NICHD P1091

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PRIMARY STATISTICAL ANALYSIS PLAN

Safety and Immunogenicity of Anti-Pneumococcal Vaccines in HIV-Infected Pregnant Women: NICHD P1091

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1 Introduction

This Primary Statistical Analysis Plan (SAP) outlines the general statistical approaches that will be used in the primary statistical analysis of NICHD P1091. The focus is on analyses that address the study's primary and secondary objectives, as well as summaries of the primary and secondary outcome measures that will be posted on ClinicalTrials.gov. It will facilitate discussion of the statistical analysis components among members of the study team and provide agreement between the team and statistician regarding the analyses to be performed and presented in the primary statistical analysis report. Detailed outlines of tables and coding descriptions that will be included in the primary statistical analysis report are included in the Analysis Implementation Plan (AIP).

Analyses for the primary statistical report will be initiated once the last participant has completed the last study visit, all laboratory data are available, all queries have been resolved, and the database has been frozen for analysis. This report will be used for submission of results to ClinicalTrials.gov. Results are required to be submitted within one year of the primary completion date (PCD), which is the date the last participant is examined for the purposes of data collection for the primary outcome measure. For this study, the PCD is based on the last study visit.

2 Key Updates to the SAP

N/A

3 Protocol Overview

3.1 Study Design

DESIGN: A double-blind, randomized, placebo-controlled study to evaluate the safety and immunogenicity of two pneumococcal vaccines in HIV-infected pregnant women in their second or third trimester on highly active antiretroviral therapy (HAART) and their infants.

SAMPLE SIZE: Approximately 345 Human Immunodeficiency Virus (HIV)-infected pregnant women and their 345 infants (690 participants), equally distributed among three treatment arms to obtain ≥ 100 evaluable pairs/arm (300 total pairs, or 600 total participants).

REGIMEN: **Step 1.** Pregnant women will be randomized between ≥ 14 weeks (14 weeks 0 days) to < 33 weeks (32 weeks 6 days) of gestation to one of three blinded treatment arms (administered on Day 0):

- Arm 1A: pneumococcal polysaccharide 23-valent vaccine (PPV-23);
- Arm 1B: pneumococcal conjugate 10-valent vaccine (PCV-10); or
- Arm 1C: placebo.

Step 2. Women randomized to Arm 1C (placebo) who complete Step 1 will be screened for entry into Step 2 and will be randomized to receive PPV-23 (Arm 2A) or PCV-10 (Arm 2B) at 24 weeks after delivery. The women who received active vaccine during pregnancy (Arms 1A and 1B) will stop study at 24 weeks after delivery.

Step 3. Women who were initially randomized to Arm 1C and meet an exclusion criterion for Step 2 due to new pregnancy will be enrolled in Step 3 and receive open label PCV-10 at the last study visit (which coincides with Step 1 24 weeks post-delivery).

All infants will receive PCV-10 per local standard of care.

STUDY DURATION: Up to 60 weeks for women (approximately 28 weeks pre-delivery; 32 weeks post-delivery) and up to 28 weeks for infants.

3.2 Study Objectives and Outcome Measures

Primary objectives and outcome measures:

1. To assess the safety of the PCV-10 and PPV-23 vaccines in HIV-infected pregnant women on HAART.

   - Outcome measures:

   Maternal:

   - Grade ≥ 3 AEs up to 4 weeks after vaccination (in Steps 1 and 2)
   - Grade ≥ 3 AEs judged to be related to the study treatment (in Steps 1 and 2) throughout the study
   - Grade 4 AEs or death after week 4 after vaccination (in Step 1)

   Neonatal:

   - Grade ≥ 3 AEs
   - Congenital defects

- HIV infections
- Pneumonia or IPD

2. To compare the immunogenicity of PCV-10 with PPV-23 vaccines in HIV-infected pregnant women on HAART.

   - Outcome measure:
     - Raw values and fold change in ELISA-measured IgG PNC antibody concentrations from baseline to week 4 in Step 1 to ≥ 1 serotype. Serotypes measured by ELISA are: 1, 4, 5, 6B, 7F, 14, 23F and 33F.

3. To compare the level of Pneumococcal (PNC) antibodies at 8 weeks of life in infants born to mothers who received PCV-10 or PPV-23 vaccines.

   - Outcome measures:
     - ELISA-measured IgG PNC antibody levels ≥ 0.35ug/mL at 8 weeks of age for ≥ 1 serotype from those listed above.

Secondary objectives and outcome measures:

1. To compare the level of transplacentally transferred vaccine-serotype PNC antibodies in infants born to mothers who received PCV-10 or PPV-23 versus placebo.

   - Outcome measure: Average ratio of infant/mother ELISA-measured IgG PNC antibody levels across the serotypes listed above, measured at birth/delivery

2. To compare the immunogenicity of PCV-10 and PPV-23 vaccines with placebo in HIV-infected pregnant women on HAART.

   - Outcome measure: ELISA-measured IgG PNC antibody concentrations at week 4 in Step 1, in all treatment groups

3. To compare the persistence of vaccine-serotype PNC anti-capsular antibodies for up to 24 weeks after delivery in HIV-infected women vaccinated with PCV-10, PPV-23 or placebo.

   - Outcome measure: ELISA-measured IgG PNC antibody concentrations at labor&delivery and week 24 post-delivery in Step 1, in all treatment groups

4. To compare maternal antibody responses to PPV-23 or PCV-10 administered during pregnancy with responses to PPV-23 or PCV-10 administered 24 weeks postpartum.

   - Outcome measure: ELISA-measured IgG PNC antibody concentrations at week 4 in

Step 1 and at week 4 in Step 2, in the women who received PPV-23 or PCV-10

5. To evaluate the effect of the following factors on the magnitude and persistence of the maternal antibody responses to PCV-10 and PPV-23: maternal age, ethnicity, cluster of differentiation 4 (CD4), cluster of differentiation 8 (CD8), plasma HIV RNA and gestational age at immunization.

    - Outcome measure: ELISA-measured IgG PNC antibody concentrations at week 4 in Step 1, in the women who received PPV-23 or PCV-10, and the following variables (measured at week 0):
        - maternal age,
        - ethnicity,
        - cluster of differentiation 4 (CD4),
        - cluster of differentiation 8 (CD8),
        - plasma HIV RNA and
        - gestational age.

6. To assess potential interference of maternal antibodies with infant vaccine-serotype PNC anti-capsular antibody responses after the first 2 doses of PCV-10 and determine if interference of maternal antibodies differs in PCV-10 from PPV-23 and from placebo recipients.

    - Outcome measure: ELISA-measured IgG PNC antibody concentrations at weeks 16 and 24 in infants

4 Definitions

4.1 Baseline

Study Day 0 is defined as the vaccination date. The values used for baseline summaries will be the last evaluation on or before the vaccination date.

4.2 Analysis Populations

Any mother participants found to be ineligible and who the study team determine should not be included in any analyses, will be included in accrual and eligibility summaries only. Protocol deviations will be summarized but should not result in any participants being excluded from analyses.

Safety population: Safety analyses will be as-treated and include all women who received study vaccination and all infants who were born alive.

Immunogenicity population: The primary immunogenicity analyses will use an as-treated approach, limited to women who received study vaccination and all infants who were born alive. In addition, the primary immunogenicity analysis in infants will be restricted to those who did not receive the PCV-10 vaccination prior to the week 8 evaluation. If more than one child is born to a pregnant woman, one child will be randomly selected to be included in the primary immunogenicity analyses.

For the immunogenicity analysis in secondary objective #6, infants who did not receive the PCV-10 vaccinations within the correct windows will be excluded. The windows are described below in section 5.1.

5 Statistical Methods

Baseline characteristics will be summarized by treatment group but with no statistical comparisons comparing arms.

Statistical tests will not be adjusted for interim monitoring or multiple comparisons. The Chi-square tests will be used to compare rates of response following vaccination between the vaccinated groups and placebo group. The statistical tests will be two-sided with a nominal significance level of 0.05. Categorical data will be summarized using N (%) and 90% or 95% confidence intervals (CIs), and continuous data using N, min, Q1, median, Q3, max, and mean (STD) (when appropriate) and 95% CI.

Any modifications to outcome measures after the team has seen data collected after entry will be identified as *post hoc* in the analysis report.

5.1 Visit and Evaluation Schedule

Maternal Schedule:

Study visits for women were conducted on Day 0 (day of vaccination), week 1 (with a window of +3 days), week 4 and at labor and delivery (L&D) (each with a window of +7 days), and at 24 weeks post-delivery (with a window of ±28 days) or as needed for unscheduled visits.

At week 24 post-delivery, the women had the possibility of registering to Step 2 or Step 3.

Infant Schedule:

Study visits for infants were conducted at birth (with a window of +7 days), week 8, which should be $\leq$ 7 days before the 1st dose of PCV-10 (with a window of +14 days), week 16, which should be $\leq$ 7 days before the 2nd dose of PCV-10 (with a window of $\pm$ 28 days), week 24, which

should be ≥ 28 days after the 2nd dose of PCV-10 (with a window of 28 days), or for Invasive Pneumococcal Disease (IPD).

5.2 Safety Primary Objectives

Only mothers who received vaccination and infants who were born alive will be included in the safety analyses.

The number and proportion of women and children experiencing at least one primary safety outcome measure will be summarized by treatment group with 90% CIs. The types of primary safety outcome measures that occur will be summarized.

5.3 Immunogenicity Primary Objectives

Maternal:

This is an as-treated analysis including only the women who have been vaccinated.

Summaries will include: (i) the proportion (%) and 95% CI of women vaccinated with PCV-10 or with PPV-23 vaccines who had a ≥two-fold increase to ≥ 1 serotype in ELISA-measured IgG PNC antibody concentrations from baseline to 28 days after immunization in Step 1 (as measured at study week 4). The difference in proportions between the vaccinated groups will be assessed using a Chi-Square test; (ii) the proportion (%) and 95% CI of women vaccinated with PCV-10 or with PPV-23 vaccines who had ELISA-measured IgG PNC antibody levels ≥ 0.35ug/mL at week 4 after immunization in Step 1 to ≥ 1 of the serotypes listed above.

Infants:

This is an as-treated analysis including only the infants born to women who have been vaccinated and those who have received the PCV-10 vaccination prior to the week 8 study visit.

Summaries will include the proportion (%) and 95% CI of infants born to mothers who received PCV-10 or PPV-23 vaccines who had ELISA-measured IgG PNC antibody levels ≥ 0.35ug/mL at 8 weeks of age for ≥ 1 serotype listed above. The difference in proportions between the two groups will be assessed using a Chi-Square test.

In the case of twins, one child will be chosen at random for the primary immunogenicity analysis. Sensitivity analyses will repeat these summaries in the event that twins are enrolled in the study, re-doing the analysis using the other sibling.

5.4 Secondary Objectives

Summaries will include:

i) means (or medians if data are not normally distributed) and 95% CI of mean ratio of infant/mother ELISA-measured IgG PNC antibody levels across the serotypes listed above, measured at birth/delivery;

ii) Summary table with proportion (%) and 95% CI of women in the each treatment group who had a ≥two-fold increase to each serotypes in ELISA-measured IgG PNC antibody concentrations from baseline to week 4 after immunization in Step 1;

iii) Summary table with proportion (%) and 95% CI of women by treatment arm who had ELISA-measured IgG PNC antibody levels ≥ 0.35ug/mL at week 4 after immunization in Step 1, at labor&delivery, and at week 24 post-delivery in Step 1 to ≥ 1 of the serotypes listed above;

iv) Summary table with proportion (%) and 95% CI of women who had a two-fold increase to ≥ 1 serotype in ELISA-measured IgG PNC antibody concentrations from baseline to week 4 after immunization in Step 1 vs the women who achieved this from entry to Step 2 until week 4 post immunization in Step 2 (for each of the two vaccines). The analyses will exclude the women who delivered prior to week 4 in Step 1;

v) Correlations between ELISA-measured IgG PNC antibody concentrations at weeks 4 in Step 1, in the women who received PPV-23 or PCV-10, and the following variables (measured at week 0): maternal age, ethnicity, cluster of differentiation 4 (CD4) count, cluster of differentiation 8 (CD8) count, plasma HIV RNA and gestational age;

vi) Summary table with proportion (%) and 95% CI of infants born to mothers who received PCV-10 or PPV-23 vaccines who had ELISA-measured IgG PNC antibody levels ≥ 0.35ug/mL at 16 and 24 weeks of age for ≥ 1 serotypes listed above;

vii) Summary table with mean (95% CI) number of serotypes with levels ≥ 0.35ug/mL at weeks 16 and 24 of age in study infants.

6 Report Components

Detailed descriptions of the content of each of the following sections are given in the AIP.

1. Accrual
2. Baseline characteristics
3. Study status
4. Protocol deviations
5. Data timeliness and completeness
6. Safety:
    a. Primary safety outcomes
    b. Deaths
    c. Hospitalizations
    d. Concomitant medications
7. Primary immunogenicity outcomes
8. Secondary outcomes

7 Core Writing Team

Protocol Co-Chairs:	Adriana Weinberg
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8 Timetable for primary analysis and manuscript preparation

Event	Weeks from primary completion date (PCD)
Primary completion date (PCD)	PCD
Laboratory Assays Completed	PCD + 7 months
Database clean-up complete	PCD + 8 months
Primary analysis report to Study Team. Primary analysis complete (PAC)	PCD + 9 months (PAC)
Draft manuscript submitted	PAC + 3 months
ClinicalTrials.gov results due	PCD + 1 year

9 Version History

Version	Changes Made	Effective Date
1.0		1/28/2019