Official Protocol Title:	A Phase II, Double-Blind, Randomized, Multicenter Trial to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Compared to Prevnar 13™ in Healthy Infants
NCT number:	NCT02987972
Document Date:	15-SEP-2016

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TITLE:

A Phase II, Double-Blind, Randomized, Multicenter Trial to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Compared to Prevnar 13™ in Healthy Infants

IND NUMBER: 14115
EudraCT NUMBER: 2016-001117-25

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
4.2.3.3	Exploratory Biomarker Research	Section 4.2.3.2 Exploratory Biomarker Research was removed.	This section was removed as it is not applicable to this study. This section was inadvertently included in the initial protocol.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.2.3.1	Immunogenicity Endpoints	#3 and #4 were removed	They are not trial immunogenicity endpoints
7.1.1.8.2	Concomitant Vaccinations	The following sentence was added: "Combination MMRV vaccines should not be given in this study; however, MMR and Varicella vaccines are permitted if administered concomitantly in 2 separate limbs."	Statement was inadvertently left out of previous version of the protocol.
7.1.3.2	Blood collection for Immunogenicity Assays	"pneumo-specific" was added and "to all 15 vaccine serotypes included in V114" was removed.	To ensure that all necessary serotypes will be tested
7.1.3.3	Future Biomedical Research Samples	"which would routinely be discarded after the main study is over" was removed.	Incorrect sentence in the context of V114 development.

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Safety/Immunogenicity of Different Lots of V114 vs. Prevnar 13™ in Infants
Sponsor Product Identifiers	V114 Generic name not yet assigned
Trial Phase	II
Clinical Indication	Prevention of pneumococcal disease
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Intramuscular
Trial Blinding	Double-blind
Vaccination Groups	Subjects will be randomly assigned to receive V114 Lot 1, V114 Lot 2, or Prevnar 13™ (control). See Section 5.2 for a detailed description of the V114 lots).
Number of trial subjects	Approximately 1,050 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 2 years from the time that written informed consent is provided for the first subject until the last subject's last study-related phone call or visit. For purposes of analysis and reporting, the overall trial ends when the Sponsor receives the last serological results.
Duration of Participation	Each subject will participate in the trial for approximately 11 to 14 months from the time the parent/legal guardian signs the informed consent form (ICF) through the final contact. Each subject will receive 4 doses of the trial vaccine given at approximately 2, 4, 6, and 12 to 15 months of age. After each vaccination, the trial subject will be observed for 30 minutes and followed for 14 days for injection site and systemic adverse events (AEs). Serious adverse events (SAEs) will be collected from the time the consent form is signed through 30 days post-dose 4 (PD4) and/or completion of the subject's participation in the trial, see Section 7.2 for details. Blood samples will be collected 1 month following dose 3, immediately prior to dose 4, and 1 month following dose 4.

Randomization Ratio	1:1:1

A list of abbreviations used in this document can be found in Section 12.4.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, randomized, double-blind trial to evaluate the safety, tolerability, and immunogenicity of 2 different lots of V114 in healthy infants to be conducted in conformance with Good Clinical Practices (GCPs). Prevnar 13™ (pneumococcal 13-valent conjugate vaccine [diphtheria CRM_{197} protein], Wyeth Pharmaceuticals, Inc., Philadelphia, Pa) will serve as the active control. This trial will enroll approximately 1,050 healthy infants 6 to 12 weeks (≥42 to ≤90 days) of age. Subjects will be randomly assigned to receive V114 Lot 1 (n=350), V114 Lot 2 (n=350) or Prevnar 13™ (n=350). (See Section 5.2 for a detailed description of the V114 lots).

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

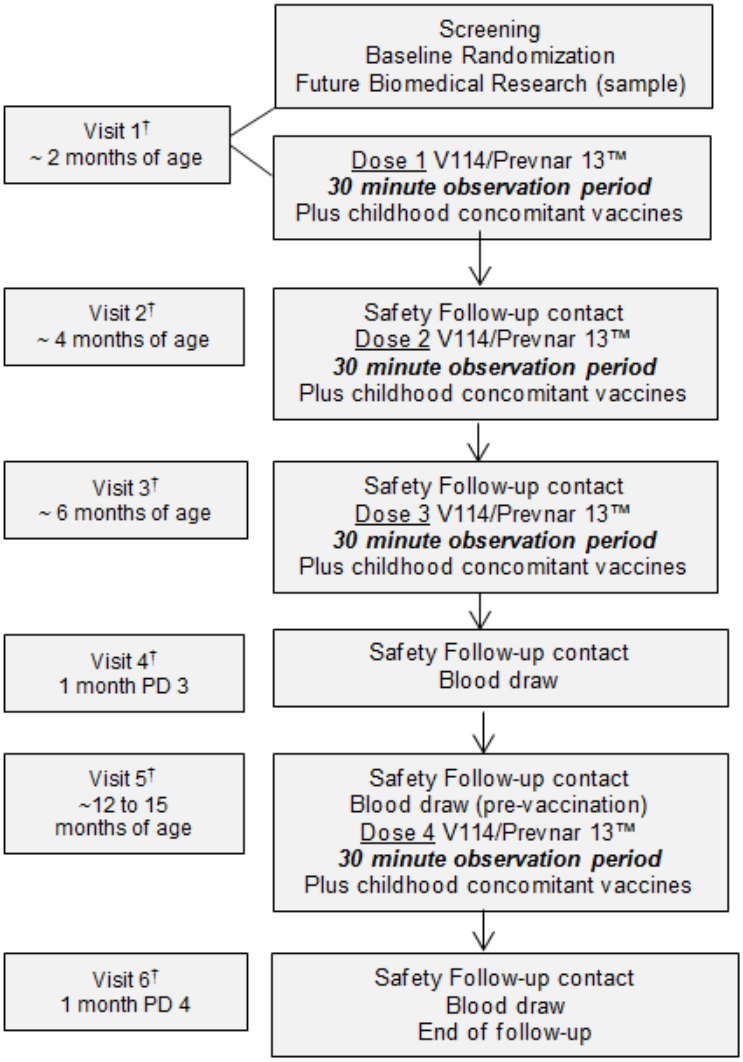
The safety and tolerability profile of V114 will be carefully monitored throughout the trial by both the SPONSOR in accordance with standard procedures and by an external Data Monitoring Committee (eDMC). (Details regarding in-house blinding of SPONSOR personnel can be found in Section 5.2.3. 'Trial Blinding').

Any trial subject with a serotype-specific anti-pneumococcal immunoglobulin G (IgG) value, as measured by pneumococcal electrochemiluminescence (Pn ECL) assay below 0.35 µg/mL for serotype 19A (individually) or below 0.35 µg/mL for 4 or more of the other serotypes in common with Prevnar 13™ at 1 month post-dose 3 (PD3) will be discontinued from the study and offered an additional dose of licensed pneumococcal conjugate vaccine outside of this protocol. See Section 5.6 (Rescue Medications & Supportive Care) for additional details of the rescue plan.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is shown in Figure 1.



†Refer to Protocol Section 6.0 Trial Flow Chart for acceptable age ranges and/or visit windows

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In healthy infants receiving one of the 2 V114 lots or Prevnar 13™ at approximately 2, 4, 6, and 12-15 months of age:

1. **Objective:** To describe the safety and tolerability profiles of 2 different lots of V114 [Lot 1 (V114-1), Lot 2 (V114-2)], after each dose.

2. **Objective:** To demonstrate that V114 (either V114-1 or V114-2) is non-inferior to Prevnar 13™ for the 13 shared serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), based on the proportion of subjects meeting serotype-specific immunoglobulin G (IgG) threshold value of ≥0.35 µg/mL at 1 month post-dose 3 (PD3).

   Hypothesis: The proportion of subjects receiving V114 (either V114-1 or V114-2) who have serotype specific IgG ≥0.35 µg/mL, as measured by the Pn ECL assay, for each of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F at 1 month PD3 is non-inferior to that for recipients of Prevnar 13™.

   [The statistical criterion for non-inferiority corresponds to the lower bound of the adjusted 95% CI of the proportion difference (V114 minus Prevnar 13™) being greater than -0.15 for each of the 13 shared serotypes.]

3. **Objective:** To evaluate the serotype-specific IgG geometric mean concentrations (GMCs) of V114-1, V114-2, and Prevnar 13™, and the IgG GMC ratios between each of the two V114 lots and Prevnar 13™ for all 15 serotypes included in V114 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) at 1 month PD3.

3.2 Secondary Objective(s) & Hypothesis(es)

1. **Objective:** To evaluate the serotype-specific IgG GMCs of V114-1, V114-2, and Prevnar 13™, and the IgG GMC ratios between each of the two V114 lots and Prevnar 13™ for all 15 serotypes included in V114 at pre-dose 4 and 1 month post-dose 4 (PD4).

3.3 Exploratory Objective(s)

1. To evaluate the serotype-specific IgG response rates of V114-1, V114-2, and Prevnar 13™, and the differences in IgG response rates between each of the two V114 lots and Prevnar 13™ for the 2 serotypes unique to V114 (22F and 33F) at 1 month PD3 and all 15 serotypes included in V114 at pre-dose 4 and 1 month PD4. The serotype-specific IgG response rate will be based on the proportion of subjects achieving serotype-specific IgG ≥0.35 µg/mL as measured by the Pn ECL assay.
2. To describe the proportions of subjects with opsonophagocytic killing activity (OPA) titer ≥8 and OPA geometric mean titers (GMTs) as measured by MOPA-4 assay in subjects receiving V114-1, V114-2, and Prevnar 13™ for all 15 serotypes included in V114 at 1 month PD3, pre-dose 4, and 1 month PD4.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on V114.

4.1.1 Pharmaceutical and Therapeutic Background

The investigational Merck pneumococcal conjugate vaccine, hereafter referred to as V114, is a 15-valent conjugate vaccine that contains all 13 pneumococcal serotypes contained in Prevnar 13™ (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F), and 2 additional pneumococcal serotypes (22F, 33F). The pneumococcal serotypes contained in V114 will provide broader coverage of the current leading serotypes associated with pneumococcal disease worldwide. The vaccine is designed to meet continuing medical and public health global needs for pneumococcal conjugate vaccines as well as to address the emergence of pneumococcal disease caused by serotypes not contained in currently licensed pneumococcal conjugate vaccines. The pneumococcal serotype composition of V114 is based on the need to maintain coverage of the serotypes included in Prevnar 13™, and to add serotypes guided by current epidemiology data and emerging trends [1].

Streptococcus pneumoniae (pneumococcus) is a major worldwide cause of morbidity and mortality and is responsible for more than half of all community-acquired pneumonia (CAP), otitis media, bacteremia and meningitis cases [2]. Bacteremia and meningitis are referred to as invasive pneumococcal disease (IPD). In 2006, the World Health Organization (WHO) estimated that pneumococcus caused the deaths of at least 1.5 million people annually [2]. In 2009, pneumococcus accounted for over 1 million deaths in children <5 years of age, mostly in developing countries [3, 4].

Three licensed pneumococcal conjugate vaccines have been licensed since 2000. The 7-valent Prevnar™, conjugated to diphtheria toxoid mutant (PCV7-CRM_{197}) was first licensed and introduced into national childhood vaccination schedules in the US, European Union (EU), and several other countries. Since then, a 10-valent (PCV10), and a 13-valent (PCV13-CRM_{197}) pneumococcal conjugate vaccine have also been licensed. PCV13-CRM197 was approved in the EU in 2009, the US in 2010, and subsequently in other countries worldwide. The vaccine is licensed globally as Prevnar 13™ and Prevenar 13™, and in this protocol the vaccine will be referred to by the name Prevnar 13™. In 2009 PCV10 marketed as Synflorix™ (pneumococcal 10-valent conjugate vaccine [Non-Typeable *Haemophilus influenzae* (NTHi) protein D, diphtheria or tetanus toxoid conjugates], GlaxoSmithKline Biologicals s.a., Rixensart, Belgium) was licensed in Europe and other countries worldwide. Synflorix™ contains the serotypes contained in Prevnar™ conjugated to 3 different carrier proteins, plus 3 additional capsular polysaccharide conjugates (serotypes 1, 5, and 7F). This vaccine is currently not licensed in the US. According to the US pediatric vaccination schedule, licensed PCV is administered to infants in a 3-dose infant primary series (at approximately 2, 4, and 6 months of age), followed by a toddler (fourth) dose at age 12 to 15 months of age.

PCV7 was highly effective in preventing invasive pneumococcal disease (IPD) caused by the serotypes included in the vaccine in children targeted for the vaccine [5], in providing moderate protection against pneumococcal acute otitis media (AOM) [6] and pneumonia [7]. Widespread use of PCV7 also decreased transmission of pneumococcal disease caused by vaccine serotypes in individuals not targeted by the vaccination program [8, 9]. PCV10 and PCV13 were licensed on the basis of immunogenicity and reactogenicity profiles comparable with that of PCV7. Despite the above mentioned public health benefits of PCV7 [10], serotype replacement emerged as an important public health concern as new serotypes begin to fill the niche created by the suppression of nasopharyngeal colonization of vaccine serotypes [11]. In the US, serotype 19A was, for instance, a leading causative pneumococcal serotype of IPD and respiratory disease several years ago [12, 13]. More recently, IPD cases caused by serotypes 22F and 33F, the 2 additional serotypes contained in V114 (not contained in Prevnar 13™) have also increased. Although only contributing for 1.2% of all IPD cases in US children under 5 years of age in 1998-1999 [14], IPD caused by these 2 serotypes increased to approximately 9.6% and 29% of IPD cases by 2006-2007 and 2011, respectively [15]. This phenomenon of serotype replacement substantiates the need for the development of more broadly-based pneumococcal conjugate vaccines.

4.1.2 Pre-clinical Trials

Preclinical immunogenicity studies of V114 formulations have been conducted in 2 animal models (refer to the V114 IB).

4.1.3 Clinical Trials

Several clinical trials of a single dose (toddlers, young and older adults) and 4-dose series (infants) of V114 have been conducted to evaluate the safety and immunogenicity of various formulations of V114 containing different amounts of pneumococcal polysaccharide and aluminum adjuvant. Trial results showed that V114 displays an acceptable safety profile and induces serotype-specific antibodies (IgG and OPA) to all 15 serotypes included in the vaccine (See IB for additional information).

4.1.4 Information on Other Trial-Related Therapy

In this trial, Prevnar 13™ will be administered as one of the trial vaccines, to serve as the active comparator. In addition to the administration of trial vaccine (V114 or Prevnar 13™), other pediatric vaccines will be administered concomitantly according to the recommended schedule for sites in the United States and according to local, regional, and/or country guidelines outside of the United States.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Safety and immunogenicity of several formulations of V114 containing different concentrations of pneumococcal capsular polysaccharide and aluminum adjuvant were evaluated in small Phase I/II clinical trials involving a small number of adults and infants. The leading formulation displaying acceptable safety profile and optimal immune responses in these studies will be evaluated in a larger number of infants in V114-008. This trial is designed to select the optimal quality attributes of the vaccine contained in either V114 lot to be tested in subsequent phases of V114 clinical development. The trial will enroll healthy infants at approximately 2 months of age, consistent with current recommendation of routine vaccination with PCV in early childhood.

4.2.2 Rationale for Dose Selection/Regimen

[redacted]

4.2.2.1 Rationale for the Use of Comparator

Placebo-controlled clinical studies, for new PCVs, are no longer feasible given the proven clinical efficacy and widespread use of licensed pneumococcal conjugate vaccine worldwide. Prevnar 13™ is currently the only recommended vaccine for the prevention of pneumococcal disease in infants in the US and is also used in many other countries worldwide. It will be used as the active comparator in this trial.

4.2.3 Rationale for Endpoints

4.2.3.1 Immunogenicity Endpoints

Serum will be collected at 3 pre-specified time points during the trial:

1) Approximately 1 month PD3
2) Pre-dose 4
3) Approximately 1 month PD4

Sera will be used for the following measurements:

(1) IgG responses using the Pn ECL assay.

(2) Functional antibody activity, OPA, will be measured using the MOPA-4 assay in the first 50% of infant subjects enrolled at US investigator sites who have sufficient serum volume at PD3 to perform both the PnECL and MOPA-4 assays. OPA will be conducted at Pre-Dose 4 and PD4 for all of the subjects who had OPA performed at PD3 and for which there is sufficient volume.

There are two primary immunogenicity endpoints in this trial:

(1) The serotype-specific IgG responses (proportion of responders achieving IgG reference level of ≥0.35 μg/mL) induced by V114-1, V114-2, and Prevnar 13™, by Pn ECL assay at 1 month following receipt of the third dose of the trial vaccine for the 13 serotypes shared with Prevnar 13™.

The use of the ≥0.35 μg/mL threshold value has been recommended as an acceptable threshold value for evaluating the clinical performance of pneumococcal conjugate vaccines [16], [17].

(2) The IgG GMCs for all 15 serotypes included in V114 at 1 month post-dose 3.

Other immunogenicity endpoints include:

(1) The serotype-specific responses for V114-1, V114-2, and Prevnar 13™, based on IgG GMCs by Pn ECL assay immediately prior (pre-dose 4) and 1 month following receipt of the fourth dose of the study vaccine for all 15 serotypes included in V114.

(2) The serotype-specific responses for V114-1, V114-2, and Prevnar 13™, based on the proportion of subjects meeting the serotype-specific threshold value of ≥0.35 μg/mL by Pn ECL assay at 1 month following receipt of the third dose of the study vaccine for the two serotypes unique to V114, and immediately prior (pre-dose 4) and 1 month following receipt of the fourth dose of the study vaccine for all 15 serotypes included in V114.

Functional antibody activity, OPA, will also be evaluated in approximately 50% of infants enrolled at US study sites with sufficient serum available at PD3 to perform both the Pn ECL assay and the OPA testing on all 15 serotypes in V114. Pre-dose 4 and PD4 OPA measurements will be conducted for all of the subjects who had PD3 OPAs performed and for which there is sufficient serum. The proportion of subjects meeting OPA titer ≥8 and the OPA GMTs at PD3 and separately at pre-dose 4 and PD4 will be summarized for each serotype.

Primary immunogenicity endpoints for the comparison of pneumococcal conjugate vaccines in children are based on immunoglobulin (IgG) antibodies responses. Such responses are consistent with the recommendations from the World Health Organization (WHO) and many regulatory agencies worldwide and include serotype-specific measurements of the following endpoints: a) the proportion of subjects achieving IgG antibody concentrations ≥0.35 μg/mL four weeks after third dose; and b) the IgG geometric mean antibody concentration (GMC) measured 4 weeks after the third and fourth doses. For new serotypes not included in licensed pneumococcal conjugate vaccine used as comparator, non-inferiority comparisons are made to the lowest response rate observed to any vaccine serotype among recipients of the licensed vaccine.

4.2.3.2 Safety Endpoints

Adverse events (AEs) will be documented on a validated vaccination report card (VRC). The VRC was developed to be administered electronically via a hand-held device. All AEs will be assessed for intensity.

1. Trial subjects will be observed for 30 minutes postvaccination for any immediate AEs.
2. Solicited injection-site AEs (redness, swelling, hard lump, and pain/tenderness) and solicited systemic AEs (irritability, drowsiness, hives/welts, and appetite lost) will be collected Day 1 to Day 14 after each vaccination.
3. Any other unsolicited systemic or injection-site AEs will be collected Day 1 to Day 14 after each vaccination.
4. Serious AEs will be collected from the time the consent form is signed through 30 days PD4 and/or completion of the subject's participation in the trial. Refer to Section 7.2.2.1 for complete detail on serious AE data collection.
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 postvaccination.

The 14-day safety follow-up period for AEs occurring following receipt of each dose of the trial vaccine is consistent with other clinical trials evaluating the safety of licensed pneumococcal conjugate vaccines in healthy infants.

Safety Monitoring

Safety and tolerability profiles will be carefully monitored throughout the trial by the SPONSOR in accordance with standard procedures and also by an external Data Monitoring Committee (eDMC). Please see Section 7.3.2 Data Monitoring Committee for details regarding the composition, roles and responsibilites of the eDMC.

In order to evaluate the safety profile of V114 in infants, VRC-prompted injection-site adverse events (redness, swelling, hard lump [rated by size] and pain/tenderness) and VRC-prompted systemic adverse events (irritability, drowsiness, appetite lost, hives/ welts) will be recorded for 14 days. If a hard lump at the injection site is present for 72 hours, the subject's parent/legal guardian should immediately contact the site to schedule an appointment with the trial site for an evaluation within 48 hours, where the trial doctor will diagnose the injection-site reaction (e.g., induration or nodule). If hives/welts (urticaria) occur, the subject's parent/legal guardian should immediately contact the site to schedule an appointment with the trial site for an evaluation within 48 hours, where the trial doctor will determine whether the hives/welts represent an urticarial-like eruption. Unsolicited systemic or injection-site adverse events or serious adverse events will be collected from Day 1 through Day 14 after each vaccination. Serious adverse events (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 trial at 30 days after the last dose of trial vaccine will be collected (see Section 7.2 for details). Any immediate adverse events occurring in the 30 minutes postvaccination observation period will be recorded. Information about any medications, including any analgesic/antipyretic use on the day of

vaccination that the subject receives, should be documented throughout the trial on the VRC for the 14-day safety follow-up period following each vaccination.

4.2.3.3 Future Biomedical Research

[redacted]

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from vaccination during participation, as clinical trials are designed to provide information about the safety and efficacy of an investigational medicine.

A subset of subjects will receive Prevnar 13™ which is the standard of care and is serving as the active comparator in this trial. V114 is aimed at providing comparable immune responses to Prevnar 13™ for the shared serotypes while providing additional coverage for the 2 serotypes (22F and 33F) unique to V114. It is unknown if the investigational V114 will have the same benefit as Prevnar 13™. As a possible rescue medication in this trial, subjects who fail to achieve adequate immune responses to serotype 19A (individually) or to 4 or more other serotypes in common between Prevnar 13™ and V114 following the third dose of trial vaccine will be offered an additional dose of licensed pneumococcal conjugate vaccine as soon as possible after serology results are available. (See Section 5.6 Rescue Medications & Supportive Care for additional details).

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Healthy male and female infants approximately 2 months of age (between 42 and 90 days old) (inclusive) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be healthy (based on medical history and physical examination) male or female infant approximately 2 months of age (42 days to 90 days), inclusive.
2. Have a parent/legal guardian who understands the trial procedures, alternate treatments available, and risks involved with the trial.
3. Have a parent/legal guardian who is able to read, understand, and complete the VRC and voluntarily agree to participate by giving written informed consent.
4. A parent/legal guardian also acknowledges that they:
    a. will attend all scheduled visits
    b. comply with the trial procedures, and
    c. have access to a telephone.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

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

1. Had prior administration of any pneumococcal vaccine.
2. Has a known hypersensitivity to any component of the pneumococcal conjugate vaccine, or any diphtheria toxoid-containing vaccine.
3. *Had a recent febrile illness (rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) occurring within 72 hours prior to receipt of trial vaccine.
4. Has a known or suspected impairment of immunological function.
5. Has a history of congenital or acquired immunodeficiency (e.g. splenomegaly).
6. Has or his/her mother has a documented human immunodeficiency virus (HIV) infection.
7. Has or his/her mother has a documented hepatitis B surface antigen – positive test.
8. Has known or history of functional or anatomic asplenia.
9. Has a history of failure to thrive.

10. Has known or history of a coagulation disorder contraindicating intramuscular vaccination.
11. Has a history of autoimmune disease including systemic lupus erythematosus, anti-phospholipid syndrome, Behcet's disease, autoimmune thyroid disease, polymyositis and dermatomyositis, scleroderma, type 1 diabetes mellitus, and other autoimmune disorders.
12. Has a known neurologic or cognitive behavioral disorder, including encephalitis/myelitis, acute disseminating encephalomyelitis, pervasive development disorder, and related disorders.
13. *****Meets one or more of the following systemic corticosteroid exclusion criteria:
    - Has received systemic corticosteroids (equivalent of ≥ 2 mg/kg total daily dose of prednisone or ≥ 20 mg/d for persons weighing > 10 kg) for ≥ 14 consecutive days and has not completed this course of treatment at least 30 days prior to trial randomization.
    - Has received systemic corticosteroids within 14 days prior to the first dose of vaccine at randomization.
    - Is expected to require systemic corticosteroids within 30 days after each vaccination during conduct of the trial..
14. *****Has received other licensed non-live vaccines within the 14 days before receipt of first dose of trial vaccine.
15. *****Has received a licensed live virus vaccine within the 30 days prior to receipt of first dose of trial vaccine.
16. Had prior receipt of a blood transfusion or blood products, including immunoglobulins.
17. Has participated in another clinical trial of an investigational product before the beginning or anytime during the duration of the current clinical trial. Subjects enrolled in observational studies may be included; these will be reviewed on a case-by-case basis for approval by the SPONSOR.
18. Has a 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.
19. Cannot be adequately followed for safety according to the protocol plan.
20. Has a parent/legal guardian who is unlikely to adhere to trial procedures, keep appointments, or is planning to relocate during the trial.
21. Has any other reason that in the opinion of the investigator may interfere with the evaluation required by the trial.
22. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Vaccination(s)

The vaccines to be used in this trial are outlined below in Table 1.

Table 1 Trial Vaccinations

Trial Vaccines	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Vaccination Period	Use
V114-1 (Lot 1)	0.5 mL	1	Intramuscular injection[1]	Each subject will receive 4 doses of the trial vaccine given at approximately 2, 4, 6, and 12 to 15 months of age.	Investigational
V114-2 (Lot 2)	0.5 mL	1	Intramuscular injection[1]	Each subject will receive 4 doses of the trial vaccine given at approximately 2, 4, 6, and 12 to 15 months of age.	Investigational
Prevnar 13™	0.5 mL	1	Intramuscular injection[1]	Each subject will receive 4 doses of the trial vaccine given at approximately 2, 4, 6, and 12 to 15 months of age.	Active Comparator

[1]Each trial vaccine is to be injected into the deltoid muscle of the upper arm.

Trial vaccination (first dose of trial vaccine) will be given on the day of treatment allocation/randomization or as close as possible to the date on which the subject is allocated/assigned.

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

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.2 Timing of Dose Administration

Subjects must be afebrile for at least 72 hours prior to vaccination. In this trial, V114-1, V114-2, or Prevnar 13™ will be administered as an 0.5-mL intramuscular injection at Visit 1 (approximately 2 months of age [≥42 or ≤90 days of age]), Visit 2 (4 months of age to 1 day prior to 5 months of age), Visit 3 (6 months of age to 1 day prior to 7 months of age) and Visit 5 (12 months of age to 1 day prior to 16 months of age). The day of the first trial vaccination is considered Day 1 of the trial for each subject. Sites should confirm date of birth with subject's parent/guardian and ensure that the age of the subject on the date of vaccination falls within the appropriate age range for each vaccination visit. Subjects should be observed for 30 minutes following vaccination.

Other pediatric vaccines will be administered concomitantly on the same day as trial vaccine according to the recommended schedule. Concomitant oral vaccines may be administered prior to the trial vaccine and other injectable concomitant vaccines. Precautions must be taken to prevent choking during the administration of oral vaccines as aspiration of oral vaccines could occur if the baby is crying or is agitated after receiving the injectable vaccine. Concomitant injectable vaccines should be administered on the same day as trial vaccine and after the trial vaccine has been administered. To avoid any confounding results, non-trial injectable vaccines should not be administered in the same limb as trial vaccine.

5.2.3 Trial Blinding

A double-blind/masking technique will be used. V114 will be dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the vaccination or clinical evaluation of the subjects are unaware of the group assignments.

All other MRL employees directly involved with the conduct of this trial will remain blinded to the subject level treatment assignment, and will receive only group level summaries of immunogenicity and safety data from the analyses.

Note: Because the trial vaccine and Prevnar 13™ have a different appearance, a member of the trial site staff will be unblinded for the purpose of receiving, maintaining, and preparing/administering the trial vaccine. In order to avoid bias, the unblinded trial personnel will have no further contact with trial subjects for any trial-related procedures/assessments after administration of trial vaccines, which includes all safety follow up procedures. Contact between subjects and unblinded trial personnel after vaccination administration is strictly prohibited.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Vaccine Allocation

Randomization will occur centrally using an interactive response technology (IRT), which may consist of interactive voice response system / integrated web response system (IVRS/IWRS). There will be two V114 arms and one Prevnar 13™ arm. Subjects will be randomly assigned in a 1:1:1 ratio to one of the two V114 vaccination groups or control (Prevnar 13™), respectively.

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed and Prohibited)

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

Any concurrent medication or medical treatment must be recorded on the appropriate electronic case report form (eCRF). During the influenza season, it is anticipated that trial subjects 6 months of age and older may be given an influenza vaccine. Influenza vaccine should be administered either 14 days prior to or 30 days after the administration of the trial vaccine.

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

The trial vaccines (V114 and Prevnar 13™) will be administered at approximately 2, 4, 6, and 12 to 15 months of age. On the day of vaccination, it is important to record the use of any analgesic or antipyretic use on the VRC and appropriate eCRF.

Subjects should not receive systemic corticosteroids (equivalent of ≥2 mg/kg total daily dose of prednisone or ≥20 mg/d for persons weighing >10 kg for ≥14 consecutive days) starting from 14 days prior to vaccination through 30 days after each vaccination. Topical, ophthalmic and inhaled steroids are permitted.

Other pediatric vaccines will be administered concomitantly according to the recommended schedule. These concomitant non-trial vaccinations will be recorded on the appropriate eCRF.

Concomitant vaccines (oral or injectable) should be administered on the same day as trial vaccine. Concomitant oral vaccines may be administered prior to the trial vaccine and other injectable concomitant vaccines. Precautions must be taken to prevent choking during the administration of oral vaccines. Other pediatric injectable vaccines administered concomitantly should be given after the trial vaccine. To avoid any confounding results, non-trial injectable vaccines should not be administered in the same limb as trial vaccine. Documentation of which limb was used for the administration of trial vaccine should be recorded on the appropriate eCRF. As the trial is reporting injection-site AEs from the trial vaccine (and not from the concomitant vaccines), this information should also be recorded on the VRC to inform the parent/legal guardian of the appropriate limb to monitor for AEs ONLY related to the trial vaccine.

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

5.6 Rescue Medications & Supportive Care

Infant subjects who fail to achieve adequate serologic responses following the third dose of trial vaccine will be offered an additional dose of licensed pneumococcal conjugate vaccine outside of this protocol. Any trial subject with serotype-specific pneumococcal IgG (as measured by Pn ECL assay) below 0.35 µg/mL for serotype 19A (individually) or 4 or more serotypes in common between V114 and Prevnar 13™ at 1 month PD3, will be given one dose of licensed pneumococcal conjugate vaccine as soon as possible after serological results are available. All subjects who meet the rescue criterion must be discontinued from the trial prior to administering the additional dose of licensed pneumococcal conjugate vaccine. The discontinuation date should be the date the parent/legal guardian was notified of the child's meeting the rescue criterion. Adverse events or changes to medical history occurring after the 14 days of safety follow up for Dose 3 and the discontinuation should be reported in the database; no additional immunogenicity blood sample should be drawn. If an SAE occurs between the 14 days of safety follow up for Dose 3 and the discontinuation, that event must be reported. The serologic threshold value of 0.35 µg/mL was recommended by a WHO expert panel as an acceptable threshold value for evaluating the clinical performance of pneumococcal conjugate vaccines in infants [16], [17]. Adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

5.7 Diet/Activity/Other Considerations

No special dietary restrictions apply to this trial.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Vaccination

Discontinuation of vaccination does not represent withdrawal from the trial.

As certain data on clinical events beyond vaccination discontinuation may be important to the study, they must be collected until the end of the study, even if the subject has discontinued vaccination. Therefore, subjects who discontinue trial vaccination prior to completion of the vaccination will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.3 – Discontinued Subjects Continuing to be Monitored in the Trial. Subjects who discontinue after Visit 4 (due to lack of efficacy or other reasons) are not required to continue to be monitored and will not be requested to return for a final monitoring visit.

Subjects may discontinue treatment at any time for any reason or be dropped from vaccination at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from vaccination by the investigator or the Sponsor if vaccination is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at vaccination discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from vaccination but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue vaccination.
- The subject's treatment assignment has been unblinded by the investigator, Merck subsidiary or through the emergency unblinding call center.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the subject at unnecessary risk from continued administration of study drug/vaccine.

For subjects who are discontinued from vaccination but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.3 – Discontinued Subjects Continuing to be Monitored in the Trial for those procedures to be completed at each specified visit.

Discontinuation from vaccination is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart vaccination.

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or subject's legally acceptable representative withdraws consent from the trial.
- The subject is lost to follow-up.
- Any infant subject that fails to achieve adequate serologic responses, as described in Section 5.6, will be discontinued from the trial.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when written informed consent is provided for the first subject. The patient participation portion of the trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall trial ends when the Sponsor receives the last serology assay result.

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

The eDMC will be provided with the following stopping rules as guidance for temporarily halting or terminating the trial:

All serious adverse events will be reviewed by the eDMC chairperson. If any of the following events occurs, administration of trial vaccine will be temporarily discontinued until a thorough review of accumulated safety data is undertaken by the eDMC, the investigator, and /or the SPONSOR's representative. Early trial termination may result from this review.

- 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 trial;
- Event which in the opinion of the investigator and/or safety monitoring committee contraindicates further dosing of additional subjects.

Conclusions about the overall safety of the investigational product will otherwise be determined from any SAE and solicited systemic AEs with a severe intensity rating, regardless of relationship to vaccination. The relationship to trial vaccine is determined by the trial investigator.

The trial site and SPONSOR's personnel directly involved in the conduct of the trial will remain blinded as to the treatment allocation of the trial subject.

5.12 Subject Completion

A subject will be considered "completed" and reported as such on the appropriate eCRFs when he/she has received the required vaccinations and the final safety follow-up visit (Visit 6) has been completed.

6.0 TRIAL FLOW CHART

Visit Number:	1[,l]	2[a,l]	3[l]	4[l]	5[l]	6[l]
Visit Timing:	Age:~2 months DOSE 1	Age:~ 4 months DOSE 2	Age:~6 months DOSE 3	~1 month after Visit 3	Age:~12 to 15 months DOSE 4	~1 month after Visit 5
Visit Window[j]:	≥42 days of age to ≤90 days of age	4 months of age to 1 day prior to 5 months of age	6 months of age to 1 day prior to 7 months of age	28 to 42 days PD3	12 months of age to 1 day prior to 16 months of age	28 to 42 days PD4
Administrative Procedures						
Informed Consent[b]	X					
Informed Consent for Future Biomedical Research (FBR)[c]	X					
Inclusion/Exclusion Criteria	X					
Subject Identification Card	X					
Medical History	X					
Update Medical History (New condition not already recorded as medical history or adverse events)		X	X	X	X	X
Prior Medication[m]	X					
Concomitant Medication Review		X	X	X	X	X
Vaccination Allocation/Randomization in IRT[d]	X					
Trial Vaccine Administration[d]	X	X	X		X	
Childhood Vaccines[e]	X	X	X		X	
Provide Electronic Vaccination Report Card (VRC)	X					
Review VRC data[f]		X	X	X		X
Clinical Procedures/Assessments						
Full Physical Examination	X	X	X		X	
Obtain Temperature[g]	X	X	X		X	
30 Minutes Postvaccination Observation Period[k]	X	X	X		X	
Adverse event Monitoring[f]	X	X	X	X	X	X
Assess for Serious Adverse events[f]	X	X	X	X	X	X
Laboratory Procedures/Assessments						
Collect blood samples for immunogenicity assays (4-5 mL) [h,]				X	X[i]	X
Collect Buccal Swabs for Future Biomedical Research [c]	X					

a. For all vaccination visits (Visits 1, 2, 3 and 5), trial coordinator should review the electronic Vaccination Report Card (VRC) in the vendors database at 14 days postvaccination (0 to plus 5 day window) and call the parent/legal guardian if there is a need to address questions (document phone call in trial chart). The site will review VRC with parent/legal guardian at next visit.
b. Consent must be obtained prior to any trial procedures.
c. Informed consent for future biomedical research samples must be obtained before the collection of the buccal swab DNA samples. Buccal swab DNA samples for analysis should be obtained prior to the vaccination, on Day 1, on randomized subjects only, or at a later date as soon as the informed consent is obtained.
d. In order to avoid bias, the unblinded trial personnel will have no further contact with trial subjects for any trial-related procedures/assessments following administration of the trial vaccines. This includes all safety follow-up procedures. Contact between subjects and unblinded trial personnel after vaccination administration is strictly prohibited. The study vaccine should be removed from the refrigerator no more than 1 hour before vaccination and time of removal and time of vaccination should be noted in subject's chart.
e. Concomitant (or routine pediatric) vaccines are to be given according to recommended schedule. Any injectable concomitant vaccines provided at the visit must be given after the trial vaccine and in a separate limb, may be given during the 30-minute observation period, and do not require additional observation time. Concomitant oral vaccines may be administered prior to the trial vaccine and other injectable concomitant vaccine.
f. Adverse events (serious and non-serious) are to be reported from Day 1 to 14 days following each vaccination. Serious Adverse events are to be reported from treatment/randomization through 30 days following the last study vaccination.
g. Pre-vaccination temperatures taken by trial staff at Visits 1, 2, 3 and 5. Subjects who have febrile illness (rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) occurring at or within 72 hours of Visits 1, 2, 3 and 5 must be rescheduled. Parent/legal guardian to measure and record temperature per VRC instructions.
h. Leftover serum samples collected from the main trial will be stored for future use if the FBR consent is signed.
i. Collect blood prior to vaccination.
j. Day of first trial vaccination = Day 1 of trial. To calculate visit windows for subsequent trial vaccinations, confirm subject DOB and ensure the age of the subject will fall within the appropriate age range for each trial visit.
k. Start and stop time for the 30 minute post vaccination observation period must be noted in subject chart.
l. Subjects who discontinue the study early may be asked to return for a post-trial visit, see Section 7.1.5.3 for details.
m. Record prior medications taken by the subject within 30 days before first vaccination.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject's legally acceptable representative. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

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

A copy of the signed and dated consent form should be given to the subject's legally acceptable representative before that subject's participation in the trial.

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

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

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject's legally acceptable representative, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject's legally acceptable representative.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

The legally acceptable representative for each subject will be given a Subject Identification Card identifying the subject as a participant in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the legally acceptable representative for each subject with the Subject Identification Card immediately after written informed consent is provided. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained at baseline by the investigator or qualified designee. At all subsequent trial visits (Visit 2, 3, 4, 5, and 6) the investigator or qualified designee will record any condition not already recorded as baseline medical history or adverse events on the update medical history eCRF.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before first vaccination.

7.1.1.5.2 Concomitant Medications

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

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

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

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

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

7.1.1.8 Trial Compliance

7.1.1.8.1 Study Vaccination

All subjects will be given a card, at the time of screening, identifying them as participants in a research study. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

Unblinded study personnel not otherwise involved in the conduct of the study will prepare and administer the study vaccine. Unblinded study personnel should not have contact with subjects for any study-related procedures/assessments after administration of study vaccines, which includes all safety follow up procedures. Of note, all vaccine must be stored at 2°C to 8°C (35.6°F to 46.4°F). The syringes must remain refrigerated (2 to 8ºC) until the time of administration; study vaccine must be administered within one (1) hour of removal from the refrigerator or discarded and replaced via the IRT system.

Prior to administration of study vaccine (V114 Lot 1, V114 Lot 2, or Prevnar 13™), shake vigorously to obtain a homogenous white suspension. If appearance is otherwise, do not administer. Do not use the vaccine if it cannot be resuspended. Visual inspection of study vaccine for particulate matter and discoloration prior to administration should be completed. The study vaccine should not be used if particulate matter or discoloration is found. Partial or empty vaccine syringes should be properly discarded as biohazardous waste. Investigator sites should follow instructions for the Clinical Supplies Return Form and contact your SPONSOR representative for review of shipment and form before shipping.

All safety and immunogenicity assessments will be conducted by blinded personnel, and the subject or subjects' parents/guardians will be blinded to the study vaccine received by the study subject. Vaccination information, such as Component Identification Number and time of vaccination, must be recorded on the appropriate eCRF as per the Data Entry Guideline (DEG) instructions.

Subjects will be randomly assigned to 1 of 3 vaccination arms:

(1) V114 Lot 1

(2) V114 Lot 2

(3) Prevnar 13™

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

The vaccines should be administered at a 90° angle in the anterolateral thigh muscle using the provided syringes with the following needle length and gauge specifications[1] : 1 inch needle, 22 to 25 gauge for infants (2-6 months) and 1 to 1¼ inch needle, 22 to 25 gauge for toddlers (12 to 15 months). (See CDC Pink Book, Appendix D for additional details).

To ensure that parents do not become confused regarding the location of the study vaccine injection-site, Doses 1, 2, and 3 of the study vaccine are to be administered in the same limb (e.g., if the study vaccine is provided in the right thigh for dose 1, subsequent doses should also be provided in the right thigh). Dose 4 may be administered in the deltoid region instead of the thigh, at the discretion of the investigator[2]. If an abnormality (i.e., rash) is observed at the site where the previous dose of the study vaccine was administered, it is permissible to use the anterolateral muscle of the other limb to administer the following dose of the study vaccine. (See attachment, CDC Pink Book, Appendix D for additional details).

7.1.1.8.2 Concomitant Vaccinations

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

[1] Needles provided in Prevnar 13™ blister packages may also be used.

[2] Per investigator discretion, dose 4 can be administered in the deltoid muscle instead of the anterolateral thigh muscle; if given in the deltoid muscle, the needle length should be 5/8 to 1 inch (a 5/8 inch needle may be used only if the skin is stretched tight, subcutaneous tissue is not bunched, and injection is made at a 90-degree angle).

The study vaccines will be administered at approximately 2, 4, 6, and 12 to 15 months of age. Other pediatric vaccines will be administered concomitantly according to the mandated schedule in the site's country/region. These concomitant non-study vaccinations will be recorded on the appropriate eCRF. Combination MMRV vaccines should not be given in this study; however, MMR and Varicella vaccines are permitted if administered concomitantly in 2 separate limbs.

Concomitant vaccines (oral or injectable) should be administered on the same day as study vaccine. Concomitant oral vaccines may be administered prior to the study vaccine and other injectable concomitant vaccines. Precautions must be taken to prevent choking during the administration of oral vaccines. Concomitant injectable vaccines should be administered after the study vaccine. To avoid any confounding results, non-study injectable vaccines 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. As we are requesting the reporting of injection-site adverse experiences from the study vaccine (and not from the concomitant vaccines), this information should also be recorded on the VRC to inform the parent/legal guardian of the appropriate limb to monitor for adverse experiences ONLY related to the study vaccine.

During the influenza season, it is anticipated that trial subjects 6 months of age and older may be given an influenza vaccine. Influenza vaccine should be administered either 14 days prior to or 30 days after the administration of the trial vaccine.

7.1.1.9 Dispense Electronic Vaccination Report Cards

The vaccination report card was developed to be administered electronically via a hand-held device. This item was structured as recommended in the final FDA Patient Reported Outcome (PRO) Guidance. The investigator or delegate will train the subject's parent/legal guardian in the use of the electronic vaccination report card prior to dispensing it at Visit 1. Body temperatures, injection-site AEs, VRC-prompted systemic complaints, other complaints or illnesses, and medications will be recorded on the VRC throughout the study. The investigator or delegate will review the data captured on the VRC with the parent/legal guardian at Visit 2 through Visit 6.

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examinations

A full physical examination will be performed at Visits 1, 2, 3, and 5.. Any clinically significant abnormality will be recorded on the appropriate eCRF.

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

Findings related to the physical examinations should be documented in the subject chart/source documentation.

7.1.2.2 Temperature

Pre-vaccination rectal temperatures will be taken by trial staff at Visits 1, 2, 3, and 5. Subjects who have febrile illness (rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) occurring at or within 72 hours of Visits 1, 2, 3 and 5 must be rescheduled. Rectal is the preferred method of obtaining subject's temperature. Axillary (underarm) is an acceptable method but temperature needs to be confirmed by rectal measurement. 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. 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. Use of temporal or tympanic thermometers to collect temperature for this study is prohibited.

The subject's parent/legal guardian will be asked to record a rectal temperature reading on the VRC from Day 1 through Day 7 following each vaccination. Temperature measurement must be recorded in the VRC if fever is suspected during Day 8 through Day 14.

7.1.2.3 Assess Adverse Experiences

Study subjects will be observed for 30 minutes postvaccination for any immediate AEs. 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 eCRF. Instructions on completing the VRC will be reviewed with each study subject's parent/legal guardian. Injection-site and systemic AEs occurring Day 1 through Day 14 following each vaccination will be recorded by the subject's parent/legal guardian on the electronic VRC; this includes VRC-prompted injection-site AEs (redness, swelling, hard lump, and pain/tenderness) and VRC-prompted systemic AEs (irritability, drowsiness, appetite lost, hives or welts). See Section 7.2 for detailed information concerning the assessment and recording of AEs.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

There are no laboratory safety evaluations required by the protocol.

7.1.3.2 Blood Collection for Immunogenicity Assays

Subjects will have blood drawn (approximately 4-5 mL) at 3 time points: (1) approximately 1 month following the third study vaccination (PD3), (2) immediately prior to administration of the fourth study vaccination, and (3) approximately 1 month following the fourth study vaccination (PD4). Sera will be used to measure vaccine-induced pneumococcal-specific immune responses (IgG and opsonophagocytic killing activity [OPA]). These serum samples will be assayed using the Meso-Scale Discovery MSD Pn ECL assay, which was developed by Merck & Co., Inc. for the measurement of pneumococcal capsular polysaccharide IgG antibodies. Serum samples will also be assayed using a 4-Fold Multiplex Opsonophagocytic Assay which Merck has developed and implemented in collaboration with PPD PPD. If a serum sample does not have enough volume for both the IgG and OPA testing, the IgG testing will take priority. OPA will be evaluated in approximately 50% of subjects enrolled at US investigator sites with sufficient PD3 sera available to perform both the PnECL and the OPA testing on all 15 serotypes in V114. OPAs will be conducted at pre-dose 4 and at PD4 for all of the subjects who had PD3 OPAs performed and for which there is sufficient serum. Any remaining sera will be retained for future biomedical research (e.g., pneumococcal assay development) providing the future biomedical research (FBR) consent has been signed.

Pneumococcal Electrochemiluminescence (Pn ECL) Assay

The purpose of the Pn ECL assay is to detect serum IgG antibody to the pneumococcal polysaccharides (PnPs) serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, and 33F before and after vaccination with PnPs containing vaccine(s). The serotypes are assayed in a group of 7 (types 1, 5, 6A, 7F, 19A, 22F, 33F) and a group of 8 (types 3, 4, 6B, 9V, 14, 18C, 19F, 23F). Antibodies to these serotypes are measured in mass units (µg/mL) read from a standard curve prepared from a pool of adult serum, collected postvaccination with a PPV23 and referred to as 007sp.

The assay is based on the MSD™ technology which employs multi-spot microtiter plates fitted with a series of electrodes associated with the bottom of the well. Serotype-specific PnPs are spotted to the MSD™ plates and used as the solid phase antigen. Experimental, control, and standard curve sera are pre-adsorbed with pneumococcal cell wall polysaccharide (CPs) and non-vaccine heterologous serotype PnPs (types 25 and 72) to reduce the nonspecific antibody response in the assay, and subsequently incubated in the PnPs antigen-coated wells. Anti-PnPs, which bind to the solid phase PnPs, are subsequently detected with a ruthenium-labeled anti-human IgG conjugate. Plates are read by measure of the chemiluminescent signal emitted from the ruthenium tag upon electrochemical stimulation initiated at the electrode surfaces of the microplates. The intensity of the luminescence is directly proportional to the amount of anti-PnPs in the sample.

Standard curves are prepared from the human Pneumococcal Standard Reference Serum, 007sp (Center for Biologics Evaluation and Research, U.S. FDA). The following standard and controls are run in each assay: (a) a 12-point standard curve which includes a serum diluent blank and an 11-point, 2.5-fold dilution series of 007sp that begins with an initial dilution of 1:400; (b) two different dilutions (1:1000 and 1:10,000) of Giebink serum 16 (G16) and one dilution (1:1000) of Giebink serum 5 (G5), both individual human immune sera obtained after vaccination with PPV23 by [redacted]; (c) a serum sample from a previous Merck clinical trial tested at 1:10,000 dilution.

Clinical testing on the Pn ECL assay will be performed at Merck Research Laboratories (MRL) or its designated partners that are qualified to perform the assay.

Multiplex Opsonophagocytic Assay (MOPA-4)

The 4-Fold Multiplexed Opsonophagocytic Killing Assay for antibodies against *Streptococcus pneumoniae* (MOPA-4) is used to measure sera of patients vaccinated with multivalent pneumococcal vaccines for antibody titers (opsonic activity/killing) against the capsular polysaccharides for specific *S. pneumoniae* serotypes. The method is multiplexed permitting testing of 4 serotypes 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 MOPA-4. 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 (pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 18C, 19F, 22F, 23F, and 33F; strains 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 results are reported as the reciprocal of the dilution. The MOPA-4 was developed and published by [redacted].

Merck has been involved in the development and implementation of the MOPA-4 in collaboration with [redacted] and with [redacted] Both labs are qualified to generate clinical results and one of them will support MOPA-4 testing for this study.

Clinical testing on the MOPA assay will be performed at Merck Research Laboratories (MRL) or its designated partners that are qualified to perform the assay.

7.1.3.3 Future Biomedical Research Samples

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover serum samples collected in the main study.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from vaccination prior to completion of the vaccination regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Any infant subject fails to achieve adequate serologic responses, as described in Rescue Medications & Supportive Care Section 5.6, will be discontinued from the trial prior to administering the additional dose of licensed pneumococcal conjugate vaccine.

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.1.2 Failure To Return For Scheduled Visits and/or Unable to Contact The Subject

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

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.
- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

7.1.4.2 Subject Blinding/Unblinding

When the investigator or delegate needs to identify the vaccine used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a subject's treatment assignment, the investigator or delegate must enter the intensity of the adverse experiences observed, the relation to study vaccine, the reason thereof, etc., in the medical chart etc. Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study vaccine, but should continue to be monitored in the trial.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update vaccine disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Other trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded. Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study vaccine, but should continue to be monitored in the trial.

7.1.4.3 Domiciling

Infant subjects will report to the Clinical Research Unit (CRU) on the day of the administration of study vaccine (Visit 1, 2, 3, and 5) and remain in the unit for 30 minutes postvaccination. At the discretion of the investigator, subjects may be requested to remain in the CRU longer. Infants will return to the CRU at Visits 4 and 6 for blood draws.

7.1.4.4 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Refrigerators
- -20° freezers
- Centrifuges

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Screening procedures will be performed at Visit 1. A separate screening visit is not required.

7.1.5.2 Vaccination Visits

Subjects will be required to come to the clinic for 6 visits. See Section 6.0 for details.

7.1.5.3 Discontinued Subjects Continuing to be Monitored in the Trial

Subjects who discontinue from the trial after visits 1, 2, 3 or 5 (vaccination visits) but agree to continue to be monitored in the trial will be requested to return for a final monitoring visit. Subjects who discontinue after Visit 4 (due to lack of efficacy or other reasons) are not required to continue to be monitored and will not be requested to return for a final monitoring visit.

Subjects returning for a final monitoring visit will be required to return to clinic approximately 14 days after the last vaccination for the post-trial visit. The following will be completed at this visit: review of VRC data, and adverse event monitoring. If the post-trial visit occurs less than 14 days after the last vaccination, a subsequent follow-up phone call should be made at 14 days post the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. 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.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of allocation/randomization through 14 days (42 days for live attenuated vaccines) following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days (42 days for live attenuated vaccines) thereafter, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

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

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other serious criteria are met.

If a dose of Sponsor's product 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 adverse event using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Immediate Reporting of Adverse Events to the Sponsor

7.2.2.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

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

Refer to Table 2 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following the last study vaccination, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event 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 the Sponsor if the event is either:

1. A death that occurs prior to the subject completing the trial, but outside the time period specified in the previous paragraph.

or

2. A serious adverse event that is considered by an investigator who is a qualified physician to be vaccine related.

All subjects with serious adverse events must be followed up for outcome.

7.2.2.2 Events of Clinical Interest

There are no Events of Clinical Interest being collected in this trial.

7.2.3 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 2. The investigator's assessment of causality is required for each adverse event. Refer to Table 2 for instructions in evaluating adverse events.

Table 2 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities) **Injection site redness or swelling or hard lump from the day of vaccination through Day 14 post-vaccination will be evaluated by maximum size.**
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose that:	
	†**Results in death; or**	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event 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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements; **or**	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the test vaccine to be discontinued?	
Relationship to test vaccine	Did the test vaccine cause the adverse event? The determination of the likelihood that the test vaccine caused the adverse event 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 event 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 event:	
	Exposure	Is there evidence that the subject 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?
	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?
	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

Relationship to test vaccine (continued)	**The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)**	
	Dechallenge	(not applicable for vaccines)
	Rechallenge	Was the subject reexposed to the test vaccine in this trial? 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 trial is a single-dose vaccine trial.) 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, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial 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.		
Record one of the following:		**Use the following criteria as guidance (not all criteria must be present to be indicative of a vaccine relationship).**
Yes, there is a reasonable possibility of vaccine relationship.		There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to the administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause.
No, there is not a reasonable possibility of vaccine relationship		Subject did not receive the test vaccine OR temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)

7.2.4 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the eDMC regarding the trial.

7.3.2 Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor this trial at approximately 4 separate time points, two of which will only contain trial safety data. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.11.

Trial Design Overview	A Phase II, Double-Blind, Randomized, Multicenter Trial to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Compared to Prevnar 13™ in Healthy Infants
Treatment Assignment	This is a double-blind trial with three vaccination groups. Subjects will be randomized to V114 Lot 1 (V114-1), V114 Lot 2 (V114-2), and Prevnar 13™ with the ratio 1:1:1.
Analysis Populations	1. Immunogenicity: Per-protocol (PP). 2. Safety: All Subjects as Treated (ASaT)
Primary Endpoints	1. The proportion of subjects meeting serotype-specific IgG ≥0.35 µg/mL for the 13 serotypes shared with Prevnar 13™ measured by the Pn ECL assay at 1 month post-dose 3 2. The serotype-specific IgG GMC for all 15 serotypes included in V114 measured by the Pn ECL assay at 1 month post-dose 3
Secondary Endpoint	The serotype-specific IgG GMC for all 15 serotypes included in V114 measured by the Pn ECL assay at pre-dose 4 and 1 month post-dose 4.
Statistical Methods for Key Immunogenicity Analyses	To address the primary objective #2, a V114 formulation will be considered non-inferior to Prevnar 13™ if the lower bound of the two-sided 95% confidence interval (CI) of the between-treatment difference (V114 – Prevnar 13™) in the proportion of subjects with PD3 IgG ≥0.35 µg/mL for the 13 serotypes in common between V114 and Prevnar 13™ is > -0.15. The Miettinen and Nurminen approach [21] will be used. To address the primary objective #3, the within-group IgG GMC along with two-sided 95% CIs will be computed for all 15 serotypes included in V114. Additionally, GMC ratios (V114/Prevnar 13™) along with two-sided 95% CIs will be computed for each of the two V114 lots (V114-1 and V114-2) for all 15 serotypes included in V114. The 95% CI for the ratio will be calculated.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a three-tier approach. The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints include solicited injection-site adverse events (redness, hard lump, swelling, and pain/tenderness) and systemic adverse events (irritability, drowsiness, hives/welts, appetite loss) during Day 1 to Day 14 postvaccination. For Tier 1 safety endpoints (those adverse events specifically prompted for on the VRC), point estimates, risk differences with 95% CIs and corresponding p-values will be provided. Adverse events not defined as Tier 1 (specific terms as well as system organ class terms) will be classified as belonging to "Tier 2" or "Tier 3". Tier 2 parameters (adverse events that occur in at least 4 subjects in any vaccination group) will be assessed via point estimates and risk differences with 95% CIs; only point estimates by group will be provided for Tier 3 safety parameters. In this trial, temperatures collected from Day 1 through Day 7 will be treated as Tier 2 events.

Interim Analysis	An interim analysis of the immunogenicity will be performed in this trial when ~100% PD3 safety follow-up completed and ~100% PD3 immunogenicity results (IgG responses) are available. An internal statistician, statistical programmer, and clinical scientist not assigned to the protocol will be unblinded throughout the duration of the trial to perform the interim analysis. Group summaries of the IgG results will be reviewed by the project team; however, the project team will not be unblinded at the subject level. The Sponsor's trial team will use the results to make scientific decisions regarding future studies. It may also inform certain scientific consultations. The Haybittle-Peto rule [18][19] using 1-sided significance level of α=0.0005 will be utilized to account for the interim analysis. The final analysis will still be evaluated at a 1-sided significance level of α =0.025.
Multiplicity	The type I error for the primary immunogenicity analyses will be controlled at the one-sided significant level of 0.025 by testing hypotheses related to V114-1 and hypotheses related to V114-2 simultaneously using a Hochberg approach [20].
Sample Size and Power	Approximately 1050 subjects will be enrolled, with approximately 350 subjects in each of the three vaccination groups. There is >90% power to declare non-inferiority to Prevnar 13™ for the common serotypes and superiority for the non-common serotypes for at least one of the V114 lots based on the proportion of subjects meeting the serotype-specific IgG $\geq$0.35 µg/mL. This power assumes an 85% evaluability rate (~298 subjects per group), a non-inferiority margin of -0.15 in the difference (V114 – Prevnar 13™), and a serotype-specific true the response rate based on the group level results from the V114-003 CSR, the V114-004 interim analysis and the knowledge of the V114 formulation that will be used in this trial.

8.2 Responsibility for Analyses/In-House Blinding

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

This trial will be conducted as a double-blind trial without complete in-house blinding procedures. Section 5.2.3 specifies the roles and responsibilities of the site and Sponsor personnel who will be unblinded during the trial. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for trial treatment assignment. Randomization will be implemented using interactive response technology (IRT).

With the exception of the unblinded CRA who will monitor and reconcile the trial vaccine, all other MRL employees directly involved with the conduct of this trial will remain blinded to the subject's treatment assignment until medical/scientific review of all safety and immunogenicity data has been performed, protocol deviations have been identified, and data have been declared final and complete.

The planned interim analysis is described in Section 8.7. The results of interim analysis will not be shared with the investigators prior to the completion of the trial. Subject-level unblinding will be restricted to the internal unblinded statistician and unblinded statistical programmer performing the interim analysis. Group summaries will be reviewed by the Sponsor's trial team in order to make scientific decisions for future studies.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the trial are stated in Section 3.0.

8.4 Analysis Endpoints

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

8.4.1 Immunogenicity Endpoints

The primary immunogenicity endpoints include:

(1) The proportion of subjects with serotype-specific IgG ≥0.35 µg/mL measured by the Pn ECL assay at 1 month post-dose 3 for the 13 common serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F) between V114 and Prevnar 13™ in recipients of either lot of V114 and Prevnar 13™.

(2) The IgG GMCs for the 13 common serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F) between V114 and Prevnar 13™, and 2 serotypes unique to V114 (22F and 33F) in recipients of either lot of V114 and Prevnar 13™, based on the serotype-specific IgG responses as measured by the Pn ECL assay at 1 month post-dose 3.

The secondary and exploratory immunogenicity endpoints include:

(1) The proportion of subjects with serotype-specific IgG ≥0.35 µg/mL measured by the Pn ECL assay at 1 month post-dose 3 for the 2 serotypes unique to V114 (22F and 33F) in recipients of either lot of V114 and Prevnar 13™.

(2) The IgG GMCs for all 15 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, and 33F) in recipients of either lot of V114 and Prevnar 13™, based on the serotype-specific IgG responses as measured by the Pn ECL assay at pre-dose 4 and 1 month post-dose 4.

(3) The proportion of subjects with serotype-specific IgG ≥0.35 µg/mL measured by the Pn ECL assay at pre-dose 4 and 1 month post-dose 4 for the 13 common serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F) between V114 and Prevnar 13™, and 2 serotypes unique to V114 (22F and 33F) in recipients of either lot of V114 and Prevnar 13™.

(4) The proportion of subjects with serotype-specific OPA titer ≥8 and OPA GMTs as measured by the MOPA-4 assay at 1 month post-dose 3, pre-dose 4, and 1 month post-dose 4 for all 15 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F and 33F) in recipients of either lot of V114 and Prevnar 13™.

8.4.2 Safety Analysis Endpoints

Refer to Section 4.2.3.2 for the description of the safety measures in this trial.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs. Tier 1 events for this trial consist of the solicited injection-site and solicited systemic AEs.

8.5 Analysis Populations

8.5.1 Immunogenicity Analysis Populations

The Per-Protocol (PP) population will serve as the primary population for the analysis of immunogenicity data in this trial. The PP population consists of those subjects who are not considered as protocol violators. Violations include but are not limited to: failure to receive the scheduled doses [at least 28 days between doses 1 and 2 and between doses 2 and 3 (for PD3, Pre-dose 4, and PD4 PP analyses), and dose 4 at 12 months to 15 months of age (for PD4 PP analyses)] of correct clinical material, and lack of valid serology results available from 28 to 42 days following the dose being analyzed. The final determination on protocol violations will be made prior to unblinding of the database and will be documented in a separate memo.

The Full Analysis Set (FAS) population will also be used for supplementary analysis of the primary analyses. The FAS population consists of all randomized subjects who received at least one vaccination and have at least one serology result. Subjects will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data.

8.5.2 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this trial. The ASaT population consists of all randomized subjects who received trial vaccine. Subjects will be included in the group corresponding to the clinical material they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the group to which they are randomized. Subjects who receive incorrect clinical material will be included in the group corresponding to the clinical material actually received.

8.6 Statistical Methods

For immunogenicity analyses, unless otherwise specified, all statistical tests will be conducted at the α=0.05 (two-sided) level. Results that will be considered to be statistically significant (versus nominally significant) after consideration of the strategy for controlling type-I errors, are described in Section 8.8, Multiplicity.

8.6.1 Statistical Methods for Immunogenicity Analyses

The immunogenicity analyses will be conducted for each serotype separately.

For the primary hypothesis, a V114 lot will be considered non-inferior to Prevnar 13™ if the lower bound of the two-sided 95% confidence interval (CI) for the between-treatment difference (V114 - Prevnar 13™) in the proportion of subjects meeting serotype-specific IgG ≥0.35 µg/mL at 1 month post-dose 3 for the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A and 23F) in common between V114 and Prevnar 13™ is >-0.15 (15 percentage point non-inferiority margin). The proposed 15 percentage point provides adequate precision around the primary immunologic endpoints and greater confidence in predicting the outcome of the Phase III pivotal study. The Miettinen and Nurminen approach will be used.

The within-group IgG GMC along with two-sided 95% CIs will be computed for all 15 serotypes included in V114. Point estimates of GMCs are the exponentiated estimates of the mean natural log concentrations. The confidence limits for GMCs are the exponentiated confidence limits for the mean natural log concentrations, based on 1-sample t-distributions. Additionally, GMC ratios (V114/Prevnar 13™) along with two-sided 95% CIs will be computed for each of the two V114 lots (V114-1 and V114-2) relative to Prevnar 13™ for all 15 serotypes included in V114. The 95% CI for the ratio will be calculated using the t-distribution with the variance estimate derived from a linear model utilizing the log-transformed antibody titers as the response and a single term for vaccination group (including the subjects from both V114 lots and Prevnar 13™).

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

Table 3 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Objectives			
Proportion of subjects with PD3 IgG ≥0.35 µg/mL for the 13 common serotypes between V114 and Prevnar 13™	Non-inferiority of V114 compared with Prevnar 13™ , based on difference in percentages (Miettinen and Nurminen)	PP [Primary] FAS [Supportive]	Missing data will not be imputed
The PD3 IgG GMCs for all 15 serotypes included in V114	• Within-group GMCs and 95% CI • GMC ratio (V114/Prevnar 13™) and 95% CI (t-distribution with the variance estimate from a linear model including the subjects from both V114 lots and Prevnar 13™)	PP [Primary] FAS [Supportive]	Missing data will not be imputed
Secondary Objectives			
The pre-dose 4 and PD4 IgG GMCs for all 15 serotypes included in V114	• Within-group GMCs and 95% CI • GMC ratio (V114/Prevnar 13™) and 95% CI (t-distribution with the variance estimate from a linear model including the subjects from both V114 lots and Prevnar 13™)	PP	Missing data will not be imputed
GMC = Geometric Mean Concentration GMFR = Geometric mean fold rise from Day 1. PP = Per-protocol FAS = Full Analysis Set CI = Confidence interval			

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events. Comparisons will be made between the V114 lots and Prevnar 13™ following each dose, and across all doses as outlined below.

The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. For Tier 1 safety endpoints (those adverse events specifically prompted on the VRC), point estimates, risk differences with 95% CIs and corresponding p-values will be provided. Tier 2 parameters will be assessed via point estimates and risk differences with 95% CIs. These analyses will be performed using the Miettinen and Nurminen method. Only point estimates by group will be provided for Tier 3 safety parameters.

Tier 1 safety endpoints include solicited injection-site adverse events (redness, swelling, hard lump, and pain/tenderness) during Day 1 to Day 14 postvaccination, and solicited systemic adverse events (irritability, drowsiness, hives/welts, appetite loss) during Day 1 to Day 14 postvaccination.

Adverse events (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 vaccination group exhibit the event; all other adverse events will belong to Tier 3. In this trial, temperatures collected from Day 1 through Day 7 will be treated as Tier 2 events and will be summarized.

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

For this protocol, the broad clinical adverse event categories consisting of the percentage of subjects with any adverse event, a vaccine-related adverse event, with a serious adverse event, with an adverse event which is both vaccine-related and serious, and who died or discontinued due to an adverse event will be considered Tier 2 endpoints.

Table 4 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Comparison	Descriptive Statistics
Tier 1	Injection-site redness (Days 1 to 14)	X	X	X
	Injection-site swelling (Days 1 to 14)	X	X	X
	Injection-site pain or tenderness (Days 1 to 14)	X	X	X
	Injection-site hard lump (Days 1 to 14)	X	X	X
	Irritability (Days 1 to 14)	X	X	X
	Drowsiness (Days 1 to 14)	X	X	X
	Hives/welts (Days 1 to 14)	X	X	X
	Appetite loss(Days 1 to 14)	X	X	X
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 or SOCs‡ (incidence ≥4 of subjects in one of the vaccination groups)		X	X
	Body temperature (Day 1 to 7)		X	X
Tier 3	Specific AEs or SOCs‡ (incidence <4 of subjects in all vaccination groups)			X

† Adverse event (AE) references refer to both Clinical and Laboratory AEs.
‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
SOC=System Organ Class
X= results will be provided.

8.6.3 Summaries of Demographics and Baseline Characteristics

The comparability of the vaccination groups for each relevant demographic and baseline characteristic will be assessed by the use of summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects randomized and vaccinated, and the reasons for discontinuation (including subjects discontinued for meeting the rescue criterion), will be displayed by group. Demographic variables (e.g., age), prior and concomitant therapies and vaccines will be summarized by group.

8.7 Interim Analyses

An interim analysis of the immunogenicity will be performed in this trial when ~100% PD3 safety follow-up completed and ~100% PD3 immunogenicity results (IgG responses) are available.. Group summaries of the IgG results will be reviewed; however, the project team will not be unblinded at the subject level. The Sponsor's trial team will use the results to make scientific decisions regarding future studies. The conduct of this trial will not be altered by the interim analysis. The Haybittle-Peto rule using 1-sided significance level of $\alpha = 0.0005$ will be utilized to account for the interim analysis. The final analysis will still be evaluated at a 1-sided significance level of $\alpha = 0.025$.

The endpoints, timing, and purpose of the interim analysis are summarized in Table 5.

Table 5 Summary of Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
• Proportion of subjects with PD3 IgG ≥0.35 µg/mL for all 15 serotypes in V114 • The PD3 IgG GMCs for all 15 serotypes included in V114 • PD3 percentage of subjects with any AE, a vaccine related AE, a serious AE, and an AE which is both vaccine-related and serious, and who died or discontinued due to an AE.	~100% PD3 safety follow-up completed and ~100% PD3 immunogenicity results (IgG responses) are available	Inform scientific decisions for future studies

8.8 Multiplicity

Non-inferiority tests will be conducted for the 13 shared serotypes between V114 and Prevnar 13™. The overall success for each of the V114 lots requires demonstrating non-inferior to Prevnar 13™ for each of the 13 serotypes. This approach controls the overall type I error within each lot, therefore no multiplicity adjustment will be required within each lot.

The type I error for the primary immunogenicity analysis will be controlled at the one-sided significant level of 0.025 by testing V114-1 and V114-2 simultaneously using a Hochberg approach, which is summarized in Figure 2.

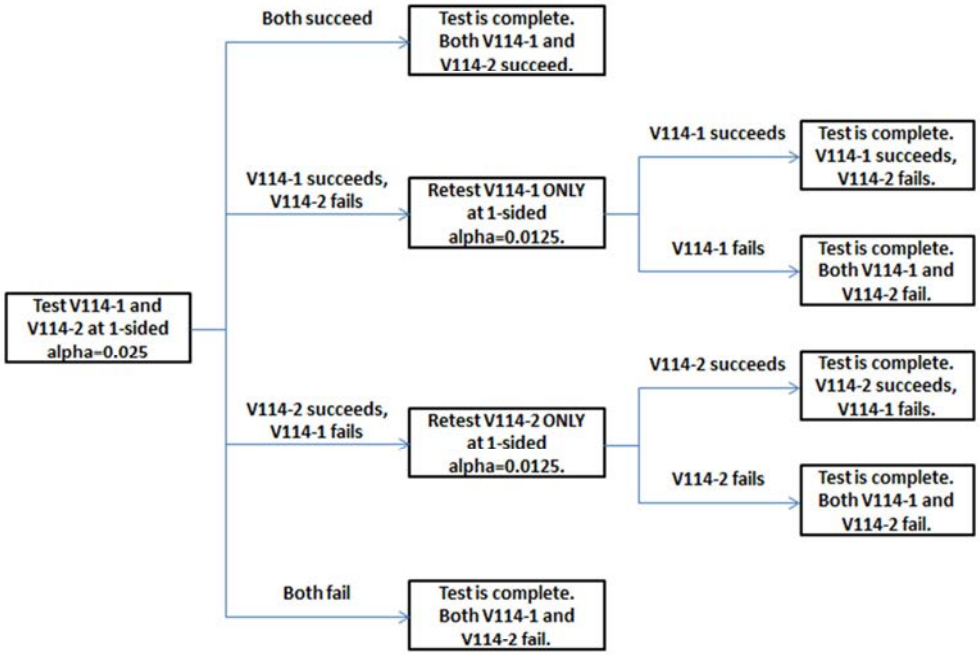


Figure 2 Diagram of the Multiplicity Adjustment

Both lots will first be tested using a 1-sided alpha of 0.025 respectively. If all tests for both lots are significant (p-value < 0.025) or at least one test for both lots is non-significant (p-value ≥ 0.025), testing is complete. However, if one lot is successful at the 1-sided alpha of 0.025 and the other is not, the successful lot will be re-tested at a more stringent 1-sided alpha of 0.0125 (0.025/2). The level of the confidence interval will align with the type I error during the re-testing procedure, i.e., the 97.5% CI will be provided if only one of the two lots succeeds. Testing in this manner controls the type I error for the primary immunogenicity analysis at the 1-tailed α=0.025.

The Haybittle-Peto rule using 1-sided significance level of α =0.0005 will be utilized to account for the interim analysis. The final analysis will still be evaluated at a 1-sided significance level of α =0.025 as described in Section 8.7.

No multiplicity adjustments will be made for the safety comparisons.

8.9 Sample Size and Power Calculations

8.9.1 Immunogenicity Analyses

Approximately 1050 subjects will be enrolled, with approximately 350 subjects in each of the three vaccination groups. For the primary immunogenicity hypotheses, the power is simulated based on the Hochberg approach. There is >90% power to declare non-inferiority to Prevnar 13™ for the 13 common serotypes between V114 and Prevnar 13™ and superiority for the two serotypes unique to V114 for at least one of the V114 lots based on the proportion of subjects meeting the serotype-specific IgG ≥0.35 µg/mL. This power assumes an 85% evaluability rate (~298 subjects per group), a non-inferiority margin of -0.15 for the difference (V114 – Prevnar 13™), and a serotype-specific true percentage of the response rate based on the group level results from the V114-003 CSR, the V114-004 interim analysis and the knowledge of the V114 formulation that will be used in this trial. Based on this knowledge, it was conservatively assumed that the true response rates of V114 will be 0.05 lower than that of Prevnar 13™ for serotypes 6A, 6B, and 19A, 0.20 higher for serotype 3, and the same for the remaining serotypes. The assumption of the true percentage for each serotype can be found in Table 6.

Note that the overall power is sensitive to the assumed response rate of V114 for the serotypes which are assumed to have lower response rates (6A, 6B, and 19A). For example, if the V114 response rate for 6B is decreased from 0.82 to 0.80 (0.07 lower than that of Prevnar 13™), the power will be ~80%.

Further details are provided in the sSAP.

Table 6 [redacted]

[redacted]

8.9.2 Safety Analyses

For safety comparisons, all subjects are expected to be evaluable. If no serious adverse event is observed among the 350 subjects in each vaccination group, this trial provides 97.5% confidence that the true serious adverse event rate is <1.05% (1 out of every 95 subjects).

The probability of observing at least one serious adverse event in this trial depends on the number of subjects enrolled and the incidence rate of serious adverse events in the general population. If the incidence rate of a serious adverse event is 1 of every 217 recipients of the vaccine (0.46%), then there is an 80% chance of observing at least one such serious adverse event among 350 subjects in the vaccine group. If the incidence rate is 1 of every 505 recipients (0.2%), there is a 50% chance of observing at least one serious adverse event.

For safety comparisons, risk differences between any 2 vaccination groups that could be detected with an 80% probability are summarized in Table 7 for a variety of hypothetical true incidence rates. These calculations assume there are 350 subjects for safety in both groups and are based on a 2-sided significance level of α =0.05. No multiplicity adjustments were made in these calculations.

Table 7 Differences in Incidence of Adverse event Rates between the Two Vaccination Groups That Can be Detected With an ~80% Probability and a Two-Sided Significance Level of 0.05

True Incidence Rate of Adverse events in V114 (%) N=350	True Incidence Rate of Adverse events in Prevnar 13™ (%) N=350	Detectable Percentage Point Difference in Incidence Rates of Adverse events
2.5	0.1	2.4
6.2	2.0	4.2
10.7	5.0	5.7
17.3	10.0	7.3
23.3	15.0	8.3
29.1	20.0	9.1
40.1	30.0	10.1
NOTE: The incidence rates for each vaccination group are hypothetical.		

8.10 Subgroup Analyses and Effect of Baseline Factors

The GMC responses as measured by Pn ECL to all 15 serotypes contained in V114 will be summarized by vaccination group in each country subgroup, in order to assess potential differences by this factor.

8.11 Extent of Exposure

The number of subjects vaccinated will be summarized by vaccination group.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 8.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
V114 Lot 1	0.5 mL dose sterile suspension for I.M. injection	Provided centrally by the Sponsor
V114 Lot 2	0.5 mL dose sterile suspension for I.M. injection	Provided centrally by the Sponsor
Prevnar 13™	0.5 mL dose sterile suspension for I.M. injection	Provided centrally by the Sponsor

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Sites will receive open label single dose syringe kits. Each kit will contain 1 syringe.

9.3 Clinical Supplies Disclosure

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

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask vaccine identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Vaccine identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded to treatment assignment. Subjects whose treatment assignment has been unblinded (by the investigator, Merck subsidiary, or through the emergency unblinding call center) must be discontinued from study drug, but should continue to be monitored in the trial.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign vaccine to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) 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 trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. 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 authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines 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.

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (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 trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

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

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

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

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research Samples will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

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

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com).

Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Buccal swab specimens will be collected inside the cheek with no associated venipuncture to obtain the specimen. Therefore, there will not be an additional risk for the subject.

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

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Trial Visit:	Visit 4	Visit 5	Visit 6
Blood Parameter	**Approximate Blood Volume (mL)**		
ECL/OPA Assay	5 mL	5 mL	5 mL
Expected Total (mL)	5 mL	5 mL	5 mL

12.4 List of Abbreviations

AEs	Adverse Events
AOM	Acute Otitis Media
ASaT	All subjects as treated
CAP	Community Acquired Pneumonia
CDC	Centers for Disease Control and Prevention
CIs	Confidence Intervals
CP	Cell wall polysaccharide
CRA	Clinical Research Associate
CRU	Clinical Research Unit
CSR	Clinical Study Report
DEG	Data Entry Guideline
eCRF	Electronic Case Report Form
eDMC	external Data Monitoring Committee
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ERC	Ethics Review Committee
EU	European Union
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
GCPs	Good Clinical Practices
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	Institute of Child Health
IGG	Immunoglobulin G
IPD	Invasive Pneumococcal Disease
IRB	Institutional Review Board
IRT	interactive response technology
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
MOPA-4	Multiplexed OPA Assay
MRL	Merck Research Laboratories
MSD	Meso-Scale Discovery
NTHi	Non-Typeable *Haemophilus influenzae*
OPA	Opsonophagocytic Killing Activity
PCV	Pneumococcal Conjugate Vaccine
PD1	Postdose 1
PD3	Postdose 3
PD4	Postdose 4
Pn ECL	Pneumococcal Electrochemiluminescence
PnPs	Pneumococcal Polysaccharides
PP	Per-protocol
PRO	Patient Reported Outcome]

SAE	Serious Adverse Event/Experience
SOC	System Organ Class
SOPs	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
UAB	PPD
US	United States
VRC	Vaccination Report Card
WHO	World Health Organization

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	