IMPAACT P1112

Primary Statistical Analysis Plan

Version 3.0

Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous (SC) VRC01, VRC01LS, and VRC07-523LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies, in HIV-1-Exposed Infants

Protocol Version 4.0, CM#1, LOA#1

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This is IMPAACT P1112 SAP Version 3.0 with names of authors and names of publication writing team members redacted.

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Version History

Version	Changes Made	Date Finalized
1	Original Version	5 August 2015
2	SAP for Week 24 analysis for Dose Group 1 and 2 Limited analyses to the week 24 for Dose Groups 1 and 2	26 May 2017
3	Update to Protocol Version 4.0, CM #1 and LOA #1 Section 1.1: expended the wording. Section 2: Updated study Schema and added info about completed Dose Groups. Added Section 3: Outcome Measures. Section 5: Updated the content of the report and moved some details to the AIP.	28 August 2020

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures that will be included in the primary manuscript(s), and which address the safety primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches that will be used in the analysis of the study. It has been developed to facilitate discussion of the statistical analysis components among the study team, and to provide agreement between the study team and statistician regarding the statistical analyses to be performed and presented in the primary analysis report. It also describes the results for the primary and secondary safety outcome measures that will be posted on ClinicalTrials.gov. The PK outcome measures will be analyzed and summarized separately by the study pharmacologist.

Detailed outlines of tables and coding descriptions that will be included in the Primary Analysis Report are included in the Analysis Implementation Plan (AIP).

Two Primary Analyses Reports will be prepared for this study. Analyses for the first Primary Analysis Report will be finalized once the last participant in Dose Group 5, Cohort 2 has completed the Week 16 study visit, all queries have been resolved, and the study database closure/data lock has been completed. Analyses for the second Primary Analysis Report will be finalized once the last participant has completed the last study visit, all queries have been resolved, and the study database closure/data lock has been completed.

Outlines of analyses for other objectives and outcome measures not included in the Primary SAP will be provided in a separate SAP.

1.2 Version History

This SAP was updated to new SDAC template and updated to include all treatment groups in Version 4.0 of the protocol. Details about analyses were moved to the AIP.

2 Study Overview

2.1 Study Design

DESIGN:	Open-label, dose-escalating, Phase 1, multicenter trial of VRC01 (VRC-HIVMAB-060-00-AB), VRC01LS (VRCHIVMAB080-00-AB), and VRC07-523LS (VRC-HIVMAB075-00-AB)

SAMPLE SIZE: N=79 mother-infant pairs, 13 per Dose Groups 1, 2 and 3; 20 per Dose Groups 4 and 5 (10 per each cohort)

Description of Dose Groups		
	N	**Dose of VRC01, VRC01LS, or VRC07-523LS**
Dose Group 1	13	20 mg/kg SC X1 VRC01
Dose Group 2	13	40 mg/kg SC X1 VRC01
Dose Group 3	13	40 mg/kg SC for initial dose 20 mg/kg SC monthly of VRC01 for at least 6 months (24 weeks) and no more than 18 months (72 weeks) while breastfeeding
Dose Group 4	10 10	Cohort 1: Non-breastfeeding Single dose at birth of VRC01LS to be administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Cohort 2: Breastfeeding Initial dose at birth of VRC01LS to be administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Second dose of 100 mg VRC01LS at Week 12 to be administered SC if the infant has not achieved complete cessation of breastfeeding
Dose Group 5	10 10	Cohort 1: Non-breastfeeding Single dose at birth of VRC07-523LS to be administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Cohort 2: Breastfeeding Initial dose at birth of VRC07-523LS to be administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Second dose of 100 mg VRC07-523LS at Week 12 to be administered SC if the infant has not achieved complete cessation of breastfeeding

POPULATION: Infants born to HIV-1-infected women who meet all maternal inclusion and exclusion criteria and who are ≥ 36 weeks gestation; ≥ 2kg birth weight; less than 72 hours of age; and meet the study definition of increased risk of HIV infection. Additional exclusion criteria for infants also apply (see protocol Section 4.0). The mothers will be enrolled as well, but only the infants will receive the VRC01/VRC01LS/VRC07-523LS immunization(s) and be followed on the study. All infants will receive

prophylactic antiretroviral therapy (ART) treatment per local standard of care.

REGIMEN:

Infants in Dose Group 1 received a single VRC01 (human monoclonal antibody) 20 mg/kg subcutaneous injection less than 72 hours after birth.

Infants in Dose Group 2 received a single subcutaneous VRC01 dose of 40 mg/kg less than 72 hours after birth.

Infants in Dose Group 3 received a subcutaneous VRC01 dose of 40 mg/kg less than 5 days after birth for the initial dose and 20 mg/kg SC monthly.

Non-breastfeeding infants in Dose Group 4, Cohort 1 received a single subcutaneous VRC01LS dose (< 4.5 kg: 80 mg; ≥ 4.5 kg: 100 mg) as soon as possible and less than 72 hours after birth. Breastfeeding infants in Dose Group 4, Cohort 2 received subcutaneous VRC01LS (< 4.5 kg: 80 mg; ≥ 4.5 kg: 100 mg) as soon as possible and no longer than 5 days after birth for the initial dose and a second dose (100 mg) at Week 12 if the infant has not achieved complete cessation of breastfeeding. Complete cessation of breastfeeding is defined as no exposure to breastmilk for 28 days.

In Dose Group 5, infants will enroll into one of two separate cohorts: Cohort 1 (non-breastfeeding) or Cohort 2 (breastfeeding). Non-breastfeeding infants in Dose Group 5, Cohort 1 will receive a single subcutaneous VRC07-523LS dose (< 4.5 kg: 80 mg; ≥ 4.5 kg: 100 mg) as soon as possible and less than 72 hours after birth. Breastfeeding infants in Dose Group 5, Cohort 2 will receive subcutaneous VRC07-523LS (< 4.5 kg: 80 mg; ≥ 4.5 kg: 100 mg) as soon as possible and no longer than 5 days after birth for the initial dose and a second dose (100 mg) at Week 12 if the infant has not achieved complete cessation of breastfeeding. Complete cessation of breastfeeding is defined as no exposure to breastmilk for 28 days.

TREATMENT DURATION:

VRC01: One day for Dose Groups 1 and 2.
VRC01: For Dose Group 3, all have received monthly doses for at least 6 months. Infants who continue to receive breastmilk will receive monthly doses through the complete cessation of breastfeeding up to a maximum of 72 weeks (19 doses).
VRC01LS: All infants in Dose Group 4 received a single dose at birth. Infants in Dose Group 4, Cohort 2 will receive a second dose at Week 12 if they have not achieved complete cessation of breastfeeding.
VRC07-523LS: All infants in Dose Group 5 will receive a single dose at birth. Infants in Dose Group 5, Cohort 2 will receive a second dose at Week 12 if they have not achieved complete cessation of breastfeeding.

NOTE: It is expected that serum levels will remain detectable for > 1 month after the final dose of VRC01 and at least 6 months after the final dose of VRC01LS or VRC07-523LS.

STUDY DURATION: Dose Groups 1 and 2: minimum of 48 weeks
Dose Group 3: 96 weeks
Dose Group 4: 96 weeks
Dose Group 5: 96 weeks

2.2 Study Objectives

This Primary SAP addresses the following primary and secondary objectives listed in the study protocol. Other study objectives in the protocol will be addressed in subsequent analysis plans.

OBJECTIVES:

Primary: In HIV exposed infants at increased risk for peripartum or breastfeeding HIV transmission:

1. To assess safety of single subcutaneous dose (20 mg/kg or 40 mg/kg) of VRC01 (Dose Groups 1 and 2).
2. To determine pharmacokinetic profile of single dose, subcutaneous VRC01 (Dose Groups 1 and 2). **– This objective will be addressed in a separate PK report.**
3. To assess safety of monthly subcutaneous doses of VRC01 (Dose Group 3).
4. To determine pharmacokinetic profile of monthly subcutaneous doses of VRC01 (Dose Group 3). **– This objective will be addressed in a separate PK report.**
5. To assess safety of one and two subcutaneous doses of VRC01LS (Dose Group 4, Cohorts 1 and 2).
6. To determine pharmacokinetic profile of one and two subcutaneous doses of VRC01LS (Dose Group 4, Cohorts 1 and 2). **– This objective will be addressed in a separate PK report.**
7. To assess safety of one and two subcutaneous doses of VRC07-523LS (Dose Group 5, Cohorts 1 and 2).
8. To determine pharmacokinetic profile of one and two subcutaneous doses of VRC07-523LS (Dose Group 5, Cohorts 1 and 2) **– This objective will be addressed in a separate PK report.**

Secondary:

1. To examine the anti-VRC01 antibody production following immunization.
2. To examine the anti-VRC01LS antibody production following immunization.
3. To examine the anti-VRC07-523LS antibody production following immunization.

The PK objectives will be analyzed and reported in a separate report, created by the study pharmacologist.

2.3 Overview of Formal Interim Monitoring

The study team will monitor the safety of the study participants through calls where adverse events and toxicity reports presenting laboratory and clinical data collected throughout follow-up for the infants enrolled are reviewed. After the first infant enrolled into Dose Group 3 reached the Week 24 milestone, the team began reviews of available safety data of adult and pediatric protocols of VRC01 (from P1112 database and most recent safety reports available from the other protocols) every 6 months. These reviews will continue and include infants in Dose Groups 4 and 5 and data on VRC01LS and VRC07-523LS. In addition, if any of the stopping rules for safety listed in the protocol are met, the study will be reviewed by an independent Study Monitoring Committee (SMC) according to IMPAACT Standard Operation Procedure (SOP) on Study Data and Safety Monitoring.

3 Outcome Measures

3.1 Primary Outcome Measures

Through Day 28 for Dose Groups 1, 2, Cohort 1 in Dose Groups 4 and 5; Week 24 for Dose Group 3; and Week 16 for Cohort 2 in Dose Groups 4 and 5:

- Death
- Grade 3 or higher adverse events
- Vaccine-related Grade 3 or higher adverse events
- HIV infection

Number (%) participants in each category will be summarized for each treatment group.

3.2 Secondary Outcome Measures

From the end of the observation period in the primary outcome measure through the end of follow-up:

- Death
- Grade 3 or higher adverse events
- Vaccine-related Grade 3 or higher adverse events
- HIV infection

Number (%) participants in each category will be summarized for each treatment group.

From vaccine administration to end of follow-up:

- Development of anti-VRC01 antibodies (yes/no)
- Development of anti-VRC01LS antibodies (yes/no)
- Development of anti-VRC07-523LS antibodies (yes/no)

4 Analysis principles

Since the study is not blinded and the dose cohorts will be enrolled sequentially, the data will be presented separately by dose cohort. All subjects who received immunization will be included in the safety and immunology analyses. Exact methods will be used when calculating the 90% CI around proportion estimates of safety data.

5 Report Contents

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

1. Accrual
   a. Table with number enrolled
   b. Table with enrollment by month
   c. Table with enrollment by site

The following tables will be restricted to only the participants who received immunization.

2. Selected characteristics of participants at baseline
   a. Summary of key characteristics including gender, race, ethnicity, birth weight, age (in days) at randomization, and type of ARV at the time of delivery.

3. Protocol deviations (text)
   a. Summary of serious protocol deviations reportable per standard IMPAACT policies

4. Study and immunization status (table or text)
   a. Number receiving immunizations
   b. Number off study prematurely, by reason and arm

5. Days between randomization and immunization
   a. Table showing the number of hours between birth and first immunization.

6. Missed or partial visits
   a. Table showing the number of missed visits and visits conducted remotely due to COVID

7. Primary Safety Outcomes as discussed in Section 3.1
   Through Day 28 for Dose Groups 1, 2, Cohort 1 in Dose Groups 4 and 5; Week 24 for Dose Group 3; and Week 16 for Cohort 2 in Dose Groups 4 and 5:
   a. Number of deaths
   b. Number of participants who experienced Grade 3 or higher adverse events
   c. Number of participants who experienced treatment-related Grade 3 or higher adverse events
   d. Number of participants who became HIV infected

   Number (%) of participants meeting each category, along with exact 90% CI, will be presented.

8. Secondary Safety Outcomes as discussed in Section 3.2

   From the end of the observation period in the primary outcome measure through the end of follow-up:

   a. Number of deaths
   b. Number of participants who experienced Grade 3 or higher adverse events
   c. Number of participants who experienced treatment-related Grade 3 or higher adverse events
   d. Number of participants who became HIV infected

   Number (%) of participants meeting each category, along with exact 90% CI, will be presented.

9. Table summarizing local reactions at the injection site
10. Anti-VRC01 Antibody Data
    a. The number of infants in each dose group who develop anti–VRC antibodies will be summarized descriptively.