IMPAACT 2008

Primary Statistical Analysis Plan

Version 2.0

Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

(Version 2.0, LOA#2)

ClinicalTrials.gov Identifier: NCT03208231

May 13, 2020

This is IMPAACT 2008 SAP Version 2.0 with names of authors, names of publication writing team members and analysis timeline redacted

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1 Version History

Version	Changes Made	Date Finalized
1.0	Original Version	April 9, 2018
1.0	Original Version reviewed to ensure no changes necessary after LOA#1	February 21, 2019
2.0	Responding to changes outlined in LOA#2 • Added new sensitivity analyses to efficacy • Added wider windows to Week 24, 36 and 48 • Clarified definition of baseline in VRC01 arm	May 13, 2020

2 Introduction

2.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcomes measures of IMPAACT 2008 that will be included in the primary manuscript, and which address the primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches that will be used in the analysis. 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 statisticians regarding the statistical analyses to be performed and presented in the primary statistical analysis report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov. Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Statistical Analysis Report are included in the Analysis Implementation Plan (AIP). A separate Statistical Analysis Plan for Other Objectives and Outcome Measures will be developed once results for the Primary and Secondary Objectives are known, and analyses will be presented in a separate report. Data for the Primary Statistical Analysis Report will be downloaded once the last infant has completed the Week 16 study visit, required laboratory measurements are in the DMC database, all queries have been resolved, and the database frozen for analysis.

The Primary Statistical Analysis Report will be used for submission of results to ClinicalTrials.gov. Results for primary outcomes 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 14 weeks of infant follow-up. Results for secondary outcome measures are due one year after the last participant reaches Week 16. A second submission to ClinicalTrials.gov will be done once all follow-up is complete to update the adverse event tables.

2.2 Version History

Version 2.0 of the SAP includes additional sensitivity analyses for the primary efficacy outcome measure. These were added as it became evident that some infants with good adherence were developing resistance to antiretrovirals and not on adequate therapy. Therefore the 'per-protocol' primary analysis would not necessarily be capturing only infants on optimal ARV therapy. This Version also clarified the definition of baseline and widened the acceptable study visits windows for Weeks 24, 36 and 48 (widened in response to disruptions at the site due to COVID-19).

3 Study Overview

3.1 Study design

IMPAACT 2008 is a Phase I/II, multisite, two-arm, randomized, controlled, open-label study to evaluate the safety and antiviral activity of VRC01 administered within 12 weeks of birth to HIV-infected infants on ART. Infants are stratified by whether their initial ART regimen includes an integrase inhibitor, and randomized with equal probability to receive (Arm 1) or not receive (Arm 2) VRC01. VRC01 will be administered at study entry and Weeks 2, 6, and 10. All infants must have initiated combination antiretroviral therapy (ART) within 14 days before study entry. Infants will be followed for 48 weeks. Infants' mothers may optionally be enrolled in the study for one-time specimen collection at study entry for exploratory evaluations.

This is a small study with limited ability to detect rare safety events. With 34 infants in each Arm, there is a 29% chance of observing at least one adverse event with a true underlying rate of 1%, and a more than 83% chance of seeing at least one adverse event with higher (>5%) underlying rates. The study will have adequate power (>87%) to detect meaningful differences between the two Arms in changes in HIV-1 DNA of 1.0 $\log_{10}$ copies/ml.

The planned enrollment was 68 infants. In March 2020, due to the outbreak of COVID-19, accrual was closed prematurely with 61 infants enrolled. The smaller enrollment may reduce power to detect differences between Arms for the primary efficacy outcome measure.

3.2 Hypotheses

1. A regimen of four doses of VRC01 (40 mg/kg per dose) will be safe among HIV-1-infected infants initiating ART.

2. HIV-1-infected infants who receive a regimen of four doses of VRC01 (40 mg/kg per dose) in addition to ART will experience a greater decrease in the concentration of HIV-1 DNA in PBMCs at four weeks after the final dose compared to infants who do not receive VRC01.

3.3 Study objectives and outcome measures

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.

The primary objectives are to assess the:

1. safety of VRC01 administered with ART (cumulatively through Week 14)

   Outcome measure: grade 3 or higher adverse events including reactogenicity outcomes, abnormal laboratory test results, signs, symptoms, and diagnoses occurring from randomization through Week 14. Events resulting in death are grade 5.

2. effect of VRC01 on HIV-1 DNA concentrations in PBMCs (change from Week 0 to Week 14)

   Outcome measure: change in HIV-1 DNA concentration in PBMCs from Week 0 to Week 14.

The secondary objective is:

1. to assess the pharmacokinetics of VRC01 (through Week 16, Arm 1 only).

   Outcome measures: VRC01 trough concentrations at Weeks 2, 6, 10, 14 and 16 in Arm 1 (VRC01).

3.4 Study monitoring

Safety will be monitored in real time by the Clinical Management Committee (CMC) and at pre-defined time points by the IMPAACT Study Monitoring Committee (SMC) for early safety (when five infants in Arm 1 have completed their Week 3 visit), pharmacokinetics (when six infants in Arm 1 have received their first two doses of VRC01 with PK results up to Week 6), antiviral activity (when half the infants have reached Week 14 (based on HIV-1 RNA rather than the primary outcome measure HIV-1 DNA, as the HIV-1 DNA data will be run in batch once the last infant reaches Week 16)), and at least yearly. *Ad hoc* SMC reviews may be requested by the CMC if pre-defined safety criteria occur.

This is a small Phase I/II study so will not use formal interim statistical stopping rules. If initial declines in HIV-1 RNA are small enough to raise concern with the SMC, additional testing on viral susceptibility to VRC01 and antiretroviral concentrations will be obtained and reviewed to determine whether enrollment and vaccinations should continue.

4 Definitions

4.1 Baseline

“Study entry” or “baseline” is defined as the randomization date. The value used for baseline (Week 0) will be the last evaluation on or before the randomization date.

4.2 Analysis populations

Any infants found to be ineligible and who the study team determines should not be included in any analyses will be included in screening, accrual and eligibility summaries only.

Safety population: Safety analyses will be intent-to-treat and include all eligible infants randomized including all multiplets.

Efficacy population: Primary efficacy analyses will use a per-protocol approach, limited to infants who do not interrupt ART for more than three consecutive days prior to the Week 14 visit and, if randomized to receive VRC01 (Arm 1), who receive at least the first scheduled dose of VRC01, and who have evaluable outcome measures at Weeks 0 and 14. If more than one infant from the same pregnancy is enrolled, one infant will be randomly selected to be included in the primary efficacy analysis.

5 Statistical methods

5.1 General considerations

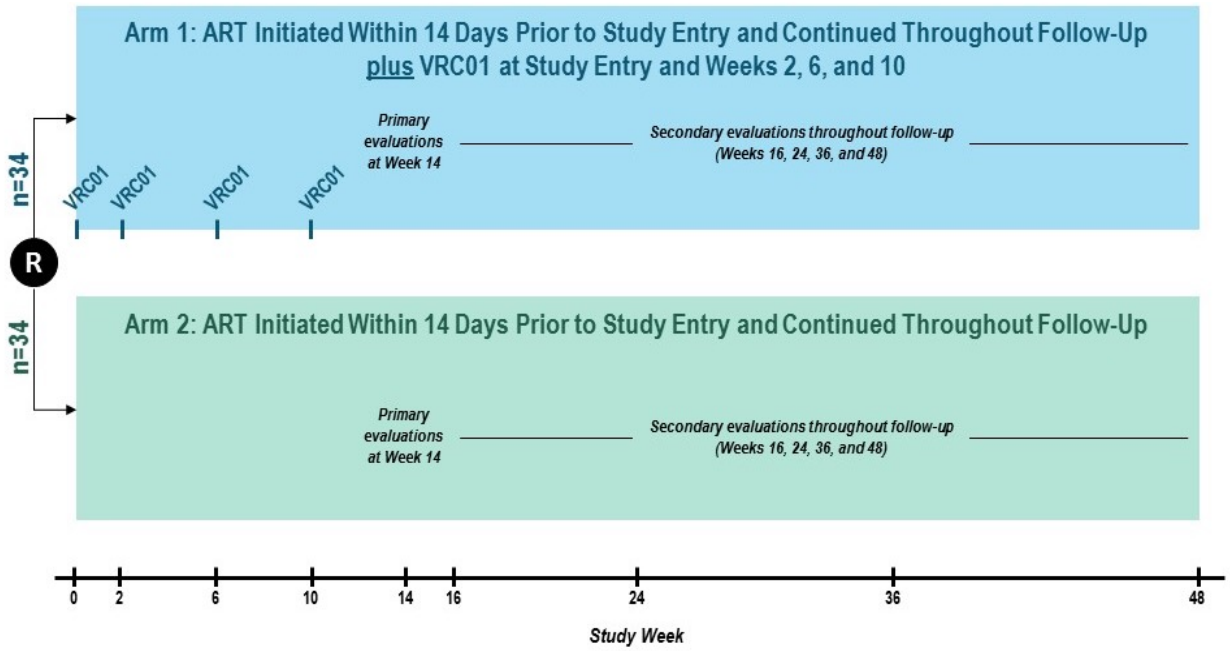
Baseline characteristics will be summarized by arm, but there will be no statistical comparisons comparing arms because of the randomized study design.

Statistical tests (all two-sided) will not be adjusted for interim monitoring, multiple comparisons or stratification by whether the initial ART regimen includes an integrase inhibitor. Significance levels p-value < 0.05 will be highlighted in the text, but must be interpreted with caution, since there will be many statistical tests which will increase the chance of spuriously significant p-values. Categorical data will be summarized using N (%), and continuous data using N, min, Q1, median, Q3, max, and mean (standard deviation (SD)) (when appropriate). Any modifications to outcome measures after the team has seen data that were collected after entry will be identified as such in the analysis report.

5.2 Visit schedule and analysis windows

The VRC01 administration and clinic visit schedules are summarized in Figure 1.

Figure 1: VRC01 administration and clinic visit schedules



VRC01 administration occurs at Weeks 0, 2 (±3 days), 6 (±7 days), and 10 (±7 days). Additional clinic visits are scheduled at Weeks 1 (±3 days), 3 (±3 days), 7 (±3 days), 11 (±3 days), 14 (targeted to take place on Day 98, with a preferred window of ±7 to +14 days), 16 (targeted to take place on Day 112, with an allowable window of -7 to +14 days), 20 (±14 days), 24 (±14 days), 36 (±14 days), and 48 (±14 days) (days are relative to randomization date). Three days after visits when VRC01 is administered, mothers (or caregivers) are contacted by study staff to report their infant's reactogenicity assessments. The allowable window for each three-day contact is -1 to +3 days. If Grade 1 or higher reactogenicity signs or symptoms are reported, mothers are instructed to return to the study clinic with their infants as soon as possible (within 48 hours) for further evaluation.

Letter of Amendment #2 was issued April 22, 2020 in response to COVID-19. To allow additional flexibility with the timing of study visits, the allowable windows for the Week 24 and 36 visits were broadened from ± 2 weeks to ± 6 weeks, and for the Week 48 visit from ± 2 weeks to -6 to +12 weeks. Visits conducted outside the allowable windows were preferred to completely missed visits.

To ensure consistent exposure time across participants, post-entry analyses include all data collected up to and including 16 weeks post randomization (14 weeks plus the 14 days allowed for the Week 14 clinic visit to take place), so analyses may include data collected at the Week 16 clinic visit. For the primary safety outcome measure, for example, all laboratory measurements collected, and signs, symptoms and diagnoses with onset dates up to 16 weeks post-randomization will be included.

For summaries of data by clinic visit, analysis visit windows will be formed around each study visit using the midpoints between adjacent weeks as cutoffs, and potentially including assessments collected outside the recommended visit windows described above. If there are multiple evaluations within the window for a given visit and only one evaluation will be summarized, then the evaluation closest to the scheduled study week will be used, and the earlier measurement will be used if there are two measurements equidistant from the scheduled week.

5.3 Analyses of outcomes measures

5.3.1 Primary safety outcome

This analysis will be conducted in the safety population defined in Section 4.2. The number and proportion of infants experiencing at least one primary safety outcome measure will be summarized by Arm with exact 95% confidence intervals (CIs), both including and excluding the reactogenicity events which can only occur in Arm 1 (VRC01). Differences in proportions between Arms in systemic safety outcomes only will be summarized with an exact 95% CI on the difference. Proportions in Arm 1 will also be summarized only including events assessed by the CMC as related to VRC01 and by type of event (e.g., anemia/neutropenia and other). The types of primary outcome measures will be summarized. Deaths and serious adverse events (SAEs) will be listed. Reactogenicity events will be summarized in Arm 1 by maximum grade, maximum diameter and time to resolution.

5.3.2 Primary efficacy outcome

This is an analysis in the per-protocol efficacy population defined in Section 4.2. In the case of multiplets, one infant will be chosen at random for the primary analysis.

Site staff will interview caregivers to determine if ART was not taken consistently. It is likely that not all infants who did not take ART consistently will be identified through these interviews, and that some non-adherent infants will be included in the primary analysis.

HIV-1 DNA concentrations are measured at entry and Week 14. Values will be $\log_{10}$-transformed. For values below the assay detection limit, a value of one half the lower assay limit will be imputed. For values above the detection limit, the upper limit of the assay will be imputed. Summaries will include (i) the proportion of values below/above the assay limit at Week 0 and Week 14, (ii) $\log_{10}$ HIV-1 DNA at Week 0 and Week 14, and (iii) change from Week 0 to Week 14. Changes will be compared by Arm using parametric/non-parametric tests as appropriate. Similar summaries will be conducted using HIV-1 RNA at all timepoints up to Week 14.

Sensitivity analyses will repeat the efficacy summaries for HIV-1 DNA:

i. in the event that multiplets are enrolled in the study, re-doing the analysis using the other sibling(s),
ii. restricting the VRC01 Arm to those who received all four injections,
iii. excluding infants who received suboptimal antiretroviral treatment,
iv. excluding infants whose baseline virus is resistant to VRC01 neutralization, as identified at the time when HIV-1 DNA concentrations are determined,
v. in the intent-to-treat population including all participants randomized to the study regardless of vaccine receipt and ART adherence,
vi. using the last available time point before Week 14 if HIV-1 DNA concentration in PBMCs is missing at Week 14, and
vii. with adequate ARV levels as determined by the team pharmacologist.

How the treatment difference is modified by other covariates will be assessed using multivariable linear regression including main effects for treatment, each covariate, and their interaction. A full list of covariates of interest will be identified by the team prior to analysis and may include entry age, site, ARV backbone (NVP or LPVr), time on ARVs, CD4% and HIV-1 RNA level, and number of VRC01 doses received.

5.4 Secondary VRC01 PK outcome

VRC01 trough concentrations will be summarized using geometric means and 90% confidence intervals at Weeks 2, 6, 10, 14 and 16. Values below the lower limits of the assay will be set to the lower limit. Summaries will be compared to those generated from other VRC01 studies (IMPAACT P1112). Based on currently available data, Week 6 concentrations are predicted to fall within the range of 20-70 mcg/mL.

6 Report components

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

1. Study entry
    a. Screening
    b. Enrollment
    c. Eligibility and stratification errors
2. Baseline characteristics
3. Protocol deviations
4. Study status
5. Study treatment (VRC01) status
6. Changes/interruptions to antiretroviral regimen up to Week 14
7. Adherence
8. Childhood vaccinations up to Week 14
9. Safety:
    a. Primary safety outcome
    b. Local injection site reactions (VRC01 Arm)
    c. Deaths
    d. Overall safety
10. Primary efficacy outcome (HIV-1 DNA)
    a. Evaluability
    b. Primary efficacy outcome
    c. Sensitivity analyses
11. CD4% at Week 14 and change from baseline
12. HIV-1 RNA up to Week 14
13. VRC01 PK concentrations