This is IMPAACT 2007 SAP Version 2.0 with names of authors, names of publication, writing team members, and analysis timeline redacted

Statistical Analysis Plan

Version 2.0

IMPAACT 2007

Phase I Safety and Pharmacokinetic Study of Maraviroc in HIV-1-Exposed Infants at Risk of Acquiring HIV-1 Infection

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1 Purpose of the Analysis Plan

This Analysis Plan outlines the components of the primary and secondary data analysis for IMPAACT 2007. The focus is on analyses of administrative, baseline, and safety data needed to address the study's primary and secondary objectives, and the analyses to assess whether safety guidelines have been met at interim and final accrual to Cohorts 1 and 2. This document focuses on analyses necessary for scientific purposes; any additional analyses needed for the regulatory purposes of the pharmaceutical sponsor will be specified in a separate document. The procedures and reports involved with protocol team monitoring of safety data during regular team calls are not fully described in this document (see the Study Monitoring Plan for details concerning monitoring). The pharmacology data will be analyzed separately by the protocol pharmacologist. The purpose of this analysis plan is:

- to ensure that the protocol team is aware of all the major issues that will be in the proposed analyses, and agrees on the contents of these analyses; and
- to specify how we intend to investigate the study questions listed in the protocol objectives and the way that data are to be analyzed and presented.

This analysis plan, therefore, includes the key analyses which might lead to modification or termination of the study and which also form the core of any presentation or publication used to disseminate the primary conclusions of the study. It is, however, recognized that this analysis plan may be modified by the core study team as new information becomes available outside of the study, or to reflect recommendations made by the Study Monitoring Committee (SMC).

2 Protocol Overview

This is a Phase I safety, tolerability, pharmacokinetics (PK), and dose-finding study of maraviroc solution during the first six weeks of life for infants born to HIV-1 infected mothers. The objectives of the study are accomplished through two sequential dosing cohorts stratified by maternal use of efavirenz (EFV).

2.1 Study Population

Infants born to HIV-1 infected mothers and are receiving a single or combination antiretroviral (ARV) regimen for prevention of perinatal HIV-1 transmission that does not include a potent cytochrome P450 CYP3A4 inhibitor or inducer (mother will also be enrolled in the study but will not receive study drug).

2.2 Sample Size

Up to 72 mother-infant pairs to achieve a target of 36 evaluable infants receiving the final recommended dose of maraviroc.

2.3 Stratification

Cohort 1: Stratified by infant *in utero* exposure to maternal EFV, with concurrent enrollment of both strata.

Up to 36 mother-infant pairs to achieve a target of 12 evaluable infants (6 in each stratum) receiving the dose of maraviroc that passes safety and PK guidelines for the relevant stratum and is recommended for Cohort 2.

Stratum 1A: n = 6-18 infants without *in utero* exposure to maternal EFV (no EFV exposure during the eight weeks immediately prior to delivery).

Stratum 1B: n = 6-18 infants with *in utero* exposure to maternal EFV (EFV exposure for a minimum of two weeks immediately prior to delivery).

Cohort 2: Stratified by infant exposure to maternal EFV after birth, with enrollment of each stratum opening upon dose selection from the corresponding stratum in Cohort 1.

Up to 36 mother-infant pairs to achieve a target of 24 evaluable infants (12 in each stratum) receiving the final recommended dose of maraviroc that passes safety and PK guidelines for the relevant stratum.

Stratum 2A: n = 12-18 infants without any exposure to maternal EFV either *in utero* (no EFV exposure during the eight weeks immediately prior to delivery) and if breastfeeding while breastfeeding.

Stratum 2B: n = 12-18 breastfeeding infants with exposure to maternal EFV both *in utero* and after birth while breastfeeding (EFV exposure for a minimum of two weeks immediately prior to delivery and while breastfeeding).

2.4 Study Drug

Cohort 1: Single doses of maraviroc solution at two time points: within 3 days of life and at one week (7-14 days) of life. The initial starting dose for this cohort will be 8 mg/kg; dose adjustment may occur as needed based on experience within the cohort.

Cohort 2: Based on evaluation of the Cohort 1, Stratum 1A and Stratum 1B safety and PK data, the initial daily dose of maraviroc oral solution to be administered in Cohort 2, Stratum 2A and Stratum 2B, participants in IMPAACT 2007 will be 8 mg/kg dose given twice daily. Dose adjustments for the cohort may occur as needed based on experience within the cohort.

2.5 Study Duration

Approximately 28 months total. Accrual is expected to require approximately 24 months and enrolled infants will be followed for four months.

2.6 Study Objectives

Primary Objectives:

- To evaluate the safety and tolerability of maraviroc solution, during the first six weeks of life, when administered with ARV prophylaxis to HIV-1 exposed infants at risk of acquiring HIV-1 infection with and without exposure to maternal EFV.
- To evaluate the pharmacokinetics of maraviroc solution, during the first six weeks of life, when administered with ARV prophylaxis to HIV-1 exposed infants at risk of acquiring HIV-1 infection with and without exposure to maternal EFV.
- To determine an appropriate dose of maraviroc solution during the first six weeks of life.

Secondary Objectives:

- To assess safety through 16 weeks of life following administration of maraviroc solution during the first six weeks of life.
- To determine age-related changes in maraviroc pharmacokinetic parameters during the first six weeks of life.
- To explore the impact of maraviroc treatment on viral tropism in the event of perinatal transmission of an X4/dual-mixed tropic strain of HIV.

3 Outline of Planned Analysis

This section contains the details of the analyses for the Interim and the Final Statistical Reports, which will include:

- The primary analyses will be done for each stratum based on infants who were exposed to the final selected dose and will be restricted to data from the initial dose of maraviroc through week 6 of life.
- Secondary analyses will include all infants, in subgroups for each dose received, and will include data from the initial dose of maraviroc through Week 16 of life

Note: Please see Section 6.0 for details on these analyses.

When applicable, separate summary tables will be generated for the women and their infants. Separate summary tables will be generated for each subgroup within a cohort. Summary statistics for subgroups of infants will be provided alongside the overall cohort summary statistics. Infant subgroups will be defined as Stratum 1A and 1B for Cohort 1, and Stratum 2A and 2B for Cohort 2.

The interim and final full stratum/cohort safety reports will be prepared for the core team and, when applicable, for the SMC. These reports will include information concerning Screening and Entry, Participant and Study Status, Baseline, and Safety summary tables. Unless otherwise noted the SDAC final report will contain all summary tables.

The analysis of the PK data will be performed by the protocol pharmacologists and is, thus, not included in this document.

IMPAACT 2007 will be using CDISC standards for data submission. Therefore data will be derived from SDTM into ADaM datasets to be used for analysis. Variables listed in this document use the SDTM naming conventions. Some variables may differ for regulatory submissions and will be specified as such.

Validation requirements as per SDAC SOPs will be as follows:

a. All dataset creation programs will be validated with double coding for the primary safety endpoints.
b. All study-specific formats will be validated.
c. Validation of analysis programs is specified in the following subsections.

For all analyses, the following will be calculated:

Relative day based on the first initial maraviroc dose (RFXSTDTC)

- ADAYDOSE=(DATE-RFXSTDTC) to be used for scientific analyses
- ADY= (DATE-RFXSTDTC+1) to be used for regulatory submissions

Relative day based on birthdate

- ADAYBRTH= (DATE-BIRTHDATE) to be used for scientific analyses
- ADAY=(DATE-BIRTHDATE) to be used for regulatory submission

Analysis Week is based on Birth Date:

COHORT 1

Week based on SOE[c]	Target Study Day (Protocol Allowed Window)	Analysis Window[d]
Week 0 (Screening and/or Entry)[a]	Day 0-3[b]	Day 0 to 3
Week 1	Day 7 (7-14)	Day 4 to (18 or 1 day before Week 2 visit)
Week 2 (Cohort 1: "7 Day Post Dose Safety")	7 days after receiving the last dose of study drug (+/- 3)	4-10 days after receiving the last dose of study drug
Week 6 (Cohort 1)	Day 35 (35-42)	1 day after Week 2 visit to Day 77
Week 16 (Cohort 1)	Day 112 (112-140)	Day 78 to 140
Early Study Discontinuation	Study day of last visit	Last study visit day

[a] *Screening and enrollment must occur within 3 days of birth, and can occur at the same visit.*
[b] *Day 0 is defined as the infant's date of birth and all follow-up visits are scheduled from this date with the exception of the 7 Days Post Dose Safety Visit.*
[c] *Analysis study week will be calculated from the date of birth, or Day 0*
[d] *If a visit falls out of the protocol defined time, then this column will be used to allow for the specific visit.*

COHORT 2

Week based on SOE [c]	Target Study Day (Protocol Allowed Window)	Analysis Window[d]
Week 0 (Screening and/or Entry)[a]	Day 0-3[b]	Day 0 to 3
Week 1	Day 7 (7-14)	Day 4 to 18
Week 4 (Cohort 2)	Day 28 (21-31)	Day 19 to 34
Week 6 (Cohort 2)	Day 35 (35-42)	Day 35 to 63
Week 12 (Cohort 2)	Day 84 (77-91)	Day 64 to 98
Week 16 (Cohort 2)	Day 112 (112-140)	Day 99 to 140
Early Study Discontinuation	Study day of last visit	Last study visit day

[a] *Screening and enrollment must occur within 3 days of birth, and can occur at the same visit.*
[b] *Day 0 is defined as the infant's date of birth and all follow-up visits are scheduled from this date.*
[c] *Analysis study week will be calculated from the date of birth, or Day 0*
[d] *If a visit falls out of the protocol defined time, then this column will be used to allow for the specific visit.*

Unscheduled visits, or visits outside of the visit window, will be defined in ADaM datasets using a decimal value of AVISITN and a corresponding AVISIT of labeled "Unscheduled Week X".

4 Data Summaries

4.1 Screening and Entry

Purpose:
To give a summary of the accrual progress of the study during interim and accrual summary for final analyses.

Analysis Program Validation:
Not required.

Data:
Date and institution of enrollment and eligibility status will be from the SES/Mastertables*; Comments related to Safety and PK exclusion will be from STUDMONR tables. Reasons for screening failures and non-enrollment will be from the SCR0054 CRF. Off-treatment reasons are from Permanent Discontinuation of Study Drug (PE4005) CRF. Off-study reasons are from Off-Study (F1601) CRF.

* Per 2007 MSWB, this includes the following original table source: PATIENT, SCASE, STEP, CURENT, CMINST, ANSTAB. Note that these will be in the DM domain.

Analysis:

4.1.1 Accrual

- Tables: Mother-infant pair accrual (Overall and by Stratum within a Cohort, at the dose being evaluated):
    - Accrual by month and by site (dates of first and last enrollment will be indicated in the text or a footnote.)
    - Accrual by stratification within a cohort
    - Total accrual

- Screening failures
    - Table: Summary of Reasons for Non-enrollment (also by Month, and Site).

4.1.2 Eligibility Violations and Analysis Status

- Listings of mother and infant eligibility criteria violations and analysis exclusions which will include (i) enrolling site; (ii) reason for eligibility violation or analysis exclusions; and (iii) team decision on whether to include in the safety/PK analyses; (iv) cohort stratification indicators.

Table 1: Eligibility Violation and Analysis Exclusion Example

Count	Enrolling site	Participant	Cohort	EFV exposure	Strat	Maraviroc dosing	Reason	Eligibility Violation	Safety Analysis Status	PK Analysis Status
1	XXX	MOTHER	1	N/A	1A	N/A	XXX	Yes	N/A	N/A
		CHILD	1	No	1A	XXX	XXX	Yes	Include*	Exclude
2	YYY	MOTHER	1	N/A	1B	N/A	YYY	No	N/A	N/A
		CHILD	1	Yes	1B	XXX	YYY	No	Include	Include

**If the participant has received the study drug, then for safety purposes, their data will be report and used in sensitivity analyses.*

4.2 Participant and Study Status

Purpose:
To describe infant study status, including whether they are on study, and whether they are evaluable for analysis.

Analysis Program Validation:
Not required.

Data:
Infant study status will be from PSTAT in CASE table. Accrued and safety/PK evaluable infants information will be from STATUS, STUDYMONR tables and ADM0022 CRF. Off-treatment reasons are from Permanent Discontinuation of Study Drug (PE4005) CRF. Off-study reasons are from Off-Study (F1601) CRF.

Analysis:

a) Study Status of the Infants:
   Table: For all enrolled participants, cross-tabulation (number and proportion) of infant study status (e.g. on/off treatment, on/off study, death)
   Table: Summary Table and listing of off-study reasons for infants

   Table: Summary Table and listing of off-treatment reasons for infants

b) Number of Infants Accrued and Evaluable for PK/Safety Analysis (by stratum by cohort and overall)

Table 2: Number of Cohort 1 Infants Accrued and were Evaluable for PK/Safety Analysis (mock-up table)

	Cohort 1A	Cohort 1B	Overall
Infants accrued	**N(%)**	**N(%)**	**N(%)**
Infants evaluable for safety analysis[a]	**N(%)**	**N(%)**	**N(%)**
Infants evaluable for PK analysis[b]	**N(%)**	**N(%)**	**N(%)**

[a] Based on infants who received at least one dose of maraviroc.
[b] Based on team determination

Note: Similar table will be generated for Cohort 2 with appropriate column labels appropriate for Cohort 2 strata.

4.3 Baseline Characteristics

Purpose:
To describe maternal and infant baseline characteristics (demographic, health status and other key parameters).

Analysis Program Validation:
Not required, but code review is recommended

Data:
Baseline is defined as the latest measurement before or on the day of first dose of Maraviroc. The following are the CRFs/tables for this section:

- Mother baseline data:
  - Demographic: race/ethnicity, age — SES/Master Table
- Infant baseline data:
  - Birth weight, birth length, APGAR score at 1 minute — NBW0014
  - Gestational age at delivery — NBW0014
  - ALT, AST, total bilirubin, creatinine — LBW0151
  - Platelet count, hemoglobin, WBC — LBW0150

Analysis:

a) For mothers: Demographics
   - Age (years): N, N missing, median, 25th and 75th percentiles, min, max, mean, standard deviation
   - Race (separate Ethnicity)
   - Ethnicity (used in the eligibility screening): N (%) by category
   - Entry ARV regimen: N (%)

b) For infants:
   Demographics/Characteristics
   - Gender
   - Race
   - Ethnicity
   - Gestational age at birth: N, N missing, median, 25th and 75th percentiles, min, max, mean, standard deviation
   - Birth weight (gram): N, N missing, median, 25th and 75th percentiles, min, max, mean, standard deviation
   - Birth length (cm): N, N missing, median, 25th and 75th percentiles, min, max, mean, standard deviation
   - APGAR score at 1 minute: N, N missing, median, 25th and 75th percentiles, min, max

Laboratory Values At Baseline

- ALT/SGPT (ukat/L): N, N missing, median, 25th and 75th percentiles, min, max
- AST/SGOT (ukat/L): N, N missing, median, 25th and 75th percentiles, min, max
- Total Bilirubin (umol/L): N, N missing, median, 25th and 75th percentiles, min, max
- Creatinine (umol/L): N, N missing, median, 25th and 75th percentiles, min, max
- Platelet count (10^9/L): N, N missing, median, 25th and 75th percentiles, min, max
- Hemoglobin (g/L): N, N missing, median, 25th and 75th percentiles, min, max
- WBC (10^9/L): N, N missing, median, 25th and 75th percentiles, min, max

c) Baseline Summaries:

- When appropriate, three sets of baseline characteristics summary tables will be generated for: (i) overall enrollments, (ii) safety evaluable participants and (iii) PK evaluable participants. Infant summary tables will include summary statistics for each stratum and overall.

Table 3: Cohort 1 Infant Baseline Characteristics (mock-up table)

Characteristics		**Cohort 1A**	**Cohort 1B**	**Overall**
Birth Weight (g)	**N**	N (X%)	N (X%)	N (X%)
	N missing	N (X%)	N (X%)	N (X%)
	Min-Max	X - Y	X - Y	X – Y
	Median (Q1-Q3)	X (Y –Z)	X (Y – Z)	X (Y- Z)
	Mean (std dev)			
Additional rows for the rest of the baseline characteristics				

Note: Similar table will be generated for Cohort 2 with appropriate column labels appropriate for Cohort 2 strata of infants.

4.4 Data Completeness for Safety Data

Purpose:
To summarize data completeness according to the scheduled visits for infant safety data.

Analysis Program Validation:
Not required.

Data:
Infant observed visit data are from the following CRFs: LBW0150 (LBDTC, AEDTC) for hematologies, LBW0151 (LBDTC, AEDTC) for liver chemistries, and ADE0003 (AEDTC) for signs/symptoms and diagnoses.

Analysis:

a) Infant Safety Data Collection Schedule and Visit Windows for Cohort 1 and 2

Table 4: Infant Safety Data Collection Schedule for Cohort 1

Study Visit	Screen	Entry	Week 1	7 Days Post Dose Safety	Week 6	Week 16 or Early Study Discontinuation
Visit Window	0 – 3 days	0 – 3 days	7 – 14 days	+/- 3days	35 – 42 days	112 – 140 days
Analysis Window	0 to 3	0 to 3	4 to 18 (or 1 day before Week 2 visit)	4-10 days after receiving the last dose of study drug	1 day after Week 2 visit to 77	78 to 140
Hematologies (LBW01050)	X		X	X	X	X
Liver Chemistries (LBW0151)	X		X	X	X	X
Signs/Symptoms and Diagnoses (ADE0003)	X		X	X	X	X

Table 5: Infant Safety Data Collection Schedule for Cohort 2

Study Visit	Screen/Entry	Week 1	Week 4	Week 6	Week 12	Week 16 or Early Study Discontinuation
Visit Window	0 – 3 days	7 – 14 days	21 – 31 days	35 – 42 days	77 – 91 days	112 – 140 days
Analysis Window	0-3	4 to 18	19 to 34	35 to 63	64 to 98	99 to 140
Hematologies (LBW0150)	X	X	X	X	X	X
Liver Chemistries (LBW0151)	X	X	X	X	X	X
Signs/Symptoms and Diagnoses (ADE0003)	X	X	X	X	X	X

b) Data Completeness Summaries of Infant Safety Data

Table: Frequency of infant expected and observed clinic visits with completed forms of IMPAACT 2007 Hematologies (LBW0150), Liver Chemistries (LBW0151), Signs/Symptoms and Diagnoses (ADE0003).

Note: Separate tables will be created for infant subgroups and overall.

5 Primary and Secondary Analyses

Procedures

Safety data will include death, signs/symptoms, diagnoses and laboratory test results, which will include results of evaluations specified in the protocol and results from the infant's clinical care.

Note: If an infant has unevaluable PK data, which reflects uncertainty about appropriate exposure to the study drug, then the infant will be replaced and will be excluded from both the PK and safety analyses during the dose-evaluation. However, the infant may be allowed to continue on study drug and will be followed through week 16. It may be necessary to prefer sensitivity analyses on the final data to test whether the results of the final safety analysis are consistent with and without this infant's data.

5.1 Safety Analysis for SDAC Final Report

Purpose:
To list the endpoints and tables of primary and secondary safety analyses for the SDAC final report.

Primary Safety Endpoints (from the initial maraviroc dose through week 6 of life)

- For dose finding purposes: Any life threatening adverse event, including death, assessed as at least possibly related to the study drug, adverse events of grade 3 or higher judged by the Core Protocol team to be probably or definitely related to the study drug, or that result in permanent discontinuation of study drug due to an adverse event, judged by Core Protocol Team to be at least possibly related to study drug. (Cohort 1: through 7 Day Post Dose Visit; Cohort 2: through Week 6 visit)

- For analysis purposes: Any life threatening adverse event, including death, assessed as at least possibly related to the study drug, adverse events of Grade 3 or higher judged by the Core Protocol team to be probably or definitely related to the study drug, or that result in permanent discontinuation of study drug due to an adverse event, judged by the Core Protocol Team, to be at least possibly related to study drug. (Cohort 1 and Cohort 2: through Week 6 Visit).

Secondary Safety Endpoints (from the initial maraviroc dose through week 16 of life)
Safety:

- For analysis purposes: Any life threatening adverse event, including death, assessed as at least possibly related to the study drug, adverse events of Grade 3 or higher judged by the Core Protocol team to be probably or definitely related to the study drug, or that result in permanent discontinuation of study drug due to an adverse event, judged by the Core Protocol Team to be at least possibly related to the study drug**.**

Primary Outcome Measures (from the initial maraviroc dose through week 6 of life)

- Safety: All adverse events (all severity grades).

Secondary Outcome Measures (from the initial dose of maraviroc through week 16 of life)

- Safety: All adverse events (all severity grades).
- Tropism: (1) Infant's viral tropism after expose to maraviroc (infants who are HIV-1 infected only); (2) Viral tropism at entry (mothers of infants who are HIV-1 infected only).

Analysis Program Validation:

Code review required. Primary/Secondary analyses for both primary/secondary safety endpoints will require double coding.

Data:
Infant safety data are adverse clinical and laboratory events reported on the following CRFs: Hematology (LBW0150), Liver Chemistries (LBW0151), Signs/Symptoms and Diagnosis (ADE0003) and Death (PE1414). The following variables in the SDAC SAS datasets will be used: AETERM, LBTOXGR, AESEV, and AETRTREL;(team's drug attribution assessment variable) in ADE0003; and Code =40 (Subject reached protocol-defined toxicity endpoint) of Reason for Treatment Discontinuation of PE4005 CRF.

Analysis:

5.1.1 Primary Safety Analysis of Data Representing Exposure to the Final Doses Selected For Each Stratum Within a Cohort (Data from the initial maraviroc dose through week 6 of life)

The primary analyses will be conducted for each stratum within a cohort based on infants who were exposed to the final selected dose and will be restricted to data from the initial maraviroc dose through week 6 of life.

Each participant's safety data will be summarized as: the worst grade of adverse event experienced, and the worst grade of adverse event assessed as at least probably related to study drug. Frequency distributions of these safety outcomes will be presented. Also, listings of all Grade 3 or higher events will be provided, including the Core Protocol Team's attribution to the study drug, and adverse events deemed to be at least possibly related that result in permanent discontinuation of study drug.

Tables and Listings:

The safety analysis will consist of listings and descriptive statistics summarizing outcomes by strata within cohorts, bounded by exact 95% confidence intervals.

<u>Safety endpoint tables:</u>

- Tables for the primary safety endpoint for the final analysis:
  - Summary table [number (%) and 95% exact CI] and listing of life-threatening adverse events, including death, judged by the protocol team to be at least possibly related to Maraviroc

- Summary table [number (%) and 95% exact CI] and listing of adverse events of Grade 3 or 4 severity judged by the protocol team as non-life threatening, and probably related or definitely related to Maraviroc
- Summary table [number (%) and 95% exact CI] and listing of adverse events which lead to permanent termination of study treatment judged to be at least possibly related to Maraviroc.

Additional Safety Outcome Tables

- Summary table [number (%)] and listing of the worst grade adverse event experienced.
- Summary table [number (%)] and listing of the worst grade adverse event experienced assessed as at least probably related to Maraviroc.
- Summary table [number (%)] and listing of adverse events of Grade 3 or 4 severity. The listing will include the team's attribution to Maraviroc.
- Summary table [number (%)] and listing of participant deaths. The listing will include the team's attribution to Maraviroc.

Table 6: Proportion of Cohort 1 Infants Meeting the Primary Safety Endpoint (mock table)

Primary Safety Endpoints	Cohort 1A	Cohort 1B	Total
Participants who had life-threatening adverse events, including death, judged by the protocol team to be at least possibly related to Maraviroc	N (%) [95% CI]	N (%) [95% CI]	N (%) [95% CI]
Participants who had adverse events of Grade 3 or 4 severity judged by the protocol team as non-life threatening, and probably related or definitely related to Maraviroc	N (%) [95% CI]	N (%) [95% CI]	N (%) [95% CI]
Participants who had adverse events which lead to permanent termination of study treatment judged to be at least possibly related to Maraviroc.	N (%) [95% CI]	N (%) [95% CI]	N (%) [95% CI]

Note: Similar table will be generated for Cohort 2 with appropriate column labels appropriate for Cohort 2 strata.

Table 7: Proportion of Cohort 1 Infants Meet the Additional Safety Outcomes

Additional Safety Outcomes	Cohort IA	Cohort IB	Total
Participants with AEs of grade 3 or 4 severity	N (%) [95% CI]	N (%) [95% CI]	N (%) [95% CI]
Participants with death	N (%) [95% CI]	N (%) [95% CI]	N (%) [95% CI]

5.1.2 Secondary Safety Data Analyses on Final-Dose and All-Treated Participants for Final Analysis Reports (Data from the initial maraviroc dose through week 16 of life)

The secondary analyses will be conducted for each stratum within a cohort based on infants who were exposed to the final selected dose, and from all-treated participants, and will be restricted to data from the initial maraviroc dose through week 16 of life.

Tables and Listings:

The safety analysis will consist of the same analyses as detailed in Section 6.1.1.

Listings of infants' adverse events which occurred between Day 0 (birthdate) and up to when the first dose of maraviroc is taken will also be presented.

5.2 Safety Analysis for Dose Finding

Purpose:
To list the endpoints and summary tables of safety analysis for dose finding. Analyses will be generated for the full accrual of Strata 1A, 1B, 2A, 2B, and at the interim mini-cohorts, at specific doses being tested.

Analysis Program Validation:
Code review required. Primary analysis will require double coding.

Data:
Infant Safety Data are adverse clinical and laboratory events reported in Hematology (LBW0150), Liver Chemistries (LBW0151) Signs/Symptoms and Diagnosis (ADE0003) and Death (PE1414) CRFs. The following variables in the SDAC SAS datasets will be used: AETERM, LBTOXGR, AESEV, and AETRTREL; (team's drug attribution assessment variable) in ADM0003; and Code =40 (Subject reached protocol-defined toxicity endpoint) of Reason for

Treatment Discontinuation of PE4005 CRF.

Analysis:
If an infant has unevaluable PK data, which reflects uncertainty about appropriate exposure to the study drug, then the infant will be excluded from the safety analyses during the dose-evaluation, provided the infant does not have any toxicities related to Maraviroc.

AEs will exclude events classified by the team as "baseline" or "ongoing baseline" events.

a) Summary table for the interim and cohort full accrual safety reports (analysis for dose finding).

   Note: The analysis will be done for the following timeframe: Cohort 1 (through 7 Day Post Dose Visit); Cohort 2 (through Week 6 Visit).

   Table: Summary table showing number (%) [95% Exact CI] of infants who meet the safety endpoints for dose finding and possible early study discontinuation.

Table 8: Summary of Infants Meeting the Safety Endpoints for Dose Finding For Each Stratum within a Cohort

Endpoint	Number and Proportion	95% Exact CI
Life threatening adverse event including death assessed as at least possibly related to the study drug,	N (%)	
Non-life threatening Grade 3 or higher adverse event judged to be probably or definitely related to study drug	N (%)	
Permanent discontinuation of study drug due to an AE, judged to be at least possibly related to study drug	N (%)	
Meeting any of the three safety guideline endpoints	N (%)	

b) Safety Data Listing: For each starting dose within each stratum, every grade 3 or higher adverse event, and permanent treatment discontinuations due to an AE will be listed, along with participant demographics, the dose prescribed to the participant at the time of the event and the protocol team's assessment of the probability that this event was due to the study drug.

5.3 Infant Infection Testing

Purpose:
To describe the infant HIV infection status.

Analysis Program Validation:
Not required.

Data:
SCORRES where SCTESTCD=”HIVSTAT” holds the current infection status.

Analysis:
Table: Frequency and proportion of infants who become HIV- infected will be presented and bounded by 95% exact confidence intervals. The results will be presented separately for each stratum within a cohort.

Listing of HIV Nucleic Acid Test Results
All Treated Neonates

Cohort	Participant Number	Visit	RNA Specimen Relative Day	RNA Specimen Date	RNA Assay Result (copies/mL)	DNA Specimen Relative Day	DNA PCR Specimen Date	DNA Assay Result

5.4 Tropism Testing (By Strata within a Cohort and Aggregated)

Purpose:
In the event of perinatal transmission of an X4/dual-mixed tropic strain of HIV, to explore the impact of maraviroc treatment on viral tropism.

Analysis Program Validation:
Not required.

Data:
From the VIROTROP table

Analysis:
Table: Listing of Viral Tropism for HIV infected infants compared with their respective mother’s Viral Tropism at entry.

Exploratory analysis will be performed in infants who become HIV-1 infected: (1) to determine the infant’s viral tropism after exposure to maraviroc; and (2) to assess if the infant’s viral tropism matches the mother's.

Therefore, this will be a listing of the infected infant’s tropism and the corresponding tropism of the mother.

5.5 Study Monitoring Committee (SMC) Review Reports

Purpose and Mechanism: To provide accrual, toxicity and/or PK reports for the SMC review for the following occasions, as specified in the protocol:

- Routine SMC reviews of participant accrual, retention, study conduct, and safety will be performed annually.
- Ad hoc SMC Review: In the event of any unresolvable disagreement within the Core Team on an issue which would impact decision making or if the Core Team encounters any other event or trend of concern, an SMC review of the relevant data will be requested. The Core Protocol Team may choose to suspend accrual and/or administration of study drug, pending the outcome of the SMC review.

Analysis Program Validation: Code review is required. Primary analysis for primary safety endpoint will require double coding.

Data: Infant safety data are adverse clinical and laboratory events reported on the following CRFs: Hematology (LBW0150), Liver Chemistries (LBW0151), Signs/Symptoms and Diagnosis (ADE0003) and Death (PE1414). (The following variables in the SDAC SAS datasets will be used: AETERM, LBTOXGR, AESEV, AETERM, and AETRTREL;(team's drug attribution assessment variable) in ADE0003) and reasons for treatment discontinuations using PE4005 CRF

Analyses:
Summary tables and listings similar to reports mentioned above, which may include but not limited to:

- Accrual report
- Study Status Report
- Screening Failure Report
- Baseline Characteristic Report
- ARV Regimen Report (see Study Monitoring Plan Version 1.0)
- Safety Summary Report
    - Safety analyses will be based on all data available at the time of preparation of the SMC report, and adverse events will be summarized by stratum within each cohort and in aggregate for each cohort.
    - This will also include notes from the interim safety report (if interim checks on safety have been done on the strata).
- PK Report (completed by team pharmacologist)
- Retention (study/participant summary report)
- Data and specimen completeness
- Data Delinquency report (appendix)