

Official Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 When Administered Concomitantly with Influenza Vaccine in Healthy Adults 50 Years of Age or Older (PNEUFLU)
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Title Page

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Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 When Administered Concomitantly with Influenza Vaccine in Healthy Adults 50 Years of Age or Older (PNEU-FLU)

Protocol Number: 021-01

Compound Number: V114

Sponsor Name:

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Regulatory Agency Identifying Number(s):

IND	14977
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Approval Date: 01-JUN-2018

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

The primary purpose of this amendment is to remove the collection of medical device incidents from the protocol (removal of Section 6.1.1, Section 8.4.8, and Appendix 4). The implementation of the FDA guidance for reporting events related to combination products has been delayed until January 2020. Therefore, the current protocol is not within the scope of medical device reporting requirements. Other clarifications and editorial revisions were also made as shown in the Summary of Changes Table below.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
2.2.1 V114 and Pneumococcal Disease	Licensure dates for Prevnar 13™ were added to the third paragraph. Revisions were made in the fourth paragraph to better align with the cited literature.	Revisions made for accuracy.
5.2 Exclusion Criteria	The number of exclusion criterion 23 has been corrected to 22.	Correction of a typographical error.
6.1.1 Medical Devices 8.4.8 Medical Device Incidents (Including Malfunctions) 10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting	Sections removed.	The implementation of the FDA guidance for reporting events related to combination products has been delayed until January 2020. Therefore, the current protocol is not within the scope of medical device reporting requirements.

Section # and Name	Description of Change	Brief Rationale
6.5 Concomitant Therapy	Concomitant corticosteroid rules were updated to align with other protocols in the V114 program.	Updates necessary for program consistency.
8.1.10 Telephone Contact Questionnaire 1.3 Schedule of Activities (SoA)	<p>The text in Section 8.1.10 was revised as follows:</p> <p>Original: All participants to collect additional information based on a will be contacted by telephone at Month 7 to complete the Telephone Contact Questionnaire provided by the Sponsor. Data to be reported from on this discussion questionnaire will include SAEs and/or any updates to previously reported safety information.</p> <p>Revised: Site personnel will contact study participants 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.</p> <p>The revised text was also added to the SoA.</p>	Revisions were made to clarify the process for administering the telephone contact questionnaire.

Section # and Name	Description of Change	Brief Rationale
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	<p>The following text was deleted from the second paragraph in this section:</p> <p>All AEs, SAEs, and other reportable safety events must be reported by the investigator from the day of allocation/randomization to the first vaccination and from the day of each vaccination through 14 days (42 days for live attenuated vaccines) postvaccination. SAEs must also be reported throughout the duration of the individual's participation in the study, regardless of whether or not related to the Sponsor's product.</p>	Live attenuated vaccines are not provided as part of the study.
8.5 Treatment of Overdose	<p>The definition of overdose was revised as follows:</p> <p>Original: In this study, an overdose is any dose higher than 1 dose of any individual study vaccine during the individual's participation in the study.</p> <p>Revised: In this study, an overdose is the administration of more than 1 dose of any individual study vaccine in any 24-hour period.</p>	Revisions made for accuracy.

Section # and Name	Description of Change	Brief Rationale
9.6.2 Statistical Methods for Safety Analyses, Table 5	Tier 2 safety endpoint was revised as follows (changes in bold): “Any SAE and vaccine-related AE” was changed to “ Any vaccine-related SAE ”	Table was revised to align with safety analysis plan and text under Tier 2 Events.
Throughout	Editorial revisions	Changes are minor and have not been summarized individually.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 When Administered Concomitantly with Influenza Vaccine in Healthy Adults 50 Years of Age or Older (PNEU-FLU)

Short Title: Safety and Immunogenicity of V114 Administered Concomitantly with Influenza Vaccine

Acronym: PNEUmococcal Conjugate Vaccine Trials: V114-021 (PNEU – FLU)

Hypotheses, Objectives, and Endpoints:

The following objectives and endpoints will be evaluated in healthy adults ≥ 50 years of age.

Primary Objectives	Primary Endpoints
<ul style="list-style-type: none">- Objective: To evaluate the safety and tolerability of V114 and quadrivalent influenza vaccine (QIV) when administered concomitantly compared with V114 and QIV when administered nonconcomitantly with respect to the proportion of participants with adverse events (AEs).	<p>Following any vaccination:</p> <ul style="list-style-type: none">- Solicited injection-site AEs from Day 1 through Day 5 postvaccination- Solicited systemic AEs from Day 1 through Day 14 postvaccination- Vaccine-related serious adverse events (SAEs) from Day 1 through Month 7
<ul style="list-style-type: none">- Objective: To compare the serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination with V114 administered concomitantly with QIV versus V114 administered nonconcomitantly with QIV. <p>Hypothesis (H1): V114 administered concomitantly with QIV is noninferior to V114 administered nonconcomitantly with QIV as measured by serotype-specific OPA GMTs at 30 days postvaccination with V114.</p> <p>(the statistical criterion for noninferiority requires the lower bound of the 2-sided 95% confidence interval [CI] of the OPA GMT ratio [concomitant/nonconcomitant] to be greater than 0.50)</p>	<ul style="list-style-type: none">- Serotype-specific OPA responses for the 15 serotypes in V114 at 30 days postvaccination with V114

<p>- Objective: To compare the strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV administered concomitantly with V114 versus QIV administered nonconcomitantly with V114.</p> <p>Hypothesis (H2): QIV administered concomitantly with V114 is noninferior to QIV administered nonconcomitantly with V114 as measured by strain-specific HAI GMTs at 30 days postvaccination with QIV.</p> <p>(the statistical criterion for noninferiority requires the lower bound of the 2-sided 95% CI of the HAI GMT ratio [concomitant/nonconcomitant] to be greater than 0.50)</p>	<p>- Strain-specific HAI responses for the 4 strains in QIV at 30 days postvaccination with QIV</p>
<p>Secondary Objectives</p>	<p>Secondary Endpoints</p>
<p>- Objective: To evaluate the serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination with V114 administered concomitantly with QIV compared with V114 administered nonconcomitantly with QIV.</p>	<p>- Serotype-specific IgG responses for the 15 serotypes in V114 at 30 days postvaccination with V114</p>
<p>- Objective: Within each vaccination group, to evaluate the serotype-specific Geometric Mean Fold Rises (GMFRs) and proportions of participants with a ≥ 4-fold rise from baseline (prevaccination with V114) to 30 days postvaccination with V114 for both OPA and IgG responses for participants administered V114 concomitantly with QIV and participants administered V114 nonconcomitantly with QIV.</p>	<p>- Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at prevaccination with V114 and 30 days postvaccination with V114</p>

- Objective: Within each vaccination group, to evaluate the strain-specific (1) GMFRs from baseline (prevaccination with QIV) to 30 days postvaccination with QIV, (2) proportions of participants with an HAI titer $\geq 1:40$ 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 V114 and participants administered QIV nonconcomitantly with V114.	- Strain-specific HAI responses for the 4 strains in QIV at prevaccination with QIV and 30 days postvaccination with QIV
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Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Pneumococcal disease
Population	Healthy adults, 50 years of age or older
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Masking	Participant Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 9 to 10 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last serology assay result.

Number of Participants:

Approximately 1200 participants will be randomized, with approximately 600 participants in each intervention group.

Intervention Groups and Duration:

Intervention Groups	Intervention Group Name	Vaccine	Dose Strength	Dose Frequency	Route of Admin.	Vaccination Regimen	Use
	Concomitant Group	V114	Refer to IB	Single Dose	IM Left arm	Single Dose at Visit 1 (Day 1)	Experimental
		QIV	Refer to product labeling	Single Dose	IM Right arm	Single Dose at Visit 1 (Day 1)	Experimental
		Placebo	NA	Single Dose	IM Left arm	Single Dose at Visit 2 (Day 30)	Experimental
	Nonconcomitant Group	Placebo	NA	Single Dose	IM Left arm	Single Dose at Visit 1 (Day 1)	Experimental
		QIV	Refer to product labeling	Single Dose	IM Right arm	Single Dose at Visit 1 (Day 1)	Experimental
		V114	Refer to IB	Single Dose	IM Left arm	Single Dose at Visit 2 (Day 30)	Experimental
	IB = Investigator's Brochure; IM = intramuscular; NA = not applicable; QIV = quadrivalent influenza vaccine (seasonal inactivated).						
Total Number	2 intervention groups						
Duration of Participation	Each participant will participate in the study for approximately 7 months from the time the participant signs the Informed Consent Form (ICF) through the final contact.						

Study Governance Committees:

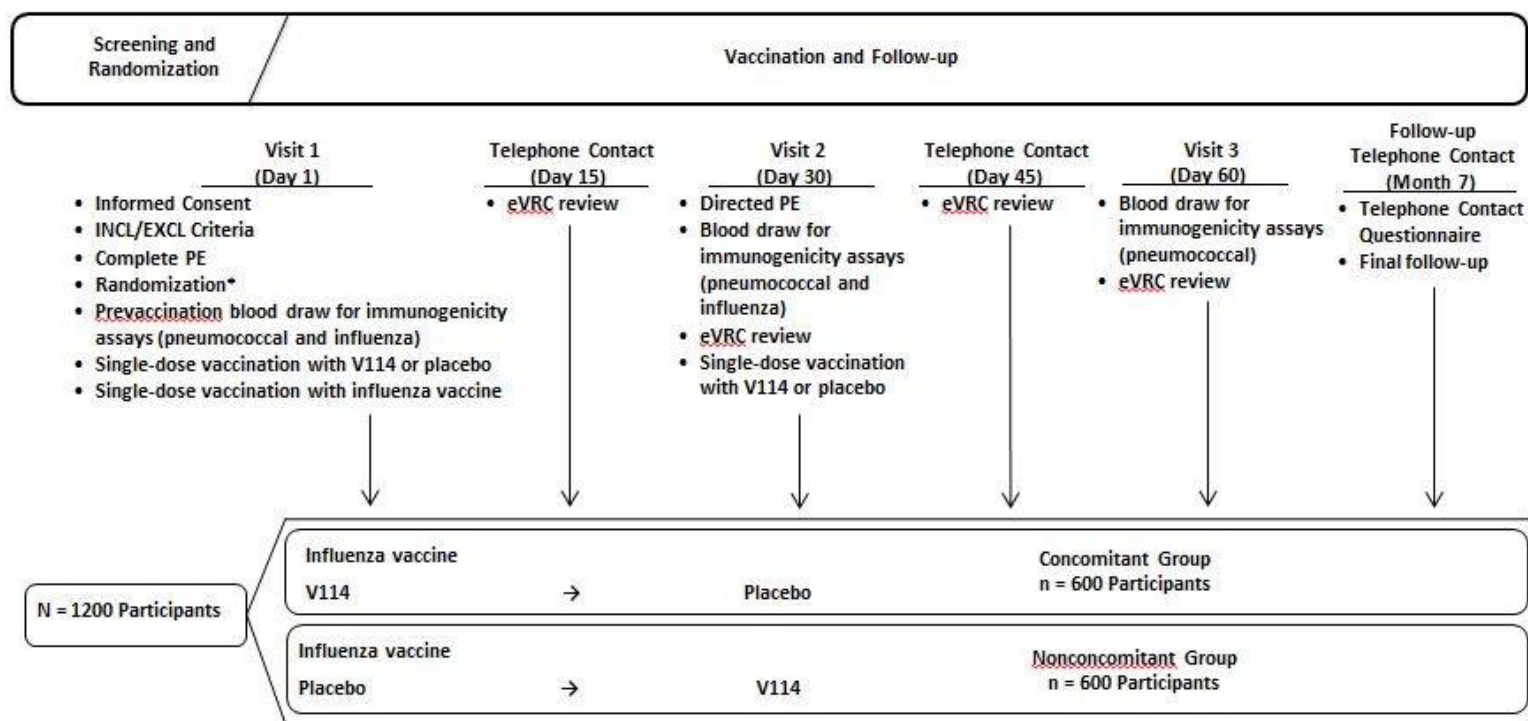
Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in [Figure 1](#).



INCL/EXCL = Inclusion/Exclusion

PE = Physical Examination

eVRC = electronic Vaccination Report Card

Note: V114 and placebo are administered under double-blind conditions.

* Randomization is stratified by age and history of prior PNEUMOVAX™23 vaccination.

Figure 1 V114-021 Study Design

1.3 Schedule of Activities (SoA)

Study Period	Intervention					Follow-up	Comments
Visit Number:	1	Telephone Contact	2	Telephone Contact	3	Telephone Contact	
Scheduled Time:	Day 1	Day 15	Day 30	Day 45	Day 60	Month 7	
Visit Window:		Day 15 to Day 19 after Visit 1 ^a	Day 30 to Day 44 after Visit 1 ^a	Day 15 to Day 19 after Visit 2 ^b	Day 30 to Day 44 after Visit 2 ^b	Day 166 to Day 194 after Visit 2 ^b	
Administrative and General Procedures							
Screening Procedures							
Informed Consent	X						Consent must be obtained before any study procedures.
Informed Consent for Optional Assay Development Blood Samples (Selected Study Sites Only)	X						Consent for optional assay development blood samples must be obtained before any of these samples are collected from a participant.
Informed Consent for Future Biomedical Research	X						Consent for future biomedical research samples must be obtained before the blood sample (DNA sample) is collected.
Assignment of Screening Number	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						The participant’s medical history for the 5 years prior to study entry will be reviewed. History of tobacco use will also be collected for all participants.
Post-Enrollment Procedures							
Assignment of Randomization Number	X						
Participant Identification Card	X						
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X	X	X		
V114 or Placebo Administration (Blinded) – Left Arm	X		X				At Visit 1 (Day 1), participants will receive a single dose of either (blinded) V114 or placebo; at Visit 2, participants will receive a single dose (blinded) of the other (ie, placebo or V114, respectively).
Seasonal Inactivated Quadrivalent Influenza Vaccine (QIV) Administration (Open-label) – Right Arm	X						At Visit 1 (Day 1), participants will receive a single dose of QIV.

Study Period	Intervention					Follow-up	Comments
Visit Number:	1	Telephone Contact	2	Telephone Contact	3	Telephone Contact	
Scheduled Time:	Day 1	Day 15	Day 30	Day 45	Day 60	Month 7	
Visit Window:		Day 15 to Day 19 after Visit 1 ^a	Day 30 to Day 44 after Visit 1 ^a	Day 15 to Day 19 after Visit 2 ^b	Day 30 to Day 44 after Visit 2 ^b	Day 166 to Day 194 after Visit 2 ^b	
Provide electronic Vaccination Report Card (eVRC)	X						Participants will be provided an eVRC at Visit 1 (Day 1) to record adverse events (AEs) and body temperature measurements. Instructions for using the eVRC will be reviewed with the participant.
Review eVRC Data with Participant		X	X	X	X		
Collect eVRC from Participant					X		
Complete Telephone Contact Questionnaire						X	Site personnel will contact study participants to collect additional information based on a Telephone Contact Questionnaire provided by the Sponsor. Data to be reported from this discussion will include serious adverse events (SAEs) and/or any updates to previously reported safety information.
Safety Procedures							
Complete Physical Examination	X						To be performed by the investigator or medically qualified designee before vaccine is administered.
Directed Physical Examination			X				To be performed by the investigator or medically qualified designee before vaccine is administered.
Pregnancy Test – if applicable	X		X				A pregnancy test consistent with local requirements (sensitive to at least 25 IU beta human chorionic gonadotropin, β -hCG) must be performed before administration of study vaccine in females who are of reproductive potential. Urine or serum tests can be used, and results must be negative before vaccination can occur.
Body Temperature Measurement Before Vaccination	X		X				Each participant's body temperature must be taken before vaccination. Participants who present with fever (oral or tympanic temperature $\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]; axillary or temporal temperature $\geq 99.4^{\circ}\text{F}$ [$\geq 37.4^{\circ}\text{C}$]; or rectal temperature $\geq 101.4^{\circ}\text{F}$ [$\geq 38.6^{\circ}\text{C}$]) will have the vaccination delayed until fever is resolved for 72 hours.
30-Minute Postvaccination Observation Period	X		X				To be performed by blinded study site personnel only.

Study Period	Intervention					Follow-up	Comments
Visit Number:	1	Telephone Contact	2	Telephone Contact	3	Telephone Contact	
Scheduled Time:	Day 1	Day 15	Day 30	Day 45	Day 60	Month 7	
Visit Window:		Day 15 to Day 19 after Visit 1 ^a	Day 30 to Day 44 after Visit 1 ^a	Day 15 to Day 19 after Visit 2 ^b	Day 30 to Day 44 after Visit 2 ^b	Day 166 to Day 194 after Visit 2 ^b	
AE Monitoring	X	X	X	X	X	X	AEs (serious and nonserious) are to be reported from Days 1 through 14 following each vaccination. SAEs and deaths are to be reported throughout the duration of an individual's study participation.
Immunogenicity Procedures							
Serum for Pneumococcal Immunogenicity Assay (Including Retention Serum)	X		X		X		Blood samples must be collected before study vaccination when applicable. After completion of opsonophagocytic activity (OPA) and electrochemiluminescence (ECL) testing, serum samples will be stored to conduct any additional study-related testing as required by regulatory agencies or the Sponsor. Leftover sera from the study may be used for the development and/or validation of pneumococcal assays after completion of all study-related immunogenicity testing; this applies only to sera received from randomized study participants who provided consent for future biomedical research.
Serum for Influenza Immunogenicity Assay (Including Retention Serum)	X		X				Blood samples must be collected before study vaccination where applicable. After completion of hemagglutination inhibition (HAI) testing, serum samples will be stored to conduct any additional study-related testing as required by regulatory agencies or the Sponsor. Leftover sera from the study may be used for the development and/or validation of pneumococcal assays after completion of all study-related immunogenicity testing; this applies only to sera received from randomized study participants who provided consent for future biomedical research.
Future Biomedical Research							
Blood-(DNA) for Future Biomedical Research	X						Collected from randomized participants who provided consent for future biomedical research (Section 8.8).
Assay Development Samples							
Serum for Optional Assay Development (Selected Study Sites Only)	X				X		Collected from randomized participants (target of approximately 120 participants) who provided consent for Assay Development Sample collection (Section 8.10).

^a When scheduling the Telephone Contact (Day 15) and Visit 2 (Day 30), the visit window "Day 1" is the date of Visit 1.

^b When scheduling the Telephone Contact (Day 45), Visit 3 (Day 60), and the Follow-up Telephone Contact (Month 7), the visit window "Day 1" is the date of Visit 2.

2 INTRODUCTION

Merck Sharp & Dohme Corp. (MSD) is developing an investigational 15-valent pneumococcal conjugate vaccine (PCV) (referred to as V114) for prevention of pneumococcal disease caused by the serotypes contained in the vaccine. V114 contains the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) present in the licensed vaccine Prevnar 13™ (pneumococcal 13-valent conjugate vaccine [diphtheria CRM₁₉₇ protein], Wyeth Pharmaceuticals, a subsidiary of Pfizer, Inc., Philadelphia, PA), plus 2 additional serotypes (22F, 33F).

2.1 Study Rationale

This clinical study will evaluate the safety, tolerability, and immunogenicity of V114 when administered concomitantly with influenza vaccine in healthy participants ≥ 50 years of age. This population is at elevated risk for pneumococcal disease and its associated morbidity and mortality [Drijkoningen, J. J 2014] [Matias, G., et al 2014], as well as the morbidity and mortality associated with influenza infection.

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 Prevnar 13™ 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].

Individuals in the target age population of this study may have received prior vaccination with PNEUMOVAX™23, a pneumococcal vaccine containing the polysaccharides of 23 pneumococcal 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) and no adjuvant or carrier proteins. In the United States, PNEUMOVAX™23 is recommended for immunocompetent adults 19 to 64 years of age who have certain chronic medical conditions, including chronic heart disease, chronic liver disease, chronic lung disease, diabetes mellitus, smoking and alcohol abuse. In order to allow a comprehensive assessment of the concomitant administration of V114 and influenza vaccine in pneumococcal vaccine-naïve adults, this study will enroll participants with and without prior PNEUMOVAX™23 vaccination. In accordance with recommendations regarding the interval between vaccinations with PNEUMOVAX™23 and a PCV, participants must have received PNEUMOVAX™23 at least 12 months prior to study enrollment.

This study is designed to evaluate the safety and tolerability of a single dose of V114 when administered concomitantly and nonconcomitantly (ie, 30 days after) with influenza vaccine. It will also evaluate whether V114 can be administered concomitantly with influenza vaccine without impairing the antibody response to the 15 serotypes contained in V114 and to the 4 influenza viruses contained in the seasonal inactivated quadrivalent influenza vaccine

(QIV). This study will also contribute to the overall safety database and immunogenicity data for V114 to support initial licensure in adults.

2.2 Background

2.2.1 V114 and Pneumococcal Disease

Refer to the Investigator's Brochure (IB) for V114 for more detailed background, including information on pneumococcal disease burden.

Streptococcus pneumoniae is a significant cause of disease worldwide, with clinical manifestations including pneumonia, meningitis, otitis media, sinusitis, and sepsis. Adults with comorbid conditions, in particular immunocompromised individuals, have a higher incidence of invasive pneumococcal disease (IPD) morbidity and mortality in all age groups compared to adults without the comorbid conditions [Lexau, C. A., et al 2005].

Currently licensed PCVs (eg, Prevnar™, Synflorix™, and Prevnar 13™) were first implemented in infant immunization programs in many countries worldwide. Prevnar™ was first licensed in 2000 and later replaced by Prevnar 13™ in 2009 for the European Union and in 2010 for the United States. Although Prevnar 13™ is indicated for children and adults, Synflorix™ is only indicated for children up to 5 years of age. Widespread use of PCVs has reduced the burden of pneumococcal disease caused by the serotypes contained in the vaccines in children who were targeted by the vaccination programs and unvaccinated individuals from other age groups (herd protection) [Centers for Disease Control and Prevention 2008] [Ruckinger, S., et al 2009] [Farrell, D. J., et al 2007] [Pilishvili, Tamara, et al 2010] [Lexau, C. A., et al 2005] [Metlay, J. P., et al 2006] [Whitney, Cynthia G., et al 2003] [Moore, M. R., et al 2015] [Lepoutre, A., et al 2015] [Weiss, S., et al 2015] [Martinelli, D., et al 2014] [Guevara, M., et al 2016] [Waight, P. A., et al 2015] [Jokinen, J., et al 2015] [Palmu, A. A., et al 2015] [Wagenvoort, G. H., et al 2016]. Prevnar 13™ was also shown to be efficacious against vaccine-type nonbacteremic pneumococcal pneumonia and IPD in adults ≥65 years of age [Bonten, M. J., et al 2015]. These study results were the basis of the recommendation from the Advisory Committee on Immunization Practices for the sequential administration of Prevnar 13™ followed at least 12 months later by PNEUMOVAX™23 in adults ≥65 years of age [Tomczyk, S., et al 2014] [Kobayashi, M., et al 2015].

Although cases of IPD have decreased following implementation of PCVs, an increase in IPD caused by serotypes not covered by currently available vaccines has been observed. V114 contains 2 additional serotypes (22F, 33F) compared with Prevnar 13™. The selection of 22F and 33F was primarily based on epidemiological importance of these 2 additional serotypes. Recent data from the United States suggest that 22F is the most common serotype not included in Prevnar 13™ in adults ≥18 years of age, causing 13% of IPD cases. Serotype 33F is associated with an additional 5% of IPD cases [Moore, M. R., et al 2015]. Data from the United Kingdom also showed that, in 2013/2014, 22F and 33F are frequent serotypes in adults ≥65 years of age, accounting for approximately 10% and 4% of IPD cases in that age group, respectively [Waight, P. A., et al 2015]. Data from 2014 reported in the 2016 annual

epidemiological report on IPD by the European Centre for Disease Prevention and Control showed that both serotypes 22F and 33F are among the most common serotypes causing IPD [European Centre for Disease Prevention and Control 2016].

The serotypes included in V114 will provide broad coverage of the leading serotypes associated with pneumococcal disease worldwide. V114 is designed to meet continuing medical and public health needs for PCVs globally, as well as to address the emergence of pneumococcal disease caused by serotypes not contained in currently licensed PCVs. V114 is designed to offer broader serotype coverage than Prevnar 13™ against pneumococcal disease in both pediatric and adult populations.

2.2.1.1 Influenza Disease

Influenza occurs annually, typically circulating in the United States in late fall through early spring, in epidemic outbreaks of varying severity. The majority of influenza cases are not associated with any significant complications. However, the risk for complications, such as pneumonia, hospitalization, and death are higher for individuals ≥ 65 years of age, young children, and persons of any age with certain underlying health conditions [Grohskopf, L. A., et al 2016].

Annual mean rates of hospitalizations due to influenza in the United States between 1993 and 2008 were 63.5 per 100,000 person-years. The highest rates were observed in adults ≥ 65 years of age (309 per 100,000 person-years) [Zhou, H., et al 2012]. In the United States alone, influenza infection has been responsible for 3,000 to 49,000 deaths each season (from the 1976-77 through the 2005-06 seasons) [Centers for Disease Control and Prevention (CDC) 2010] and 55,000 to 431,000 hospitalizations annually (from the 1979-80 through 2000-01 seasons) [Thompson, W. W., et al 2004].

Influenza illness may be prevented through vaccination. Antibody responses are often lower in individuals ≥ 65 years of age than in younger adults, and some studies have shown statistically significant decline in titers in individuals ≥ 65 years of age during the first 6 months postvaccination [Kunzel, W., et al 1996] [Song, J. Y., et al 2010]. While vaccine effectiveness can vary, recent studies showed that vaccination reduces the risk of influenza illness by about 40% to 60% among the overall population during seasons when most circulating influenza viruses are like the vaccine viruses [Grohskopf, L. A., et al 2015].

2.2.2 Preclinical and Clinical Studies

Refer to the IB for information on completed preclinical and clinical studies conducted with V114.

2.2.3 Information on Other Study-related Therapy

2.2.3.1 Seasonal Inactivated Quadrivalent Influenza Vaccine

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

The QIV protects against the influenza viruses that research indicates will be most common during the upcoming season, and includes antigens from influenza A (H1N1) virus, influenza A (H3N2) virus, influenza B/Victoria virus, and influenza B/Yamagata virus.

In the United States, annual influenza vaccination is recommended for all individuals ≥ 6 months of age [Grohskopf, L. A., et al 2017]. Most countries in the European Union recommend annual influenza vaccination for individuals at risk for influenza associated morbidity and mortality, such as children, older adults, pregnant women and individuals with chronic diseases, and for health care workers [ECDC 2017].

2.3 Benefit/Risk Assessment

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

While the impact of concomitant administration of V114 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 2018/2019 influenza season through participation in this study based on the experience of concomitant administration of Prevnar 13™ and influenza vaccines [Frenck, R. W. Jr., et al 2012] [Schwarz, T. F., et al 2011] [Schwarz, T. F. 2013].

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and the Informed Consent Form (ICF).

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

The following objectives and endpoints will be evaluated in healthy adults ≥ 50 years of age.

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> Objective: To evaluate the safety and tolerability of V114 and quadrivalent influenza vaccine (QIV) when administered concomitantly compared with V114 and QIV when administered nonconcomitantly with respect to the proportion of participants with adverse events (AEs). 	<p>Following any vaccination:</p> <ul style="list-style-type: none"> Solicited injection-site AEs from Day 1 through Day 5 postvaccination Solicited systemic AEs from Day 1 through Day 14 postvaccination Vaccine-related serious adverse events (SAEs) from Day 1 through Month 7
<ul style="list-style-type: none"> Objective: To compare the serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination with V114 administered concomitantly with QIV versus V114 administered nonconcomitantly with QIV. <p>Hypothesis (H1): V114 administered concomitantly with QIV is noninferior to V114 administered nonconcomitantly with QIV as measured by serotype-specific OPA GMTs at 30 days postvaccination with V114.</p> <p><i>(the statistical criterion for noninferiority requires the lower bound of the 2-sided 95% confidence interval [CI] of the OPA GMT ratio [concomitant/nonconcomitant] to be greater than 0.50)</i></p>	<ul style="list-style-type: none"> Serotype-specific OPA responses for the 15 serotypes in V114 at 30 days postvaccination with V114

Objectives	Endpoints
<ul style="list-style-type: none"> Objective: To compare the strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV administered concomitantly with V114 versus QIV administered nonconcomitantly with V114. <p>Hypothesis (H2): QIV administered concomitantly with V114 is noninferior to QIV administered nonconcomitantly with V114 as measured by strain-specific HAI GMTs at 30 days postvaccination with QIV.</p> <p><i>(the statistical criterion for noninferiority requires the lower bound of the 2-sided 95% CI of the HAI GMT ratio [concomitant/nonconcomitant] to be greater than 0.50)</i></p>	<ul style="list-style-type: none"> Strain-specific HAI responses for the 4 strains in QIV at 30 days postvaccination with QIV
Secondary	
<ul style="list-style-type: none"> Objective: To evaluate the serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination with V114 administered concomitantly with QIV compared with V114 administered nonconcomitantly with QIV. 	<ul style="list-style-type: none"> Serotype-specific IgG responses for the 15 serotypes in V114 at 30 days postvaccination with V114
<ul style="list-style-type: none"> Objective: Within each vaccination group, to evaluate the serotype-specific Geometric Mean Fold Rises (GMFRs) and proportions of participants with a ≥ 4-fold rise from baseline (prevaccination with V114) to 30 days postvaccination with V114 for both OPA and IgG responses for participants administered V114 concomitantly with QIV and participants administered V114 nonconcomitantly with QIV. 	<ul style="list-style-type: none"> Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at prevaccination with V114 and 30 days postvaccination with V114

Objectives	Endpoints
<ul style="list-style-type: none"> Objective: Within each vaccination group, to evaluate the strain-specific (1) GMFRs from baseline (prevaccination with QIV) to 30 days postvaccination with QIV, (2) proportions of participants with an HAI titer $\geq 1:40$ 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 V114 and participants administered QIV nonconcomitantly with V114. 	<ul style="list-style-type: none"> Strain-specific HAI responses for the 4 strains in QIV at prevaccination with QIV and 30 days postvaccination with QIV

4 STUDY DESIGN

4.1 Overall Design

Approximately 1200 participants will be randomly assigned in a 1:1 ratio to receive either V114 with concomitant QIV or V114 with nonconcomitant QIV. Randomization will be stratified by age (50 to 64 years, 65 to 74 years, and 75 years or older; at least 50% of the participants will be 65 years of age or older) and by history of prior PNEUMOVAX™23 vaccination (yes and no; at least 50% of participants are to be PNEUMOVAX™23-naïve).

Participants enrolled in the concomitant group will receive V114 (blinded) in the left arm and QIV (open label) in the right arm on Day 1, and then will receive placebo (blinded) in the left arm 30 days later at Visit 2 (Day 30).

Participants enrolled in the nonconcomitant group will receive placebo (blinded) in the left arm and QIV (open label) in the right arm on Day 1, and then will receive V114 (blinded) in the left arm 30 days later at Visit 2 (Day 30).

Participants will be followed for local and systemic AEs through Day 14 following each vaccination. Information for SAEs and deaths, regardless of whether the events are considered to be vaccine-related by the investigator, will be collected from the time consent is signed through completion of participation in the study. An external Data Monitoring Committee (DMC) will conduct a periodic review of safety and tolerability data for the adult V114 Phase 3 program. A description of the structure, function, and guidelines for decision-making by 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 immediately before the first V114 or placebo vaccination and the QIV vaccination at Visit 1 (Day 1), before vaccination at Visit 2 (Day 30), and at Visit 3 (Day 60).

After completion of OPA, electrochemiluminescence (ECL), and HAI testing, serum samples will be stored to conduct any additional study-related testing as required by regulatory agencies or the Sponsor. Leftover sera from the study may be used for the development and/or validation of pneumococcal assays after completion of all study-related immunogenicity testing; this applies only to sera received from randomized study participants who provided consent for future biomedical research.

Adult participants at selected study sites who consent (target of approximately 120 participants) will have 2 optional additional blood samples drawn (50 mL at each of Visits 1 and 3) to support further development, validation, and performance of anti-pneumococcal antibody assays.

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

4.2 Scientific Rationale for Study Design

This study is conducted in a population (healthy adults ≥ 50 years of age) at elevated risk for pneumococcal and influenza disease and associated morbidity and mortality [Drijkoningen, J. J 2014].

The concomitant and nonconcomitant administration of V114 and QIV in this study allows for meaningful comparisons of safety, tolerability, and immunogenicity between the 2 administration types.

In order to demonstrate that concomitant administration of V114 and QIV does not adversely affect the antibody response to or safety profile of either vaccine, concomitant and nonconcomitant administration groups are being generated in this study through the use of a placebo to V114. A saline placebo is being used to maintain blinded vaccine administration on Day 1 and Day 30. Both groups of randomized participants will receive V114 in the study.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

4.2.1.1.1 Pneumococcal Immunogenicity Endpoints

Sera from participants will be used to measure vaccine-induced, serotype-specific OPA and IgG responses for all 15 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) included in V114 using the Multiplexed Opsonophagocytic Assay (MOPA) assay and pneumococcal electrochemiluminescence (PnECL) assay.

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, and therefore is considered an important immunologic surrogate for protection against IPD in adults. It is noted that threshold values that correlate with protection in adults have not been defined for either assay.

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 to a homologous or related influenza virus and 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 demonstrated 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 primary endpoints.

4.2.1.2 Safety Endpoints

The safety endpoints evaluated in this study were selected based on the product's safety profile demonstrated in previous studies, published data from marketed PCVs, and feedback received from regulatory agencies during product development. The electronic Vaccination Report Card (eVRC) used to record AEs during the postvaccination periods, as defined in Section 8.1.9, was structured as recommended in the final US Food and Drug Administration Patient Reported Outcome Guidance [U.S. Food and Drug Administration 2009].

Details on the safety endpoints evaluated in this study can be found in Section 8.3.4 and Section 9.4.2.

Details on AEs, including definitions and reporting requirements, can be found in Appendix 3.

4.2.1.3 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research 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 this future biomedical research substudy are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

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

4.3 Justification for Dose

The dosing regimen of V114 is similar to that used in previous adult V114 clinical studies in which 1 dose has resulted in a robust immune response (refer to the V114 IB for more detailed information on dose selection).

The dose of QIV for use in this study is the approved dose.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, 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 serology assay result.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Healthy adult males and females (≥ 50 years of age) will be enrolled in this study.

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. The participant is in good health. Any underlying chronic illness must be documented to be in stable condition.

Demographics

2. Participant is male or female ≥ 50 years of age.

Female Participants

3. A female participant is eligible to participate if she is not pregnant (Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:
 - a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.OR
 - b. A WOCBP who agrees to use 1 of the contraceptive methods as defined in Appendix 5 during the treatment period and for at least 6 weeks after the last dose of study intervention.

Informed Consent

4. The participant provides written informed consent for the study.
The participant may also provide consent for future biomedical research and/or Assay Development Sample collection. However, the participant may participate in the main study without participating in future biomedical research or Assay Development Sample collection.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. 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 before Visit 1 (Day 1).
2. Known hypersensitivity to any component of pneumococcal polysaccharide vaccine, PCV, or any diphtheria toxoid-containing vaccine.

3. Known hypersensitivity to any component of influenza vaccines, including egg protein, or following a previous dose of any influenza vaccine.
4. 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).
5. Has experienced Guillain-Barré syndrome within 6 weeks of receiving a previous influenza vaccination.
6. Coagulation disorder contraindicating intramuscular vaccinations.
7. * Recent febrile illness (defined as oral or tympanic temperature $\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]; axillary or temporal temperature $\geq 99.4^{\circ}\text{F}$ [$\geq 37.4^{\circ}\text{C}$]; or rectal temperature $\geq 101.4^{\circ}\text{F}$ [$\geq 38.6^{\circ}\text{C}$]) or received antibiotic therapy for any acute illness occurring within 72 hours before receipt of study vaccine.
8. History of malignancy ≤ 5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
9. A WOCBP who has a positive urine or serum pregnancy test before the first vaccination at Visit 1 (Day 1).

Prior/Concomitant Therapy

10. Prior administration of any PCV (eg, Prevnar 13™) or is expected to receive any pneumococcal vaccine during the study outside of the protocol.
11. Prior administration of PNEUMOVAX™23 ≤ 12 months before Visit 1.
Note: individuals who received PNEUMOVAX™23 > 12 months prior to Visit 1 are eligible for this study.
12. Previous receipt of influenza vaccine during the 2018/2019 flu season or expected to receive any influenza vaccine during the study outside of the protocol.
13. Received systemic corticosteroids (≥ 20 mg/day prednisone equivalent) for ≥ 14 consecutive days and has not completed intervention at least 30 days before study entry.
14. Received systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) within 14 days before vaccination. (Note: Topical, ophthalmic, intra-articular or soft-tissue [eg, bursa, tendon steroid injections], and inhaled/nebulized steroids are permitted).
15. Receiving immunosuppressive therapy, including chemotherapeutic agents used to treat cancer or other conditions, and interventions associated with organ or bone marrow transplantation, or autoimmune disease.
16. *Received any non-live vaccine within the 14 days before receipt of any study vaccine or is scheduled to receive any non-live vaccine within 30 days following receipt of any study vaccine.

17. *Received any live vaccine within 30 days before receipt of any study vaccine or is scheduled to receive any live vaccine within 30 days following receipt of any study vaccine.
18. Received a blood transfusion or blood products, including immunoglobulin within the 6 months before receipt of study vaccine or is scheduled to receive a blood transfusion or blood product within 30 days of receipt of study vaccine. Autologous blood transfusions are not considered an exclusion criterion.

Prior/Concurrent Clinical Study Experience

19. 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.

Other Exclusions

20. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence as assessed by the study investigator.
21. Has history or current evidence of any condition, therapy, lab 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.
22. 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, the Day 1 Visit 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 Consolidated Standards of Reporting Trials (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 (V114, placebo, and QIV) 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](#).

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength	Dosage Level	Route of Admin	Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Concomitant Group	Experimental	V114	Biological/ Vaccine	Sterile suspension (prefilled syringe)	Refer to IB	0.5 mL	IM Left arm	Single Dose at Visit 1 (Day 1)	Experimental	IMP	Central
Concomitant Group	Experimental	QIV ^a	Biological/ Vaccine	Sterile solution (prefilled syringe)	Refer to product labeling	0.5 mL	IM Right arm	Single Dose at Visit 1 (Day 1)	Experimental	IMP	Central
Concomitant Group	Experimental	Placebo (Sterile Saline)	Biological/ Vaccine	Ampule	N/A	0.5 mL	IM Left arm	Single Dose at Visit 2 (Day 30)	Experimental	IMP	Central
Nonconcomitant Group	Experimental	Placebo (Sterile Saline)	Biological/ Vaccine	Ampule	N/A	0.5 mL	IM Left arm	Single Dose at Visit 1 (Day 1)	Experimental	IMP	Central
Nonconcomitant Group	Experimental	QIV ^a	Biological/ Vaccine	Sterile solution (prefilled syringe)	Refer to product labeling	0.5 mL	IM Right arm	Single Dose at Visit 1 (Day 1)	Experimental	IMP	Central
Nonconcomitant Group	Experimental	V114	Biological/ Vaccine	Sterile suspension (prefilled syringe)	Refer to IB	0.5 mL	IM Left arm	Single Dose at Visit 2 (Day 30)	Experimental	IMP	Central

^a Fluarix Quadrivalent (Influenza Vaccine)

Admin = administration; IB = Investigator's Brochure; IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; QIV = quadrivalent influenza vaccine (seasonal inactivated).

The definition of IMP and NIMP is based on guidance issued by the European Commission. Regional and/or country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in [Table 1](#) will be provided per the "Sourcing" column depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number.

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

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

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to receive either V114 concomitantly with QIV or V114 nonconcomitantly with QIV.

6.3.2 Stratification

Treatment allocation/randomization will be stratified according to the following factors at time of randomization:

- Age (50 to 64 years of age, 65 to 74 years of age, and ≥ 75 years of age). At least 50% of the participants will be ≥ 65 years of age.
- History of prior PNEUMOVAX™23 vaccination (Yes and No). At least 50% of participants will be PNEUMOVAX™23-naïve.

6.3.3 Blinding

A double-blinding technique will be used. V114 and placebo will be prepared and/or dispensed by an unblinded pharmacist or unblinded qualified study site personnel. The participant and the investigator who is involved in the clinical evaluation of the participants will remain blinded to the group assignments.

Because the V114 and placebo have a different appearance, a member of the study site staff will be unblinded for the purposes of receiving, maintaining, preparing and/or dispensing, and administering these study vaccines. QIV will also be prepared and/or dispensed and administered by unblinded study site staff for consistency even though it will be provided open-label in this study. In order to avoid bias, the unblinded study personnel will have no further contact with study participants for any study-related procedures/assessments after administration of study vaccines, which includes all safety follow up procedures. Additionally, blinded site personnel will not be present in the exam room when study vaccines are administered. Contact between participants and unblinded study personnel after vaccination administration is strictly prohibited.

Blinded site personnel will be responsible for all safety and immunogenicity follow-up procedures after vaccine administration.

An unblinded Clinical Research Associate will monitor vaccine accountability at the study site. All other Sponsor personnel or delegate(s) and Merck Research Laboratories employees 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 plan for V114 or placebo and QIV vaccinations at Visit 1 (Day 1) and placebo or V114 vaccination at Visit 2 (Day 30) 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 time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medication or vaccination 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.

Listed below (items 1 to 4) are specific restrictions for concomitant therapy or vaccination during the course of the study:

1. Any administration of a nonstudy pneumococcal vaccine is prohibited during the study.
2. Live and non-live vaccines may only be administered prior to or following the receipt of study vaccine according to the time frames specified in exclusion criteria (Section 5.2).
Vaccines should not be given within 30 days after receipt of study vaccine.
Participants should not receive an influenza vaccine during the 2018/2019 flu season outside of the study.
3. Participants should not receive systemic corticosteroids (≥ 20 mg/day prednisone equivalent for ≥ 14 consecutive days) starting from 30 days prior to through 30 days following each study vaccination. Note: Topical, ophthalmic, intra-articular or soft-tissue (eg, bursa, tendon steroid injections), and inhaled/nebulized steroids are permitted.
4. Participants should not receive systemic corticosteroids exceeding physiologic replacement doses (prednisone equivalent dose > 5 mg/day) within 14 days before any vaccination. Note: 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.

6.6 Dose Modification (Escalation/Titration/Other)

No dose modification is allowed in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

This study is blinded but supplies are provided open label; therefore, an unblinded pharmacist or unblinded qualified study site personnel will be used to maintain the blinding of study staff who are directly involved in the clinical evaluation of participants in the study. 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). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/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.

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 prior to completion of the protocol-specified vaccinations will still continue to participate in the study as specified in Section 1.3 and Section 8.13.3, unless the participant withdraws consent (Section 7.2).

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.

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

- The participant 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 with placebo/V114 vaccine at Visit 2 (Day 30).

For participants who are discontinued from study intervention but continue to be monitored in the study, see Section 1.3 and Section 8.13.3 for those procedures to be completed at each specified visit.

Discontinuation from study intervention is “permanent.” Once a participant is discontinued, he/she 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 withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment 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 future biomedical research, 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 prespecified 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 or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Study 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.
- 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.

Table 2 shows the approximate blood volumes drawn by study visit and by sample type. The maximum amount of blood collected from each participant at each study visit for immunogenicity assessments will not exceed 40 mL and the total amount of blood for the entire study will not exceed 120 mL. For those participants that consent to future biomedical research, an additional blood sample of approximately 8.5 mL will be taken. For those at selected study sites who consent to provide optional assay development blood samples (target of approximately 120 participants), additional blood samples of approximately 50 mL will be taken at Visit 1 (Day 1) and Visit 3 (Day 60).

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 Types

Study Visit	Visit 1 Day 1	Visit 2 Day 30	Visit 3 Day 60
Blood parameter	Approximate Blood Volume (mL)		
Serum for immunogenicity assays (including retention serum)	40 mL	40 mL	40 mL
Blood (DNA) for future biomedical research	8.5 mL	N/A	N/A
<i>Optional assay development blood samples^a</i>	<i>50 mL</i>	<i>N/A</i>	<i>50 mL</i>
Expected total ^a	48.5 mL	40 mL	40 mL
^a Optional assay development blood samples will be obtained from a total of only approximately 120 participants and therefore the volumes associated with these samples are not included in the Expected total values. For participants who consent to provide optional assay development blood samples, the total blood volumes drawn will be approximately 98.5 mL, 40 mL, and 90 mL at Visit 1, Visit 2, and Visit 3, respectively. DNA = deoxyribonucleic acid			

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant prior to participating in a clinical study or future biomedical research. 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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant 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 dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The 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 future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant.

8.1.1.3 Consent and Collection of Blood Samples for Optional Assay Development

At selected study sites (target of approximately 120 participants), the investigator or medically qualified designee will explain the consent for the optional assay development blood samples to the participant, answer all of his/her questions, and obtain written 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.

If the participant meets any of the exclusion criteria with an asterisk (*), Visit 1 (Day 1) may be rescheduled for a time when these criteria are not met.

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 written informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare 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 before vaccination at Visit 1 (Day 1). The participant's medical history for the 5 years prior to Visit 1 (Day 1) will be obtained to ensure that the participant satisfies the inclusion and exclusion criteria of the study. History of tobacco use will also be collected for all participants.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review and record prior vaccinations and medications taken by the participant within 30 days before the first dose of study vaccine at Visit 1 (Day 1).

Any history of prior PNEUMOVAX™23 vaccination will be reviewed and recorded.

8.1.5.2 Concomitant Medications

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

New and/or concomitant medications taken after Visit 1 (Day 1) and nonstudy vaccines received since Visit 1 will be recorded with the eVRC as specified in Section 8.3.4.

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 prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.13.1.

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 allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

V114 or placebo will be administered at Visit 1 (Day 1) and placebo or V114 will be administered at Visit 2 (Day 30). QIV will be administered at Visit 1 (Day 1).

V114 should be removed from the refrigerator no more than 1 hour before vaccination. The time of removal and time of vaccination should be documented in the participant's chart.

Unblinded study personnel not otherwise involved in the conduct of the study will prepare and administer V114 or placebo and QIV at the study site. QIV will be administered open-label.

Prior to administration of V114, the unblinded pharmacist should shake the product vigorously to obtain a homogenous white suspension. If white-colored insoluble particle appears, the unblinded pharmacist should use rapid, horizontal hand shaking for 5 to 10 seconds while holding the syringe in between the thumb and index finger until complete resuspension. This action should be repeated, as necessary. If appearance is otherwise, the vaccine should not be administered. The vaccine should not be used if the vaccine cannot be resuspended.

For QIV, study personnel should follow the preparation and administration instructions for Fluarix Quadrivalent (influenza vaccine) as specified in the product label.

Study vaccine will be administered as a single 0.5-mL intramuscular injection in the deltoid region of the participant's arm. Vaccination information, such as Component Identification Number and time of vaccination, must be recorded on the appropriate electronic case report form (eCRF) per the Data Entry Guidelines.

All safety and immunogenicity assessments will be conducted by blinded personnel, and the participant will be blinded to the intervention (ie, V114 then placebo vs placebo then V114).

8.1.8.1 Timing of Dose Administration

Vaccinations may be administered at any time of day, and without regard to timing of meals.

Each participant's body temperature must be taken before each vaccine administration. Individuals who present with fever (oral or tympanic temperature $\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]; axillary or temporal temperature $\geq 99.4^{\circ}\text{F}$ [$\geq 37.4^{\circ}\text{C}$]; or rectal temperature $\geq 101.4^{\circ}\text{F}$ [$\geq 38.6^{\circ}\text{C}$]) will have the vaccination delayed until fever is resolved for at least 72 hours.

The collection of blood samples and administration of pregnancy tests (if applicable) must be done before each vaccine administration.

All participants will be observed for 30 minutes after each vaccination for any immediate reactions. This observation must be performed by blinded site personnel for all study vaccines (Section 1.3 and Section 6.3.3).

8.1.9 Electronic Vaccination Report Card

The eVRC was developed to be administered electronically via a hand-held device. This item was structured as recommended in the final Food and Drug Administration Patient Reported Outcome Guidance [U.S. Food and Drug Administration 2009]. The investigator or delegate will train the participant in the use of the eVRC at Visit 1 (Day 1).

Temperatures, injection-site reactions, vaccine-specific complaints, other complaints or illnesses, and concomitant medications or vaccinations will be recorded on the eVRC as described in Section 1.3 and Section 8.3.4. The investigator or delegate will review the data captured on the eVRC with the participant at Telephone Contact (Day 15), Visit 2 (Day 30), Telephone Contact (Day 45), and Visit 3 (Day 60).

For the AEs outlined above, the investigator will use the information provided by the participant both on the eVRC, and verbally at the time of eVRC review, to apply the appropriate assessment of intensity and toxicity as described in Appendix 3.

8.1.10 Telephone Contact Questionnaire

Site personnel will contact study participants 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 prior to completion of the protocol-specified vaccinations should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit (Visit 3 [Day 60]) should be performed if the participant can attend during the Day 30 window or the Day 60 window. If the participant withdraws at any other time, the Month 7 Telephone Contact activities should be performed (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 future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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 drug 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. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity/toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that 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 principal 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 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. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that 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 is 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 vaccine-induced OPA and IgG for serotypes included in V114. These endpoints will be tested for all blood draws. 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 GMTs. 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.

Measurement of serotype-specific IgG will be measured using the PnECL v2.0 assay to assess the concentration of binding antibodies to capsular polysaccharide of *S. pneumoniae* for the serotypes included in the study vaccines.

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

8.2.1 Multiplex Opsonophagocytic Assay (MOPA)

The MOPA, developed and published by Professor Moon Nahm (Director of the United States World Health Organization pneumococcal serology reference laboratory and National Institutes of Health pneumococcal reference laboratories), is a multiplexed OPA assay capable of measuring 4 serotypes at a time, against a total of 16 serotypes of pneumococci [Burton, Robert L. and Nahm, Moon H. 2006]. The OPA 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. The ability of the assay to simultaneously test 4 serotypes/run 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 $\geq 50\%$ bacterial killing, as determined by comparison to assay background controls. MSD has developed and optimized the MOPA in a high throughput microcolony platform. The MOPA assay for all 15 V114 serotypes has undergone validation. The validation study evaluated various performance parameters of the assay including precision, relative accuracy/dilutional linearity, and specificity. The validation results were evaluated against prespecified acceptance criteria for each of the parameters.

8.2.2 Electrochemiluminescence (ECL)

MSD has developed and optimized a multiplex, ECL-based detection method for the quantitation of IgG serotype-specific antibodies to the 15 pneumococcal polysaccharide serotypes contained in V114. The PnECL v2.0 assay is based on the Meso-Scale Discovery technology, which employs disposable multi-spot microtiter plates. The benefits of the ECL multiplex technology over the prior enzyme-linked immunosorbent assay methodology include speed, equivalent or better sensitivity, increased dynamic range, the ability to multiplex, and reduction in required serum sample and reagent volumes. The measurement of

immune responses to the 15 serotypes included in V114 is performed using an assay format consisting of 2 groups of 7 and 8 serotypes each. The PnECL v2.0 assay for all 15 serotypes has undergone validation. The validation study evaluated various performance parameters of the assay including precision, ruggedness, relative accuracy, dilutional linearity, selectivity, and specificity. The validation results were evaluated against pre-specified acceptance criteria for each of the parameters.

8.2.3 Hemagglutination Inhibition (HAI) Assay

The HAI assay is based on the World Health Organization (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 (RBCs), causing them to agglutinate. It is a traditional method to measure vaccine-induced antibodies to hemagglutinin that bind to the hemagglutinin molecule, thereby inhibiting hemagglutination. The HAI test is generally performed using microtiter plates. In a first step, 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 RBCs, the degree of inhibition of agglutination compared to strain-specific reference sera is being 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. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn by visit and by sample type per participant, can be found in Section 8.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) before vaccination at Visit 1 (Day 1). A directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) before vaccination at Visit 2 (Day 30).

Investigators should pay special attention to clinical signs related to previous illnesses.

8.3.2 Pregnancy Test

A pregnancy test consistent with local requirements (sensitive to at least 25 IU beta human chorionic gonadotropin [β -hCG]) must be performed before vaccination at Visit 1 (Day 1) and Visit 2 (Day 30) in WOCBP as described in Section 1.3. Urine or serum tests can be used, and results must be negative before vaccination can occur.

8.3.3 Body Temperature Measurement

Each participant's body temperature must be taken before vaccination, as described in Section 1.3.

Oral body temperatures will also be documented by participants using their eVRC during the eVRC-specified postvaccination follow-up period (Section 8.3.4).

For this study, any oral or tympanic temperature $\geq 100.4^{\circ}\text{F}$ ($\geq 38.0^{\circ}\text{C}$), axillary or temporal temperature $\geq 99.4^{\circ}\text{F}$ ($\geq 37.4^{\circ}\text{C}$), or rectal temperature $\geq 101.4^{\circ}\text{F}$ ($\geq 38.6^{\circ}\text{C}$) will be considered an AE of fever. All fevers must be reported Day 1 through Day 14, unless the fever is a symptom of another reported AE.

8.3.4 Safety Assessments and Use of the eVRC

All participants will be observed for 30 minutes after each 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.

Participants will use the eVRC (Section 8.1.9) to document the following information:

- Oral body temperatures measured Day 1 (day of vaccination) through Day 5 postvaccination;
- Solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain) Day 1 through Day 5 postvaccination;
- Solicited systemic AEs (muscle pain/myalgia, joint pain/arthritis, headache, and tiredness/fatigue) Day 1 through Day 14 postvaccination;
- Any other injection-site or systemic AEs Day 1 through Day 14 postvaccination; and
- Concomitant medications and nonstudy vaccinations Day 1 to Day 14 postvaccination

8.3.5 Clinical 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.
- 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 (AEs), Serious Adverse Events (SAEs), 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 or surrogate).

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 remain responsible for following up AE, 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 consent form is signed but before allocation/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 treatment, or a procedure.

All AEs, SAEs, and other reportable safety events must be reported by the investigator from the day of allocation/randomization to the first vaccination and from the day of each vaccination through 14 days postvaccination. SAEs must also be reported throughout the duration of the individual's participation in the study, regardless of whether or not related to the Sponsor's product.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is either:

1. A death that occurs prior to the participant completing the study.

OR

2. An SAE that is considered by an investigator who is a qualified physician to be vaccine related.

Investigators are not obligated to actively seek AE or SAE 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 he/she 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](#).

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

Type of Event	<u>Reporting Time Period:</u> Consent to Randomization/ Allocation	<u>Reporting Time Period:</u> Randomization/ Allocation through Protocol- Specified Follow-up Period	<u>Reporting Time Period:</u> After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event	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
Serious Adverse Event	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: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Events of Clinical Interest	There are no Events of Clinical Interest for this study.			Not applicable
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

Care will be taken not to introduce bias when detecting AE and/or SAE 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 AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, 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 towards 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. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (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 SAE) 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. Pregnancy outcomes of 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

This is not applicable to this study.

8.4.7 Events of Clinical Interest (ECIs)

There are no events of clinical interest for this study.

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.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

All reports of overdose must be reported by the investigator within 5 calendar days to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the electronic data collection (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

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

8.9 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.10 Optional Assay Development Blood Sample Collection

Each participant enrolled at the selected study sites will be asked to provide optional assay development blood samples until approximately 120 participants have consented.

Each participant providing consent will have a 50-mL sample of blood collected at Visit 1 (Day 1) and Visit 3 (Day 60) (100 mL total). These additional blood samples will be used to establish a proficiency panel for a particular assay, 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 Biomarkers

Biomarkers are not evaluated in this study.

8.12 Medical Resource Utilization and Health Economics

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

8.13 Visit Requirements

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

8.13.1 Screening

Screening procedures will be conducted at Visit 1 (Day 1) as outlined in Section 1.3.

8.13.2 Treatment Period/Vaccination Visit

Requirements during the treatment period are outlined in Section 1.3.

8.13.3 Discontinued Participants Continuing to be Monitored in the Study

A participant may discontinue from study intervention (ie, vaccination) but continue to participate in subsequent protocol visits as outlined in Section 1.3, as long as the participant does not withdraw consent. Protocol-specified activities, including blood draws for immunogenicity assessments and AE monitoring, should occur at these visits.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to unblinding, changes are made to hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a Supplemental Statistical Analysis Plan and referenced in the Clinical Study Report (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, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 When Administered Concomitantly with Influenza Vaccine in Healthy Adults 50 Years of Age or Older (PNEU – FLU)
Intervention Assignment	Participants will be randomly assigned in a 1:1 ratio to V114 with concomitant QIV or V114 with nonconcomitant QIV, respectively. Randomization will be stratified into 6 groups according to the participant's age (50 to 64 years, 65 to 74 years, and ≥ 75 years) and history of prior PNEUMOVAX™23 vaccination (Yes and No) at the time of randomization as described in Section 6.3.2.
Analysis Populations	Immunogenicity: Per Protocol (PP) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	Immunogenicity: <ul style="list-style-type: none"> Serotype-specific OPA GMTs at 30 days postvaccination with V114 Strain-specific HAI GMTs at 30 days postvaccination with QIV Safety: <ul style="list-style-type: none"> Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, tenderness/pain) from Day 1 through Day 5 following any vaccination Proportion of participants with solicited systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, and tiredness/fatigue) from Day 1 through Day 14 following any vaccination Proportion of participants with vaccine-related SAEs from Day 1 to Month 7
Key Secondary Endpoints	<ul style="list-style-type: none"> Serotype-specific IgG GMCs at 30 days postvaccination with V114

Statistical Methods for Key Immunogenicity Analyses	<p>Immunogenicity analyses will be conducted for each of the 15 pneumococcal serotypes in V114 and each of the 4 influenza strains in QIV separately.</p> <p>The primary objective (to compare the serotype-specific OPA GMTs at 30 days postvaccination with V114 between participants administered V114 concomitantly with QIV versus participants administered V114 nonconcomitantly with QIV) will be assessed via the following noninferiority hypotheses:</p> <p>H_0: $GMT_1/GMT_2 \leq 0.50$ versus H_1: $GMT_1/GMT_2 > 0.50$</p> <p>where GMT_1 is the serotype-specific OPA GMT for the concomitant group and GMT_2 is the serotype-specific OPA GMT for the nonconcomitant group. The primary objective (to compare the strain-specific HAI GMTs at 30 days postvaccination with QIV between participants administered QIV concomitantly with V114 versus participants administered QIV nonconcomitantly) will be assessed via the following noninferiority hypotheses:</p> <p>H_0: $GMT_1/GMT_2 \leq 0.50$ versus H_1: $GMT_1/GMT_2 > 0.50$</p> <p>where GMT_1 is the strain-specific HAI GMT for the concomitant group and GMT_2 is the strain-specific HAI GMT for the nonconcomitant group. The serotype-specific OPA GMTs at 30 days postvaccination with V114 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 15 serotypes in V114 and strain-specific HAI GMT ratios for each of the 4 strains in QIV, respectively. Serotype-specific OPA GMT ratios and strain-specific HAI GMT ratios estimation, 95% CIs, and results from the hypothesis tests (i.e., 1-sided p-values) will be calculated using a constrained longitudinal data analysis (cLDA) method utilizing data from both vaccination groups. Estimation of the serotype-specific IgG GMC ratios and 95% CIs will be calculated using the cLDA method.</p>
Statistical Methods for Key Safety Analyses	<p>P-values (Tier 1 endpoints) and 95% CIs (Tier 1 and Tier 2 endpoints) will be provided for between-group differences in the percentage of participants with events; these analyses will be performed using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].</p>
Interim Analyses	<p>To support the periodic review of safety and tolerability data across the V114 Phase 3 program, an external unblinded statistician will provide unblinded interim safety summaries to an independent external DMC for their review. There are no plans to conduct an interim analysis of unblinded immunogenicity data in this study.</p>
Multiplicity	<p>The overall success of the study requires demonstrating success on all 15 pneumococcal serotypes and all 4 influenza strains included in the primary immunogenicity hypotheses. This approach controls the 1-sided type-I error rate at 0.025, and no multiplicity adjustment is required.</p>

Sample Size and Power	Immunogenicity: This study will randomize approximately 600 participants into the concomitant group and 600 participants into the nonconcomitant group and has approximately 87% power overall for demonstrating noninferiority of OPA GMT ratio for the 15 pneumococcal serotypes included in V114 and noninferiority of HAI GMT ratio for the 4 influenza strains in QIV at an overall 1-sided 2.5% alpha-level. Safety: Section 9.9.2 provides information about the ability of this study to estimate the incidence of AEs within and between the concomitant and nonconcomitant group.
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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.

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

9.4.1 Immunogenicity Endpoints

A description of immunogenicity assessments is contained in Section 8.2.

The primary immunogenicity analysis endpoints include:

- Serotype-specific OPA GMTs at 30 days postvaccination with V114
- Strain-specific HAI GMTs at 30 days postvaccination with QIV

The secondary immunogenicity analysis endpoints include:

- Serotype-specific IgG GMCs at 30 days postvaccination with V114
- Serotype-specific GMFRs and proportions of participants with a 4-fold rise from baseline (prevaccination with V114) to 30 days postvaccination with V114 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 $\geq 1:40$ 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 $\geq 1:10$) or (2) a HAI titer of $\geq 1:40$ at 30 days postvaccination with QIV among participants who are seronegative at baseline (HAI titer $< 1:10$)

9.4.2 Safety Endpoints

A description of safety measures is contained in Sections 8.3 and 8.4. The analysis of safety results is described in Section 9.6.2.

The safety analysis endpoints include:

- Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, tenderness/pain) from Day 1 through Day 5 following any vaccination
- Proportion of participants with solicited systemic AEs (muscle pain/myalgia, joint pain/arthritis, headache, and tiredness/fatigue) from Day 1 through Day 14 following any vaccination
- Proportions of participants with the broad AE categories consisting of any AE, a vaccine-related AE, a SAE, a death, an AE which is both vaccine-related and serious, an AE which leads to discontinuation
- Proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 5 following any vaccination

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

The Per-Protocol (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 endpoints. Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Failure to receive any study vaccine at Visit 1 (Day 1)
- Failure to receive correct clinical material as per randomization schedule at Visit 1 (Day 1) (ie, participants who were cross-treated)
- Receipt of a prohibited medication or prohibited vaccine prior to study vaccination

Additional 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 any study vaccine at Visit 2 (Day 30)
- Failure to receive correct clinical material as per randomization schedule at Visit 2 (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 (as described in Section 1.3)

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. 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 Full Analysis Set (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 All Participants as Treated (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. This will be the group to which they are randomized except for participants who take incorrect study vaccination; such participants will be included in the group corresponding to the study vaccination actually received. If a participant received the same vaccine at Visit 1 and Visit 2 due to the incorrect medication administration, resulting in the administration of 2 doses of V114 or 2 doses of placebo, this participant's data would be excluded from APaT and would be 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

Statistical testing and inference for immunogenicity and safety analyses are described in Section 9.6.1 and Section 9.6.2, respectively. Unless otherwise stated, all statistical tests will be conducted at the $\alpha=0.05$ (2-sided) level. Section 9.6.3 describes how demographic and baseline characteristics will be summarized.

9.6.1 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the primary and secondary immunogenicity objectives.

Immunogenicity analyses will be conducted for each of the 15 pneumococcal serotypes in V114 and each of the 4 influenza strains in QIV separately.

The primary objective (to compare the serotype-specific OPA GMTs at 30 days postvaccination with V114 between participants administered V114 concomitantly with QIV versus participants administered V114 nonconcomitantly with QIV) will be assessed via the following noninferiority hypotheses:

$$\begin{aligned} H_0: \text{GMT}_1/\text{GMT}_2 &\leq 0.50 \text{ versus} \\ H_1: \text{GMT}_1/\text{GMT}_2 &> 0.50, \end{aligned}$$

where GMT_1 is the serotype-specific OPA GMT for the concomitant group and GMT_2 is the serotype-specific OPA GMT for the nonconcomitant group. A ratio of 0.50 corresponds to a 2.0-fold decrease of OPA GMT in the concomitant group as compared with the nonconcomitant group. This same statistical criterion has been previously applied to evaluate Prevnar 13™ when administered concomitantly with influenza vaccine [Frenck, R. W. Jr., et al 2012] [Schwarz, T. F., et al 2011] [Schwarz, T. F. 2013]. Rejecting the null hypothesis (H_0) at the 1-sided $\alpha=0.025$ level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (concomitant/ nonconcomitant) being >0.50 and would lead to the conclusion

that the OPA responses in the concomitant group are noninferior to the nonconcomitant group for the 15 pneumococcal serotypes.

The primary objective (to compare the strain-specific HAI GMTs at 30 days postvaccination with QIV between participants administered QIV concomitantly with V114 versus participants administered QIV nonconcomitantly) will be assessed via the following noninferiority hypotheses:

H_0 : $\text{GMT}_1/\text{GMT}_2 \leq 0.50$ versus

H_1 : $\text{GMT}_1/\text{GMT}_2 > 0.50$,

where GMT_1 is the strain-specific HAI GMT for the concomitant group and GMT_2 is the strain-specific HAI GMT for the nonconcomitant group. A ratio of 0.50 corresponds to a 2.0-fold decrease of HAI GMT in the concomitant group as compared with the nonconcomitant group. This same statistical criterion has been previously applied to evaluate influenza vaccine when administered concomitantly with Prevnar 13™ [Frenck, R. W. Jr., et al 2012] [Schwarz, T. F., et al 2011] [Schwarz, T. F. 2013] [U.S. Department of Health & Human Services 2018]. Rejecting the null hypothesis (H_0) at the 1-sided $\alpha=0.025$ level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (concomitant/ nonconcomitant) being >0.50 and would lead to the conclusion that the influenza HAI responses in the concomitant group are noninferior to the nonconcomitant group for the 4 influenza strains.

To address the 2 primary immunogenicity objectives, the serotype-specific OPA GMTs at 30 days postvaccination with V114 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 15 serotypes in V114 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 (i.e., 1-sided p-value) will be calculated using a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [Liang, K-Y and Zeger, S. L. 2000] utilizing data from both vaccination groups. In this model, the response vector consists of the log-transformed baseline and 30 days postvaccination antibody titers. The repeated-measures model will include terms for vaccination group, time, the interaction of time-by-vaccination group (with a restriction of the same baseline mean across groups), age stratum (i.e., 50 to 64 years, 65 to 74 years, and ≥ 75 years) at baseline, history of prior PNEUMOVAX™23 stratum (i.e., Yes and No), age stratum-by-time interaction, and history of prior PNEUMOVAX™23 stratum-by-time interaction. This model will allow for different baseline means for each stratum, but restrict the baseline mean within both the age stratum levels and the history stratum levels to be the same for both vaccination groups. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted (or residual) 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.

A similar statistical approach will be used to evaluate the serotype-specific IgG GMCs at 30 days postvaccination with V114 for participants administered V114 concomitantly with QIV and participants administered V114 nonconcomitantly 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 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 V114 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 4](#).

Table 4 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach [†]	Statistical Method [‡]	Analysis Population	Missing Data Approach
Primary Endpoints				
OPA GMTs at 30 days postvaccination with V114	P	cLDA [§] (estimate, 95% CI)	PP	Model-based
	S		FAS	
HAI GMTs at 30 days postvaccination with QIV	P	cLDA [§] (estimate, 95% CI)	PP	Model-based
	S		FAS	
Secondary Endpoints				
IgG GMCs at 30 days postvaccination with V114	P	cLDA [§] (estimate, 95% CI)	PP	Model-based
OPA GMTs and IgG GMCs at baseline (prevaccination with V114) and 30 days postvaccination with V114	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
GMFRs and %s of participants with a ≥4- fold rise from baseline (prevaccination with V114) to 30 days postvaccination with V114 for both OPA and IgG responses	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
HAI GMTs at baseline (prevaccination with QIV) and 30 days postvaccination with QIV	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
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

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach [†]	Statistical Method [‡]	Analysis Population	Missing Data Approach
%s of participants with HAI titer $\geq 1:40$ at 30 days postvaccination with QIV	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
%s 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
[†] P = Primary approach; S = Supportive approach. [‡] Statistical models are described in further detail below: [§] Constrained longitudinal data analysis (cLDA) model with terms for vaccination group, time, the interaction of time-by-vaccination, age stratum at baseline, history of prior PNEUMOVAX™23 stratum, age stratum-by-time interaction, and history of prior PNEUMOVAX™23 stratum-by-time interaction. CI = confidence interval; FAS = Full Analysis Set; GMC = Geometric Mean Concentration; GMFR = geometric mean fold rise; GM = Geometric Mean Titer; IgG = Immunoglobulin G; OPA= opsonophagocytic activity; PP = Per-Protocol; HAI= hemagglutination inhibition; QIV = quadrivalent influenza vaccine (seasonal inactivated).				

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.

The analysis of safety results following any vaccination will follow a tiered approach (Table 5). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) are either pre-specified as “Tier 1” endpoints, or will be classified as belonging to “Tier 2” or “Tier 3” based on the number of events observed.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs to be provided for between-group differences in the proportion of participants with events; these analyses will be performed using the unstratified Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method. For this protocol, solicited injection-site AEs (redness/erythema, swelling, tenderness/pain) from Day 1 through Day 5 following any vaccination and solicited systemic AEs (muscle pain/myalgia, joint pain/arthritis, headache, and tiredness/fatigue) from Day 1 through Day 14 following any vaccination are considered Tier 1 events.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (also via the unstratified M&N method [Miettinen, O. and Nurminen, M. 1985]).

Membership in Tier 2 requires that at least 4 participants in any vaccination group exhibit the event. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when vaccination groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events.

In addition to individual events that occur in 4 or more participants in any vaccination group, the broad AE categories consisting of the proportion of participants with any AE, a vaccine-related AE, a SAE, an AE which is both vaccine-related and serious, discontinuation due to an AE, and the proportion of participants who died will be considered Tier 2 endpoints. The proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points will also be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by vaccination group are provided for Tier 3 safety parameters.

Table 5 Analysis Strategy for Safety Parameters Following Any Vaccination

Safety Tier	Safety Endpoint	p-Value	95% CI for Between-Group Comparison	Descriptive Statistics
Tier 1	Injection-site redness/erythema (Days 1 to 5)	X	X	X
	Injection-site swelling (Days 1 to 5)	X	X	X
	Injection-site tenderness/pain (Days 1 to 5)	X	X	X
	Muscle pain/myalgia (Days 1 to 14)	X	X	X
	Joint pain/arthritis (Days 1 to 14)	X	X	X
	Headache (Days 1 to 14)	X	X	X
	Tiredness/fatigue (Days 1 to 14)	X	X	X

Safety Tier	Safety Endpoint	p-Value	95% CI for Between-Group Comparison	Descriptive Statistics
Tier 2	Any AE [†]		X	X
	Any vaccine-related AE [†]		X	X
	Any SAE [†]		X	X
	Any vaccine-related SAE [†]		X	X
	Discontinuation due to AE [†]		X	X
	Death [†]		X	X
	Maximum temperature measurements meeting the Brighton Collaboration cut points (Days 1 to 5)		X	X
	Specific AEs by SOC and PT [‡] (incidence ≥ 4 of participants in 1 of the vaccination groups)		X	X
Tier 3	Specific AEs by SOC and PT [‡] (incidence < 4 of participants in all of the vaccination groups)			X
[†] These endpoints are broad adverse event 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. [‡] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints. AE = adverse event; PT = preferred term; SAE = serious adverse event; SOC = system organ class; X = results will be provided.				

In addition to the analyses following any vaccination, point estimates by vaccination group will be provided for injection-site AEs following V114 and following QIV separately. That is, the proportion of participants with injection-site AEs following administration of V114 will include AEs reported from Day 1 through Day 5 following V114 administration in the limb corresponding to the location of V114 administration. Similarly, the proportion of participants with injection-site AEs following administration of QIV will include AEs reported from Day 1 through Day 5 following QIV administration in the limb corresponding to the location of QIV administration.

Additionally, the systemic AEs in the 14 days following each vaccination time point for each vaccination group will be summarized. That is, descriptive summaries of systemic AEs will include AEs reported from Day 1 through Day 14 following administration of

1. V114 and QIV in the concomitant group at Visit 1 (Day 1)
2. QIV with placebo in the nonconcomitant group at Visit 1 (Day 1)
3. Placebo alone in the concomitant group at Visit 2 (Day 30)
4. V114 alone in the nonconcomitant group at Visit 2 (Day 30)

Safety analyses will be based on the observed data (ie, with no imputation of missing data).

9.6.3 Demographic and Baseline Characteristics

The comparability of the vaccination groups for each relevant demographic and baseline characteristic will be assessed by the use of 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, and gender), baseline characteristics, prior and concomitant vaccinations and therapies 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 adult V114 Phase 3 program will be conducted by an independent, unblinded, external DMC. A description of the structure, function, and guidelines for decision-making by 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. There are no plans to conduct an interim analysis of unblinded immunogenicity data in this study. However, unblinded immunogenicity data will be made available to the DMC upon request to enable a benefit-risk assessment.

Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to intervention assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician performing the interim analysis. The DMC will serve as the primary reviewer of the results of the safety interim analyses and will make recommendations for discontinuation of the study or protocol modifications to an executive committee 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, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the intervention level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the external unblinded statistician. Additional logistical details will be provided in the DMC Charter.

Intervention-level results from the safety interim analysis 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 interim analyses.

9.8 Multiplicity

The overall success of the study requires demonstrating success on all 15 pneumococcal serotypes and all 4 influenza strains included in the primary immunogenicity hypotheses. This approach controls the 1-sided type-I 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 600 participants into the concomitant group and 600 participants into the nonconcomitant group and has approximately 87% power for demonstrating noninferiority of the serotype-specific OPA GMT ratios for the 15 pneumococcal serotypes included in V114 and >99.9% 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. Because the 2 hypotheses are assumed to be independent and the success of the study requires that the statistical criteria be met for both hypotheses, the overall power for the primary immunogenicity hypotheses is estimated to be approximately 87% ($=0.87 \times >0.999$).

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

- 90% evaluability rate (approximately 540 evaluable participants per treatment group) for both primary endpoints (OPA GMT ratios and HAI GMT ratios).
- The underlying OPA GMT ratio is 0.80 (concomitant/nonconcomitant) for the 15 pneumococcal serotypes. The assumption for this ratio is based on results of studies evaluating the administration of Prevnar 13™ with concomitant influenza vaccines.
- The variabilities for OPA titers in both concomitant group and nonconcomitant group are the same as that observed in V114-006. The standard deviations of the natural log titers for the 15 pneumococcal serotypes in V114 range from 1.33 to 2.24. The lowest estimated GMT ratios (concomitant group/nonconcomitant group) that would still meet the noninferiority margin range from 0.59 to 0.65.
- The HAI antibody responses are the same as those observed in a prior Merck study.

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 a 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 600 participants in the concomitant group if the underlying incidence of a SAE is 0.27% (1 of every 373 participants receiving the vaccine). There is a 50% chance of observing at least 1 SAE among 600 participants in the concomitant group if the underlying incidence of a SAE is 0.12% (1 of every 866 participants receiving the vaccine). If no SAEs are observed among 600 participants in the concomitant group, this study will provide 97.5% confidence that the underlying percentage of participants with a SAE is <0.61% (1 in every 163 participants) in the concomitant group.

Table 6 summarizes the percentage point differences between the 2 vaccination groups that could be detected with 80% probability for a variety of hypothetical underlying incidences of an AE. These calculations assume 600 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 (1990) [Farrington, C. P. 1990]; no multiplicity adjustments were made.

Table 6 Differences in Incidence of AE Rates between the 2 Vaccination Groups That Can be Detected With an ~80% Probability (Assuming 2-sided 5% alpha level with 600 Participants in each Group)

Incidence of Adverse Event		Risk Difference
Nonconcomitant Group (%)	Concomitant Group (%)	Percentage Points
0.1	1.6	1.5
2.0	5.0	3.0
5.0	9.1	4.1
10.0	15.4	5.4
15.0	21.2	6.2
20.0	26.8	6.8
30.0	37.6	7.6
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. Based on an asymptotic method (Farrington and Manning [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). Examples of possible subgroup classification variables include age (50 to 64 years, 65 to 74 years, and ≥ 75 years) and history of PNEUMOVAX™23 vaccination (Yes and No). Further details of subgroup analyses will be documented in the Supplemental Statistical Analysis Plan.

9.11 Compliance (Medication Adherence)

Given that participants will receive just a single dose of V114 and a single dose of QIV, 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 V114 and the number and proportion of randomized participants administered QIV.

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 and Dohme Corp., a subsidiary of Merck & Co., Inc. (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 of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and 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 (eg, 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 (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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 to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of 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 fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified 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. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

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. Unless required by law, only the investigator, Sponsor (or representative), 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 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 (eg, 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, commonly 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

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 report form 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 prior to 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 Scientific Advisory Committee

This study was developed in collaboration with a Scientific Advisory Committee (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.

10.1.4.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

10.1.4.3 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.

10.1.5 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 International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, 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 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 trial directive 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 directive 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, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); 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 Studies.

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 signed ICF, 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. 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 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 7](#) will be performed according to local requirements.
- 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 7 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Other Screening Tests	Serum or urine β -hCG pregnancy test (as needed for WOCBP)
β -hCG = β human chorionic gonadotropin; WOCBP = woman/women of childbearing potential	

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

10.3.1 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 (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, 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, or are considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.7 for protocol-specific exceptions.

10.3.2 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 pre-existing condition that has not worsened is not an SAE. A pre-existing 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.

10.3.3 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

10.3.4 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/Toxicity

- 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 intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
 - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
 - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies definitely acting like something is wrong).
 - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).
- Injection-site redness/erythema or swelling from the day of vaccination through Day 5 postvaccination will be evaluated by maximum size.
- The investigator will make an assessment of toxicity for each AE and SAE (and other reportable event) reported during the study. A toxicity 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 toxicity 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."

Injection-Site AE Toxicity Grading Scale

Injection Site Reaction to Study Vaccine/Placebo ^a	Grade 1	Grade 2	Grade 3	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 B	Size measured as C or D	Size measured as E→	Necrosis or exfoliative dermatitis or results in ER visit or hospitalization
Induration/Swelling	Size measured as B	Size measured as C or D	Size measured as E→	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
Any injection-site reaction that begins ≥ 6 days after receipt of study vaccine/placebo				
Pain/tenderness Erythema/Redness Induration/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

Abbreviations: AE = adverse event; ER = emergency room; eVRC = electronic Vaccine Report Card; SAE = serious adverse event

^a Based upon information provided by the patient on the eVRC and verbally during VRC review. Erythema/Redness and Induration/Swelling are specific injection-site AEs with size designations of letters A through E→, based upon a graphic in the eVRC. Size A is not assigned a toxicity grade; however, injection-site AEs that measure size A should be reported as adverse experiences. If the participant has an ER visit or is hospitalized for any injection-site AE, that AE is to be assigned a toxicity grade of 4, regardless of the size measured.

Specific Systemic AE Toxicity 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

Abbreviations: ER = emergency room

Other Systemic AE Toxicity 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

Abbreviations: ER = emergency room; eVRC = electronic Vaccine Report Card; SAE = serious adverse event

^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) Toxicity Grading Scale

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

^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 Sponsor's product cause the AE?
- The determination of the likelihood that the Sponsor's product 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 initialled 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 upon the available information.
- **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
 - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product 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 Sponsor's product? 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 re-exposed to the Sponsor's product 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, or (2) the study is a single-dose vaccine study; or (3) Sponsor's product(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 SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT 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 Sponsor's product 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 his/her 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 Sponsor's product relationship).
- Yes, there is a reasonable possibility of Sponsor's product relationship:
- There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
- No, there is not a reasonable possibility of Sponsor's product relationship:

- Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- 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 his/her 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.

10.3.5 Reporting of AE, SAE, 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 electronic data collection (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 e-mail 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 Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

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

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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
 - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal 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 Contraception Requirements

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use 1 of the contraception methods described in [Table 8](#) consistently and correctly during the protocol-defined time frame in Section 5.1.

Table 8 Contraceptive Methods

Acceptable Contraceptive Methods <i>Failure rate of >1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> • Male or female condom with or without spermicide • Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent^a <i>Failure rate of <1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> • Combined (estrogen- and progestogen- containing) hormonal contraception^b <ul style="list-style-type: none"> ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
<ul style="list-style-type: none"> • Progestogen only hormonal contraception^b <ul style="list-style-type: none"> ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency <i>Failure rate of <1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> • Progestogen- only contraceptive implant^b • Intrauterine hormone-releasing system (IUS)^b • Intrauterine device (IUD) • Bilateral tubal occlusion
<ul style="list-style-type: none"> • Vasectomized partner A vasectomized partner 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.
<ul style="list-style-type: none"> • 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.
<p>Notes:</p> <p>Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.</p> <p>^a Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).</p> <p>^b If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.</p>

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

1. Definitions

- 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.
- Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.²
- Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.²
- DNA: Deoxyribonucleic acid.
- RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 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 drugs/vaccines may interact with
- 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.

- Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research substudy

- Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants 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.

- 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.

- 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

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' 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 gender, age, medical history and treatment outcomes are 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 which 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

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing 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 this substudy. 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

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main 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 utilized 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

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

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

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

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@merck.com.

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10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
APaT	All Participants as Treated
β-hCG	beta-human chorionic gonadotropin
CAPiTA	Community-Acquired Pneumonia Immunization Trial in Adults
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
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECL	electrochemiluminescence
eCRF	electronic case report form
EDC	electronic data collection
EMA	European Medicines Agency
EOC	Executive Oversight Committee
eVRC	Electronic Vaccination Report Card
FAS	Full Analysis Set
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HIV	Human Immunodeficiency Virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation Good Clinical Practice
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IMP	investigational medicinal product
IPD	invasive pneumococcal disease
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MOPA	Multiplexed Opsonophagocytic Assay
MSD	Merck Sharp & Dohme Corp.
NIMP	non-investigational medicinal product
OPA	opsonophagocytic activity
PCV	pneumococcal conjugate vaccine
PnECL	pneumococcal electrochemiluminescence
PP	Per-Protocol

Abbreviation	Expanded Term
PT	preferred term
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SLAB	supplemental laboratory test
SoA	schedule of activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
US	United States
WOCBP	woman/women of childbearing potential

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