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TITLE:

A Multicenter, Double-Blind Study of the Safety, Tolerability, and Immunogenicity of Pneumococcal Conjugate Vaccine (V114) Compared to Prevnar™ in Healthy Adults and Toddlers

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: I

US IND NUMBER: 14115

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

To obtain additional sera from adult subjects to support further development, validation, and performance of anti-pneumococcal antibody assays.

OTHER CHANGES INCLUDED IN THE AMENDMENT:

Section 1.3 – To add rationale for extension study
Section 1.4 – To add additional blood draw at Visit 4
Section 1.6 – To add Visit 4 to the study flow chart
Section 2.1.2 - To add objective for the extension study
Section 2.4.1 – To add additional blood draw at Visit 4
Section 2.5 - To add reason for use of additional serum
Section 3.1.1 – To add extension study rationale
Section 3.2.4.1.1 – To add consent form must be obtained
Section 3.2.4.4 – To clarify allocation number assignments
Section 3.2.4.5 – To add additional blood draw at Visit 4
Section 3.4.5.2 – To add serious adverse experience text for extension phase
Section 3.3 – To add reason for use of additional serum

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1. SUMMARY

1.1 TITLE

A Multicenter, Double-Blind Study of the Safety, Tolerability, and Immunogenicity of Pneumococcal Conjugate Vaccine (V114) Compared to Prevnar™ in Healthy Adults and Toddlers

1.2 INDICATION

The proposed indication for V114/Pneumococcal Conjugate Vaccine (PCV) is the prevention of pneumococcal disease caused by *S. pneumoniae* due to capsular serotypes included in the vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) in infants and toddlers.

1.3 SUMMARY OF RATIONALE

Redacted

¹ Prevnar is a trademark of Wyeth Pharmaceuticals Inc., Philadelphia, Pa., U.S.A.

Redacted

1.4 SUMMARY OF STUDY DESIGN

This is a multicenter, randomized, double-blind (with in-house blinding procedures), active control trial to evaluate the safety, tolerability, and immunogenicity of 15-valent pneumococcal conjugate vaccine (V114) compared to PrevnarTM in healthy adults and toddlers. Prior to enrollment of toddlers, the safety of a single dose administration of the study vaccines will be evaluated in healthy adults.

Adults will be randomly assigned to 1 of 2 treatment arms:

- (1) Merck investigational V114, aluminum-adjuvanted
- (2) PrevnarTM control arm

After completion of a safety review of the adult stage by an external Data Monitoring Committee (eDMC), toddlers who have previously completed a documented full 3-dose infant series of PrevnarTM (according to the current national vaccination schedule), will be randomized to receive 1 booster dose of study vaccine according to the respective treatment arm. During the toddler stage, study vaccines may be administered concomitantly with other licensed routine pediatric vaccines normally administered at 12-15 months of age (according to the current national vaccination schedule).

Toddlers will be randomly assigned to 1 of 3 treatment arms:

- (1) Merck investigational V114, aluminum-adjuvanted
- (2) Merck investigational V114, non-adjuvanted
- (3) PrevnarTM control arm

Adult Stage:

Safety will be assessed in 60 healthy adults (30 subjects per arm). A single 0.5 mL dose of vaccine will be administered intramuscularly. Because an exact match to the PrevnarTM syringe is not possible, unblinded study personnel not otherwise involved in the conduct of the study will administer vaccine. All safety and immunogenicity assessments will be

conducted by blinded personnel, and the subjects will be blinded to the treatment received.

The adult subjects will be followed for local and systemic adverse experiences; this includes VRC-prompted injection site adverse experiences (redness, swelling, nodules, and pain/tenderness) and VRC-prompted systemic adverse experiences (muscle pain, joint pain, and tiredness) for 14 days. Serious adverse experiences will be collected until the end of the subject's participation in the study (Day 30 postvaccination). Body temperature will be collected for 7 days postvaccination. In addition, temperature measurement will be collected if fever is suspected during Day 8 through Day 14. Blood samples (approximately 20mL) will be drawn on Day 1 immediately prior to vaccination, Day 14 postvaccination, and Day 30 postvaccination. Samples collected on Day 1 prior to vaccination and on Day 14 postvaccination will be used to perform a safety laboratory evaluation. Samples collected on Day 1 prior to vaccination and on Day 30 postvaccination will be used to measure vaccine-induced immune responses. Serum samples collected to measure immune responses will be assayed using MSD electrochemiluminescence (ECL) assay developed by Merck for the measurement of pneumococcal capsular polysaccharide IgG antibodies. Serum samples will also be assayed for functional activity using the opsonophagocytic killing assay (OPA).

Adult subjects who completed the original study will be asked to participate in the extension phase consisting of an additional study visit (V4) that will be solely restricted to the collection of an additional blood sample (40 mL) to support further development, validation and performance of anti-pneumococcal antibody assays. No subsequent safety follow-up visit is required. (See section 3.4.5.1 for reporting any serious adverse events that occur during the extension phase.)

Safety Review Prior to Toddler Enrollment

All clinical safety data (including incidence, intensity, and duration of all local and systemic adverse experiences) from the adult stage will be reviewed by an eDMC before proceeding with the evaluation of the candidate vaccine in toddlers. Adult outcome criteria for proceeding to the toddler phase will therefore include approval from the eDMC which should take into consideration the criteria proposed for stopping rules as regards the incidence and severity of serious and non-serious adverse experiences (See section 3.3.2).

Toddler Stage:

In the toddler stage of the clinical trial a 0.5 mL intramuscular (IM) dose of vaccine will be administered to healthy toddlers at 12-15 months of age, who have previously completed a full 3-dose infant series of Prevnar™ at 2, 4, and 6 months of age. The toddler stage will enroll 90 subjects (30 subjects per arm). As with the adult stage, unblinded study personnel not otherwise involved in the conduct of the study will administer the study vaccine. All safety and immunogenicity assessments will be

conducted by blinded personnel, and the subject's parent/legal guardian will be blinded to the treatment received.

The toddler subjects will be followed for local and systemic adverse experiences; this includes VRC-prompted injection site adverse experiences (redness, swelling, nodules, and pain/tenderness) and VRC-prompted systemic adverse experiences (muscle pain, joint pain, and tiredness) for 14 days. Serious adverse experiences will be collected until the end of the subject's participation in the study (Day 30 postvaccination). Body temperature will be collected for 7 days postvaccination. In addition, temperature measurement will be collected if fever is suspected during Day 8 through Day 14. Blood samples (approximately 3-5 mL) will be drawn on Day 1 immediately prior to vaccination and Day 30 postvaccination. Samples will be used to measure vaccine-induced immune responses. Serum samples will be assayed using MSD electrochemiluminescence (ECL) assay developed by Merck for the measurement of pneumococcal capsular polysaccharide IgG antibodies, and for functional activity using the opsonophagocytic killing assay (OPA).

1.5 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

Adult Stage:

Study vaccines (aluminum-adjuvanted V114, and Prevnar™, see Table 1-1) will be provided in syringes. A single 0.5 mL intramuscular dose of study vaccine will be administered to adult subjects.

Table 1-1

Vaccines To Be Studied In Phase I

Dose	Prevnar™ (w/ AlPO4)	V114 (w/ AlPO4)
Polysaccharide	16 mcg	32 mcg
Protein	20 mcg	32 mcg
Al ³⁺	125 mcg	125 mcg

Toddler Stage:

A 0.5 mL intramuscular dose of study vaccine (aluminum-adjuvanted V114, non-adjuvanted V114, and Prevnar™) will be administered to healthy toddlers at 12-15 months of age who have previously completed a full 3-dose infant series of Prevnar™ at 2, 4, and 6 months of age. Licensed routine pediatric vaccines routinely administered at 12-15 months of age may be administered concomitantly with study vaccines. Concomitant vaccinations are to be given in alternate limbs if applicable.

1.6 STUDY FLOW CHART

Adult Stage

	Visit 1 (Day 1)	Visit 2 (Day 14)	Visit 3 (Day 30)	Visit 4
Obtain written informed consent [†]	x			x
Perform physical exam and review medical history	x			
Review prior/concomitant medications	x		x	
Review inclusion and exclusion criteria	x			
Urine pregnancy test [‡]	x			
Randomization	x			
Vaccination with pneumococcal conjugate vaccine [§]	x			
Collect blood samples	x	x ^{# ††}	x ^{# ‡‡}	x^{¶¶}
Collect urine sample	x			
Distribute VRC to subject and review instructions	x			
Obtain oral or equivalent temperature measurements	x			
Collect and review VRC for adverse events ^{§§}		x	x	
[†] Consent must be obtained PRIOR to any study procedures. [‡] Urine pregnancy test (sensitive to 25 IU β-hCG) must be done prior to vaccination. [§] Vaccine will be administered by unblinded study personnel not otherwise involved in the conduct of the study. Vaccine arms include V114 (aluminum- adjuvanted) and Prevnar™ (control arm). Blood will be drawn for safety labs and for immunogenicity testing. Safety laboratory tests include CBC with differential including platelets, creatinine, alkaline phosphatase (ALK), alanine aminotransferase (ALT), bilirubin. [¶] Collect blood prior to vaccination. [#] Blood draw range: minus 1 day to plus 5 days. ^{††} Blood drawn at Visit 2 will be for safety labs only. ^{‡‡} Blood drawn at Visit 3 will be for immunogenicity testing only. ^{§§} Adverse Experiences (serious and non-serious) are to be reported Day 1 to 14 days following vaccination. Serious adverse experiences are to be reported throughout the subject's study participation (Day 30) VRC collected at Visit 2; site to solicit for any unreported SAEs since Visit 2. ^{¶¶} Blood draw at Visit 4 (40mL) is to obtain adult serum samples to support further development, validation, and performance of anti- pneumococcal-specific antibody assays. VRC-Vaccine Report Card				

Toddler Stage

	Visit 1 (Day 1)	Visit 2 (Day 30)
Obtain written informed consent [†]	x	
Perform physical exam and review medical history	x	
Review prior/concomitant medications	x	x
Review inclusion and exclusion criteria	x	
Randomization	x	
Vaccination with pneumococcal conjugate vaccine [‡]	x	
Collect blood samples for immunogenicity assays	x [§]	x
Distribute VRC to subject's parent/legal guardian and review instructions	x	
Obtain rectal temperature measurements [¶]	x	
Collect and review VRC for adverse events ^{# ††}		x
[†] Consent must be obtained PRIOR to any study procedures. [‡] Vaccine will be administered by unblinded study personnel not otherwise involved in the conduct of the study. Vaccine arms include V114 (aluminum-adjuvanted), V114 (non-adjuvanted), and Prevnar™ (control arm). [§] Collect blood prior to vaccination. Blood draw range: minus 1 day to plus 5 days. [¶] Rectal temperature is the preferred method for fever evaluation, however axillary temperature measurement is acceptable. If an axillary temperature is performed and is reported to be ≥37.8°C (≥100.0°F), it must be confirmed with a rectal temperature. [#] Adverse Experiences (serious and non-serious) are to be reported Day 1 to 14 days following vaccination. Serious adverse experiences are to be reported throughout the subject's study participation (Day 30). ^{††} Study coordinator should call parent/legal guardian 14 days postvaccination to review VRC. Site will collect VRC and review with parent/legal guardian at Visit 2. In addition, site will solicit for any unreported SAEs that may have occurred after completion of the VRC. VRC-Vaccine Report Card		

2. CORE PROTOCOL

2.1 OBJECTIVES

2.1.1 Primary Objectives

Safety

Adult Stage:

Evaluate the safety profile of a single dose of the aluminum-adjuvanted formulation of V114 pneumococcal conjugate vaccine in healthy adults.

Toddler Stage:

Evaluate the safety profile of a single booster dose of the aluminum-adjuvanted, and the non-adjuvanted formulation of V114 versus PrevnarTM administered at 12-15 months of age in healthy toddlers.

2.1.2 Secondary Objectives

Immunogenicity:

To describe the immunogenicity response to the serotypes contained in V114 in both adults and toddlers as measured by the MSD electrochemiluminescence (ECL) assay for the measurement of serotype-specific pneumococcal capsular polysaccharide IgG antibodies. Sera will also be assayed by a multiplex OPA for opsonophagocytic killing activity.

The main immunogenicity measurement is the pneumococcal capsular polysaccharide IgG concentration as measured by the electrochemiluminescence (ECL) assay, and corresponding to the 0.35 µg/mL level as measured by the internationally accepted ELISA.

Extension phase: To obtain additional sera from adult subjects for further development, validation, and performance of anti-pneumococcal-specific antibody assays.

This is a descriptive study; therefore, there is no hypothesis.

2.2 SUBJECT/PATIENT INCLUSION CRITERIA

A subject will be eligible to participate in this study if all of the following criteria apply:

Adult Stage:

- a. Adults ≥ 18 to 45 years of age in good health.
- b. Signed and dated informed consent prior to receipt of vaccine.

- c. Afebrile ($<100.4^{\circ}\text{F}$ [$<38.0^{\circ}\text{C}$] oral or equivalent) on day of vaccination
- d. Subject is able to read, understand and complete study questionnaires (i.e. the Vaccine Report Card).
- e. Subject is able to attend all scheduled visits and to comply with the study procedures.
- f. Subject has access to a telephone.
- g. Females must have a negative urine pregnancy test.

Toddler Stage:

- a. Healthy toddlers, 12-15 months of age who have previously completed a documented full 3 dose infant series of Prevnar™ at 2, 4, and 6 months of age.
- b. Subject's parent/legal guardian understands the study procedures, alternate treatments available and risks involved with the study, and voluntarily agree to participate by giving written informed consent.
- c. Afebrile, with a rectal temperature $<38.1^{\circ}\text{C}$ ($<100.5^{\circ}\text{F}$) or axillary temperature $<37.8^{\circ}\text{C}$ ($<100.0^{\circ}\text{F}$) on day of vaccination.
- d. Subject's parent/legal guardian is able to read, understand, and complete study questionnaires (i.e., the Vaccination Report Card).
- e. Subject is able to attend all scheduled visits and to comply with the study procedures.
- f. Subject's parent/legal guardian has access to a telephone.

2.3 SUBJECT/PATIENT EXCLUSION CRITERIA

A subject will not be eligible to participate in this study if any of the following criteria apply:

Adult Stage

- a. Receipt of any pneumococcal polysaccharide vaccine at any time or receipt of polysaccharide conjugate vaccine after the second year of life.
- b. Known hypersensitivity to any component of the pneumococcal conjugate vaccine.
- c. Known or suspected immunocompromised persons, including persons with congenital immunodeficiency, HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure (most

recent serum creatinine values in medical record ≥ 3 mg/dL), nephritic syndrome, or other conditions associated with immunosuppression such as organ or bone marrow transplant.

- d. Functional or anatomic asplenia.
- e. History of autoimmune disease including multiple sclerosis (MS), systemic lupus, polymyositis, inclusion body myositis, dermatomyositis, Hashimoto's thyroiditis, Sjogren's syndrome, rheumatoid arthritis, other autoimmune disorders.
- f. History of chronic fatigue syndrome.
- g. Known neurologic or cognitive behavioral disorders including multiple sclerosis (MS), MS-like disease, encephalitis/myelitis, acute disseminating encephalomyelitis (ADEM), pervasive developmental disorder, and related disorders.
- h. Subject has a coagulation disorder contraindicating IM vaccination.
- i. Use of any immunosuppressive therapy (Note: topical and inhaled/nebulized steroids are permitted). Subjects on corticosteroids should be excluded if they are receiving or are expected to receive, in the period from 30 days prior to Visit 1 through Visit 2, systemic doses greater than required for physiological replacement, i.e., >5 mg of prednisone (or equivalent) daily and for >2 weeks. Excluded immunosuppressive therapies also include chemotherapeutic agents used to treat cancer or other conditions, and treatments associated with organ or bone marrow transplantation, or autoimmune disease.
- j. Any underlying illness that would complicate evaluation and completion of this study.
- k. Any licensed non-live virus vaccine administered within the 14 days prior to receipt of study vaccine or is scheduled to receive any other licensed vaccine within 30 days following receipt of study vaccine. (Exception: Inactivated influenza vaccine may be administered during the study, but must be given at least 7 days prior to receipt of the study vaccine or at least 15 days after receipt of the study vaccine.)
- l. Subject has received a licensed live virus vaccine within 30 days prior of receipt of study vaccine or is scheduled to receive vaccination with a licensed live virus vaccine within 30 days of receipt of study vaccine.
- m. Subject has received diphtheria toxoid within 6 months prior to receipt of study vaccine.
- n. Prior receipt of a blood transfusion or blood products including immune globulin administered within the 6 months before receipt of study vaccine.

- o. Investigational drugs or vaccines received within the 2 months before receipt of study vaccine.
- p. Participation in another clinical study within 42 days before the beginning or anytime during the duration of the current clinical study.
- q. Recent hospitalization for acute illness within the 3 months before receipt of study vaccine.
- r. History of invasive pneumococcal disease (positive blood culture, positive cerebrospinal fluid culture, or other sterile site.) or known history of other culture positive pneumococcal disease.
- s. History of febrile illness (≥ 100.40 F [≥ 38.00 C] oral or equivalent) occurring within 72 hours before receipt of study vaccine.
- t. Subject is pregnant or breastfeeding or expecting to conceive within the projected duration of the study. Female subjects of reproductive potential must have been using 2 acceptable methods of birth control for 2 weeks prior to enrollment, and agree to use 2 acceptable methods of birth control for 1 month after vaccination. (Acceptable methods of birth control include use of hormonal contraceptives, intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, tubal ligation, condoms, or abstinence).
- u. Any subject who cannot be adequately followed for safety according to the protocol plan.
- v. Subject is unlikely to adhere to study procedures, keep appointments, or is planning to relocate during the study.
- w. Any other reason that in the opinion of the investigator may interfere with the evaluation required by the study.

Toddler Stage

- a. Have received less than the full 3-dose infant series of Prevnar™ or 3rd dose less than 2 months before study vaccine.
- b. Known hypersensitivity to any component of the pneumococcal conjugate vaccine.
- c. Known or suspected impairment of immunological function.
- d. Subject has a history of congenital or acquired immunodeficiency (e.g. splenomegaly)
- e. Subject or his/her mother has documented HIV infection.

- f. Functional or anatomic asplenia.
- g. History of autoimmune disease including multiple sclerosis (MS), systemic lupus, polymyositis, inclusion body myositis, dermatomyositis, Hashimoto's thyroiditis, Sjogren's syndrome, rheumatoid arthritis, other autoimmune disorders.
- h. Known neurologic or cognitive behavioral disorders including multiple sclerosis (MS), MS-like disease, encephalitis/myelitis, acute disseminating encephalomyelitis, pervasive developmental disorder, and related disorders.
- i. Receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks prior to vaccination. (Note: Toddlers on topical and inhaled/nebulized steroids may participate in the study.) Use of systemic steroids are only permitted when the subject is receiving less than 2mg/kg per day of prednisone (or its equivalent), or less than 20mg/d if they weigh more than 10kg and are not otherwise immunocompromised.
- j. Subject has received other licensed non-live vaccines administered within the 14 days before receipt of study vaccine
- k. Subject has received a licensed live virus vaccine within 30 days prior of receipt of study vaccine (Exception: Influenza virus vaccine given according to recommended guidelines within 7 days of receiving study vaccine).
- l. Prior receipt of a blood transfusion or blood products, including immunoglobulins.
- m. Investigational drugs or vaccines received within the 2 months before receipt of study vaccine.
- n. Participation in another clinical study within 42 days before the beginning or anytime during the duration of the current clinical study.
- o. History of invasive pneumococcal disease (positive blood culture, positive cerebrospinal fluid culture, or other sterile site) or known history of other culture positive pneumococcal disease.
- p. A recent (<72 hours) febrile illness (rectal temperature $\geq 38.1^{\circ}\text{C}$ [$\geq 100.5^{\circ}\text{F}$]) occurring within 48 hours before receipt of study vaccine.
- q. History of failure to thrive.
- r. Subject has a coagulation disorder contraindicating IM vaccination.
- s. Subject and his/her mother is documented hepatitis B surface antigen- positive.

- t. Any toddler who cannot be adequately followed for safety according to the protocol plan.
- u. Subject's parent/legal guardian is unlikely to adhere to study procedures, keep appointments, or is planning to relocate during the study.
- v. Any other reason that in the opinion of the investigator may interfere with the evaluation required by the study.

2.4 STUDY DESIGN AND DURATION

2.4.1 Summary of Study Design

This is a multicenter randomized double-blind, study to evaluate the safety, tolerability and immunogenicity of a 15-valent pneumococcal conjugate vaccine compared to Prevnar™ in healthy adults and toddlers.

Adult Stage:

A single 0.5 mL intramuscular dose of study vaccine will be administered to healthy adults. At baseline and Day 30 postvaccination, serotype-specific IgG antibody responses will be measured by an electrochemiluminescence (ECL) based detection method for serotype-specific IgG. Sera will also be assayed by OPA for antibodies with opsonophagocytic killing activity against pneumococcal serotypes present in the study vaccine. **Additional blood sample (40 mL) will be collected from adult subjects who consent to participate in the extension phase at Visit 4 to be used for further development, validation, and performance of anti-pneumococcal antibody assays.** In addition, safety laboratory tests including a complete blood count (CBC) with differential including platelets, serum creatinine, serum alkaline phosphatase (ALK), serum alanine aminotransferase (ALT), serum bilirubin and urinalysis will also be performed on Day 1 immediately prior to the administration of study vaccine and at Day 14 postvaccination (see Appendix 6.1). Safety will be evaluated in all subjects.

All eligible subjects who have consented to participate in the study will be randomized into one of the 2 treatment arms:

- (1) V114 (aluminum-adjuvanted), n=30
- (2) Prevnar™ (control arm), n=30

Study vaccine will be administered intramuscularly in a blinded fashion to each subject on Day 1 (Visit 1).

Study subjects will be observed for 30 minutes postvaccination for any immediate adverse experiences. The time at which the event occurred within the 30 minute timeframe, as well as the event itself and resolution of the event, must be recorded on the appropriate worksheet. The Vaccination Report Card (VRC) and instructions will be reviewed with each study subject. Injection site adverse experiences and systemic adverse experiences occurring Day 1 through Day 14 following each vaccination will be

recorded by each study subject on a VRC; this includes VRC-prompted injection site adverse experiences (redness, swelling, nodules, and pain/tenderness) and VRC-prompted systemic adverse experiences (muscle pain, joint pain, and tiredness). Serious adverse experiences will be collected until the end of the subject's participation in the study (Day 30 postvaccination). In addition, subjects will be asked to record an oral or equivalent temperature reading on the VRC from Day 1 to Day 7 following the vaccination. Temperature measurement must be recorded in the VRC if fever is suspected during Day 8 through Day 14. Temperature readings should be taken at approximately the same time each day.

Subjects will have blood drawn (20 mL) prior to vaccination at Day 1 (Visit 1), Day 14 (Visit 2), and Day 30 following the study vaccination (Visit 3) time points. **Additional blood sample (40 mL) will be drawn at Visit 4 for assay development, validation, and performance of anti-pneumococcal antibody assays from subjects who consent to participate in the extension phase.**

Adult Safety Review

The conduct of the clinical trial will be monitored and advised by an eDMC, consisting of experienced physicians who are not employees of the SPONSOR. The eDMC will advise the team on safety issues as they pertain to this study. After the adult stage is completed, a safety review will be conducted prior to enrollment of the toddler stage of the clinical trial. The eDMC may recommend any steps to ensure the safety of study participants and integrity of the clinical trial.

Toddler Stage:

A 0.5 mL dose of study vaccine will be administered intramuscularly to healthy toddlers at 12-15 months of age who have previously completed a full 3-dose infant series of PrevnarTM. Response to the vaccines will be measured by an electrochemiluminescence (ECL) based detection method for the quantitation of serotype-specific IgG. Responses to the vaccines will also be measured by OPA for opsonophagocytic killing activity against the vaccine serotypes, if remaining sample volume permits after the ECL studies. Safety will be evaluated in all subjects.

All eligible subjects who have consented to participate in the study will be randomized into one of the 3 treatment arms:

- (1) V114 aluminum-adjuvanted, n = 30
- (2) V114 non-adjuvanted, n = 30
- (3) PrevnarTM (control arm), n = 30

Study vaccine will be administered in a blinded fashion to each subject at 12-15 months of age.

Study subjects will be observed for 30 minutes postvaccination for any immediate adverse experiences. The time at which the event occurred within the 30 minute

timeframe, as well as the event itself and the resolution of the event, must be recorded on the appropriate worksheet. Instructions on completing the VRC will be reviewed with each study subject's parent/legal guardian. Injection site adverse experiences and systemic adverse experiences occurring Day 1 through Day 14 following each vaccination will be recorded by the subject's parent/legal guardian on a VRC; this includes VRC-prompted injection site adverse experiences (redness, swelling, nodules, and pain/tenderness) and VRC-prompted systemic adverse experiences (muscle pain, joint pain, and tiredness). Serious adverse experiences will be collected until the end of the subject's participation in the study (Day 30 postvaccination). In addition, subjects will be asked to record temperature readings on the VRC from Day 1 to Day 7 following vaccination. Temperature measurement must be recorded on the VRC if fever is suspected during Day 8 through Day 14. Although axillary temperature measurement is acceptable, rectal temperature is the preferred method for fever evaluation. If an axillary temperature is performed and is reported to be $\geq 37.8^{\circ}\text{C}$ ($\geq 100.0^{\circ}\text{F}$), it must be confirmed with a rectal temperature. In this case, both axillary and rectal temperatures must be recorded on the VRC. Temperature readings should be taken at approximately the same time each day.

Subjects will have blood drawn (3-5 mL) prior to vaccination at Day 1 (Visit 1) and Day 30 following the study vaccination (Visit 2) time points.

Toddler Safety Review

The conduct of the toddler stage of the clinical trial will be monitored and advised by an eDMC. The eDMC will advise the team on safety issues as they pertain to this study. After the toddler stage is completed, a safety review will be conducted prior to continuing to the Phase II trial of the V114 program. The eDMC may recommend any steps to ensure the safety of study participants and integrity of the clinical trial.

2.4.2 Treatment Plan

Adult Stage:

Eligible subjects who have consented to participate in the study will receive a 0.5 mL dose of study vaccine administered on Day 1 (Visit 1). The study will enroll 60 adult subjects (30 subjects in each study group). Because an exact match to the Prevnar™ syringe is not possible, unblinded study personnel not otherwise involved in the conduct of the study will administer vaccine. Safety and immunogenicity assessments will be conducted by blinded personnel and the subject will be blinded to the treatment received.

Toddler Stage:

Eligible subjects whose parent/legal guardian has consented for their toddler to participate in the study will receive a 0.5 mL dose of study vaccine administered intramuscularly at 12-15 months of age. In addition, subjects may receive concomitant administration of routine pediatric vaccines regularly administered at 12-15 months of age. The study will enroll 90 toddler subjects (30 subjects per arm). Because an exact

match to the Prevnar™ syringe is not possible, unblinded study personnel not otherwise involved in the conduct of the study will administer vaccine. Safety and immunogenicity assessments will be conducted by blinded personnel and the subject's parent/legal guardian will be blinded to the treatment received.

2.5 LIST OF IMMUNOGENICITY MEASUREMENTS

Sera collected prior to vaccination and at Day 30 postvaccination for both adults and toddlers will be assayed by ECL for serotype-specific pneumococcal capsular polysaccharide antibodies to all 15 vaccine serotypes contained in the V114 vaccine. Sera will also be assayed by OPA for opsonophagocytic killing activity if remaining sample volume permits after the ECL measurements. **Sera collected at Visit 4 will be used for the development, validation, and performance of assays to measure anti-pneumococcal immune responses.** In addition, non-vaccine serotypes may be assayed in subjects with sufficient sample volume remaining after ECL and OPA measurements.

2.6 LIST OF SAFETY MEASUREMENTS

Adverse experiences will be documented on a validated VRC. All adverse experiences (AE's) will be graded for severity.

Adult and Toddler Stages:

- 1) Study subjects will be observed for 30 minutes postvaccination for any immediate adverse experiences.
- 2) Solicited injection site adverse experiences (redness, swelling, nodules, and pain/tenderness) and solicited systemic adverse experiences (muscle pain, joint pain and tiredness) will be collected Day 1 to Day 14 after each vaccination.
- 3) Any other systemic or injection site adverse experiences Day 1 to Day 14 after each vaccination.
- 4) Serious adverse experiences from the time the consent form is signed through completion of the subject's participation in the study at Day 30 after the last dose of study vaccine.
- 5) Body temperature will be measured during Day 1 to Day 7 after each vaccination. If fever is suspected, temperature will also be measured during Day 8 to Day 14.

Adults Only:

- 1) CBC with differential including platelets, serum creatinine, ALK, ALT, bilirubin, and urinalysis will be performed at Day 1 and Day 14.
- 2) Severity of AEs and safety laboratory abnormalities will be assessed according to a toxicity grading scale as mild (Grade I), moderate (Grade II), severe (Grade III), and potentially life threatening (Grade IV).

2.6.1 Safety Monitoring

Safety and tolerability will be carefully monitored throughout the study by the SPONSOR in accordance with standard procedures and also by an eDMC. The eDMC will meet at pre-specified time points: after completion of the adult stage and after completion of the toddler stage. The eDMC will review all adverse experiences, including serious adverse experiences.

The eDMC consists of experienced physicians who are not employees of the SPONSOR.

The eDMC will monitor all safety data during the study. They will have the responsibility of study surveillance to monitor safety outcome events and identify safety issues in order to make recommendations (including the potential to terminate the study) to the Merck clinical monitor. A set of safety criteria proposed as stopping rules will be used by the eDMC in their evaluation of the safety data during the conduct of the study (See section 3.3.2 Data Safety Monitoring Committee). Following the eDMC charter and the protocol-specific charter, the eDMC will meet at pre-specified time points, including after collection of safety data from adult subjects and after completion of the toddler stage. The eDMC will also meet to evaluate the safety outcomes from the toddler data at the end of the study.

2.7 DATA ANALYSIS SUMMARY

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 3.5 of the protocol details.

2.7.1 Immunogenicity Analyses

There are no immunogenicity hypotheses in this study.

The main summary of immunogenicity will be based on the percentage of subjects with serotype-specific IgG concentration ≥ 0.35 $\mu\text{g/mL}$ at baseline and Day 30 postvaccination. These data will be summarized descriptively by treatment arm. The per-protocol population will be used for the main summary.

2.7.2 Safety Analyses

There are no safety hypotheses in this study.

There are no events pre-specified as of interest, i.e., no Tier-1 events. SAEs and AEs will be summarized descriptively by treatment arm. The All-Subjects-as-Treated population will be employed for safety analyses.

3. PROTOCOL DETAILS

3.1 RATIONALE

Redacted

Product: V114
Protocol/Amendment No.: 001-10

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Redacted

Product: V114
Protocol/Amendment No.: 001-10

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Redacted

Redacted

3.2 STUDY PROCEDURES

3.2.1 Concomitant Medication(s)/Treatment(s)

Any concurrent medication or medical treatment must be recorded on the appropriate electronic case report form (eCRF). On the day of vaccination, record the time of any analgesic or antipyretic use on the appropriate eCRF.

In addition to receiving study vaccine, toddlers may also receive their normal routine pediatric vaccinations given at 12-15 months of age according to the current national vaccination schedule and recorded on the appropriate eCRF.

To avoid any confounding results, non-study injectable vaccines generally should not be administered in the same limb as study vaccine. Documentation of which limb was used for the administration of study vaccine should be recorded on the appropriate eCRF. No other investigational compound or device may be administered at any time during this study without prior approval by the SPONSOR.

If medical condition requires the use of immunoglobulin, blood, or blood products before or during a subject's participation in this study, one of the individuals listed on the SPONSOR Contact Information page must be notified immediately and any such use must be documented on the appropriate eCRF.

3.2.2 Unblinded Site Personnel

Because an exact match to the Prevnar™ syringe is not possible, at least one member of the site staff (study coordinator or pharmacist) will be unblinded to the treatment groups. The unblinded person(s) will be responsible for receiving all clinical supply shipments, monitoring the ongoing clinical supply accountability and temperature logs, and preparing and administering the clinical supplies to all subjects. The unblinded person(s) will also be responsible for entering study drug information, including time vaccine was administered, for each subject into the electronic data capturing (EDC) system on the appropriate eCRF. The unblinded person(s) will be provided with an "Unblinded Study Coordinator Administrative Binder" where documents related to the clinical supplies will be maintained (e.g., vaccine dispensing logs, vaccine daily temperature monitoring logs), etc.).

In order to avoid bias, the unblinded person(s) will not be involved in any postvaccination safety assessment procedures. The unblinded person(s) must also not disclose any information regarding the allocation of the clinical supplies to any blinded member of the site staff. No blinded member of the site staff should have contact with the clinical supplies at any point during the course of the study.

The responsibilities of the unblinded person(s) are outlined in an Unblinded Study Coordinator Guidance Document provided in both the Administrative Binder and the Unblinded Study Coordinator Administrative Binder.

3.2.3 Diet/Activity/Other

No special dietary restrictions apply to this study.

3.2.4 Procedures

3.2.4.1 Informed Consent

3.2.4.1.1 General Informed Consent

A subject (adult stage) or a subject's parent/legal guardian (toddler stage) is required to give written informed consent before a subject undergoes any study procedures. The study site personnel must thoroughly explain the details of this clinical trial and inform each subject or each subject's parent/legal guardian that participation in this study will not interfere with standard medical care. Consent must be documented by obtaining signatures of the subject or the subject's parent/legal guardian and of the person conducting the consent discussion on the consent form. Depending on local law or review committee requirements, such consent may also need to be signed by an impartial witness. A copy of the signed and dated consent form will be given to the subject or the subject's parent/legal guardian. Verification of the subject's identity and age is to be determined prior to obtaining written consent. Any government-issued photo identification will suffice for verification purposes and should be documented in the subject's file.

Should a subject or a subject's parent/legal guardian sign a consent form but not enroll in the study on that same day (i.e., no study procedures are performed), the signed consent form is valid for up to 14 days. If the subject returns after more than 14 days have elapsed, written consent must be re-obtained from the subject or the subject's parent/legal guardian.

Extension phase: A subject is required to give written informed consent before undergoing any study procedures. The study site personnel must thoroughly explain the details of this clinical trial and inform each subject that participation in this study will not interfere with standard medical care. Consent must be documented by obtaining signatures of the subject and of the person conducting the consent discussion on the consent form. A copy of the signed and dated consent form will be given to the subject.

3.2.4.1.2 Consent and Collection of Specimens for Genetic Analysis

Specimens for genetic analysis will not be collected for this trial.

3.2.4.2 Assignment of Baseline Number

Each subject with a signed informed consent form to participate in the study will be assigned a unique baseline number for identification purposes. Each subject should be assigned only one baseline number. Should the subject fail to qualify for the study, his/her baseline number must not be re-used for any other subject in the study. A subject may be re-screened at a later date; in this case, the subject should retain his/her original baseline number. Baseline numbers should be assigned sequentially from the lowest number to the highest number at each site. Baseline numbers should never be skipped and may not be reassigned for any reason.

3.2.4.3 Stratification

There will be no stratification for this study.

3.2.4.4 Randomization/Allocation

After a signed and dated consent form, the subject's medical history, physical exam and vital signs have been obtained from the subject, and all eligibility criteria have been met, the subject will be assigned an allocation number using a blinded randomization system.

Each allocation number may be used only once. Allocation numbers should not be reassigned for any reason.

Additional details on the process for randomization can be found in the Administrative Binder provided by the SPONSOR.

No new allocation number should be assigned to subjects during the extension phase. The original allocation number should be used for any subject participating in the extension phase.

A single patient/subject cannot be assigned more than 1 allocation number.

3.2.4.5 Vaccination/Evaluation/Follow-up

Prior to enrollment of toddlers, the safety of a single dose administration of the study vaccines will be evaluated in healthy adults. During the toddler stage, study vaccines may be administered concomitantly with other licensed routine pediatric vaccines (given according to the current national vaccination schedule).

During the extension study, only a blood sample will be collected; no study vaccines will be administered and no safety follow-up visit is required. (See section 3.4.5.1 for reporting any serious adverse events that occur during the extension phase.)

Adult subjects will be randomly assigned to 1 of 2 treatment arms:

- (1) Merck investigational V114, aluminum-adjuvanted
- (2) Prevnar™ control arm

Toddlers will be randomly assigned to 1 of 3 treatment arms:

- (1) Merck investigational V114, aluminum-adjuvanted
- (2) Merck investigational V114, non-adjuvanted
- (3) Prevnar™ control arm

Adult Stage:

Safety will be assessed in 60 healthy adult subjects (30 subjects per arm). A single 0.5 mL dose of vaccine will be administered intramuscularly in a blinded fashion to each subject on Day 1 (Visit 1). Because an exact match to the Prevnar™ syringe is not possible, unblinded study personnel not otherwise involved in the conduct of the study will administer vaccine. Note that the time of vaccination should be recorded on the eCRF. All safety and immunogenicity assessments will be conducted by blinded personnel, and all subjects will be blinded to the treatment received.

Safety Monitoring

Study subjects will be observed for 30 minutes postvaccination for any immediate adverse experiences. The time at which the event occurred within the 30 minute timeframe, as well as the event itself and resolution of the event, must be recorded on the appropriate worksheet. The Vaccination Report Card (VRC) and instructions will be reviewed with each study subject. Injection site adverse experiences and systemic adverse experiences occurring Day 1 through Day 14 following each vaccination will be recorded by the subject's parent/legal guardian on a VRC; this includes VRC-prompted injection site adverse experiences (redness, swelling, nodules, and pain/tenderness and VRC-prompted systemic adverse experiences (muscle pain, joint pain, and tiredness). The presence of a nodule at the injection site as defined by the Brighton Collaboration Case Definitions is discrete or well-demarcated soft tissue mass or lump that is firm and is at the injection site. There may be additional less discrete, softer swelling surrounding the nodule at the injection site, especially early in its development. There may also be tenderness and pruritus. The *absence* of abscess formation and erythema and warmth [12]. Serious adverse experiences will be collected until the end of the subject's participation in the study (Day 30 postvaccination). In addition, subjects will be asked to record an oral or equivalent temperature reading on the VRC from Day 1 to Day 7 following each vaccination. Temperature measurement must be recorded in the VRC if fever is suspected during Day 8 through Day 14. Temperature readings should be taken at approximately the same time each day.

All data fields on the VRC must be completed by the subject. To validate the authenticity of the entries, the subject will initial and date the last page of the VRC after it has been reviewed with the investigator or study staff personnel at each subsequent visit.

If discrepancies or omissions are observed during review of the VRC, the subject, not the investigator or study staff personnel, must make the corrections. Corrections are to be made with a single line through the incorrect entry, with the correct entry provided and initialed and dated by the subject. The subject should make all entries in the VRC in ink (preferably black); correction fluid and pencils should never be used. The VRC is a source document; all information provided on the VRC by the subject will be entered into the appropriate eCRF by study staff personnel.

Laboratory Samples

Blood samples (approximately 20 mL) will be drawn immediately prior to vaccination on Day 1, Day 14 postvaccination, and Day 30 postvaccination. **Additional blood samples (40 mL) will be drawn at Visit 4 to support further development, validation, and performance of assays to measure response to pneumococcal vaccine.** Samples drawn at baseline and Day 14 postvaccination will be used to perform a safety laboratory evaluation (CBC with differential including platelets, serum creatinine, serum alkaline phosphatase (ALK), serum alanine aminotransferase (ALT), serum bilirubin, and urinalysis). Samples drawn at baseline and Day 30 postvaccination will be used to measure vaccine-induced immune responses. Serum samples collected for immune response will be assayed using MSD electrochemiluminescence (ECL) assay developed by Merck for the measurement of serotype-specific pneumococcal capsular polysaccharide IgG antibodies. Serum samples will also be assayed for functional activity using the opsonophagocytic killing assay (OPA). Safety will be evaluated in all subjects following the administration of the study vaccine. **During the study extension, a blood sample will be collected at Visit 4 and will be used to develop, validate, and perform assays to measure immune responses to pneumococcal vaccine.**

Safety Review Prior to Toddler Enrollment

The conduct of the clinical trial will be monitored and advised by an external Data Monitoring Committee (eDMC) not directly involved in the conduct of the study. This committee will advise the team on safety issues as they pertain to this study.

All clinical safety data (including incidence, intensity, and duration of all local and systemic adverse experiences) from the adult stage will be reviewed by an eDMC before proceeding with the evaluation of the candidate vaccine in toddlers. Adult outcome criteria for proceeding to the toddler phase will therefore include approval from the eDMC which should take into consideration the criteria proposed for stopping rules as regards the incidence and severity of serious and non-serious adverse experiences.

Toddler Stage:

Upon successful evaluation of the adult stage safety data, the toddler stage of the clinical trial will start enrollment. A 0.5 mL intramuscular dose of study vaccine will be administered to healthy toddlers 12-15 months of age. All subjects must have previously completed the full 3-dose infant series of Prevnar™ prior to study participation. This

study will enroll 90 subjects (30 per arm). In addition, subjects are allowed to receive concomitant administration of routine pediatric vaccines regularly administered at 12-15 months of age according to the current national vaccination schedule. As with the adult stage, unblinded study personnel not otherwise involved in the conduct of the study will administer study vaccine and record the vaccination on the appropriate eCRF. Note that the time of vaccination should be recorded on the eCRF. All safety and immunogenicity assessments will be conducted by blinded personnel, and the subjects' parents/guardians will be blinded to the treatment received.

Safety Monitoring

Study subjects will be observed for 30 minutes postvaccination for any immediate adverse experiences. The time at which the event occurred within the 30 minute timeframe, as well as the event itself and resolution of the event, must be recorded on the appropriate worksheet. Instructions on completing the VRC will be reviewed with each study subject's parent/legal guardian. Injection site adverse experiences and systemic adverse experiences occurring Day 1 through Day 14 following each vaccination will be recorded by the subject's parent/legal guardian on a VRC; this includes VRC-prompted injection site adverse experiences (redness, swelling, nodules, and pain/tenderness) and VRC-prompted systemic adverse experiences (muscle pain, joint pain, and tiredness). Serious adverse experiences will be collected until the end of the subject's participation in the study (Day 30 postvaccination). In addition, the subject's parent/legal guardian will be asked to record a rectal temperature reading on the VRC from Day 1 to Day 7 following each vaccination. Temperature measurement must be recorded in the VRC if fever is suspected during Day 8 through Day 14. Although axillary temperature measurement is acceptable, rectal temperature is the preferred method for fever evaluation. If an axillary temperature is performed and is reported to be $\geq 37.8^{\circ}\text{C}$ ($\geq 100.0^{\circ}\text{F}$), it must be confirmed with a rectal temperature. In this case, both axillary and rectal temperatures must be recorded on the VRC. Temperature readings should be taken at approximately the same time each day.

The site should call parent/legal guardian 14 days postvaccination to review VRC. The VRC should be collected and reviewed with parent/legal guardian at the Day 30 study visit. All data fields on the VRC must be completed by the parent/legal guardian. To validate the authenticity of the entries, the parent/legal guardian will initial and date the last page of the VRC. Any discrepancies or omissions will be discussed with the parent/legal guardian at Visit 2. The parent/legal guardian, not the investigator or study staff personnel, must make all corrections. Corrections are to be made with a single line through the incorrect entry, with the correct entry provided and initialed and dated by the parent/legal guardian. All entries in the VRC should be made in ink (preferably black); correction fluid and pencils should never be used. The VRC is a source document; all information provided on the VRC by the parent/legal guardian will be entered into the appropriate eCRF by study staff personnel.

Laboratory Samples

Subjects will have blood drawn (approximately 3-5 mL) at 2 time points: at Visit 1 prior to vaccination and at Visit 2 (Day 30 postvaccination). Serum samples will be assayed by ECL for the quantitation of serotype-specific anti-pneumococcal IgG antibodies. Serum samples will also be assayed for functional activity by OPA if remaining sample volume permits. Safety will be evaluated in all subjects.

3.2.4.6 Blinding/Unblinding

Except for the unblinded study personnel (e.g. site pharmacist, study coordinator etc.) administering study vaccine, all study-site personnel, subjects, subject's parent/legal guardian, and SPONSOR personnel will remain blinded to the treatment group assigned to all subjects throughout the study. Members of the SPONSOR staff who will remain blinded to treatment group at the subject level throughout the duration of the study include: (1) MRL Clinical Monitor responsible for scientific conduct of the trial; (2) MRL Clinical Research Specialists (CRS) responsible for scientific conduct of the study; (3) MRL Clinical Research Associates (CRA) responsible for blinded site-monitoring activities; (4) MRL Worldwide Clinical Data Management Operations (WCDMO) personnel responsible for reviewing study data; (5) MRL project statisticians responsible for data analysis; and (6) all laboratory personnel involved in the conduct of safety and immunogenicity assays for the study.

An exact match to the Prevnar™ syringe is not possible, therefore all vaccination-related procedures will be performed by an unblinded study person (unblinded study coordinator[s] and/or pharmacist[s]). In order to avoid any potential safety reporting bias, the unblinded study coordinator will not be involved in any of the subsequent safety assessment procedures. The unblinded MRL Clinical Research Associates (CRAs) directly responsible for unblinded site-monitoring activities (monitoring clinical supplies at the site) will remain unblinded to treatment group.

Except in the case of medical necessity, a subject's vaccination should not be unblinded without the approval of the SPONSOR. If any subject is unblinded prior to completion of the study, the investigator must promptly contact the appropriate personnel designated on the SPONSOR Contact Information page, and document the circumstances on the appropriate electronic case report form (eCRF) and on the Study Unblinding Log. See section 3.6.3 for specific procedures if emergency unblinding is necessary.

In the event of unblinding (either accidental unblinding or emergency unblinding), the investigator must do the following:

- Immediately notify the SPONSOR Clinical Monitor or Clinical Research Specialist (CRS).
- Document the circumstances in the subject's study chart.

- Document the unblinding on the Patient Unblinding Log located in the Administrative Binder.

3.2.4.7 Discontinuation/Withdrawal from Study

If a subject or a subject's parent/legal guardian signs a consent form, but the subject is not randomized because he or she does not meet the criteria for being in the study, the appropriate eCRFs must be completed. Please consult the eCRF Entry Guidelines for instructions regarding the completion of the appropriate eCRFs. Furthermore, the information about subjects who are screened and are not randomized must also be documented on the Subject Participation Log located in the Administrative Binder.

If a subject wants to withdraw or a subject's parent/legal guardian wants to withdraw the subject prior to completion of the study, the subject will be followed for safety from Day 1 through Day 14 following the last dose of any study vaccine, for all adverse experiences both serious and non serious.

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject/patient has been discontinued/withdrawn due to an adverse experience (telephone or FAX). When a subject/ patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 3.4 SAFETY MEASUREMENTS - DETAILS.

3.3 IMMUNOGENICITY MEASUREMENTS

Sera will be collected from all adult and toddler subjects prior to vaccination and Day 30 postvaccination for immunogenicity testing. All serum samples will be shipped to a central laboratory for evaluation. Samples will be assayed by ECL for serotype-specific IgG antibodies to all 15 vaccine pneumococcal capsular serotypes. Sera will also be assayed by OPA for opsonophagocytic killing activity if remaining sample volume permits after the IgG measurements. In addition, non-vaccine serotypes may be assayed in serum samples if sufficient volume is available. **Serum samples obtained during the extension study may be used for the development, validation, and performance of the IgG antibody and OPA assays as well as other anti-pneumococcal assays.**

3.3.1 Clinical and Laboratory Measurements for Immunogenicity

3.3.1.1 Multiplex, Electrochemiluminescence-based Detection Assay for the Quantitation of IgG Serotype-Specific Anti-Pneumococcal Antibodies in Human Serum

The Pneumococcal (Pn) electrochemiluminescence (ECL)-based detection assay is a direct binding assay used to simultaneously quantitate IgG Pn antibody responses in sera from naturally infected individuals or sera from individuals immunized with a 23-valent pneumococcal vaccine or other PnPs containing vaccines. The assay is based on the Meso-Scale discovery (MSD) technology which employs multi-spot microtiter plates fitted with a series of electrodes associated with the bottom of each well. Using an MSD plate imager, an electrical current is placed across the plate-associated electrodes. The result is a series of electrically induced oxidation-reduction reactions involving Ruthenium and Tripropylamine (TPA) leading to a luminescent signal. The standard curve reference serum for this assay is the Pn International Reference Standard, Lot 89SF-2. A control from Pneumovax®23 immunized human subjects tested across 3 dilutions is included on each plate. Antibody concentrations are determined in a direct binding format, where the total IgG SULFO-TAG -labeled antibody binds to sample serum IgG antibodies. Test sample antibody concentration is determined by referencing their ECL response against a standard curve generated from the serially diluted 89SF-2 reference serum.

The data from the characterization of the multiplex, Pn ECL based detection assay for quantitation of serotype-specific Pn Ab's directed against serotypes 3, 4, 6B, 9V, 14, 18C, 19F, and 23F of *Streptococcus pneumoniae* suggest that the assay has excellent operating characteristics. The Pn ECL assay exhibits a wide dynamic range and provides for the ability to read concentrations down to the minimum reported concentration in the Merck ELISA of 0.1 µg/ml. The Pn antibody concentrations generated using the Pn ECL assay satisfied the WHO recommended acceptance criterion for concordance to the WHO Pn ELISA for all seven serotypes with published Pn ELISA value. The characterization of the PnECLs for the remaining serotypes will follow that utilized for the initial 8 types.

Information on the laboratory used to perform this assay will be provided in the Administrative Binder of the protocol.

3.3.1.2 Multiplexed Opsonophagocytic Killing Assay (OPA) for Antibodies against *Streptococcus pneumoniae*

The 4-Fold Multiplexed Opsonophagocytic Killing Assay for antibodies against *Streptococcus pneumoniae* (MOPA 4) is used to measure sera of patients vaccinated with multivalent *Streptococcus pneumoniae* vaccines for antibody titers (opsonic activity/killing) against the capsular polysaccharides for specific *S. pneumoniae* types. The method is multiplexed (quad) permitting 4 serotype testing per run eliminating excessive use of infant sera. The assay utilizes complement (baby rabbit source), a critical component, which requires qualification prior to use in the MOPA4. The opsonophagocytic killing assay (OPA) also utilizes HL-60 human Promyelocytic

Leukemia cells which are transformed into phagocytes for this assay. Complement is added in addition to bacterial strains (*S. pneumoniae* bacterial strains 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C 19A, 19F, 22F, 23F, and 33F; strains are tested in groups of 4) and patient sera. The ability of antibodies in patient sera, at a series of dilutions, to initiate the killing of the pneumococcal bacteria is the basis for assignment of antibody titer of the sample. The opsonization titers (OT) are defined as the serum dilution that kills 50% of bacteria and are determined using a linear interpolation algorithm.

The OPA as described by Professor Moon Nahm (Director of the US WHO and NIH pneumococcal serology reference laboratory) will be utilized to support the V114 program. The method has been published [11] and presented at the WHO OPA standardization meeting in Geneva, January 2007. Information on the laboratory to perform this assay will be provided in the Administrative Binder of the protocol.

3.3.2 Data Safety Monitoring Committee

The safety and tolerability of the clinical trial will be carefully monitored throughout the study by the SPONSOR in accordance with standard procedures and also by an eDMC. Members of this eDMC consist of experienced physicians who are not employees of the SPONSOR. The eDMC will advise the team on safety issues as they pertain to this study. The eDMC will meet at pre-specified time points; after completion of the adult stage and after completion of the toddler stage. This committee will review all adverse experiences, including serious adverse experiences. Additional logistical details will be outlined in the eDMC charter.

The eDMC will have the responsibility of study surveillance for the data, and more specifically to monitor safety outcome events and identify safety issues in order to make periodic recommendations (including the potential to terminate the study) to the Merck clinical monitor. The eDMC may recommend any steps to ensure the safety and integrity of the trial.

The eDMC will be provided with the following stopping rules as guidance for terminating the study:

Study Stopping Rules

If any of the following events occurs, administration of study vaccine will be temporarily discontinued until a thorough review of accumulated safety data is undertaken by the eDMC, the investigators, and/or the SPONSOR's representative.

- Death in any subject, unless the cause of death is due to obvious alternative etiology.
- Unexpected life-threatening event in any subject, unless due to obvious alternative etiology. Event should not have been previously observed with similar pneumococcal vaccines, or vaccines administered concomitantly in this study.

- Any serious adverse event, unless due to obvious alternative etiology, with the exception of those already reported for pneumococcal conjugate vaccines or for other concomitantly administered vaccines;
- Three or more of the same grade 3 AE (judged by the clinical investigators, medical monitor, or SPONSOR's medical expert) including injection site reactions, muscle pain, joint pain, and fatigue occurring in 20% individuals in any dose group, unless due to obvious alternative etiology;
- Event which in the opinion of the investigator and/or safety monitoring committee contraindicates further dosing of additional subjects.

Conclusions regarding safety outcome will otherwise be determined from any SAE and grade 3 solicited systemic adverse event, regardless of relationship to vaccination.

After all the adult Day 14 safety data have been collected, a safety review will be conducted by the eDMC prior to enrollment of the toddler stage. The eDMC will also review all available safety and tolerability toddler data. Progression of the study from the adult to the toddler stage requires the written approval of the eDMC. The study site and SPONSOR's personnel involved in the conduct of the study will remain blinded as to the treatment allocation of the study subject. Summaries of the safety data and a final report of the safety evaluation conducted by the eDMC will be communicated to CBER/FDA in a timely fashion.

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical and Laboratory Measurements for Safety

The safety and tolerability of the clinical trial will be carefully monitored throughout the study by the SPONSOR in accordance with standard procedures and also by the eDMC. A safety review of the adult safety data will be conducted by the eDMC, prior to enrollment of the toddler stage (see section 3.3.2). All adult adverse experiences (AEs) will be graded for severity according to a toxicity grading scale (see Attachment). Severity of clinical AE's will be assessed as mild (Grade I), moderate (Grade II), severe (Grade III), and potentially life-threatening (Grade IV). All adult AEs recorded on the VRC will then be reviewed and graded according to the toxicity grading scale by the investigator and recorded in the study records. Consistent with previous pediatric clinical trials conducted by the SPONSOR, all AEs reported for toddlers will be evaluated for severity (mild, moderate, severe) according to Table 3-2 by an investigator who is a qualified physician. Specifically, clinical adverse experiences will be graded by the subject/subject's parent/legal guardian on the VRC.

In order to evaluate the safety profile of V114 in adults and toddlers, all subjects will be followed for the solicited injection site adverse experiences of redness, swelling, nodules and pain/tenderness and solicited systemic adverse experiences of muscle pain, joint pain, and tiredness. Unsolicited systemic or injection site adverse experiences will be collected from Day 1 through Day 14 after each vaccination. All serious adverse experiences

(regardless of the investigator's assessment of causality) from the time the consent form is signed through completion of the subject's participation in the study at Day 30 after the last dose of study vaccine will be collected. Any immediate adverse experiences occurring in the 30 minutes postvaccination observation period will be recorded. Information about any medications, including time of any analgesic/antipyretic use on the day of vaccination that the subject receives should be documented throughout the study on the VRC.

VRCs will be reviewed by study personnel for completeness, accuracy, and clarity. The VRC is considered a source document and no original information recorded by the subject or the subject's parent/legal guardian should be crossed out or altered in any manner. A sample VRC can be found in the Administrative Binder. Investigators will need to make causality and intensity assessments on non-serious adverse events (NSAE) just as they typically do for all SAEs.

Sites will review with the subject or the subject's parent/legal guardian the definition of a serious adverse event (SAE) and the need to notify the site immediately if the subject experiences an SAE. SAEs should be reported by the investigator to the SPONSOR's representative within 24 hours of first notification to the study site personnel.

For adult subjects only, laboratory safety measurements of complete blood count with differential including platelets, serum creatinine, serum alkaline phosphatase (ALK), serum alanine aminotransferase (ALT), bilirubin, and urinalysis will be evaluated at Day 1 and Day 14. These laboratory values will be graded according to the toxicity grading scale.

3.4.2 Recording Adverse Experiences

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

All adverse experiences will be collected from the time the consent form is signed through 14 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter, and such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets.

3.4.3 Definition of an Overdose for This Protocol

Administration of more than 1 dose of any individual study vaccine in any 24 hour period will be considered an overdose for this protocol. An overdose should be reported to the SPONSOR immediately.

3.4.3.1 Reporting of Overdose to SPONSOR

If an adverse experience(s) is associated with (“results from”) the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology “accidental or intentional overdose without adverse effect.”

All reports of overdose with and without an adverse experience must be reported within 24 hours to one of the individuals listed on the SPONSOR contact information page found in the Administrative Binder.

3.4.4 Reporting of Pregnancy to SPONSOR

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a subject/patient (spontaneously reported to them) which occurs during the study or within 14 days of completing the study. All subjects/patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page found in the Administrative Binder.

3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

3.4.5.1 Serious Adverse Experiences

Any serious adverse experience, including death due to any cause, which occurs to any subject from the time the consent is signed through 14 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter, whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the SPONSOR contact information page found in the Administrative Binder.

Additionally, any serious adverse experience brought to the attention of an investigator who is a qualified physician at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the SPONSOR contact information page (found in the administrative binder) if the event is either:

1. A death which resulted in the subject/patient discontinuing the study
- or
2. A serious adverse experience that is considered by an investigator who is a qualified physician to be possibly, probably, or definitely vaccine related.

All subjects/patients with serious adverse experiences must be followed up for outcome.

3.4.5.2 Serious Adverse Experiences – Extension Phase

Any serious adverse experience, including death related to the protocol specified research procedure(s), which occurs to any subject entered into this study within 5 days following the procedure, must be reported within 24 hours to one of the individuals on the SPONSOR Contact Information Page found in the administrative binder.

Additionally, any serious adverse experience considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the protocol specified procedure that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the sponsor contact information page found in the administrative binder.

All subjects with serious adverse experiences related to the procedure or participation in the study must be followed to outcome.

Additionally, if through the conduct of this study, an investigator becomes aware of any serious adverse experience that is possibly, probably or definitely related to a marketed product manufactured by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., it should be reported directly to one of the persons on the sponsor contact information page. Such serious adverse experiences will not be actively solicited and will not be collected on the eCRF. Other adverse experiences will not be ascertained or evaluated in this protocol.

3.4.6 Evaluating Adverse Experiences

Refer to Table 3-2 for instructions in evaluating adverse experiences.

Table 3-2

An investigator who is a qualified physician, will evaluate all adverse experiences as to:

Maximum Intensity	Mild	awareness of sign or symptom, but easily tolerated (for pediatric studies, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric studies, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric studies, extremely distressed or unable to do usual activities) Injection site redness or swelling from the day of vaccination through Day 4 post-vacc will be evaluated by maximum size.
Seriousness	A serious adverse experience is any adverse experience occurring at any dose that:	
	† Results in death; or	
	† Is life threatening; or places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]; or	
	† Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	† Results in or prolongs an existing inpatient 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or	
	† Is a congenital anomaly/birth defect (in offspring of subject/patient taking the product regardless of time to diagnosis); or	
	Is a cancer; or	
	Is an overdose (Whether accidental or intentional.) Any overdose whether or not associated with an adverse experience must be reported within 24 hours to one of the individuals on the Contact Information Page found in the Administrative Binder.	
Duration	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
	Record the start and stop dates of the adverse experience. If less than 1 day, indicate the appropriate length of time and units	
	Did the adverse experience cause the test vaccine to be discontinued?	
Action taken	Did the test vaccine cause the adverse experience? The determination of the likelihood that the test vaccine caused the adverse experience will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet, that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test vaccine and the adverse experience based upon the available information.	
	The following components are to be used to assess the relationship between the test vaccine and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test vaccine caused the adverse experience (AE):	
	Exposure	Is there evidence that the subject/patient was actually exposed to the test vaccine such as: reliable history, acceptable compliance assessment (e.g. diary), seroconversion or identification of vaccine virus in bodily specimen?
Relationship to test vaccine	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test vaccine?
		Is the time of onset of the AE compatible with a vaccine-induced effect?

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Relationship to test vaccine (continued)	The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)	
	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
	Dechallenge	(not applicable for vaccines)
	Rechallenge	Was the subject/patient reexposed to the test vaccine in this 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.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST VACCINE, OR IF REEXPOSURE TO THE TEST VACCINE POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Study Vaccine Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test vaccine or vaccine class pharmacology or toxicology?
	The assessment of relationship will be reported on the case report forms /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 vaccine relationship).	
	Definitely related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test vaccine or test vaccine class.
	Probably related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
	Probably not related	There is evidence of exposure to the test vaccine. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The subject/patient did not receive the test vaccine. OR Temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable. OR There is another obvious cause of the AE.

3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.5 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to any of the analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

3.5.1 Responsibility for Analyses/ In-House Blinding

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

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

The SPONSOR will generate the randomized allocation schedule(s) for study vaccine assignment.

The eDMC will serve as the reviewer of results of interim summaries and will make recommendations for discontinuation of the study or modification to an executive committee of the SPONSOR. The eDMC will review blinded summaries. If subsequently requested by the eDMC, treatment-level results of interim summaries will be provided by an unblinded statistician to this committee. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details will be provided in the eDMC Charter.

Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts.

3.5.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 2.1.

3.5.3 Analysis Endpoints

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

3.5.3.1 Immunogenicity Endpoints

The main summary of immunogenicity will be based on the postvaccination percentage of subjects with ≥ 0.35 $\mu\text{g/mL}$ IgG concentration, for all serotypes. Secondary endpoints of interest are the geometric mean concentrations of IgG, the percent of subjects with OPA activity as defined by $\geq 1:8$ and the geometric mean OPA titers.

Safety Endpoints

The safety endpoints are frequencies of adverse events. For adults, safety endpoints will also include those based on chemistry, and hematology and urinalysis laboratory values.

3.5.4 Analysis Populations

3.5.4.1 Immunogenicity Analysis Populations

The Per Protocol (PP) population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of those subjects who are not considered protocol violators. Potential violations include: failure to receive the scheduled dose of correct clinical material, temperature excursions with administered treatment, and lack of valid serology results available from 29 to 35 days following dose 1.

The final determination on protocol violations will be made prior to the locking of the database and will be documented in a separate memo.

Subjects will be included in the treatment group to which they are randomized for the analysis of immunogenicity data.

Details on the approach to handling missing data are provided in Section 3.5.5, Statistical Methods.

3.5.4.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

Details on the approach to handling missing data are provided in Section 3.5.5, Statistical Methods.

3.5.5 Statistical Methods

3.5.5.1 Statistical Methods for Immunogenicity Analyses

There are no immunogenicity hypotheses for this study. Only observational comparisons will be made.

For the summary analysis of the main endpoint, the percentage of subjects who achieve the above-specified IgG level will be calculated along with 95% confidence intervals per treatment group, within both the adult and toddler cohorts. The confidence intervals will be calculated according to the Clopper-Pearson method [13].

Other summary analyses will be based on geometric mean concentrations/titers (GMC/GMTs) for both the IgG and OPA assays. The GMC/GMTs will be calculated along with 95% confidence intervals per treatment group, within both the adult and toddler cohorts. Point estimates of GMCs/GMTs are the exponentiated estimates of the mean $\log_e$ concentrations. The confidence intervals for GMCs are the exponentiated confidence intervals for the mean $\log_e$ concentrations, based on 1-sample t-distributions.

The percentage of subjects with OPA titer $\geq 1:8$ will be summarized according to the same methods described above for the main endpoint.

No data will be imputed.

3.5.5.2 Statistical Methods for Safety Analyses

There are no safety hypotheses for this study. Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), within both the adult and toddler cohorts.

The summary analysis of safety results will follow a tiered approach (Table 3-3). The tiers differ with respect to the analyses that will be performed. There are no safety parameters or adverse experiences of special interest that are identified as a priori and constitute "Tier 1" safety endpoints. Safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group (V114 versus Prevnar™) comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence

intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences.

For this protocol, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a vaccine related AE, a serious AE, an AE which is both vaccine-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. For Tier 2, 95% confidence intervals will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method (1985), an unconditional, asymptotic method [14].

Table 3-3
Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint [†]	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Vaccine-Related AE	X	X
	Any Serious and Vaccine-Related AE	X	X
	Discontinuation due to AE	X	X
	Specific AEs, SOCs (incidence ≥ 4 of subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs (incidence < 4 of subjects in all of the treatment groups)		X
[†] Adverse Experience references refer to both Clinical and Laboratory AEs. Note: SOC=System Organ Class; X = results will be provided.			

3.5.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of summary tables within both the adult and toddler cohorts. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects randomized and vaccinated, and the reasons for discontinuation will be displayed by treatment. Demographic variables (e.g., age), prior and concomitant therapies and vaccines will be summarized by treatment.

No other analyses are planned for this protocol.

3.5.6 Multiplicity

There are no hypotheses for this study; therefore, there are no multiplicity issues in that regard.

3.5.7 Sample Size and Power

There are no hypotheses for this study.

The sample size of 30 subjects/arm was chosen to allow for clinically sufficient determination of the vaccine's safety and tolerability with respect to whether further study should be pursued. For purposes of estimation of all proportions, 30 subjects/arm will result in 95% confidence intervals with half-widths between 12 and 19 percentage points. So, if there are 0 AEs observed in a treatment arm, there will be 95% confidence that the true proportion of AEs in that treatment arm is <12%.

3.5.8 Subgroup Analyses and Effect of Baseline Factors

No analyses for these factors will be performed, as none are expected to influence the results.

3.5.9 Interim Analyses

No interim analyses will be performed.

3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

3.6.1 Product Descriptions

Investigational materials will be provided by the SPONSOR as summarized in Table 3-4.

Table 3-4

Product Descriptions

Product Name & Potency	Dosage form/Contents/Route of Administration	Storage Conditions
V114 adjuvanted Pneumococcal 15-valent Conjugate Vaccine (Diphtheria CRM ₁₉₇ Protein) *†	0.5 mL dose sterile suspension for intramuscular injection	Store refrigerated 2-8°C Protect from light Do not freeze
V114 non-adjuvanted Pneumococcal 15-valent Conjugate Vaccine (Diphtheria CRM ₁₉₇ Protein) †	0.5 mL dose sterile liquid formulation for intramuscular injection	Store refrigerated 2-8°C Protect from light Do not freeze
PREVNAR® Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM ₁₉₇ Protein) *†	0.5 mL dose sterile solution for intramuscular injection	Store refrigerated 2-8°C Do not freeze

* Vaccine provided for Adult stage

† Vaccine provided for Toddler stage

3.6.2 Packaging Information

V114 adjuvanted and non-adjuvanted: Individual doses will be supplied as open-labeled single-dose syringe kits. Supplies will be affixed with a clinical label in accordance with regulatory requirements.

Prevnar™: Individual doses will be supplied as ten unit market packs. The market pack will be affixed with a clinical label in accordance with regulatory requirements. Individual syringes within the market pack will not contain a clinical label.

3.6.3 Clinical Supplies Disclosure

This study is blinded; however, unblinded site personnel will dose the subject. Therefore, clinical vaccine will be supplied as open-label. Drug identity is included in the label text.

Vaccines will be provided with blinded envelopes containing drug disclosure information. The SPONSOR will provide one sealed envelope to the investigator for each allocation number.

Disclosure envelopes must be received by a designated person at the study site and kept in a secured location to which only the investigator and designated assistants have access. The envelope should be opened only in the case of an emergency if the drug/vaccine identification information is necessary for the welfare of the subject/patient. Every effort should be made not to unblind the subject/patient unless necessary. Prior to unblinding, the investigator will attempt to contact the clinical research associate (CRA). Any unblinding that occurs at the site must be documented and the unblinded envelope retained at site. At the end of the study, all disclosure envelopes (sealed and unsealed) are to be returned to the SPONSOR.

3.6.4 Storage and Handling Requirements

Please see Product Description Table (Table 3-4). The storage conditions will be indicated on the vaccine label.

Study vaccine should be stored in a limited-access area. Blinded study personnel should not have access to study vaccine; as drug identity is included in the label text. The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range as specified on the label or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

Vaccine supplies will be shipped to the sites refrigerated. Upon receipt at the investigational site, the vaccine should be removed from the outer secondary shipping box and placed immediately into the refrigerator and stored according to the labeled storage instructions.

A temperature monitoring device is included with each refrigerated shipment. The device must be de-activated upon receipt of the shipment. Directions for de-activation are specified in the Temp Tale Form (*Instructions to Site*), which are enclosed with each shipment. The temperature monitoring device will indicate whether the shipment has remained within the specified temperature range during transit. **If the monitoring device is in alarm upon receipt, immediately notify the SPONSOR (Clinical Research Associate [CRA]) and store the product at 2-8°C until instructed otherwise.** Return the temperature monitoring device according to instructions accompanying the shipment.

If the refrigerator in which the study vaccine is stored deviates from the 2°C to 8°C (35.6°F to 46.4°F) range, study vaccinations should be suspended and the SPONSOR (CRA) should be contacted immediately. Vaccine must NOT be frozen.

It is strongly recommended that a non-frost free laboratory grade refrigerator is used to store the study vaccine. This type of refrigerator is less likely to have wide temperature fluctuations, so it will be more likely to stay within the 2°C to 8°C (35.6°F to 46.4°F) temperature range. A daily refrigerator temperature log must be maintained at the site. The refrigerator must be equipped with an appropriately calibrated min/max thermometer and/or circular chart temperature recorder. The temperature log will be reviewed by the CRA throughout the study. An appropriate back up system (i.e. alarm, generator) and study site personnel telephone numbers should be in place in the event of a refrigerator failure.

3.6.5 Standard Policies / Return of Clinical Supplies

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be administered only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount administered to the subjects, and the amount remaining at the conclusion of the study. The CRA should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all unused clinical supplies must be returned as indicated in the SPONSOR Contact Information. Partial or empty vaccine vials should be properly discarded as biohazardous waste. U.S. sites should follow instructions for the Clinical Supplies Return Form and contact your SPONSOR representative for review of shipment and form before shipping. Sites outside of the United States should check with local country Merck personnel for appropriate documentation that needs to be completed for vaccine accountability.

3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens for this protocol will be provided in the Administrative Binder.

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

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 Institutional Review Board, Ethics Review Committee, 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.

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time. ("HIPAA").

4.1.3 Confidentiality of Investigator Information

For All Studies

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site

personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the SPONSOR, and subsidiaries, affiliates and agents of the SPONSOR, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

For Multicenter Studies

In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 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 Good Clinical Practice; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study,

provide all data, and upon completion or termination of the clinical study submit any other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

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

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency 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.

In the event the SPONSOR prematurely terminates a particular trial site, the SPONSOR will promptly notify that site's IRB/IEC.

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. in the United States for

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

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, <http://clinicaltrials.gov/>. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

4.6 PUBLICATIONS

As this study is part of a multicenter trial, publications derived from this study should include input from the investigator(s) and SPONSOR personnel. Such input should be reflected in publication authorship, and whenever possible, preliminary agreement regarding the strategy for order of authors' names should be established before conducting the study. Subsequent to the multicenter publication, or 24 months after completion of the study, whichever comes first, an investigator and/or his/her colleagues may publish the results for their study site independently. However, the SPONSOR does not recommend separate publication of individual study site results due to scientific concerns.

The SPONSOR must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication guidelines.

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