumococcal serotypes contained in the vaccine.

To allow a comprehensive assessment of the concomitant administration of V116 and influenza vaccine this study will enroll participants with and without prior PPSV23 and/or PCV13 vaccination. In accordance with recommendations regarding the interval between vaccination with PPSV23 and PCV13, participants who have received a prior pneumococcal vaccine must have received PPSV23 and/or PCV13 at least 12 months prior to study enrollment.

This clinical study will evaluate the safety, tolerability, and immunogenicity of V116 when administered concomitantly with influenza vaccine in participants ≥50 years of age. This population is at elevated risk for pneumococcal disease and associated morbidity and mortality due to age-related physiological changes in the respiratory system, age-related

immunosenescence, and an increased incidence of other medical conditions associated with increased risk for pneumococcal disease [Drijkoningen, J. J 2014] [Janssens, J. P. 2004].

2.2 Background

To date, a Phase 1/2 study (V116-001) and a Phase 1 study in Japan (V116-002) have been conducted with V116. Results from the Phase 1 part of V116-001 were used to select the optimal vaccine formulation for subsequent development. Results from both studies showed that V116 is immunogenic and has acceptable safety and tolerability in healthy adults.

Refer to the IB for detailed background information on V116.

2.2.1 Pharmaceutical and Therapeutic Background

Pneumococcal disease (ie, disease caused by *S pneumoniae*) is one of the single largest vaccine-preventable causes of death in children and older adults (≥65 years of age) worldwide. PCV use in children has decreased the incidence of disease caused by vaccine serotypes and has led to indirect protection in unvaccinated individuals from other age groups. This has resulted in a decrease in hospital admissions for pneumococcal disease in adults ≥65 years of age, including estimated decreases of 29% and 34% in admissions due to IPD and noninvasive pneumococcal pneumonia, respectively [Simonsen, L., et al 2014]. In some countries, including the US, the decrease in pneumococcal disease in children vaccinated with PCV has led to the recommendation to vaccinate adults with PCVs. However, current surveillance does not definitively indicate that the use of PCVs in adults results in a similar reduction in pneumococcal disease [Matanock, A. 2018]. The residual burden of disease in the US is estimated as 24 cases of IPD per 100,000 in adults ≥65 years of age, and surveillance data estimates serotypes included in currently licensed PCVs account for approximately 23% to 50% of these cases [Centre for Disease Control and Prevention 2016] [Centers for Disease Control and Prevention 2019] [Kobayashi, M. 2021].

The residual burden of disease in adults reflects the difference in serotype distribution in adults compared with that in infants and children. An increasing incidence of disease due to serotypes not included in the licensed PCVs has been observed, particularly in adults [Miller, Elizabeth, et al 2011] [Moore, M. R., et al 2015] [Pilishvili, T. 2015] [van der Linden, M., et al 2015] [Golden, A. R., et al 2016]. Increases in IPD cases due to nonvaccine serotypes (3, 7F, and 19A after implementation of Prevnar™; 22F and 33F following widespread usage of Prevnar 13™) have been observed in both pediatric and adult (≥65 years of age) populations in the US [Hicks, L. A., et al 2007] [Pilishvili, Tamara, et al 2010] [Waight, P. A., et al 2015] [Moore, M. R., et al 2015] [Demczuk, W. H. B., et al 2013]. Similarly, due to the limited serotype coverage of the currently licensed vaccines in the EU, serotype replacement due to nonvaccine serotypes is being observed in older adults and may decrease the potential additional benefit of vaccination with currently available PCVs [European Center for Disease Prevention and Control 2018].

Serotypes were selected for inclusion in V116 based on available global epidemiology data with a primary focus on data from older adults (≥65 years of age) in the US and EU, regions with an established pediatric vaccination program. Based on 2018 surveillance data in US

adults ≥65 years of age, the serotypes selected for inclusion in V116 account for approximately 83% of all cases of IPD, 25% to 30% of which are accounted for by the serotypes unique to V116 (US CDC ABCs unpublished data 2014 to 2018) [Centre for Disease Control and Prevention 2018].

V116 includes serotypes not currently contained in any licensed pneumococcal vaccine. V116 being developed to support an indication for active immunization for the prevention of invasive disease and pneumonia caused by *S pneumoniae* serotypes 3, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older. Note that serotype 15C represents deOAc15B as the molecular structures for deOAc15B and 15C are similar. Throughout this protocol, serotype 20 refers to serotype 20A.

2.2.2 Information on Other Study-related Therapy

2.2.2.1 Quadrivalent Influenza Vaccine

Refer to approved labeling for detailed background information on the QIV used in this study.

In the US, annual influenza vaccination is recommended for all individuals ≥6 months of age [Grohskopf, L. A., et al 2017].

2.2.2.2 Pneumococcal Vaccination Guidelines

Many countries have implemented age-based and/or risk-based recommendations for pneumococcal vaccination. Age-based recommendations typically start at 65 years of age due to the increased risk of pneumococcal disease associated with age.

Prior to 2014, the US ACIP recommended that all adults ≥65 years of age receive a single dose of PPSV23. In 2014, ACIP recommended the sequential vaccination regimen of PCV13 followed by PPSV23 for all adults ≥65 years of age, with the intent to reevaluate this recommendation. The guideline was updated in 2019 to remove the recommendation for routine use of PCV13 among adults ≥65 years and continued to recommend a routine single dose of PPSV23 for adults aged ≥65 years[Matanock, A., et al 2019]. The ACIP updated the guidelines in 2021 to recommend that adults ≥65 years of age should receive either PCV15 followed by PPSV23 or PCV20 alone [Kobayashi, M., et al 2022].

Risk-based recommendations generally include individuals with an increased risk of pneumococcal disease who are categorized as immunocompetent at-risk or as high-risk. Conditions associated with immunocompetent at-risk include, but are not limited to, chronic heart disease, chronic lung disease (including chronic obstructive pulmonary disease, emphysema, and asthma), diabetes mellitus, alcoholism, chronic liver disease (including cirrhosis), and cigarette smoking. Conditions associated with high-risk include, but are not limited to, congenital or acquired asplenia, sickle cell disease/other hemoglobinopathies, chronic renal failure, congenital or acquired immunodeficiencies, generalized malignancy, hematologic malignancy, HIV infection, nephrotic syndrome, solid organ transplant, and hematopoietic stem cell transplant [Kobayashi, M., et al 2022]. In the US, recommendations

for immunocompetent at-risk individuals 19 to 64 years of age previously included a single dose of PPSV23, with the exception of individuals with cochlear implants or cerebrospinal fluid leaks, who should receive PCV13 followed by PPSV23. High-risk individuals were recommended to receive 1 dose of PCV13 followed by 1 dose of PPSV23 ≥8 weeks later, and an additional dose of PPSV23 ≥5 years later [Matanock, A., et al 2019]. Similar to the age-based recommendations, the ACIP guidelines were updated in 2021 and now recommend that immunocompetent at-risk individuals and high-risk individuals 19 to 64 years of age receive PCV15 followed by PPSV23 or PCV20 alone [Kobayashi, M., et al 2022].

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Despite the public health impact of currently available pneumococcal vaccines, pneumococcal disease in adults remains a significant unmet medical need. *S pneumoniae* is a major cause of vaccine-preventable disease worldwide, resulting in considerable morbidity and mortality [Troeger, C., et al 2018].

Vaccination with PCVs has reduced the incidence of disease caused by vaccine serotypes in the population targeted by the vaccination (primarily children <5 years of age in most countries) and has had an indirect effect in other age groups. However, in several countries, infant vaccination with PCVs has also led to increases in IPD due to serotypes not included in the licensed PCVs, particularly in adults. This has resulted in an unmet medical need in this population.

V116 is designed to provide significantly broader pneumococcal disease coverage in adults as compared with currently licensed pneumococcal vaccines and is anticipated to have a generally comparable safety profile. No clinically important safety findings have been identified to date based on data from early phase clinical studies with V116.

The benefit-risk profile for V116 supports continued evaluation.

While the impact of concomitant administration of V116 and QIV on the immune response to both vaccines is unknown and will be evaluated in this study, participants in both vaccination groups are expected to be sufficiently covered by the QIV for the 2022/2023 influenza season through participation in this study based on the experience of concomitant administration of PCV13 or PCV15 and influenza vaccines [Severance, R., et al 2021] [Frenck, R. W. Jr., et al 2012] [Schwarz, T. F., et al 2011] [Schwarz, T. F. 2013].

Previous studies have shown the additive benefit of concomitant administration of pneumococcal vaccines and influenza vaccine in elderly populations. The concomitant administration of PCVs with influenza vaccine is supported by the results of clinical studies with other PCVs [Yin, M., et al 2018]. While reduced immune responses to pneumococcal vaccines have been observed when administered concomitantly with influenza vaccine, the clinical significance of this trend is unknown [Frenck, R. W. Jr., et al 2012] [Schwarz, T. F., et al 2011] [Schwarz, T. F. 2013] [Song, J. Y., et al 2017].

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Objectives and endpoints will be evaluated in adults ≥50 years of age who are administered V116 concomitantly with QIV or V116 administered sequentially with QIV.

Primary Objective	**Primary Endpoint**
• To evaluate the safety and tolerability of V116 when administered concomitantly with quadrivalent influenza vaccine (QIV) compared with V116 administered sequentially with QIV as assessed by the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs from Day 1 through Day 5 postvaccination • Solicited systemic AEs from Day 1 through Day 5 postvaccination • Vaccine-related Serious Adverse Events (SAEs) from Day 1 through the duration of participation in the study
• To compare the serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV. **Hypothesis (H1):** V116 administered concomitantly with QIV is noninferior to V116 administered sequentially with QIV as assessed by serotype-specific OPA GMTs at 30 days postvaccination with V116. • (The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% confidence interval [CI] of the OPA GMT ratio [concomitant group/sequential group] to be >0.50).	• Serotype-specific OPA responses

• To compare the strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV administered concomitantly with V116 compared with QIV administered sequentially with V116. • **Hypothesis (H2):** QIV administered concomitantly with V116 is noninferior to QIV administered sequentially with V116 as assessed by strain-specific HAI GMTs at 30 days postvaccination with QIV. (The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% CI of the HAI GMT ratio [concomitant group/sequential group] to be greater than 0.67)	• Strain-specific HAI responses
Secondary Objectives	**Secondary Endpoints**
• To evaluate serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV.	• Serotype-specific IgG responses
• Within each vaccination group, to evaluate the serotype-specific Geometric Mean Fold Rises (GMFRs) and the proportion of participants who achieve a serotype-specific ≥4-fold rise from baseline to 30 days postvaccination with V116 for both OPA and IgG responses for participants administered V116 concomitantly with QIV and participants administered V116 sequentially with QIV.	• Serotype-specific OPA and IgG responses

• Within each vaccination group, to evaluate the strain-specific (1) GMFRs from baseline to 30 days postvaccination with QIV, (2) proportions of participants with an HAI titer ≥1:40 at 30 days postvaccination with QIV, and (3) proportions of participants that seroconvert at 30 days postvaccination with QIV for participants administered QIV concomitantly with V116 and participants administered QIV sequentially with V116.	• Strain-specific HAI responses
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
• To evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV.	• Serotype-specific OPA and IgG responses

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multisite, double-blind study of V116 in adults ≥50 years of age who receive V116 administered concomitantly with QIV or V116 administered sequentially with QIV.

Approximately 1000 participants will be randomly assigned in a 1:1 ratio to receive either V116 administered concomitantly with QIV or V116 administered sequentially with QIV. Randomization will be stratified by participant age at enrollment (50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years) and by pneumococcal vaccination status (PCV13- and PPSV23-naïve, prior receipt of PCV13 only, prior receipt of PPSV23 only, and prior receipt of both PCV13 and PPSV23). At least 50% of participants will be ≥65 years of age and at least 50% of participants will be naïve to PCV13 and PPSV23.

An eVRC will be used by all participants to record solicited injection-site AEs, solicited systemic AEs, and daily body temperature from Day 1 through Day 5 postvaccination. Unsolicited AEs will be collected through Day 30 postvaccination. All participants will be provided an electronic device or have their own electronic device configured, if compatible, to complete the eVRC.

Information for SAEs and deaths, regardless of whether the events are considered to be vaccine-related by the investigator, will be collected through completion of participation in the study.

An external DMC will conduct a periodic review of safety and tolerability data for the V116 Phase 3 program. A description of the structure and function of the DMC, along with the timing and content of the safety reviews, will be outlined in the DMC charter. Information regarding the composition of the DMC is provided in Appendix 1.

Blood samples for immunogenicity assays will be drawn on Day 1 and at 30 days after each vaccination.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This study will evaluate the safety, tolerability, and immunogenicity of V116 in adults ≥50 years of age. The population enrolled in this study is at increased risk for pneumococcal disease and its associated morbidity and mortality as the incidence of IPD is directly related to age, with over half of all cases occurring in adults ≥50 years of age [Drijkoningen, J. J 2014].

Adults with stable chronic medical conditions will be included in this study. These individuals are generally categorized as being immunocompetent at-risk, reflecting the

understanding that while they are at an increased risk of pneumococcal disease, their immune responses are not impacted by the chronic medical condition [Curcio, D., et al 2015] [Weycker, D., et al 2010] [van Hoek, A. J., et al 2012].

The concomitant and sequential administration of V116 and QIV in this study allows for meaningful comparisons of safety, tolerability, and immunogenicity between the 2 vaccination regimens.

To demonstrate that concomitant administration of V116 and QIV does not adversely affect the antibody response to or safety profile of either vaccine, blinding is being maintained through the use of a placebo. A saline placebo will be used to maintain blinded vaccine administration on Day 1 and Day 30. Both groups of randomized participants will receive V116 in the study.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

4.2.1.1.1 Pneumococcal Immunogenicity Endpoints

The immunogenicity endpoints and the associated statistical criteria are consistent with previous studies evaluating PCVs.

Sera from participants will be used to assess vaccine-induced, anti-PnPs serotype-specific OPA and IgG responses using the validated MOPA and Pn ECL assay, respectively. Immunogenicity endpoints will be evaluated for all serotypes included in V116 and for cross-reactive serotypes within a serogroup.

Several studies have shown a positive correlation between serotype-specific IgG antibody concentrations and OPA titers in children and adults [Centers for Disease Control and Prevention 2010] [Anttila, M., et al 1999] [Romero-Steiner, S., et al 1997]. OPA assesses levels of functional antibodies capable of opsonizing pneumococcal capsular polysaccharides for presentation to phagocytic cells for engulfment and subsequent killing; therefore, it is considered an important immunologic surrogate for protection against IPD in adults. It is noted that IgG antibody concentration and OPA titer threshold values that correlate with protection in adults have not been defined; however, the OPA responses are considered an accepted endpoint for the evaluation of novel pneumococcal vaccines in adults.

OPA GMTs, IgG GMCs, GMFRs, and the differences in proportions of participants with 4-fold rises in OPA and IgG responses are acceptable assessments used to evaluate novel PCVs.

Details on the immunogenicity endpoints evaluated in this study can be found in Section 9.4.1.

4.2.1.1.2 Influenza Immunogenicity Endpoints

Antibodies that block the binding of the hemagglutinin antigen of the influenza virus to host receptors contribute to natural or vaccine-induced immunity against a homologous or related influenza virus. These antibodies are generally considered to be correlates of protective immunity against influenza [Zakay-Rones, Z. 2010] [Reber, A. 2013]. The HAI assay detects antibodies that bind around the globular head of the hemagglutinin molecule, inhibiting the interaction of the virus with host cells. It has been shown that serum HAI titers are inversely correlated with the frequency of clinical influenza in vaccinated individuals. However, no defined serum antibody threshold exists and the relationship between HAI responses and protection is influenced by preexisting immunity and age [Reber, A. 2013].

HAI responses are part of the criteria that regulatory agencies use for the evaluation and the licensure of influenza vaccines [Food and Drug Administration (CDER) 2007] [European Medicines Agency 2016], with postvaccination GMTs, seroconversion, and seroprotection rates as recommended endpoints.

Details on the immunogenicity endpoints evaluated in this study can be found in Section 9.4.1.

4.2.1.2 Safety Endpoints

Safety information will be collected from all participants on an eVRC. The eVRC used to record AEs during the postvaccination periods (Section 8.1.9) is structured as recommended in the final US FDA Patient-reported Outcome Guidance [U.S. Food and Drug Administration 2009].

The safety endpoints (ie, AEs and temperature) evaluated in this study are consistent with previous studies of V116 and published data from marketed PCVs. Detailed information for the safety endpoints evaluated in this study can be found in Section 9.4.2.

Definitions and reporting requirements for AEs are provided in Appendix 3.

4.2.1.3 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

Placebo is used in this study to maintain blinding to the concomitant and sequential group assignment. The placebo is sterile saline for injection.

4.3 Justification for Dose

The V116 dose of 4 µg/each PnPs was selected based on review of safety and immunogenicity data from the Phase 1 and Phase 2 studies. In Phase 1, 2 doses of V116 were evaluated: a single dose containing 2 µg/each PnPs and a single dose of 4 µg/each PnPs. Based on the data from Phase 1, the V116 dose of 4 µg/each PnPs was selected for further evaluation in Phase 2. Results from Phase 2 showed that the V116 dose of 4 µg/each PnPs is well tolerated and generates serotype-specific immune responses. These data support the selection of the V116 dose of 4 µg/each PnPs for further development in Phase 3.

Refer to the IB for detailed background information on V116.

The dose of QIV selected for use in this study is consistent with the approved dosing and product labeling.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. The participant may have underlying chronic conditions if they are assessed to be in stable condition as per the investigator's judgment.

Demographics

2. Is male or female, ≥50 years of age, at the time of informed consent.

Female Participants

3. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP
  OR
- A WOCBP and:
  - Uses an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 6 weeks after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.2.

- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

4. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide documented informed consent for FBR and/or assay development sample collection. However, the participant may participate in the study without participating in FBR or assay development sample collection.

Additional Categories

5. The participant has the ability to complete eVRC data collection without assistance based on the judgment of the investigator.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has a history of IPD (positive blood culture, positive cerebrospinal fluid culture, or positive culture at another sterile site) or known history of other culture-positive pneumococcal disease within 3 years of Visit 1 (Day 1).
2. Has a known hypersensitivity to any component of V116 or any influenza vaccine, including diphtheria toxoid.
3. Has a known or suspected impairment of immunological function including, but not limited to, a history of congenital or acquired immunodeficiency, documented HIV infection, functional or anatomic asplenia, or history of autoimmune disease (including, but not limited to the autoimmune conditions outlined in the Investigator Trial File Binder for this study).
4. Has a coagulation disorder contraindicating intramuscular vaccination.
5. *Had a febrile illness (defined as oral or tympanic temperature ≥100.4°F [≥38.0°C] or axillary or temporal temperature ≥99.4°F [≥37.4°C]) or received antibiotic therapy for any acute illness occurring <72 hours before receipt of study vaccine.
6. Has a known malignancy that is progressing or has required active treatment <3 years before enrollment. Note: participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

Prior/Concomitant Therapy

7. Is expected to receive any pneumococcal vaccine during the study outside of the protocol.

8. Received any pneumococcal vaccine <12 months prior to enrollment (including PCV13 followed by PPSV23 and PPSV23 followed by PCV13).
9. Had prior administration of PCV15 or PCV20.
10. Received any influenza vaccine <6 months prior to enrollment or is expected to receive any influenza vaccine during the study outside of the protocol.
11. *Received systemic corticosteroids (prednisone equivalent of ≥20 mg/day) for ≥14 consecutive days and has not completed intervention ≥14 days before receipt of study vaccine. Note: physiologic replacement doses (prednisone equivalent of approximately 5 mg/day), topical, ophthalmic, intra-articular or soft-tissue (eg, bursa, tendon steroid injections), and inhaled/nebulized steroids are permitted.
12. Is currently receiving immunosuppressive therapy, including chemotherapeutic agents or other immunotherapies/immunomodulators used to treat cancer or other conditions, and interventions associated with organ or bone marrow transplantation, or autoimmune disease.
13. *Received any nonlive vaccine ≤14 days before receipt of study vaccine or is scheduled to receive any nonlive vaccine ≤30 days after receipt of study vaccine.
    Exception: SARS-CoV-2 mRNA or SARS-CoV-2 protein subunit vaccines may be administered but must be given ≥7 days before or ≥15 days after receipt of study vaccine.
14. *Received any live virus vaccine ≤30 days before receipt of study vaccine or is scheduled to receive any live virus vaccine ≤30 days after receipt of study vaccine.
15. Received a blood transfusion or blood products, including immunoglobulin ≤6 months before receipt of study vaccine or is scheduled to receive a blood transfusion or blood product before the Day 30 postvaccination blood draw is complete. Autologous blood transfusions are not considered an exclusion criterion.

Prior/Concurrent Clinical Study Experience

16. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 2 months of participating in this current study.

Diagnostic Assessments

Not applicable

Other Exclusions

17. In the opinion of the investigator, has a history of clinically relevant drug or alcohol use that would interfere with participation in protocol-specified activities.
18. Has history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might expose the participant to risk by participating in the study, confound the results of the study, or interfere with the participant's participation for the full duration of the study.
19. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

For items with an asterisk (*), if the participant meets these exclusion criteria, Visit 1 may be rescheduled for a time when these criteria are not met.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (V116, QIV, placebo) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 1. Country-specific differences are noted in Appendix 7.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin.	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Concomitant Group	Experimental	Pneumococcal 21-valent conjugate vaccine	Biological/Vaccine	Injection, Solution	4 µg of each PnPs antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B)	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Test Product	IMP	Central
Concomitant Group	Experimental	Quadrivalent influenza vaccine	Biological/Vaccine	Injection, Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Test Product	IMP	Central or Local
Concomitant Group	Experimental	Placebo (sterile saline)	Biological/Vaccine	Injection, Solution	N/A	0.5 mL	IM	Single dose at Visit 3 (Day 30)	Placebo	IMP	Central
Sequential Group	Experimental	Quadrivalent influenza vaccine	Biological/Vaccine	Injection, Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Test Product	IMP	Central or Local
Sequential Group	Experimental	Placebo (sterile saline)	Biological/Vaccine	Injection, Solution	N/A	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Placebo	IMP	Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin.	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Sequential Group	Experimental	Pneumococcal 21-valent conjugate vaccine	Biological/Vaccine	Injection, Solution	4 µg of each PnPs antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B)	0.5 mL	IM	Single dose at Visit 3 (Day 30)	Test Product	IMP	Central

Admin=administration; IM=intramuscular; IMP=investigational medicinal product; N/A=not applicable; NIMP/AxMP=noninvestigational/auxiliary medicinal product; PnPs=pneumococcal polysaccharide

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number. However, central sourcing is preferable.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.1.1 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

Specific procedures that are required for dose preparation are outlined in the Investigator Trial File Binder.

As detailed in Section 6.3.3, study vaccines will be prepared by an unblinded member of the study-site staff.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to receive V116 administered concomitantly with QIV or V116 administered sequentially with QIV.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

- Participant age at time of randomization:
  - 50 to 64 years of age
  - 65 to 74 years of age
  - 75 to 84 years of age
  - ≥85 years of age

  At least 50% of participants will be ≥65 years of age.
- Prior pneumococcal vaccination status:
  - PCV13- and PPSV23-naïve
  - Prior receipt of PCV13 only
  - Prior receipt of PPSV23 only
  - Prior receipt of PCV13 and PPSV23

At least 50% of participants will be naïve to PCV13 and PPSV23.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. V116 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, the investigator, and Sponsor personnel or delegate(s)

who are involved in the clinical evaluation of the participants are unaware of the intervention assignments.

Because V116 and placebo have a different appearance, an unblinded pharmacist (or qualified study-site personnel) will be responsible for receiving, maintaining, preparing and/or dispensing, and administering these study vaccines (Section 8.1.8). Although QIV is provided open label in this study, it will also be prepared and/or dispensed and administered by the unblinded study-site personnel for consistency.

To avoid bias, contact between the unblinded study-site personnel and study participants is strictly prohibited for any study-related procedures/assessments other than administration of study vaccines. Blinded site personnel will be responsible for all other study procedures/assessments specified in Section 1.3.

An unblinded Clinical Research Associate will monitor vaccine accountability at the study site. All other Sponsor personnel or delegate(s) directly involved with the conduct of this study will remain blinded to the participant-level intervention assignment.

See Section 8.1.12 for a description of the method of unblinding a participant during the study should such action be warranted.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified vaccination plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study (see Section 5.2). If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

It is important to record the use of any analgesic or antipyretic medication that occurs on the day of vaccination on the eVRC and appropriate eCRF.

Listed below are specific restrictions for concomitant therapy or vaccination:

- Administration of a nonstudy pneumococcal vaccine and/or a nonstudy influenza vaccine is prohibited during the study.

- Nonstudy vaccines may only be administered before or after the receipt of study vaccines according to the time frames specified in the Exclusion Criteria (Section 5.2).

- Receipt of systemic corticosteroids (prednisone equivalent ≥20 mg/day) for ≥14 consecutive days is prohibited from 14 days before any vaccination through 30 days following any vaccination. **Note**: physiologic replacement doses (prednisone equivalent of approximately 5 mg/day), topical, ophthalmic, intra-articular or soft-tissue (eg, bursa, tendon steroid injections), and inhaled/nebulized steroids are permitted.

Any deviation from the above requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Use of prior and concomitant medications/vaccinations should be recorded as described in Section 8.1.5.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification

No dose modification is allowed in this study.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is blinded but supplies are provided as open label; therefore, an unblinded pharmacist or qualified study-site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.12). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.12 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.12.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.11 and Section 8.12.3.

A participant must be discontinued from study intervention, but continue to be monitored in the study, for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance, which in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive urine or serum pregnancy test before vaccination at Visit 3.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in

Section 8.1.11. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the pre-specified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant at each visit will not exceed 99 mL, and the total amount of blood collected over the duration of the study will not exceed 258.5 mL (Table 2).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 2 Approximate Blood Volumes Drawn by Study Visit and by Sample Type

	Visit 1	Visit 3	Visit 5	Total
Parameter	**Approximate Blood Volume**			
Pneumococcal Immunogenicity assessment	30 mL	30 mL	30 mL	90 mL
Influenza Immunogenicity assessment	20 mL	20 mL	N/A	40 mL
DNA for Future Biomedical Research[a]	8.5 mL	N/A	N/A	8.5 mL
Assay development[a]	40 mL	40 mL	40 mL	120 mL
Expected total	98.5 mL	90 mL	70 mL	258.5 mL

DNA=deoxyribonucleic acid; N/A=not applicable.

[a] Samples for future biomedical research and assay development will only be obtained from participants who provide separate consent for collection of these optional samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.1.3 Consent and Collection of Specimens for Optional Assay Development

The investigator or medically qualified designee will explain the consent for the optional assay development blood samples to the participant, or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent before performing any procedure related to the optional assay development blood samples collection. A copy of the informed consent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The participant's relevant medical history for the 5 years before Visit 1 will be obtained to ensure that the participant satisfies the inclusion and exclusion criteria of the study. History of tobacco use will be collected for all participants.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee must review and record the following in the participant's source documents and on the appropriate eCRF before vaccination at Visit 1:

- Prior vaccinations and medication taken by the participant within 30 days before study vaccination at Visit 1.
- History of prior pneumococcal vaccination regardless of timing before Visit 1.
- Any analgesic or antipyretic medication taken on the day of vaccination before vaccination.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

Any analgesic or antipyretic medication taken must be recorded on the eVRC and appropriate eCRF.

The participant will use their eVRC (Section 8.1.9) to record new and/or concomitant medications taken and nonstudy vaccines received from the day of each vaccination through 30 days postvaccination.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Unblinded study personnel will prepare and administer all study vaccines (Section 6.3.3). The unblinded study personnel who administer study vaccines should not have contact with participants for any other study-related procedures/assessments.

Blinded site personnel will not be present in the examination room when study vaccines are administered.

Study vaccines should be prepared and administered by appropriately qualified members of the study personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local/state, country, and institutional guidance. Procedures for handling, preparing, and administering the unblinded vaccines are provided in the Investigator Trial File Binder.

Study vaccine will be administered according to the schedule specified in Section 1.3. V116 or placebo should be administered as a single IM injection in the deltoid region of the participant's left arm, while QIV should be administered as a single IM injection in the deltoid region of the participant's right arm. QIV will be administered open label. Adequate treatment provision, including epinephrine and equipment for maintaining an airway, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

8.1.8.1 Timing of Dose Administration

Study vaccines will be administered as indicated in Section 1.3. Vaccinations may be administered at any time of day and without regard to timing of meals.

All participants will be observed for at least 30 minutes after vaccination for any immediate reactions (Section 8.3.4). This observation must be performed by blinded site personnel (Section 6.3.3).

Participants must not have a fever reported within 72 hours before vaccination (Section 1.3 and Section 8.3.3).

Administration of pregnancy tests (if applicable) must be performed before vaccine administration.

The collection of blood samples should be performed before vaccine administration.

8.1.9 Electronic Vaccination Report Card

The eVRC is structured as recommended in the final US FDA Patient-reported Outcome Guidance [U.S. Food and Drug Administration 2009].

The participant will use the eVRC to record body temperature (Section 8.3.3), solicited injection-site AEs, and solicited systemic AEs (Section 8.4.8.1). Unsolicited AEs (Section 8.4.8.2), concomitant medications (including use of any analgesic or antipyretic

medication), and nonstudy vaccinations (Section 8.1.5.2) will also be reported. Participants will be provided an electronic device or have their own electronic device configured, if compatible, to complete the eVRC.

The investigator or delegate will review the data captured on the eVRC with the participant as indicated in Section 1.3. Any differences between data reported by the participant on the eVRC and data entered into the clinical database must be clearly explained in the participant's source documents.

8.1.10 Telephone Contact Questionnaire

Site personnel will contact the participant (or the participant's legally acceptable representative, as applicable) as indicated in Section 1.3 to collect additional information based on a Telephone Contact Questionnaire provided by the Sponsor. Data to be reported from this discussion will include SAEs and/or any updates to previously reported safety information.

8.1.11 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the vaccination regimen should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.12.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.11.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.12 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity grade of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

8.1.13 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Immunogenicity Assessments

Sera from participants will be used to measure pneumococcal vaccine-induced OPA and IgG responses and QIV-induced HAI responses. These endpoints will be tested for all

immunogenicity blood draws specified in Section 1.3. Blood collection, storage, and shipment instructions for serum samples will be provided in the operations/laboratory manual.

The MOPA will be used for measuring OPA responses. Opsonization of pneumococci for phagocytosis is an important mechanism by which antibodies to polysaccharides protect against disease in vivo. The OPA assay is a useful tool for assessing the protective function of serotype-specific antibodies and, therefore, the immunogenicity of pneumococcal vaccine formulations.

Serotype-specific IgG will be measured using the Pn ECL assay to assess the concentration of binding antibodies to capsular polysaccharide of *S pneumoniae*.

The HAI assay will be used to measure influenza vaccine-induced antibodies that inhibit hemagglutination. The HAI results reflect the degree of hemagglutination inhibition.

After completion of immunogenicity testing to evaluate the study objectives and hypotheses, serum samples will be stored to conduct any additional study-related testing as requested by regulatory agencies or the Sponsor. For participants who provide optional consent for FBR, leftover sera from the study may be used for other purposes, such as the development and/or validation of pneumococcal assays after completion of all study immunogenicity testing.

8.2.1 Multiplex Opsonophagocytic Assay (MOPA)

The MOPA is an antibody-mediated killing assay that measures the ability of human serum to kill *S pneumoniae* serotypes with the help of complement and phagocytic effector cells [Burton, Robert L. and Nahm, Moon H. 2006]. The ability of the assay to simultaneously test 4 serotypes at a time reduces the amount of serum needed for testing. The assay readout is the opsonization index, which is the reciprocal of the highest dilution that gives ≥50% bacterial killing, as determined by comparison to assay background controls. The Sponsor has developed and optimized the MOPA in a high-throughput microcolony platform, which not only covers all 21 serotypes in V116, but also includes serotypes 6C and 15B so that antibodies induced by vaccine serotypes 6A and 15C but cross-reactive to serotypes 6C and 15B, respectively, can be measured. The assay has been validated for various performance parameters of the assay including precision, ruggedness, relative accuracy/dilutional linearity, and the limit of detection of the assay.

8.2.2 Pneumococcal Electrochemiluminescence (Pn ECL)

The Sponsor has developed, optimized, and validated a multiplex, ECL-based detection method for the quantitation of IgG serotype-specific antibodies. This multiplexed ECL assay not only detects all 21 serotypes contained in V116, but also detects serotypes 6C and 15B so that antibodies induced by vaccine serotypes 6A and 15C, but cross-reactive to serotypes 6C and 15B, respectively, can be measured. The ECL assay is based on the Meso-Scale Discovery technology, which employs disposable multispot microtiter plates. Briefly, PnPs are bound to the surface of 96-well 10 plex carbon microplates, and serum containing purported anti-PnPs antibodies is added. The anti-PnPs antibodies bind to the coated plates and form an antibody-antigen complex. The bound antibody-antigen complex can be detected

using a ruthenium labeled anti-human IgG. Plates are read by measure of the chemiluminescent signal emitted from the ruthenium tag upon electrochemical stimulation initiated at the electrode surfaces of the microplates. CCI [redacted] ssay validation studies showed excellent performance operating characteristics for precision (intra- and inter-assay), dilutability, ruggedness (to different plate lots and analysts), relative accuracy, and specificity.

8.2.3 Hemagglutination Inhibition (HAI) Assay

The HAI assay is based on the WHO established method as described in the WHO Manual for the Laboratory Diagnosis and Virological Surveillance of Influenza [WHO Global Influenza Surveillance Network 2011]. The HAI assay relies on the tendency of influenza virus to bind to red blood cells, causing them to agglutinate. It is a traditional method to measure vaccine-induced antibodies to influenza that bind to the hemagglutinin molecule, thereby inhibiting hemagglutination. The HAI test is generally performed using microtiter plates. Nonspecific inhibitors of hemagglutination that occur naturally in sera are removed prior to testing. Serially diluted serum is then mixed with standardized quantities of hemagglutinin antigens compatible with the strains included in the seasonal vaccine formulation. After addition of red blood cells, the degree of inhibition of agglutination compared with strain-specific reference sera is assessed. The HAI titer is the inverse of the highest dilution of serum exhibiting complete inhibition of hemagglutination.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination and a brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard before vaccination as indicated in Section 1.3. The directed physical examination should focus on examining systems related to any ongoing conditions and/or follow-up on previously reported AEs.

Findings related to the physical examinations should be documented in the source documents. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Pregnancy Testing

A pregnancy test consistent with local requirements (sensitive to at least 25 IU hCG) must be performed before vaccination in WOCBP as described in Section 1.3.

Urine or serum tests can be used, and results must be negative before vaccination can occur. A detailed definition of WOCBP is provided in Appendix 5.

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

8.3.3 Body Temperature Measurements

Each participant's body temperature must be taken by study-site staff before vaccination as described in Section 1.3. The prevaccination temperature should be documented in the participant's source documents. Participants who have febrile illness (defined as oral or tympanic temperature ≥100.4°F [≥38.0°C]; axillary or temporal temperature ≥99.4°F [≥37.4°C]) <72 hours before vaccination must be rescheduled.

Participants will also record oral body temperature measurements using the eVRC (Section 8.1.9) from Day 1 to Day 5 after each vaccination.

8.3.4 Postvaccination Observation Period

All participants will be observed for at least 30 minutes after vaccination for any immediate reactions. If any immediate AEs are observed during this period, the time at which the event occurred within this timeframe, as well as the event itself, any concomitant medications that were administered, and resolution of the event must be recorded on the appropriate eCRF.**Clinical Safety Laboratory Assessments**

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 to 44 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before randomization, must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

All nonserious AEs and other reportable safety events (excluding pregnancy and lactation exposure) must be reported by the investigator from the day of randomization through 30 days after the first vaccination and from the time of each subsequent vaccination through 30 days postvaccination.

All pregnancies and lactation exposure during breastfeeding must be reported by the investigator from the day of randomization through 6 weeks postvaccination.

All SAEs must be reported by the investigator throughout the duration of the individual's participation in the study, regardless of whether related to the study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator

considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 3 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. – any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (important medical events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable for this study.

8.4.7 Events of Clinical Interest

There are no ECIs for this study.

8.4.8 Adverse Events on the VRC

Participants will use an eVRC to report solicited and unsolicited AEs.

The definitions of solicited and unsolicited AEs can be found in Appendix 3.

8.4.8.1 Solicited Adverse Event

Solicited AEs for this study are summarized in Table 4.

Table 4 Solicited Adverse Events

Type of Solicited Adverse Event	Predefined Solicited Adverse Events (Preferred Term)	Solicited Time Period
Injection site	• Injection-site pain or tenderness (injection-site pain) • Injection-site redness (injection-site erythema) • Injection-site swelling (injection-site swelling)	Day 1 through Day 5 postvaccination
Systemic	• Headache (headache) • Muscle aches all over body (myalgia) • Tiredness (fatigue)	Day 1 through Day 5 postvaccination

8.4.8.2 Unsolicited Adverse Events

Unsolicited AEs for this study are events that are 1) not predefined in Table 4 or 2) predefined in Table 4 but reported at any time outside the solicited period.

8.5 Treatment of Overdose

In this study, an overdose is the administration of more than 1 dose of any individual study vaccine in any 24-hour period.

No specific information is available on the treatment of overdose.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- DNA for future research
- Leftover study serum after completion of immunogenicity testing stored for future research

8.10 Optional Assay Development Blood Sample Collection

If the participant documented informed consent for the optional assay development blood samples, these samples will be used to support future development work on improving bioanalytical measurements, which requires high-volume single-donor samples to monitor performance of the assay over time.

Sample collection, storage, and shipment instructions for the optional assay development blood samples will be provided in the operations/laboratory manual.

8.11 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.12.1 Screening

Screening procedures will be conducted at Visit 1 as outlined in Section 1.3. Potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

If Visit 1 is rescheduled (see Section 5.2), a pregnancy test (if applicable); a body temperature measurement; and a review of inclusion/exclusion criteria, prior medications/vaccinations, and medical history must be repeated before vaccination.

8.12.2 Treatment Period/Vaccination Visit

Requirements during the treatment period are outlined in Section 1.3.

8.12.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

A participant who discontinues from study intervention will continue to participate in protocol-specified activities as outlined in Section 1.3, including blood draws for immunogenicity testing and AE monitoring activities, as long as the participant does not withdraw consent.

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. The protocol will be amended if, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post-hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 3 Randomized, Double-blind, Placebo-Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 When Administered Concomitantly with Influenza Vaccine in Adults 50 Years of Age or Older.
Treatment Assignment	Approximately 1000 participants will be randomly assigned in a 1:1 ratio to receive either V116 concomitantly with QIV or V116 sequentially with QIV. Randomization will be stratified based on the participant's age (50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years) and prior pneumococcal vaccination status (PCV13- and PPSV23-naïve, prior receipt of PCV13 only, prior receipt of PPSV23 only, and prior receipt of PCV13 and PPSV23) at the time of randomization.
Analysis Populations	**Immunogenicity**: PP population **Safety**: APaT population
Primary Endpoint(s)	**Immunogenicity**: • Serotype-specific OPA GMTs at 30 days postvaccination with V116 • Strain-specific HAI GMTs at 30 days postvaccination with QIV **Safety**: • Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain) from Day 1 through Day 5 postvaccination • Proportion of participants with solicited systemic AEs (muscle aches all over body/myalgia, headache, and tiredness/fatigue) from Day 1 through Day 5 postvaccination • Proportion of participants with vaccine-related SAEs from Day 1 through the duration of participation in the study
Key Secondary Endpoints	• Serotype-specific IgG GMCs at 30 days postvaccination with V116

Statistical Methods for Key Immunogenicity Analyses	Immunogenicity analyses will be conducted for each of the 21 pneumococcal serotypes in V116 and each of the 4 influenza strains in QIV separately. For the primary immunogenicity objectives: H1: The concomitant group will be considered noninferior to the sequential group if the lower bound of the 2-sided 95% CI of the OPA GMT ratio (GMT_1/GMT_2) for each of the 21 serotypes is >0.50, where GMT_1 is the serotype-specific OPA GMT for the concomitant group and GMT_2 is the serotype-specific OPA GMT for the sequential group. H2: The concomitant group will be considered noninferior to the sequential group if the lower bound of the 2-sided 95% CI of the HAI GMT ratio (GMT_1/GMT_2) for each of the 4 strains is >0.67, where GMT_1 is the strain-specific HAI GMT for the concomitant group and GMT_2 is the strain-specific HAI GMT for the sequential group. For the hypotheses H1 and H2, estimation of serotype-specific OPA GMT ratios for each of the 21 serotypes in V116 and strain-specific HAI GMT ratios for each of the 4 strains in QIV, 95% CIs, and *p*-values will be calculated using the cLDA method [Liang, K-Y and Zeger, S. L. 2000].
Statistical Methods for Key Safety Analyses	For overall safety evaluation, safety parameters will be summarized via descriptive statistics. For selected safety parameters, between-group 95% CIs will be provided for the percentage of participants using the M&N method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	To support the periodic review of safety and tolerability data across the adult V116 Phase 3 program, an external unblinded statistician will provide unblinded interim safety summaries to an independent external DMC for their review. Unblinded immunogenicity data will be made available to the DMC upon request to enable a benefit-risk assessment.
Multiplicity	This study will be considered to have met its primary immunogenicity objectives if noninferiority is demonstrated with respect to OPA GMTs for the 21 serotypes in V116 and HAI GMTs for the 4 influenza strains in QIV at a 1-sided 2.5% alpha-level. Since comparisons are made individually for each of the 21 serotypes and the 4 influenza strains, this approach controls the 1-sided type 1 error rate at 0.025, and no multiplicity adjustment is required.
Sample Size and Power	This study will randomize approximately 500 participants into the concomitant group and 500 participants into the sequential group and has approximately 90% power to demonstrate noninferiority of OPA GMT ratio for the 21 pneumococcal serotypes included in V116 and noninferiority of HAI GMT ratio for the 4 influenza strains in QIV at an overall 1-sided 2.5% alpha-level.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment. Randomization will be implemented using an IRT system.

Blinding issues related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Immunogenicity and safety endpoints that will be evaluated for within- and/or between-intervention differences are listed below.

9.4.1 Immunogenicity Endpoints

OPA and IgG responses will be measured for all 21 serotypes contained in V116 (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B), and 2 cross-reactive serotypes (6C and 15B).

HAI responses will be measured for all 4 influenza strains contained in QIV.

The primary immunogenicity endpoints include:

- Serotype-specific OPA GMTs at 30 days postvaccination with V116.
- Strain-specific HAI GMTs at 30 days postvaccination with QIV.

The secondary immunogenicity endpoints include:

- Serotype-specific IgG GMCs at 30 days postvaccination with V116.
- Serotype-specific GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with V116) to 30 days postvaccination with V116 for both OPA and IgG responses.
- Strain-specific HAI GMFRs from baseline (prevaccination with QIV) to 30 days postvaccination with QIV.
- Strain-specific proportions of participants with a HAI titer ≥1:40 at 30 days postvaccination with QIV.
- Strain-specific proportions of participants that seroconvert at 30 days postvaccination with QIV for HAI responses. Seroconversion for HAI responses is defined as achieving either (1) a ≥4-fold rise in HAI titer from baseline (prevaccination with QIV) to 30 days postvaccination with QIV among participants who are seropositive at baseline (HAI titer ≥1:10) or (2) a HAI titer of ≥1:40 at 30 days postvaccination with QIV among participants who are seronegative at baseline (HAI titer < 1:10).

The exploratory immunogenicity endpoints include the summaries of the cross-reactive immune responses to serotypes within a serogroup using serotype-specific OPA and IgG responses at 30 days postvaccination with V116.

9.4.2 Safety Endpoints

The safety endpoints for overall safety assessment that address the primary objectives include:

- Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain) from Day 1 through Day 5 postvaccination.
- Proportion of participants with solicited systemic AEs (muscle aches all over body/myalgia, headache, and tiredness/fatigue) from Day 1 through Day 5 postvaccination.
- Proportion of participants with vaccine-related SAEs from Day 1 through the duration of participation in the study.

Additional safety endpoints for overall safety assessment include:

- Proportion of participants with the broad AE categories consisting of any AE, any unsolicited AE, and any vaccine-related AE from Day 1 through Day 30 postvaccination.
- Proportion of participants with the broad AE categories consisting of any SAE, any vaccine-related SAE, discontinuation due to an AE, and death from Day 1 through the duration of participation in the study.
- Proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 5 postvaccination.

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

The PP population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s). Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Failure to receive the assigned regimen as per randomization schedule at Visit 1 (Day 1).
- Receipt of a prohibited medication or prohibited vaccine prior to study vaccination.

Additional potential deviations that may result in the exclusion of a participant from the PP population for specific immunogenicity analyses (depending on the time point) include:

- Failure to receive study vaccine at Visit 3 (Day 30).
- Failure to receive correct clinical material as per randomization schedule at Visit 3 (Day 30).
- Receipt of a prohibited medication or prohibited vaccine prior to a blood sample collection.
- Collection of a blood sample outside of the pre-specified window.

The final determination on protocol deviations that impact the immunogenicity analysis, and thereby the composition of the PP population, will be made prior to the final unblinding of the database and will be documented in a separate memo. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the PP population.

A supportive analysis using the FAS population will also be performed for the primary immunogenicity endpoint. The FAS population consists of all randomized participants who received at least 1 study vaccination and have at least 1 serology result. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the FAS population.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study vaccination. Participants will be included in the group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population. If a participant receives incorrect study vaccines resulting in a regimen that does not belong to either of the 2 designed regimens in the study, this participant's data will be excluded from the APaT population and summarized separately.

At least 1 temperature measurement obtained subsequent to study intervention is required for inclusion in the analysis of temperature.

9.6 Statistical Methods

9.6.1 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the primary and secondary immunogenicity objectives. Methods related to exploratory objectives will be described in the sSAP.

Immunogenicity analyses will be conducted for each of the 21 pneumococcal serotypes in V116 and each of the 4 influenza strains in QIV separately.

Primary Endpoint/Hypothesis (H1)

The primary objective to compare the serotype-specific OPA GMTs at 30 days postvaccination with V116 between participants administered V116 concomitantly with QIV versus participants administered V116 sequentially with QIV will be assessed via the following noninferiority hypotheses:

H0: GMT1/GMT2 $\leq$0.50 versus

H1: GMT1/GMT2 >0.50,

where GMT1 is the serotype-specific OPA GMT for the concomitant group and GMT2 is the serotype-specific OPA GMT for the sequential group. A ratio of 0.50 corresponds to a 2.0 fold decrease of OPA GMT in the concomitant group as compared with the sequential group. Rejecting the null hypothesis (H0) at the 1-sided α=0.025 level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (concomitant group/sequential group) being >0.50 and would lead to the conclusion that the OPA responses in the concomitant group are noninferior to the sequential group for the 21 pneumococcal serotypes.

Primary Endpoint/Hypothesis (H2)

The primary objective to compare the strain-specific HAI GMTs at 30 days postvaccination with QIV between participants administered QIV concomitantly with V116 versus participants administered QIV sequentially will be assessed via the following noninferiority hypotheses:

H0: GMT1/GMT2 ≤0.67 versus

H1: GMT1/GMT2 >0.67,

where GMT1 is the strain-specific HAI GMT for the concomitant group and GMT2 is the strain-specific HAI GMT for the sequential group. A ratio of 0.67 corresponds to a 1.5 fold decrease of the HAI GMT in the concomitant group as compared with the sequential group. Rejecting the null hypothesis (H0) at the 1-sided α=0.025 level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (concomitant group/sequential group) being >0.67 and would lead to the conclusion that the influenza HAI responses in the concomitant group are noninferior to the sequential group for the 4 influenza strains.

To address the 2 primary immunogenicity objectives, the serotype-specific OPA GMTs at 30 days postvaccination with V116 and strain-specific HAI GMTs at 30 days postvaccination with QIV will be compared between intervention groups separately. Comparisons will be made through the estimation of serotype-specific OPA GMT ratios for each of the 21 serotypes in V116 and strain-specific HAI GMT ratios for each of the 4 strains in QIV, respectively. Estimation of the ratios, 95% CI, and the hypothesis test (ie, 1-sided *p*-value) will be calculated using the cLDA method proposed by Liang and Zeger [Liang, K-Y and Zeger, S. L. 2000] using data from both vaccination groups. In this model, the response vector consists of the log transformed antibody titers at baseline and 30 days postvaccination. The repeated measures model will include terms for vaccination group, time, the interaction of time-by-vaccination group, age stratum (ie, 50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years) at baseline, prior pneumococcal vaccination status (ie, PCV13- and PPSV23 naïve, prior receipt of PCV13 only, prior receipt of PPSV23 only, and prior receipt of PCV13 and PPSV23), the interaction of age stratum-by-time, and the interaction of prior pneumococcal vaccination status-by-time. This model will allow for different baseline means for each stratum but restrict the baseline mean within both the age stratum levels and the prior pneumococcal vaccination status stratum levels to be the same for both vaccination groups. The term for time will be treated as a categorical variable. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted maximum likelihood to make proper

statistical inference. This model allows the inclusion of participants who are missing either the baseline or postbaseline measurements, thereby increasing efficiency.

Further details of handling sparse data in stratification variables (eg, age and prior pneumococcal vaccination status) will be described in the sSAP.

Secondary Endpoints

A similar statistical approach will be used to evaluate the serotype-specific IgG GMCs at 30 days postvaccination with V116 for participants administered V116 concomitantly with QIV and participants administered V116 sequentially with QIV.

Descriptive statistics with point estimates and within-group 95% CIs will be provided for all other immunogenicity endpoints. For the continuous endpoints, the point estimates will be calculated by exponentiating the estimates of the mean of the natural log values and the within-group CIs will be derived by exponentiating the bounds of the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within group CIs will be calculated based on the exact method proposed by Clopper and Pearson[CLOPPER, C. J. and PEARSON, E. S. 1934].

Reverse Cumulative Distribution Curves for both OPA titers and IgG concentrations at 30 days postvaccination with V116 will be graphically displayed by serotype. Reverse Cumulative Distribution Curves for HAI titers at 30 days postvaccination with QIV will be graphically displayed by strain.

A detailed analysis strategy for key immunogenicity endpoints is listed in Table 5.

Table 5 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints				
OPA GMTs at 30 days postvaccination with V116	P	cLDA[b] (estimate, 95% CI, *p*-value)	PP	Model-based
	S		FAS	
HAI GMTs at 30 days postvaccination with QIV	P	cLDA[b] (estimate, 95% CI, *p*-value)	PP	Model-based
	S		FAS	
Secondary Endpoints				
IgG GMCs at 30 days postvaccination with V116	P	cLDA[b] (estimate, 95% CI)	PP	Model-based
GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with V116) to 30 days postvaccination with V116 for both OPA and IgG responses	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
HAI GMFRs from baseline (prevaccination with QIV) to 30 days postvaccination with QIV	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
Proportions of participants with HAI titer ≥1:40 at 30 days postvaccination with QIV	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
Proportions of participants that seroconvert at 30 days postvaccination with QIV for HAI responses	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

CI=confidence interval; cLDA=constrained longitudinal data analysis; FAS=full analysis set; GMC=geometric mean concentration; GMFR=geometric mean fold rise; GMT=geometric mean titer; HAI=hemagglutination inhibition; IgG=immunoglobulin G; OPA=opsonophagocytic activity; PP=per-protocol; QIV=quadrivalent influenza vaccine.
[a] P=primary approach; S=supportive approach.
[b] cLDA model with terms for vaccination group, time, the interaction of time-by-vaccination, age stratum at baseline, prior pneumococcal vaccination status, age stratum-by-time interaction, and prior pneumococcal vaccination status-by-time interaction.

9.6.2 Statistical Methods for Safety Analyses

Safety and Tolerability will be assessed by clinical review of all relevant parameters, including AEs and postvaccination temperature measurements.

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will be performed following any vaccination. A participant with an AE after the first vaccination, the second vaccination, or both vaccinations will contribute a count of one participant for the particular AE. The summary (ie, number and percentage) by the concomitant and sequential groups will include participants with any AEs, any unsolicited AEs, any vaccine-related AEs, any SAEs, any vaccine-related SAEs, discontinuation of vaccine due to an AE, any AEs resulting in death following any vaccination. Point estimates and 95% CIs for the between-group differences (the concomitant group compared with the sequential group) in the percentages of participants with the event will be provided.

The number and percentage of participants with specific AEs will also be provided. Point estimates and 95% CIs of the differences between intervention groups in the percentages of participants with specific AEs will be provided for solicited AEs and AEs that occur in ≥1% of participants in any intervention group. Events reported by <1% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful differences.

The number and percentage of participants with maximum temperature measurements meeting the Brighton Collaboration cut point [Marcy, S. M., et al 2004] will be provided along with point estimates and 95% CIs of between-group differences.

CIs for between-group differences will be calculated using the M&N Method [Miettinen, O. and Nurminen, M. 1985]. CIs that are not associated with pre-specified hypotheses are not adjusted for multiplicity. Therefore, they should be regarded as helpful descriptive measures

for the review of the safety profile and not a formal method for assessing statistical significance of between-group differences. Rainfall plots with point estimates and 95% CIs will be displayed for AEs that occur in ≥5% of participants in the concomitant or sequential group.

The analysis strategy for safety endpoints is summarized in Table 6.

Table 6 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95 % Between-group CI	Graphical Display
Overall Safety Assessment	Solicited injection-site AE (Day 1 through Day 5 postvaccination) [a]	X	X	
	Solicited systemic site AE (Day 1 through Day 5 postvaccination) [a]	X	X	
	Any AE [b]	X	X	
	Any unsolicited AE [b]	X	X	
	Any vaccine-related AE [b]	X	X	
	Any SAE [b]	X	X	
	Any vaccine-related SAE [b]	X	X	
	Discontinuation due to AE [b]	X	X	
	Death [b]	X	X	
	Specified AEs by SOC and PT [c]	X	X	X
	Maximum temperature (Day 1 through Day 5 postvaccination) [d]	X	X	

AE=adverse event; CI=confidence interval; PT=preferred term; SAE=serious adverse event; SOC=system organ class.
[a] Solicited injection-site AEs include redness/erythema, swelling, and tenderness/pain; solicited systemic AEs include muscle aches all over body/myalgia, headache, and tiredness/fatigue.
[b] These endpoints are broad AE categories. For example, descriptive statistics for the safety endpoint of "Any AE" will provide the number and percentage of participants with at least 1 AE.
[c] Descriptive statistics, 95% between-group CI, and graphical display will be provided for specific AEs with incidence >0%, ≥1%, and ≥5% of participants respectively, in the concomitant and sequential groups.
[d] Maximum temperature measurements are categorized by Brighton Collaboration cut points.

In addition to the analyses following any vaccination, a supportive analysis of select safety endpoints will be provided after each vaccination. Point estimates by vaccination group will be provided for injection-site AEs following V116 and following QIV separately. That is, the proportion of participants with injection-site AEs following administration of V116 will include AEs reported following V116 administration in the limb corresponding to the location of V116 administration. Similarly, the proportion of participants with injection-site AEs following administration of QIV will include AEs reported following QIV administration in the limb corresponding to the location of QIV administration.

Additionally, the systemic AEs following each vaccination time point for each vaccination group will be summarized. That is, descriptive summaries of systemic AEs will include AEs reported following administration of:

- QIV and V116 in the concomitant group at Visit 1 (Day 1).
- QIV with placebo in the sequential group at Visit 1 (Day 1).
- Placebo alone in the concomitant group at Visit 3 (Day 30).

- V116 alone in the sequential group at Visit 3 (Day 30).

9.6.3 Demographic and Baseline Characteristics

The comparability of the vaccination groups for each relevant demographic and baseline characteristic will be assessed by using summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, race, ethnicity, sex, and gender), baseline characteristics, prior and concomitant vaccinations and medications will be summarized by vaccination group either by descriptive statistics or categorical tables.

9.7 Interim Analyses

A periodic review of safety and tolerability data across the V116 Phase 3 adult program will be conducted by an independent, unblinded, external DMC. A description of the structure and function of the DMC, along with the timing and content of the safety reviews, will be outlined in the DMC charter. Information regarding the composition of the DMC is provided in Appendix 1. In addition, unblinded immunogenicity data will be made available to the DMC upon request to enable a benefit-risk assessment.

The DMC will serve as the primary reviewer of the results of the ongoing safety reviews and will make recommendations for discontinuation of the study or protocol modifications to an EOC of the Sponsor (see Appendix 1 for details on the Committees Structure for this study). If the DMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC of the Sponsor (and potentially other limited Sponsor personnel) may be unblinded to results at the intervention level to act on these recommendations. The extent to which individuals are unblinded with respect to ongoing safety reviews will be documented by the external unblinded statistician. Additional logistical details will be provided in the DMC charter.

Study enrollment may be ongoing at the time of external DMC review. Blinding to intervention assignment will be maintained at all investigational sites. Participant-level unblinding will be restricted to an external unblinded statistician performing ongoing safety reviews. Intervention-level, ongoing safety reviews will be provided by the external unblinded statistician to the DMC. Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the safety reviews.

9.8 Multiplicity

The study will have met its primary immunogenicity objectives if noninferiority is demonstrated with respect to the OPA GMTs for the 21 serotypes in V116 and the HAI GMTs for the 4 influenza strains in QIV at a 1-sided 2.5% alpha-level. All hypotheses will be tested individually for each pneumococcal serotype and influenza strain at a 1-sided

0.025 alpha-level. This approach controls the 1-sided type 1 error rate at 0.025, and no multiplicity adjustment will be required.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity Analyses

This study will randomize approximately 500 participants into the concomitant group and 500 participants into the sequential group.

Primary Immunogenicity Endpoints/Hypotheses (H1 and H2)

For the primary hypotheses, this study has approximately 90% power for demonstrating noninferiority of the serotype-specific OPA GMT ratios for the 21 pneumococcal serotypes included in V116 and >99% power for demonstrating noninferiority of the strain-specific HAI GMT ratios for the 4 influenza strains in QIV at an overall 1-sided 2.5% alpha-level.

The sample size and power calculations are based on the following assumptions:

- 90% evaluability rate (approximately 450 evaluable participants per treatment group) for both primary endpoints (OPA GMT ratios and HAI GMT ratios).
- The underlying OPA GMT ratio is CCI (concomitant group/sequential group) for the 21 pneumococcal serotypes. The assumption for this ratio is based on results of studies evaluating the administration of PCVs with concomitant influenza vaccines.
- The variabilities for OPA titers in both concomitant and sequential groups are the same as those observed in V116-001 Phase 2. The standard deviations of the natural log titers for the 21 pneumococcal serotypes in V116 range from 1.06 to 1.95.
- The underlying HAI GMT ratio is CCI (concomitant group/sequential group) for the 4 influenza strains. The variabilities for HAI titers in both concomitant and sequential groups are the same as that observed in V114-021. The standard deviations of the natural log titers for the 4 influenza strains range from 1.08 to 1.41 in the concomitant group.

The 2 hypotheses are assumed to be independent. The overall power for the primary immunogenicity hypotheses is estimated to be approximately 90% (=0.909×>0.992) to achieve the pre-specified noninferiority statistical criteria for the 21 serotypes in V116 and the 4 influenza strains in QIV.

9.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying incidence of participants with an SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least 1 SAE among 500 participants in the concomitant group if the underlying incidence of an SAE is 0.32% (1 of every 311 participants receiving the vaccine). There is a 50% chance of observing at least 1 SAE among 500 participants in the concomitant group if the underlying incidence of an SAE is 0.14% (1 of every 721 participants receiving the vaccine). If no SAEs are observed

among 500 participants in the concomitant group, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is <0.74% (1 in every 136 participants) in the concomitant group.

The percentage point differences between the 2 vaccination groups that could be detected with 80% probability is summarized in Table 7 for a variety of hypothetical underlying incidences of an AE. These calculations assume 500 participants in each group and are based on a 2-sided 5% alpha-level. The calculations are based on an asymptotic method proposed by Farrington and Manning [Farrington, C. P. 1990]; no multiplicity adjustments were made.

Table 7 Differences in Incidence of AE Rates Between the 2 Vaccination Groups That Can Be Detected With an Approximate 80% Probability (Assuming 2-sided 5% Alpha-level With 500 Participants in Each Group)

Incidence of Adverse Event		**Risk Difference**
Concomitant Group (%) N=500	**Sequential Group (%) N=500**	**Percentage Points**
1.8	0.1	1.7
5.3	2.0	3.3
9.6	5.0	4.6
15.9	10.0	5.9
21.9	15.0	6.9
27.5	20.0	7.5
38.4	30.0	8.4
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. The incidences assume a 2-sided 5% alpha-level with 500 participants in each group. No multiplicity adjustments were made. The calculations are based on an asymptotic method proposed by Farrington and Manning [Farrington, C. P. 1990].		

9.10 Subgroup Analyses

Subgroup analyses will be performed for the primary immunogenicity endpoints and selected safety endpoints (summary of AEs and summary of solicited AEs). The following subgroups are planned for evaluation:

- Age (50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years of age)
- Sex
- Race
- Ethnicity
- Prior pneumococcal vaccination status (PCV13- and PPSV23-naïve, prior receipt of PCV13 only, prior receipt of PPSV23 only, and prior receipt of PCV13 and PPSV23)

Further details of subgroup analyses will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

Given that participants will receive a single dose of V116, QIV, and placebo, compliance will not be calculated. However, the number and proportion of randomized participants receiving each vaccination will be summarized (Section 9.12).

9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered V116, QIV, and placebo.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data

protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary,

authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.3 Scientific Advisory Committee (SAC)

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible,

contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 8 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)
hCG=human chorionic gonadotropin; WOCBP=women of childbearing potential	

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a VRC and that is communicated by a participant/participant's legally authorized representative who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Solicited AEs are predefined local (at the injection/administration site) and systemic events for which the participant/participant's legally authorized representative is specifically questioned, and which are noted by the participant/participant's legally authorized representative in their VRC.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of overall intensity grade for each AE and SAE (and other reportable event) reported during the study. An overall intensity grade will be assigned to injection-site AEs, specific systemic AEs, other systemic AEs, and vital sign (temperature) AEs as shown in the following tables. The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

Injection-Site AE Overall Intensity Grading Scale

Injection-Site Reaction to Study Vaccine/Placebo	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Injection-site AEs occurring Days 1 through 5 following receipt of study vaccine/placebo				
Pain/Tenderness	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Erythema/Redness	Size measured as ≤5 cm	Size measured as 5.1 to 10 cm	Size measured as >10 cm	Necrosis or exfoliative dermatitis or results in ER visit or hospitalization
Swelling	Size measured as ≤5 cm	Size measured as 5.1 to 10 cm	Size measured as >10 cm	Necrosis or ER visit or hospitalization
Other	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization

Injection-Site Reaction to Study Vaccine/Placebo	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Any injection-site reaction that begins ≥6 days after receipt of study vaccine/placebo				
Pain/Tenderness Erythema/Redness Swelling Other	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization

AE=adverse event; ER=emergency room

The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

Specific Systemic AE Overall Intensity Grading Scale

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

ER=emergency room
The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

Other Systemic AE Overall Intensity Grading Scale

Systemic Illness[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[b]
Illness or clinical AE (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and required medical intervention	ER visit or hospitalization

AE=adverse event; ER=emergency room; eVRC=electronic Vaccine Report Card; SAE=serious adverse event
The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

[a] Based upon information provided by the patient on the eVRC and verbally during the eVRC review during the primary safety follow-up period. For SAEs reported beyond the primary safety follow-up period, grading will be based upon the initial report and/or follow-up of the event.

[b] AEs resulting in death will be assessed as Grade 4.

Vital Sign (Temperature) Overall Intensity Grading Scale

Vital Signs[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)[b]	38.0 to 38.4	38.5 to 38.9	39.0 to 40.0	>40.0
(°F)[b]	100.4 to 101.1	101.2 to 102.0	102.1 to 104.0	>104.0

The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

[a] Participant should be at rest for all vital sign requirements.

[b] Oral temperature; no recent hot or cold beverages or smoking.

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based on the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a vaccine-induced effect?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?
  - **Rechallenge:** Was the participant reexposed to the study intervention in the study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose vaccine study; or (3) study intervention(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT

RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant[c] • IUS[d] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. • Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ABCs	Active Bacterial Care Surveillance
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
APaT	All-Participants-as-Treated
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
cLDA	Constrained Longitudinal Data Analysis
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CTR	Clinical Trials Regulation
deOAc	De-O-acylated
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECI	event of clinical interest
ECL	electrochemiluminescence
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EU	European Union
eVRC	electronic Vaccination Report Card
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Abbreviation	Expanded Term
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean concentration
H	hypothesis
HAI	hemagglutination inhibition
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular(ly)
IMP	investigational medicinal product
IND	Investigational New Drug
IPD	Invasive pneumococcal disease
IRB	Institutional Review Board
IRT	interactive response technology
ISO	International Organization for Standardization
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	Lactational amenorrhea method
M&N	Miettinen and Nurminen
MedDRA	Medical Dictionary for Regulatory Activities
MOPA	Mulitplexed Opsonophagocytic Assay
mRNA	messenger RNA

Abbreviation	Expanded Term
NIMP	noninvestigational medicinal product
NSAE	nonserious adverse event
OPA	opsonophagocytic activity
PCV	Pneumococcal conjugate vaccine
PCV13	Prevnar 13™ (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F)
PCV15	VAXNEUVANCE™ (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F)
PCV20	Prevnar 20™
PK	Pharmacokinetics
Pn ECL	Pneumococcal electrochemiluminescence
PnPs	Pneumococcal polysaccharide
PP	per-protocol
PPSV23	PNEUMOVAX™23 (Serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F)
QIV	quadrivalent influenza vaccine
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
US	United States
VRC	Vaccination Report Card
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

11 REFERENCES

[Anttila, M., et al 1999]	Anttila M, Voutilainen M, Jäntti V, Eskola J, Käyhty H. Contribution of serotype-specific IgG concentration, IgG subclasses and relative antibody avidity to opsonophagocytic activity against Streptococcus pneumoniae. Clin Exp Immunol 1999;118(3):402-7.	[03QY70]
[Burton, Robert L. and Nahm, Moon H. 2006]	Burton RL, Nahm MH. Development and validation of a fourfold multiplexed opsonization assay (MOPA4) for pneumococcal antibodies. Clin Vaccine Immunol 2006;13(9):1004-9.	[03QT2R]
[Centers for Disease Control and Prevention 2010]	Centers for Disease Control and Prevention. Prevention of Pneumococcal Disease Among Infants and Children - Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine; Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2010;59(RR-11):1-19.	[03RSB6]
[Centers for Disease Control and Prevention 2015]	Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. 13th ed. Hamborsky J, Kroger A, Wolfe S, editors. Washington (DC): Department of Health and Human Services (HHS); c2015. Chapter 6, Vaccine administration; p. 79-106.	[0508PV]
[Centers for Disease Control and Prevention 2019]	Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP), summary report, October 24-25, 2018. Washington (DC): Department of Health and Human Services (HHS); 2019. 190 p.	[057YZL]

[Centre for Disease Control and Prevention 2016]	Centre for Disease Control and Prevention. Active Bacterial Core surveillance (ABCs) report emerging infections program network Streptococcus pneumoniae, 2016. Atlanta (GA): Department of Health and Human Services (HHS); 2016. 1 p.	[052RDB]
[Centre for Disease Control and Prevention 2018]	Centers for Disease Control and Prevention. Active Bacterial Core surveillance (ABCs) report: emerging infections program network: Streptococcus pneumoniae, 2018. Washington (DC): Department of Health and Human Services (HHS); 2018.	[05J8JP]
[CLOPPER, C. J. and PEARSON, E. S. 1934]	Clopper CJ, Pearson ES. The use of confidence of fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[03RRVC]
[Curcio, D., et al 2015]	Curcio D, Cane A, Isturiz R. Redefining risk categories for pneumococcal disease in adults: critical analysis of the evidence. Int J Infect Dis. 2015;37:30-5.	[04VSHL]
[Demczuk, W. H. B., et al 2013]	Demczuk WHB, Martin I, Griffith A, Lefebvre B, McGeer A, Lovgren M, et al. Serotype distribution of invasive Streptococcus pneumoniae in Canada after the introduction of the 13-valent pneumococcal conjugate vaccine, 2010-2012. Can J Microbiol 2013;59:778-88.	[03XKZ6]
[Dominguez, A., et al 2013]	Dominguez A, Castilla J, Godoy P, Delgado-Rodriguez M, Saez M, Soldevila N, et al. Effectiveness of vaccination with 23-valent pneumococcal polysaccharide vaccine in preventing hospitalization with laboratory confirmed influenza during the 2009-2010 and 2010-2011 seasons. Hum Vaccin Immunother. 2013 Apr;9(4):865-73.	[04WX4B]

[Drijkoningen, J. J 2014]	Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect. 2014 May;20 Suppl 5:45-51.	[04NFHN]
[European Center for Disease Prevention and Control 2018]	European Center for Disease Prevention and Control. Surveillance report: annual epidemiological report for 2016: invasive pneumococcal disease. Stockholm (Sweden): European Center for Disease Prevention and Control (ECDC) 2018 Aug. 12 p.	[052RH8]
[European Medicines Agency 2016]	European Medicines Agency. Guideline on influenza vaccines: non-clinical and clinical module. London: European Medicines Agency. 2016. 31 p. (EMA publication; no. EMA/CHMP/VWP/457259/2014).	[04W9SY]
[Farrington, C. P. 1990]	Farrington CP, Manning G. Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk. Stat Med Vol. 9,1447-1454 (1990)	[04FS6L]
[Food and Drug Administration (CDER) 2007]	Food and Drug Administration (CDER). Guidance for Industry: clinical data needed to support the licensure of pandemic influenza vaccines. Silver Spring: U.S. Department of Health and Human Services; 2007. 17 p.	[04GKNY]
[Food and Drug Administration 2007]	Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD. Sep 2007.	[05B4S4]

[Frenck, R. W. Jr., et al 2012]	Frenck RW Jr, Gurtman A, Rubino J, Smith W, van Cleeff M, Jayawardene D, et al. Randomized, controlled trial of a 13-valent pneumococcal conjugate vaccine administered concomitantly with an influenza vaccine in healthy adults. Clin Vaccine Immunol. 2012 Aug;19(8):1296-303.	[040DGC]
[Gilchrist, S. A., et al 2012]	Gilchrist SA, Nanni A, Levine O. Benefits and effectiveness of administering pneumococcal polysaccharide vaccine with seasonal influenza vaccine: an approach for policymakers. Am J Public Health. 2012 Apr;102(4):596-605.	[040DG8]
[Golden, A. R., et al 2016]	Golden AR, Adam HJ, Zhanel GG. Invasive Streptococcus pneumoniae in Canada, 2011-2014: Characterization of new candidate 15-valent pneumococcal conjugate vaccine serotypes 22F and 33F. Vaccine. 2016 May 17;34(23):2527-30.	[04KWF0]
[Grohskopf, L. A., et al 2017]	Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Bresee JS, Fry AM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices - United States, 2017-18 influenza season. MMWR Recomm Rep. 2017 Aug 25;66(2):1-20.	[04W72Z]
[Hicks, L. A., et al 2007]	Hicks LA, Harrison LH, Flannery B, Hadler JL, Schaffner W, Craig AS, et al. Incidence of Pneumococcal Disease Due to Non-Pneumococcal Conjugate Vaccine (PCV7) Serotypes in the United States during the Era of Widespread PCV7 Vaccination, 1998-2004. J Infect Dis 2007;196:1346-54.	[03QT0G]
[Janssens, J. P. 2004]	Janssens JP, Krause KH. Pneumonia in the very old. Lancet Infect Dis. 2004 Feb;4:112-24.	[04VTNJ]

[Kobayashi, M. 2021]	Kobayashi M. Considerations for age-based and risk-based use of PCV15 and PCV20 among U.S. adults and proposed policy options. Slides presented at: Advisory Committee on Immunization Practices (ACIP) meeting; 2021 Oct 20-21; Atlanta, GA.	[07XY2V]
[Kobayashi, M., et al 2022]	Kobayashi M, Farrar JL, Gierke R, Britton A, Childs L, Leidner AJ, et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. adults: updated recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022 Jan 28;71(4):109-17.	[07YPRJ]
[Liang, K-Y and Zeger, S. L. 2000]	Liang K-Y, Zeger SL. Longitudinal data analysis of continuous and discrete responses for pre-post designs. Sankyha: The Indian Journal of Statistics 2000;62(Series B, Part 1):134-48.	[00V5V6]
[Marcy, S. M., et al 2004]	Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Connell Jones M, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004;22:551-6.	[03PVW0]
[Matanock, A. 2018]	Matanock A. Estimating pneumococcal pneumonia burden among U.S. adults and progress on the research agenda for potential policy change. Slides presented at: Advisory Committee on Immunization Practices (ACIP) Meeting; 2018 Feb 21-22; Atlanta, GA.	[05B5W5]

[Matanock, A., et al 2019]	Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged greater than or equal to 65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019 Nov 22;68(46):1069-75.	[05D5ST]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]
[Miller, Elizabeth, et al 2011]	Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. Lancet Infect Dis 2011;11(10):760-8.	[03RKY7]
[Moore, M. R., et al 2015]	Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Lexau C, Bennett NM, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis. 2015 Feb 3. [Epub ahead of print].	[043MRP]
[Pilishvili, T. 2015]	Pilishvili T, Bennett NM. Pneumococcal disease prevention among adults: strategies for the use of pneumococcal vaccines. Am J Prev Med. 2015 Dec;49(6 suppl 4):S383-90.	[04WP9S]
[Pilishvili, Tamara, et al 2010]	Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 2010;201(1):32-41.	[03R5S4]

[Reber, A. 2013]	Reber A, Katz J. Immunological assessment of influenza vaccines and immune correlates of protection. Expert Rev Vaccines. 2013;12(5):519-36.	[04W9TH]
[Romero-Steiner, S., et al 1997]	Romero-Steiner S, Libutti D, Pais LB, Dykes J, Anderson P, Whitin JC, et al. Standardization of an opsonophagocytic assay for the measurement of functional antibody activity against streptococcus pneumoniae using differentiated HL-60 cells. Clin Diagn Lab Immunol 1997;4(4):415-22.	[03NWQ5]
[Schwarz, T. F. 2013]	Schwarz TF, Schmoele-Thoma B. Assessment of functional antibacterial opsonophagocytic antibodies elicited by 13-valent pneumococcal conjugate vaccine administered concomitantly with trivalent influenza vaccine in a randomized clinical trial in adults aged >=65 years. Vaccine. 2013;31:291-4.	[04WR0V]
[Schwarz, T. F., et al 2011]	Schwarz TF, Flamaing J, Rumke HC, Penzes J, Juergens C, Wenz A, et al. A randomized, double-blind trial to evaluate immunogenicity and safety of 13-valent pneumococcal conjugate vaccine given concomitantly with trivalent influenza vaccine in adults aged >=65 years. Vaccine. 2011;29:5195-202.	[04WQY8]
[Severance, R., et al 2021]	Severance R, Schwartz H, Dagan R, Connor L, Li J, Pedley A, et al. Safety, tolerability, and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, administered concomitantly with influenza vaccine in healthy adults aged >=50 years: a randomized phase 3 trial (PNEU-FLU). Hum Vaccin Immunother. In press 2021.	[07YXZM]

[Simonsen, L., et al 2014]	Simonsen L, Taylor RJ, Schuck-Paim C, Lustig R, Haber M, Klugman KP. Effect of 13-valent pneumococcal conjugate vaccine on admissions to hospital 2 years after its introduction in the USA: a time series analysis. Lancet Respir Med. 2014 May;2(5):387-94.	[04KVRV]
[Song, J. Y., et al 2017]	Song JY, Cheong HJ, Hyun HJ, Seo YB, Lee J, Wie SH, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine and an MF59-adjuvanted influenza vaccine after concomitant vaccination in >=60-year-old adults. Vaccine. 2017;35:313-20.	[05DV3G]
[Troeger, C., et al 2018]	Troeger C, Blacker BF, Khalil IA, Rao PC, Cao S, Zimsen SRM, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018 Nov;18:1191-210.	[07XTBZ]
[U.S. Food and Drug Administration 2009]	U.S. Food and Drug Administration (CDER, CBER, CDRH). Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims [Internet]. Washington: U.S. Department of Health and Human Services; 2009. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf	[04MG9J]
[van der Linden, M., et al 2015]	van der Linden M, Falkenhorst G, Perniciaro S, Imohl M. Effects of infant pneumococcal conjugate vaccination on serotype distribution in invasive pneumococcal disease among children and adults in Germany. PLoS One. 2015 Jul 1;10(7):e0131494.	[04KVRY]

[van Hoek, A. J., et al 2012]	van Hoek AJ, Andrews N, Waight PA, Stowe J, Gates P, George R, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012 Jul;65(1):17-24.	[04NKDG]
[Waight, P. A., et al 2015]	Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MP, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015 May;15(5):535-43.	[04KTF2]
[Weycker, D., et al 2010]	Weycker D, Strutton D, Edelsberg J, Sato R, Jackson LA. Clinical and economic burden of pneumococcal disease in older US adults. Vaccine 2010;28(31):4955-60.	[03RFMJ]
[WHO Global Influenza Surveillance Network 2011]	WHO Global Influenza Surveillance Network. Manual for the laboratory diagnosis and virological surveillance of influenza [Internet]. Geneva (CH): World Health Organization; 2011. Available from: http://apps.who.int/iris/bitstream/10665/44518/1/9789241548090_eng.pdf.	[04HMD6]
[Yin, M., et al 2018]	Yin M, Huang L, Zhang Y, Yu N, Xu X, Liang Y, et al. Effectiveness and safety of dual influenza and pneumococcal vaccination versus separate administration or no vaccination in older adults: a meta-analysis. Expert Rev Vaccines. 2018;17(7):653-63.	[05FFLS]
[Zakay-Rones, Z. 2010]	Zakay-Rones Z. Human influenza vaccines and assessment of immunogenicity. Expert Rev Vaccines. 2010;9(12):1423-39.	[04W9TB]

[Zhang, Y. Y., et al 2016]	Zhang YY, Tang XF, Du CH, Wang BB, Bi ZW, Dong BR. Comparison of dual influenza and pneumococcal polysaccharide vaccination with influenza vaccination alone for preventing pneumonia and reducing mortality among the elderly: a meta-analysis. Hum Vaccin Immunother. 2016;12(12):3056-64.	[04XF37]