Official Protocol Title:	A Phase 3, Single-Arm, Open-label Clinical Study to Evaluate the Safety and Immunogenicity of 4 doses of V114 Administered to Healthy Infants in South Korea.
NCT number:	NCT04633226
Document Date:	23-Jun-2022

Title Page

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Protocol Title: A Phase 3, Single-Arm, Open-label Clinical Study to Evaluate the Safety and Immunogenicity of 4 doses of V114 Administered to Healthy Infants in South Korea.

Protocol Number: 036-02

Compound Number: V114

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

EudraCT	2020-003181-39
IND	14115

Approval Date: 23 June 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 02	23-JUN-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 01	05-OCT-2021	The primary purpose of this amendment is to reduce the number of participants in the study from an enrollment target of approximately 100 to approximately 45 due to the enrollment challenges primarily related to the COVID-19 pandemic.
Original Protocol	24-SEP-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Single-Arm, Open-label Clinical Study to Evaluate the Safety and Immunogenicity of 4 doses of V114 Administered to Healthy Infants in South Korea.

Short Title: Safety and immunogenicity of V114 in healthy infants in South Korea

Acronym: PNEU-PED KOR

Hypotheses, Objectives, and Endpoints:

The following objectives and endpoints will be evaluated in healthy infants enrolled at approximately 2 months of age (from 42 to 90 days [inclusive]) administered V114.

Primary Objectives	Primary Endpoints
- Objective: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).	- Solicited injection-site AEs from Day 1 through Day 7 postvaccination. - Solicited systemic AEs from Day 1 through Day 7 postvaccination. - Vaccine-related serious adverse events (SAEs) through completion of study participation.
- Objective: To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 30 days after Dose 3. - Objective: To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days after Dose 3.	- Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 3 (PD3).
Secondary Objectives	
- Objective: To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days after Dose 4.	- Anti-PnP serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 4 (PD4).

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Pneumococcal disease
Population	Healthy infants
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 25 months from the time the first participant (or their legally acceptable representative) provides documented informed consent/assent until the last participant's last study-related contact. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

Number of Participants:

Approximately 45 participants will be randomized.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Vaccine</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Administration</th><th>Vaccination Regimen</th><th>Use</th></tr>
<tr><td>V114</td><td>V114</td><td>Refer to IB</td><td>4 dose</td><td>IM</td><td>Single dose at Visits 1,2, 3, and 5 (~2, 4, 6, and 12-15 months of age)</td><td>Experi-mental</td></tr>
<tr><td colspan="7">Abbreviations: IB = Investigator’s Brochure; IM= intramuscular</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>1 intervention group</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 11 to 15 months from the time the participant’s parent or legally acceptable representative provides documented informed consent.</td></tr>
</table>

Study Governance Committees:

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

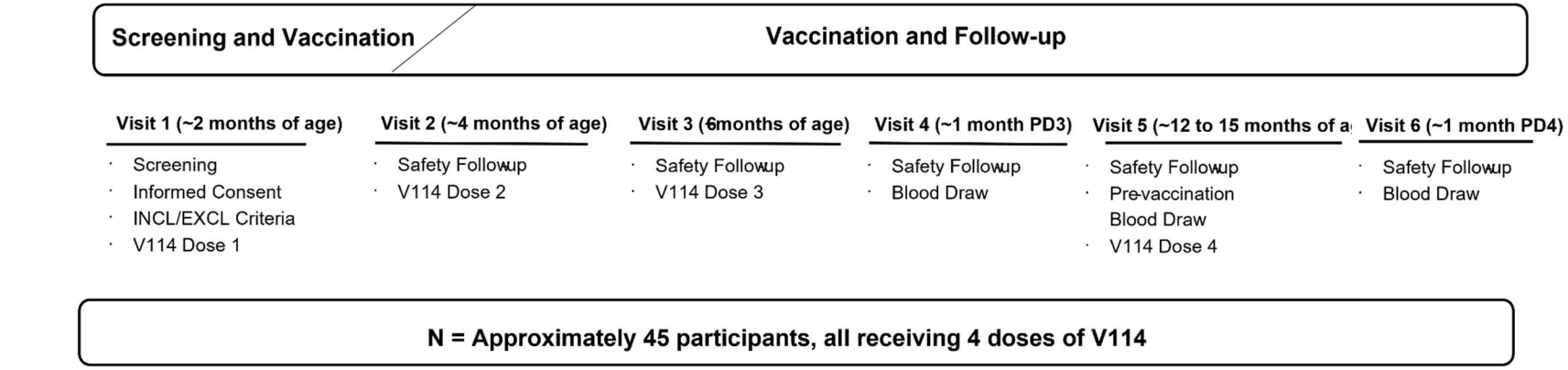
Study Accepts Healthy Volunteers: Yes

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.

Figure 1 V114-036 Study Design



INCL/EXCL = Inclusion/Exclusion Criteria

1.3 Schedule of Activities

Study Period:	**Intervention**						**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	
Scheduled Time:	**Age: ~2 months (Dose 1)**	**Age: ~4 months (Dose 2)**	**Age: ~6 months (Dose 3)**	**~1 month after Dose 3**	**Age: ~12 to 15 months (Dose 4)**	**~1 month after Dose 4**	Months of age is calculated according to the participant's birth date
Visit Window[a]	**≥42 days of age to ≤90 days of age**	**4 months of age to 1 day before 5 months of age**	**6 months of age to 1 day before 7 months of age**	**Day 28 to Day 42 Postdose 3**	**12 months of age to 1 day before 16 months of age**	**Day 28 to Day 42 Postdose 4**	
Administrative Procedures							
Screening Procedures							
Informed Consent	X						Consent must be obtained before any study procedures.
Informed Consent for FBR	X						Participation in FBR is optional and consent must be obtained before collection of buccal swab DNA samples.
Assignment of Screening Number	X						
Participant Identification Card	X						
Inclusion/Exclusion Criteria	X						Review of prior medications/vaccinations, a complete physical examination, and temperature measurement are required at Visit 1 to determine eligibility.
Medical History	X						
Postrandomization Procedures							
Assignment of Treatment/ Randomization Number	X						
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X	X	X	X	
V114 Administration	X	X	X		X		Before V114 administration, ensure the participant has no new contraindication to V114. Participants must be afebrile for at least 72 hours before V114 administration.

Study Period:	**Intervention**						**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	
Scheduled Time:	**Age: ~2 months (Dose 1)**	**Age: ~4 months (Dose 2)**	**Age: ~6 months (Dose 3)**	**~1 month after Dose 3**	**Age: ~12 to 15 months (Dose 4)**	**~1 month after Dose 4**	Months of age is calculated according to the participant's birth date
Visit Window[a]	**≥42 days of age to ≤90 days of age**	**4 months of age to 1 day before 5 months of age**	**6 months of age to 1 day before 7 months of age**	**Day 28 to Day 42 Postdose 3**	**12 months of age to 1 day before 16 months of age**	**Day 28 to Day 42 Postdose 4**	
Nonstudy Pediatric Vaccines	(X)	(X)	(X)		(X)		Sponsor will not provide nonstudy pediatric vaccines, but they are permitted to be given during the study. If given at the same time, oral vaccines are recommended to be given before the study vaccine and other injectable vaccines. Other injectable vaccines are administered after the study vaccine and in a separate limb. See Section 6.5 for details on concomitant vaccines.
Provide Paper VRC	X	X	X		X		A paper VRC will be provided to record AEs, body temperature, concomitant medications, and nonstudy vaccinations. Instructions for using the paper VRC will be reviewed with the participant's parent or legally acceptable representative. See Section 8.1.9 and 8.3.3 for details regarding the completion of the paper VRC.
Collect Paper VRC and Review VRC data with Participant's Parent or Legally Acceptable Representative		X	X	X		X	See Section 8.1.9 for details.
Safety Procedures							
Complete Physical Examination	X						To be performed by the investigator or medically qualified designee before vaccine is administered (see Section 8.3.1).
Targeted Physical Examination		X	X		X		To be performed by the investigator or medically qualified designee before vaccine is administered (see Section 8.3.1).
Body Temperature Measurement	X	X	X		X		Each participant's body temperature must be taken before vaccination (see Section 8.3.2 for method). Participants who have febrile illness at or within 72 hours of vaccination must be rescheduled.

Study Period:	**Intervention**						**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	
Scheduled Time:	**Age: ~2 months (Dose 1)**	**Age: ~4 months (Dose 2)**	**Age: ~6 months (Dose 3)**	**~1 month after Dose 3**	**Age: ~12 to 15 months (Dose 4)**	**~1 month after Dose 4**	Months of age is calculated according to the participant's birth date
Visit Window[a]	**≥42 days of age to ≤90 days of age**	**4 months of age to 1 day before 5 months of age**	**6 months of age to 1 day before 7 months of age**	**Day 28 to Day 42 Postdose 3**	**12 months of age to 1 day before 16 months of age**	**Day 28 to Day 42 Postdose 4**	
15-Minute Postvaccination Observation Period	X	X	X		X		The observation period can be extended if clinically indicated.
AE Monitoring	X	X	X	X	X	X	Nonserious AEs are to be reported from Days 1 through 14 after each vaccination. SAEs and deaths are to be reported throughout the duration of an individual's study participation.
Serum for Immunogenicity Assays (Including Retention Serum)				X		X	Blood samples must be collected before vaccination where applicable.
Collect Buccal Swabs (DNA) for FBR	X						Buccal swab DNA samples for analysis should be obtained before vaccination at Visit 1, on randomized and FBR consented participants only, or at a later date as soon as the informed consent is obtained.

AE = adverse event; DNA = deoxyribonucleic acid; paper; FBR = future biomedical research; SAE = serious adverse event; VRC = paper Vaccination Report Card; (X) = Not provided by Sponsor, but permitted in the study

[a] For calculating the visit windows, the day of vaccination is considered Day 1. To calculate visit windows for subsequent vaccinations, confirm participant date of birth and ensure the age of the participant will fall within the appropriate age range for each study visit.

2 INTRODUCTION

MSD is developing an investigational 15-valent PCV (called V114) for the prevention of pneumococcal disease caused by the serotypes 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 Prevenar 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

Pneumococcal disease remains an important worldwide concern despite the availability of PCVs. This is due to the emergence of nonvaccine serotypes that are being increasingly isolated in cases of IPD. Given the worldwide distribution, the increased proportion of nonvaccine serotypes and the value of multiple suppliers to strengthen global supply, there is a continued need to develop new PCVs with expanded serotype coverage. V114 contains all the pneumococcal serotypes contained in Prevenar 13™ plus 2 additional serotypes (22F, 33F), which have emerged as important causes of IPD and will address an unmet medical and public health need for a PCV with expanded coverage.

The purpose of this study is to show the safety and immunogenicity of a 4-dose schedule (3 doses in the infant primary series followed by 1 toddler dose) of V114 in healthy South Korean infants approximately 2 months of age (42 to 90 days of age).

The 3 + 1 PCV immunization schedule in this study is the same as that currently recommended by the South Korean NIP. It is generally recommended that Prevenar 13™ is to be given at the same time as other NIP pediatric vaccines. The concomitant administration of V114 with NIP pediatric vaccines (with the exception of influenza vaccine and LJEV vaccine as detailed in Section 6.5) will be allowed in this Phase 3 clinical study at the discretion of investigators.

2.2 Background

2.2.1 V114 and Pneumococcal Disease

Refer to the IB for V114 for detailed background information including information on pneumococcal disease burden.

Streptococcus pneumoniae remains a significant cause of disease worldwide, with clinical manifestations including meningitis, sepsis, pneumonia, sinusitis, and otitis media.

Currently, many countries worldwide have incorporated licensed PCVs (eg, Prevenar 13™ and/or Synflorix™ (pneumococcal polysaccharide conjugate vaccine [adsorbed], GlaxoSmithKline Biologicals S.A, Rixensart, Belgium) into their infant immunization programs. In South Korea, Prevenar™ was introduced as an optional vaccine in 2003 followed by Prevenar 13™ and Synflorix™ in 2010. Prevenar 13™ and Synflorix™ were then included in the South Korean NIP in 2014 [Lee, J. K., et al 2017]. Since PCVs have

been introduced into the NIP, the overall burden of IPD in children caused by vaccine serotypes has decreased [Kim, S. H., et al 2016]. Widespread use of PCVs have reduced the burden of pneumococcal disease caused by the serotypes contained in the vaccines in children who received the vaccines, as well as unvaccinated individuals through 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]. Despite this, an increase in the burden of IPD caused by serotypes not contained in currently available vaccines has been observed.

V114 contains all the pneumococcal serotypes contained in Prevenar 13™ plus 2 additional serotypes (22F, 33F). The selection of 22F and 33F was primarily based on the emergence of these 2 serotypes as important causes of IPD in the era of Prevenar 13™.

In South Korea, the prevalence of serotype 22F isolates from children ≤5 years with invasive or noninvasive pneumococcal disease during the period of 2014 to 2016 was 2.4% [Park, D. C., et al 2019]. In 2013 the prevalence of IPD caused by serotype 33F in children under 18 years of age was 5.6%. [Cho, E. Y., et al 2016]. Of particular concern is the high degree of invasiveness of serotype 22F and 33F compared with other serotypes not currently covered by licensed PCVs, resulting in both being associated with serious clinical outcomes. Furthermore, serotypes 22F and 33F have shown relative resistance to certain antibiotics used in the treatment of community acquired pneumonia [Golden, A. R., et al 2016]. Thus, it is anticipated that vaccination with V114 will contribute further to prevention of disease in both children and adults due to clinically important strains of *S. pneumoniae* compared with Prevenar 13™.

The additional serotypes contained in V114 will provide broader coverage against 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 address the emergence of pneumococcal disease caused by serotypes not contained in currently licensed PCVs.

2.2.2 Preclinical and Clinical Studies

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

2.3 Benefit/Risk Assessment

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

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The following objectives and endpoints will be evaluated in healthy infants enrolled at approximately 2 months of age (from 42 to 90 days [inclusive]) administered V114.

Objectives	Endpoints
Primary	
• Objective 1: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs from Day 1 through Day 7 postvaccination. • Solicited systemic AEs from Day 1 through Day 7 postvaccination. • Vaccine-related serious adverse events (SAEs) through completion of study participation.
• Objective: To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 30 days after Dose 3. • Objective: To evaluate the anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) at 30 days after Dose 3.	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 3 (PD3).
Secondary	
• Objective: To evaluate the anti-PnPs serotype-specific IgG GMCs at 30 days after Dose 4.	• Anti-PnP serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 4 (PD4).

4 STUDY DESIGN

4.1 Overall Design

This is a single-arm, multisite, open-label study of V114 in healthy infants in South Korea. Approximately 45 infants will be enrolled to receive V114.

A 0.5 mL intramuscular dose of V114 will be administered to healthy infants at approximately 2, 4, 6, and 12 to 15 months of age.

Participants will be followed for injection-site and systemic AEs through Day 7 after each vaccination with V114. Information for SAEs and deaths, regardless of whether the events are considered vaccine related by the investigator, will be collected from the time consent is signed through completion of participation in the study.

Blood samples for immunogenicity assays will be collected at 2 time points: (1) 30 days after the completion of the 3-dose primary series (PD3), and (2) 30 days after Dose 4 (PD4).

After completion of immunogenicity testing to evaluate the study objectives, serum samples will be stored to conduct any additional study-related testing as required by regulatory agencies or the Sponsor. For study participants whose parent or legally acceptable representative provided consent for future biomedical research leftover sera from the study may be used for other purposes such as the development and/or validation of pneumococcal assays after completion of all study-related immunogenicity testing.

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

The global pediatric V114 Phase 3 program, with over 9 studies, and including approximately 5228 individuals has accumulated comprehensive safety and immunogenicity data, comparing V114 to Prevenar 13™ PCV13. These data are sufficient for filing and licensure in South Korea; further comparator data are not needed. However, no South Korean infants or children participated in the global V114 pediatric program.

The purpose of this study is to show the safety and immunogenicity of a 4-dose schedule (3 doses in the infant primary series followed by 1 toddler dose) of V114 in healthy South Korean infants approximately 2 months of age (42 to 90 days of age).

The safety and immunogenicity endpoints, including the duration of the safety follow-up period, are consistent with previous studies evaluating PCVs evaluating safety and immunogenicity in an infant population. These infants are at increased risk for pneumococcal disease and its associated morbidity and mortality [Drijkoningen, J. J 2014]. The enrollment of infants in this study is intended to assess safety and immunogenicity in a population that is representative of children receiving commercially available PCVs.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

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

The use of the serotype-specific IgG antibody level of ≥0.35 µg/mL has been recommended by a WHO expert panel as an acceptable threshold value for evaluating the clinical performance of PCVs after a routine childhood vaccination regimen [World Health Organization 2008] [World Health Organization 2005]. The response rate (ie, the proportion of participants meeting the serotype-specific IgG threshold value of ≥0.35 µg/mL) is a primary endpoint in this study.

Anti-PnPs serotype-specific IgG responses will be measured at 2 time points:

- Approximately 30 days after Dose 3 to evaluate the immune response to the primary vaccination series (IgG GMCs and IgG response rates)
- Approximately 30 days after Dose 4 to evaluate anamnestic antibody responses (IgG GMCs)

4.2.1.2 Safety Endpoints

The safety endpoints evaluated in this study were selected based on the product's safety profile shown in previous studies, published data from marketed PCVs, and guidance from regulatory agencies during product development. The VRC used to record AEs during the postvaccination periods, as defined in Section 8.1.9, was structured as recommended in the final Food and Drug Administration Guidance for Industry: Patient-Reported Outcome Measures [U.S. Food and Drug Administration 2009].

Details on the safety endpoints evaluated in this study can be found in Section 8.3.3 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 FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

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

FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.3 Justification for Dose

The dose and dosing schedule of V114 is similar to that used in previous pediatric V114 clinical studies, which showed safety and comparable immune responses to those of Prevenar 13™. Refer to V114 IB for details on dosing schedule.

The 3 + 1 PCV immunization schedule in this study is the same as that currently used by the South Korean NIP.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative provides documented consent. The overall study ends when the last participant completes the last study-related contact, 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 laboratory result or at the time of final contact with the last participant, whichever comes last.

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Healthy male and female infants approximately 2 months of age, from 42 to 90 days (inclusive) 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

A participant will be eligible for inclusion in the study if the participant:

1. Is healthy (based on a review of medical history and physical examination) based on the clinical judgment of the investigator.

Demographics

2. Is a South Korean male or female, approximately 2 months of age, from 42 days to 90 days inclusive, at the time of signing the informed consent.

Informed Consent/Assent

3. Has a parent or legally acceptable representative who understands the study procedures, alternate treatments available, and risks involved with the study and voluntarily agrees to participate by providing documented informed consent. The parent or legally acceptable representative may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has a history of IPD (positive blood culture, positive cerebrospinal fluid culture, or other sterile site) or known history of other culture positive pneumococcal disease.

2. Has a known hypersensitivity to any component of the PCV, any component of the licensed pediatric vaccines to be administered concomitantly in the study, or any diphtheria toxoid-containing vaccine.

3. *Had a recent febrile illness (rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) occurring within 72 hours before receipt of study vaccine.

4. Has a known or suspected impairment of immunological function, including congenital or acquired immunodeficiency.

5. Has or his/her mother has a documented HIV infection.

6. Has or his/her mother has a documented hepatitis B surface antigen – positive test.

7. Has known or history of functional or anatomic asplenia.

8. Has a health or developmental disorder that, based on the clinical judgment of the investigator, could affect evaluation of the vaccine.

9. Has a bleeding disorder contraindicating intramuscular vaccination.

10. Has a history of autoimmune disease.

11. Has a known or suspected history of neurologic disorder, including encephalitis/myelitis, acute disseminating encephalomyelitis and related disorders.

Prior/Concomitant Therapy

12. Has received a dose of any pneumococcal vaccine before study entry.

13. *Meets 1 or more of the following systemic corticosteroid exclusion criteria:

    a. Has received systemic corticosteroids (equivalent of ≥2 mg/kg total daily dose of prednisone or ≥20 mg/d for persons weighing >10 kg) for ≥14 consecutive days and has not completed this course of treatment at least 30 days before the first dose of study vaccine at treatment/randomization.

    b. Has received or is expected to receive systemic corticosteroids within 14 days before any dose of study vaccine.

    c. Is expected to require systemic corticosteroids within 30 days after any study vaccination during conduct of the study.

    Note: Topical, ophthalmic, and inhaled steroids are permitted.

14. *Has received a licensed nonlive vaccine within 14 days before receipt of study vaccine or is scheduled to receive any licensed nonlive vaccine within 14 days after receipt of study vaccine.
    Exception: Inactivated influenza vaccine may be administered, but must be given at least 7 days before receipt of study vaccine or at least 15 days after receipt of study vaccine. Participant may receive nonstudy pediatric licensed nonlive vaccines on the same day as study vaccine is given (Day 1).

15. *Has received a licensed live vaccine within 28 days before receipt of study vaccine or is scheduled to receive any live vaccine within 14 days after receipt of study vaccine.
    Exception: Participant may receive nonstudy pediatric licensed live vaccines on same day as study vaccine is given (Day 1).

16. Has received a blood transfusion or blood products, including immunoglobulins.

Prior/Concurrent Clinical Study Experience

17. Has participated in another clinical study of an investigational product before the beginning or anytime during the duration of the current clinical study. Participants

enrolled in observational studies may be included; these will be reviewed on a case by case basis for approval by the Sponsor.

Other Exclusions

18. Has any other reason that, in the opinion of the investigator, may interfere with the evaluation required by the study. Reasons may include, but are not limited to, being unable to keep appointments or planning to relocate during the study.

19. Is or has an immediate family member (eg, parent/legal guardian, sibling) who is investigational site or Sponsor staff directly involved with this study.

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

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (V114) 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 intervention to be used in this study is outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin.	Vaccination Regimen	Use	IMP/ NIMP	Sourcing
V114	Experimental	V114	Biological/ Vaccine	Sterile Suspension	Refer to IB	0.5 mL	IM	Single dose at Visits 1, 2, 3, and 5 (~2, 4, 6, and 12 to 15 months of age, respectively)	Experimental	IMP	Central
The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification 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. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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 to administer the proper dose to each participant. The rationale for selection of dose 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

Participants in this study will be allocated by nonrandom assignment and will receive a treatment/randomization number.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the vaccine administered.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified vaccination plan for V114 indicated in Section 1.3 require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

If a medical condition requires the use of a prohibitive steroid regimen, immunoglobulin, blood, or blood products during a participant's participation in this study, 1 of the individuals listed on the Sponsor Contact Information page must be notified as soon as possible. Any concurrent medication or medical treatment must be recorded on the appropriate eCRF. It is important to record the use of any analgesic or antipyretic use that occurs on the day of vaccination on the paper VRC and appropriate eCRF.

Nonstudy pediatric vaccines are permitted to be administered according to local recommended schedule, regional, and/or country guidelines, and according to the restrictions outlined in Section 5.2.

During influenza season, it is anticipated that participants 6 months of age and older may be given an influenza vaccine. Influenza vaccine should be administered either 7 days before or 15 days after the administration of the study vaccine.

It is anticipated that participants 12 months of age and older may be given LJEV, which should be administered either more than 28 days before or more than 14 days after the administration of the study vaccination dose 4. If LJEV is to be given at Visit 6, it should be administered after the blood collection.

Other nonstudy concomitant vaccines (oral or injectable) can be administered on the same day as V114. Nonstudy oral concomitant vaccines should be given before V114 and other injectable concomitant vaccines. Precautions must be taken to prevent choking during the administration of oral vaccines. Other pediatric injectable vaccines administered concomitantly should be given after V114, and in a separate limb.

It is recommended that V114 be administered in the right thigh. To avoid any confounding results, nonstudy injectable vaccines should not be administered in the same limb as V114. Documentation of which limb was used for the administration of V114 should be recorded on the appropriate eCRF. As the study is reporting injection-site AEs for V114 (and not from nonstudy pediatric vaccines), this information should also be recorded on the paper VRC to inform the parent or legally acceptable representative of the appropriate limb to monitor for AEs related to the V114.

No other investigational compound or device may be administered at any time during this study without prior approval by the Sponsor.

6.5.1 Rescue Medications and Supportive Care

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

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 after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

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 vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.10 and Section 8.11.3.

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

- The participant 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.

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.10. 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's legally acceptable representative and reschedule the missed visit. If the participant's legally acceptable representative is

contacted, the participant's legally acceptable representative 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's legally acceptable representative at each missed visit (eg, telephone calls and/or a certified letter to the participant's legally acceptable representative 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 (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

Approximately 5 mL of blood will be drawn at each of Visits 4, and 6 for immunogenicity assays. The maximum amount of blood collected from each participant over the duration of the study will not exceed 10 mL.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent, and assent if applicable, from each potential participant or their legally acceptable representative prior to participating in this 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 documented informed consent is in place.

8.1.1.1 General Informed Consent/Assent

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

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

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

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

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

8.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

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

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. The investigator should consult with the Sponsor's Clinical Director for any questions about participant eligibility.

If the participant meets any of the Exclusion Criteria with an asterisk (*), Visit 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 documented informed consent/assent. At the time of intervention treatment/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a 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. Note: Birth weight and gestational age will be documented in the participant's medical history.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 Concomitant Medications

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

If a medical condition requires the use of a prohibitive steroid regimen, immunoglobulin, blood, or blood products during a participant's participation in this study, one of the individuals listed on the Sponsor Contact Information page must be notified as soon as possible. Any concurrent medication or medical treatment must be recorded on the appropriate eCRF.

It is important to record any analgesic or antipyretic use that occurs on the day of vaccination on the paper VRC and appropriate eCRF. Concomitant medications taken after Visit 1 and nonstudy vaccines received since Visit 1 will be recorded in the paper VRC as specified in Section 8.3.3.

The administration of nonstudy pediatric vaccines during the study should be recorded on the appropriate eCRF. To avoid any confounding results, concomitant injectable vaccines should not be administered in the same limb as V114. Documentation of which limb was used for the administration of V114 must be recorded on the paper VRC (Section 8.1.9 and Section 8.3.3) and appropriate eCRF.

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 treatment/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 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Before each vaccine administration, the investigator (or designee) must review medical history to ensure that the participant has no new contraindication to the vaccine(s) scheduled to be given. This information should be documented in the participant's medical record.

Study vaccine will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

Study vaccines should be prepared and administered by appropriately qualified members of the study personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local/state, country, and institutional guidance.

Study vaccines 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 medical record.

If the V114 is provided as a syringe: Before administration of study vaccine, the investigator (or designee) should shake vigorously to obtain a homogenous white suspension. If white-colored insoluble particle appears, the investigator (or designee) 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 the appearance is otherwise, the vaccine should not be administered.

If V114 is provided as a vial: Before administration of study vaccine, the investigator (or designee) should use rapid, horizontal hand -shaking for up to 5 seconds while holding the vial in between the thumb and index finger to obtain a homogenous white suspension. This action should be repeated, as necessary. If the appearance is otherwise, the vaccine should not be administered.

The vaccine should not be used if the vaccine cannot be resuspended.

A 0.5-mL intramuscular dose of study vaccine will be administered to healthy South Korean infants at approximately 2, 4, 6, and 12 to 15 months of age. It is recommended that the study vaccines are administered in the right thigh. Documentation of which limb was used for the administration of V114 should be recorded on the appropriate eCRF. This information should also be recorded on the paper VRC to inform the participant's parent or legally acceptable representative of the appropriate limb to monitor for AEs related to V114.

If an abnormality (ie, rash) is observed at the site where the previous dose of the study vaccine was administered, it is permissible to use the anterolateral muscle of the other limb to administer the following dose of the study vaccine. Adequate treatment provision, including epinephrine and equipment for maintaining an airway, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

8.1.8.1 Timing of Dose Administration

V114 will be administered as indicated in Section 1.3. All participants will be observed for at least 15 minutes after each vaccination for any immediate reactions. This observation must be performed by site personnel for V114 (Section 1.3).

Participants must be afebrile for at least 72 hours before each V114 administration (Section 1.3 and Section 8.3.2).

8.1.9 Vaccination Report Card

The investigator or delegate will train the participant's parent or legally acceptable representative in the use of the paper VRC as indicated in Section 1.3.

After providing paper VRC, contact the participant's parent or legally acceptable representative at least once at approximately Day 3 poststudy vaccination, to ensure timely completion of paper VRC during Day 1 to Day 7 for solicited injection-site AEs, solicited systemic AEs and temperature. The main purpose of the contact is to ensure the participant's legally acceptable representative records on the paper VRC and to answer any questions related to VRC. While these contacts are not for collection of AEs, if any potential SAE information is reported it should be reviewed during the contact.

The investigator or delegate will review the data captured on the paper VRC with the participant's parent or legally acceptable representative as indicated in Section 1.3. For the AEs outlined above, the investigator will use the information provided by the participant's parent or legally acceptable representative on the paper VRC, and verbally at the time of VRC review, to apply the appropriate assessment of intensity as described in Appendix 3.

8.1.10 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 as outlined in the Section 1.3 and Section 8.11.3.

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

8.1.10.1 Withdrawal From Future Biomedical Research

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

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

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.12 Calibration of Equipment

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

8.2 Immunogenicity Assessments

Pneumococcal Electrochemiluminescence assay will be used to measure vaccine-induced, anti-PnPs serotype-specific immune responses for all 15 serotypes included in V114.

Blood collection, storage and shipment instructions for serum samples will be provided in the operations/laboratory manual.

8.2.1 Pneumococcal Electrochemiluminescence

The Sponsor has developed and optimized a multiplex, ECL-based detection method for the quantitation of IgG serotype-specific antibodies to the 15 PnPs serotypes contained in V114. The PnECL v2.0 assay is based on the Meso Scale Discovery technology, which employs disposable multispot microtiter plates. The benefits of the ECL multiplex technology over the prior ELISA 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 prespecified acceptance criteria for each of the parameters.

The WHO Expert Committee on Biological Standardization has recommended that in-house assays used in immunogenicity studies designed to evaluate protection against IPD be bridged to the WHO reference assay to maintain the link between immune responses to vaccination and the clinical demonstration of protective efficacy against IPD conferred by the 7 conjugated polysaccharides in Prevenar™. In 2012 and 2014, the Sponsor formally bridged

the original PnECL assay to the WHO IgG ELISA to determine the PnECL threshold values that correspond to 0.35 µg/mL in the WHO ELISA for each of the 7 Prevenar™ serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) and for each of the additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A) in Prevenar 13™.

A confirmatory study was performed to formally bridge the optimized PnECL assay (v2.0) to the WHO reference ELISA, and to assess the PnECL threshold values that correspond to 0.35 µg/mL measured using the WHO ELISA for each of the serotypes in V114, including the Prevnar 13™ serotypes and serotypes 22F and 33F, which were not previously assessed. The bridging of the optimized PnECL to the WHO ELISA is complete, and the data showed good concordance between the PnECL and WHO ELISA around the 0.35 µg/mL threshold value for all 15 serotypes. It is recommended that a single PnECL threshold value of 0.35 µg/mL be applied to each of the 15 serotypes.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected 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) at Visit 1 for all participants. A targeted physical examination will be performed at subsequent vaccination visits as indicated in Section 1.3. Any clinically significant abnormality will be recorded on appropriate eCRF.

The complete and targeted physical examination procedures both include obtaining vital signs (heart rate, respiratory rate, and temperature), auscultation of the heart and lung, and examination of the abdomen. In addition, a full physical examination will include an assessment of the head, eyes, ears, nose and throat, skin, lymph nodes, neurological system, and musculoskeletal system.

Findings related to the physical examinations should be documented in the participant's medical record/source documentation.

8.3.2 Body Temperature Measurements

Prevaccination temperatures will be taken by study personnel as indicated in Section 1.3. Participants who have febrile illness (rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) at or within 72 hours of study vaccination must be rescheduled.

The participant's parent or legally acceptable representative will be asked to record the participant's temperature reading on the paper VRC from Day 1 through Day 7 after each vaccination.

Rectal is the preferred method of obtaining participant's temperature at prevaccination and on the paper VRC. Axillary (underarm) is an acceptable method, but temperature needs to be confirmed by rectal measurement if fever is detected. If an axillary temperature is reported to be ≥37.8°C (≥100.0°F), a rectal temperature must be taken. In this case, both axillary and rectal temperatures must be recorded on the paper VRC. Temperature readings should be taken at approximately the same time each day if possible. Use of temporal or tympanic thermometers to collect temperature for this study is prohibited.

8.3.3 Safety Assessment and Use of the Paper VRC

All participants will be observed for at least 15 minutes after each vaccination for any immediate reactions. The observation period can be extended if clinically indicated. 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.

The limb that was used for the administration of V114 will be recorded in the paper VRC (Note: the study will report injection-site AEs from V114 only, not from concomitant injectable vaccines; the location of V114 administration can be used by the participant's parent or legally acceptable representative to monitor the appropriate limb for injection-site AEs related to V114).

Participant's parent or legally acceptable representative will use the paper VRC (Section 8.1.9) to document the following information:

- Rectal/axial temperatures measured Day 1 (day of vaccination) through Day 7 after each vaccination
- Solicited injection-site AEs (swelling, redness, pain or tenderness, and hard lump) Day 1 through Day 7 postvaccination
- Solicited systemic AEs (irritability, drowsiness, appetite lost, and hives or welts) Day 1 through Day 7 postvaccination
- Any other unsolicited injection-site or systemic AEs Day 1 through Day 14 postvaccination
- Use of any analgesic or antipyretic on the day of vaccination
- Concomitant medications and nonstudy vaccinations Day 1 to Day 14 postvaccination

8.3.4 Clinical Safety Laboratory Assessments

There are no laboratory safety evaluations required by the protocol.

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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

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

All 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:

- A death that occurs prior to the participant completing the study, but outside the time period specified in the previous paragraph.

OR

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

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and 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 2.

Table 2 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. - any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

NSAE=nonserious adverse event; SAE=serious adverse event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities 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. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

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

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of 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

Information in this section is not applicable since participants are infants.

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

There are no events of clinical interest in 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.

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 EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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.

8.6 Pharmacokinetics

Pharmacokinetics parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.8.1 Planned Genetic Analysis Sample Collection

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

8.9 Future Biomedical Research Sample Collection

If the participant's parent or legally acceptable representative provides documented informed consent for future biomedical research, the following specimens will be obtained as part of future biomedical research:

- DNA for future research
- Leftover main study serum from immunogenicity assay stored for future research

8.10 Health Economics Medical Resource Utilization and Health Economics

Medical resource utilization and health economics are not evaluated in this study.

8.11 Visit Requirements

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

8.11.1 Screening

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

8.11.2 Treatment Period/Vaccination Visit

Requirements during the treatment period are outlined in Section 1.3.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

A participant may discontinue from study intervention (including receipt of V114), but continue to participate in protocol-specified, AE-monitoring activities as outlined in Section 1.3, as long as the participant's parent or legally acceptable representative does not withdraw consent. Blood draws for immunogenicity testing could occur if agreed to by the participant's parent or legally acceptable representative at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but before final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, Single-Arm, Open-label Clinical Study to Evaluate the Safety and Immunogenicity of 4 doses of V114 Administered to Healthy Infants in South Korea
Treatment Assignment	Participants will be allocated to V114.
Analysis Populations	Immunogenicity: Per-Protocol Safety: All Participants as Treated

Primary Endpoint(s)	**Immunogenicity:** • Anti-PnPs serotype-specific IgG response rates (proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL) at 30 days PD3 • Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 **Safety:** • Proportion of participants with solicited injection-site AEs (swelling, redness/erythema, tenderness/pain, and hard lump/induration) from Day 1 through Day 7 after vaccination with V114 • Proportion of participants with solicited systemic AEs (irritability, drowsiness/somnolence, appetite lost/decreased appetite, and hives or welts/urticaria) from Day 1 through Day 7 after vaccination with V114 • Proportion of participants with vaccine-related SAEs from Day 1 through completion of study participation
Key Secondary Endpoints	Anti-PnPs serotype-specific IgG GMCs at 30 days PD4
Statistical Methods for Key Immunogenicity Analyses	Immunogenicity analyses will be conducted for each of the 15 pneumococcal serotypes in V114 separately. To address the primary immunogenicity objectives, estimation of the IgG response rates and GMCs will include descriptive summaries and 95% CIs at 30 days PD3. A similar statistical approach will be used to evaluate the IgG GMCs at 30 days PD4.
Statistical Methods for Key Safety Analyses	The analysis strategy for safety parameters after each vaccination is described in Section 9.6.2. Safety parameters will be summarized via descriptive statistics. In addition, for select safety parameters, 95% CIs will be provided.
Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	**Immunogenicity:** This study will allocate approximately 45 participants to V114. It is assumed that approximately 38 participants will be evaluable for immunogenicity analyses at 30 days PD3 (85% evaluability rate), and approximately 36 participants will be evaluable for immunogenicity analyses at 30 days PD4 (80% evaluability rate). There are no hypotheses to be evaluated, but Section 9.9.1 provides information about the expected variability of the IgG GMCs given the sample size.

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 trial is being conducted as a nonrandomized, open-label study; ie, subjects, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the treatment/randomization schedule(s) for study treatment assignment. Treatment/randomization will be implemented using an IRT system.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. This is an estimation study and no formal hypothesis testing will be performed.

9.4 Analysis Endpoints

Immunogenicity and safety endpoints that will be summarized are listed below.

9.4.1 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements after any vaccination with V114.

The safety endpoints include:

- Proportion of participants with solicited injection-site AEs (swelling, redness/erythema, tenderness/pain, and hard lump/induration) from Day 1 through Day 7 after any vaccination with V114
- Proportion of participants with solicited systemic AEs (irritability, drowsiness/somnolence, hives or welts/urticaria, and appetite loss/decreased appetite) from Day 1 through Day 7 after any vaccination with V114
- Proportions of participants with the broad AE categories consisting of any AE and a vaccine-related AE from Day 1 through Day 7 after any vaccination with V114
- Proportions of participants with an SAE, a vaccine-related SAE, and discontinuation due to an AE, and death from Day 1 through completion of study participation
- Participants body temperature measured from Day 1 through Day 7 after any vaccination with V114

9.4.2 Immunogenicity Endpoints

A description of immunogenicity assessments is contained in Section 8.2.

The immune responses will be measured for each of the following serotypes contained in V114: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F. The primary immunogenicity endpoints include:

- Proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3.

- Anti-PnPs serotype-specific IgG GMCs at 30 days PD3.

The secondary immunogenicity analysis endpoints include:

- Anti-PnPs serotype-specific IgG GMCs at 30 days PD4.

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

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

- Failure to receive primary infant series vaccination (V114 Doses 1, 2, and 3) as per vaccination schedule

- Receipt of prohibited medication or prohibited vaccine before study vaccination

Additional potential deviations that may result in the exclusion from the PP immunogenicity analyses at a particular time point include:

- Failure to receive Dose 4 of V114 according to vaccination schedule required at the time point for the analysis

- Failure to receive the scheduled doses of V114 with the specified intervals/time window (at least 28 days between Doses 1 and 2 and between Doses 2 and 3 [for PD3 analysis], 12 months to 1 day before 16 months of age for Dose 4 [for PD4 analyses])

- Receipt of prohibited medication or prohibited vaccine before a blood sample collection

- Collection of blood sample at the time point for the analysis outside the prespecified window (as described in Section 1.3)

The final determination on protocol deviations, and thereby the composition of the PP population, will be made before the final database lock.

A supportive analysis using the FAS population may also be performed for the primary immunogenicity endpoints. The FAS population consists of all randomized participants who received at least 1 study vaccination and have at least 1 serology result.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study vaccination.

At least 1 temperature measurement obtained after 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. 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 separately. To address the primary immunogenicity objectives, evaluation of the IgG response rates and GMCs at 30 days after the third dose of V114 will include descriptive summaries and 95% CIs. For IgG response rates, the CIs will be calculated based on the exact binomial method proposed by Clopper and Pearson [CLOPPER, C. J. and PEARSON, E. S. 1934]. For IgG GMCs, point estimates will be calculated by exponentiating the estimates of the mean of the natural log values. The CIs will be derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

To address the secondary immunogenicity objective, evaluation of the IgG GMCs at 30 days after the fourth dose of V114 will include descriptive summaries and 95% CIs.

The primary and secondary endpoints may be summarized separately as soon as complete data for the specified time points become available.

A detailed analysis strategy for immunogenicity endpoints is listed in Table 3.

Table 3 Analysis Strategy for Key Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints				
IgG response rates at 30 days PD3	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
IgG GMCs at 30 days PD3	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoint				
IgG GMCs at 30 days PD4	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

† P=Primary approach; S=Supportive approach.
CI = confidence interval; FAS = Full Analysis Set; GMC = geometric mean concentration;
IgG = immunoglobulin G; PP = Per-Protocol.

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 strategy of safety parameters is summarized in Table 4. The proportion of participants with solicited injection-site AEs (swelling, redness/erythema, tenderness/pain, and hard lump/induration from Day 1 to Day 7 postvaccination) and solicited systemic AEs (irritability, drowsiness/somnolence, hives or welts/urticaria, and appetite loss/decreased appetite from Day 1 to Day 7 postvaccination) will be provided along with the corresponding CIs (based on the exact binomial method proposed by Clopper and Pearson [CLOPPER, C. J. and PEARSON, E. S. 1934]). In addition, the broad AE categories consisting of the proportion of participants with any AE, a vaccine-related AE, an SAE, a vaccine-related SAE, discontinuation due to an AE, and the proportion of participants who died will be summarized in the same manner. The proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points (from Day 1 through Day 7) [Marcy, S. M., et al 2004] will also be provided along with the corresponding 95% CIs. Point estimates will be provided for all other safety parameters (specific AE terms and system organ class terms).

Medical device incidents due to syringe, if any, will be listed.

The safety parameters may be summarized separately as soon as complete data become available at 30 days after the third dose of V114 and 30 days after the fourth dose of V114.

Table 4 Analysis Strategy for Safety Parameters

Safety Endpoint	95% CI	Descriptive Statistics
Injection-site redness/erythema (Day 1 to Day 7) †	X	X
Injection-site swelling (Days 1 to 7) †	X	X
Injection-site tenderness/pain (Days 1 to 7) †	X	X
Injection-site hard lump/induration (Days 1 to 7) †	X	X
Irritability (Days 1 to 7) †	X	X
Drowsiness/somnolence (Days 1 to 7) †	X	X
Hives or welts/urticaria (Days 1 to 7) †	X	X
Appetite loss/decreased appetite (Days 1 to 7) †	X	X
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 7)	X	X
Specific AEs by SOC and PT		X

AE = adverse event; CI = confidence interval; PT = preferred term; SAE = serious adverse event; SOC = system organ class; X = results will be provided.

† Includes solicited events only.

‡ 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.

9.6.3 Demographic and Baseline Characteristics

The relevant demographic and baseline characteristics will be assessed using summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, prior and concomitant vaccinations and therapies will be summarized either by descriptive statistics or categorical tables.

9.7 Interim Analyses

There are no planned interim analyses for this study.

9.8 Multiplicity

No adjustment will be made for multiplicity.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity Analyses

This is a descriptive study. This study will randomize approximately 45 participants to receive V114. It is assumed that approximately 38 participants will be evaluable for PP immunogenicity analyses at 30 days PD3 (based on an 85% evaluability rate), and 36 participants will be evaluable for PP immunogenicity analyses at 30 days PD4 (based on an 80% evaluability rate).

The width of the 95% CIs for the serotype-specific IgG GMCs depends on the sample size, variability of the natural log concentrations, and the magnitude of the IgG GMC. In Table 5, the 95% CIs for various hypothetical IgG GMCs at 30 days PD3 and various hypothetical standard deviation estimates for the natural log titers are displayed.

Table 5 95% CIs for Varying Hypothetical IgG GMCs and Varying Standard Deviations

Standard Deviation of Natural Log Titers[†]	Serotype-specific IgG GMC[†]		
	1	5	10
1.0	(0.73, 1.37)	(3.64, 6.87)	(7.28, 13.74)
1.5	(0.62, 1.61)	(3.10, 8.06)	(6.21, 16.11)
2.0	(0.53, 1.89)	(2.65, 9.44)	(5.29, 18.89)

Based on 38 evaluable participants.

[†] The estimates of the standard deviation and IgG GMCs are representative of those observed in a previous MSD study.

CI = confidence interval; GMC = geometric mean concentration; IgG = immunoglobulin G.

9.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying incidence of participants with an SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least 1 SAE among 45 participants if the underlying incidence of an SAE is 3.5% (1 of every 28 participants receiving the vaccine). There is a 50% chance of observing at least 1 SAE among 45 participants if the underlying incidence of an SAE is 1.5% (1 of every 65 participants receiving the vaccine). If no SAEs are observed among 45 participants, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is <7.9% (1 in every 13 participants).

9.10 Subgroup Analyses

Subgroup analyses (eg, sex = female vs male) will be performed for the primary immunogenicity endpoints and selected safety endpoints (summary of AEs). Details of subgroup analyses will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

The number and proportion of randomized participants receiving V114 will be summarized.

9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered V114.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. 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 (or individuals acting on behalf of MSD) 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 Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus

source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the 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.

10.1.6 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 Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

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

Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

Not applicable

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, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent 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 8.4.6 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

- 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 used 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 erythema/redness, or swelling or hard lump/induration from the day of vaccination through Day 7 postvaccination will be evaluated by maximum size.

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 AEs, SAEs, and Other Reportable Safety Events to the Sponsor

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

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

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure 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 and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

Not applicable.

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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 with which drugs/vaccines may interact
- The biology of disease

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes 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 future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

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 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@MSD.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@MSD.com.

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3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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10.7 Appendix 7: Country-specific Requirements

Not Applicable

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ACCP	American College of Chest Physicians
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
APaT	All Participants as Treated
AR	adverse reaction
ART	antiretroviral therapy
ATD	accelerated titration design
ATP	adenosine triphosphate
BCG	Bacillus Calmette–Guérin
BDS	blood drug screen
BICR	blinded independent central review
BID	twice daily
BMI	body mass index
BP	blood pressure
CAC	Clinical Adjudication Committee
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CF	compact flash
CG	Cockcroft-Gault
CHS	cough hypersensitivity syndrome
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
CSD	Cough Severity Diary
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DAIDS	Division of AIDS
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
ECL	electrochemiluminescence
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection

Abbreviation	Expanded Term
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic patient-reported outcomes
EQ-5D	EuroQoL-5D
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
FEV1	forced expiratory volume in 1 second
FAS	Full Analysis Set
FFPE	formalin-fixed, paraffin embedded
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
GMC	geometric mean concentration
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	imaging CRO
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IND	Investigational New Drug
IO	immuno-oncology
IPD	Invasive pneumococcal disease
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
IWRS	integrated web response system
KPS	Karnofsky performance status
LAM	lactational amenorrhoea method

Abbreviation	Expanded Term
LCQ	Leicester Cough Questionnaire
LJEV	Live Japanese encephalitis vaccine
mAb	monoclonal antibody
MAD	maximum administered dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCI	National Cancer Institute
NCS	not clinically significant
NEAB	noneosinophilic bronchitis
NIP	National Immunization Program
NSCLC	non-small cell lung cancer
NDA	New Drug Application
NOAEL	no observed adverse effect level
OR	objective response
ORR	objective response rate
OS	overall survival
OSF	on-site formulation
OTC	over-the-counter
PBPK	physiologically-based PK
PCV	pneumococcal conjugate vaccine
PD3	postdose 3
PD4	postdose 4
PD-1	programmed cell-death 1
PD-L1	programmed cell-death ligand 1
PD-L2	programmed cell-death ligand 2
PET	positron emission tomography
PFS	progression free survival
PGIC	Patient Global Impression Change
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PnECL	pneumococcal electrochemiluminescence
PO	orally
PnP	pneumococcal polysaccharide
PP	per-protocol
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
QOL	quality of life
QP2	Department of Quantitative Pharmacology and Pharmacometrics
RCC	refractory chronic cough
RNA	ribonucleic acid
rP2D	recommended Phase 2 dose
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Expanded Term
siDMC	Standing Internal Data Monitoring Committee
SIM	Site Imaging Manual
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TMDD	target-mediated drug disposition
UACS	upper airway cough syndrome
UCC	unexplained chronic cough
UDS	urine drug screen
URTI	upper respiratory tract infection
V	volume of distribution
VAS	Visual Analog Scale
VRC	paper Vaccination Report Card
VS	vital sign
WBC	white blood cell
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

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