This is the IMPAACT P1090 SAP Version 3.0 with names of authors, names of publication writing team members and analysis timeline redacted

IMPAACT P1090
A Phase I/II, Open-Label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Etravirine (ETR) in Antiretroviral (ARV) Treatment-Experienced HIV-1 Infected Infants and Children, Aged ≥ 2 Months to <6 Years

Statistical Analysis Plan
(For Protocol Version 5.0 with Letter of Amendment #1 Dated March 30, 2018)
Version 3.0

Weeks 24 and 48 Primary Analyses
(Week 240 Secondary Analysis)

Date
February 27, 2019

1 INTRODUCTION

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures of P1090 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. It is recognized that this statistical analysis plan (SAP) may be modified by the Study Team as new information becomes available.

The P1090 SAPs, Version 1 (dated 11/30/2011), Version 2 (dated12/7/2018), and the current version, do not address the interim data analyses for Janssen's submissions to regulatory agencies. As mentioned in P1090 protocol section 8.6324, Janssen performs these interim data analyses for their regulatory submissions, using P1090 study datasets provided to Janssen by the IMPAACT Data Management Center.

Data for the Primary Statistical Analysis Report will be downloaded once the last participant of the last cohort has completed the Week 48 study visit, all queries have been resolved, and the database frozen for analysis. The Primary Statistical Analysis Reports 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 48 weeks of treatment. A second submission to ClinicalTrials.gov will be done within one year after the last enrolled participant reaches Week 288 the last visit of the long-term safety follow-up) at which time point the adverse event tables will be updated.

2 STUDY DESIGN

This is a Phase I/II, multicenter, open label 48 week pharmacokinetic, safety, tolerability and antiviral study of etravirine in combination with at least 2 active ARVs, including a boosted PI and NRTIs for treatment experienced HIV-1-infected infants and children $\geq$ 2 months to < 6 years cohorts.

The study will, in a sequential manner, accrue subjects for an initial dose finding intensive PK component for age related cohorts. It is expected that approximately 50 subjects will be accrued, to yield a minimum of 36 evaluable subjects (a minimum of 12 subjects in each cohort). Up to 18 subjects may be enrolled into Cohort I. The total sample size will depend upon the number needed to complete the dose finding stage of the study and the number of subjects required for regulatory approval of etravirine in these populations.

Evaluable will be defined as having been treated exclusively on the dose determined to be optimal for a given age cohort and having either completed 24 (or 48) weeks of exposure to the study drug or having been classified as a safety failure, due to a study drug related adverse event occurring during the first 24 (or 48) weeks of treatment.

The P1090 core protocol team will be responsible for reviewing the PK and safety data and approving the dose selection for each full and mini-cohort. The P1090 core protocol team will consist of the protocol chair and co-chairs, clinical trials specialist, NIAID and NICHD Medical Officers, data manager, pharmacologists, pharmacist, statisticians and Janssen representatives.

This study is designed to determine the appropriate etravirine dose for HIV-1-infected infants and children and to evaluate the PK, safety and tolerability of etravirine in this population. Etravirine (ETR) will be administered as 25 mg scored tablets and/or 100 mg tablets swallowed as a whole or dispersed in an appropriate liquid vehicle (see Section 5.2). ETR will be started concurrently with an optimized background regimen (OBR), while OBR will be based on clinical status, treatment history, resistance data and availability of appropriate pediatric dosing and formulations.

Children will be stratified by age, as follows:

- Cohort I: ≥ 2 year to < 6 years who are treatment experienced*
- Cohort II: ≥ 1 year to < 2 years who are treatment experienced*
- Cohort III: ≥ 2 months to < 1 year who are treatment experienced*, †

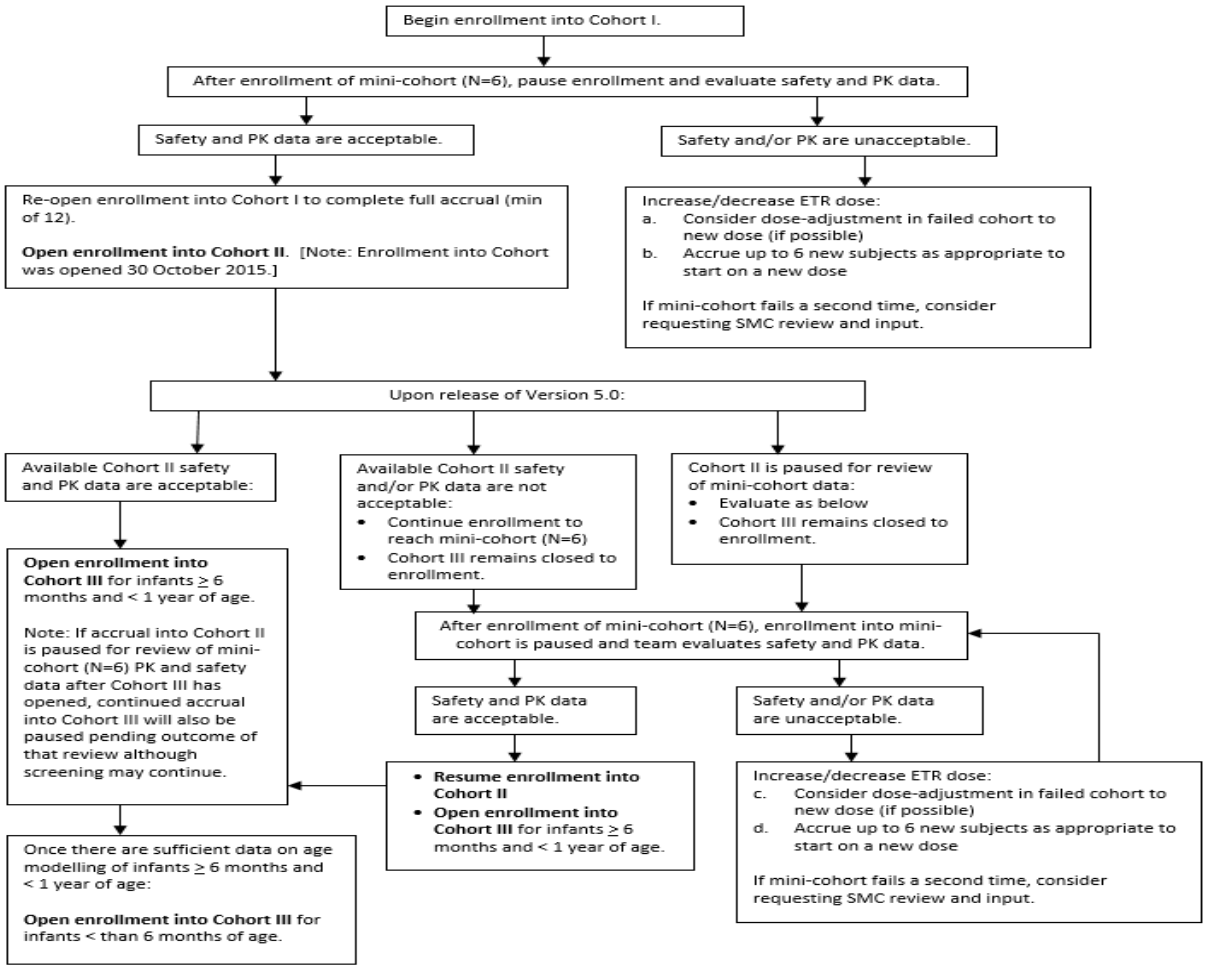
*Treatment experienced children on a failing combination antiretroviral regimen (containing at least 3 ARVs) for at least 8 weeks OR Treatment experienced children on a treatment interruption of at least 4 weeks with a history of virologic failure while on a combination antiretroviral regimen (containing at least 3 ARVs)

† Subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects between 6 months and 1 year of age.

3 STUDY ALGORITHM

General Guidelines:

- Younger mini-cohorts will open when the mini-cohort (6) from the previous older cohort passes the safety (≤ 28 day data) & Day 7-12 PK evaluation (see Section 3.3)



4 STUDY OBJECTIVES

Primary Objectives:

1. To evaluate the pharmacokinetics of etravirine in combination with an OBR in HIV-infected children aged ≥ 2 months to < 6 years
2. To determine the safety and tolerability of etravirine in combination with an OBR through 48 weeks of therapy.
3. To determine the appropriate dose of etravirine in combination with an OBR for children aged ≥ 2 months to < 6 years.

Secondary Objectives:

1. To assess the antiretroviral activity of ETR containing regimens through 48 weeks of therapy.
2. To determine the immunological changes (change in CD4 percent and absolute count; CD4/CD8 ratio and percent) through 48 weeks of ETR therapy in combination with an OBR.
3. To determine changes in viral drug resistance during 48 weeks of ETR therapy in combination with an OBR.
4. To assess the relationship between ETR pharmacokinetics and the antiviral activity and safety of ETR containing regimens.\
5. To explore the relationship between subject-specific gene CYP profile, sex, age, weight, race, HIV regimen (e.g., boosted PI) and HIV response markers and pharmacokinetics of ETR.

5 ENDPOINTS AND OUTCOME MEASURES

Primary Endpoints:

Toxicity Endpoints:
- Termination from treatment due to a suspected adverse drug reaction (SADR)
- Adverse events of Grade 3 or higher severity
- Death

Pharmacokinetic Endpoint:
- Failure to meet PK targets (specified in Section 9.0)

Secondary Endpoints:
- Adverse events of Grade 3 or higher severity judged to be at least possibly attributable to the study medications
- Confirmed failure to suppress plasma HIV-1 RNA to ≤ 400 copies
- AND
- Failure to achieve at least a 2 log reduction (from baseline) in HIV-1 RNA at weeks 24 and/or 48 (confirmed in 1 to 4 weeks)
- Treatment discontinued due to toxicity or virologic failure
- Change in optimized background regimen due to virologic failure
- New onset OI or AIDS diagnosis
- Decline in absolute CD4 percent of > 5% any time after 12 weeks of therapy

Primary Response Variables:
• Pharmacokinetic parameters - AUC12h

Secondary Response Variables:
• Plasma HIV-1 RNA (copies/mL)
• CD4 counts and percent
• CD4/CD8 ratio and percent
• Genotypic and phenotypic measures of resistance at virologic failure and at early discontinuation
• Pharmacokinetic parameters - C12h and Cmax

Exploratory Response Variables:
• Patient-specific CYP gene profiles.

6 STATISTICAL METHODS AND RESULTS

6.1 *Administrative Data: Accrual and Baseline Demographics*

- Frequency tables on accrual in aggregate and broken down by cohort
- Reasons/frequencies for treatment discontinuation in aggregate and broken down by cohort
- Deaths (if any): Frequency, list of patients and complete etiologies
- Baseline Demographics: provides descriptive statistics for some of the variables of interest such as: gender, race and/or ethnicity, weight, age, RNA and CD4 (count and percentage) in aggregate and broken down by cohort

6.2 Safety

- Summary of Dose Finding Data (Through Week 4 – the point up to which the safety criteria are applied)

  Descriptive statistics summarizing the safety data during the dose finding phase of the study. The safety data will be broken down by cohort and will present the results of the safety evaluations applied to each starting dose tested within each cohort, including information indicating which starting doses have passed or failed the safety guidelines. For each starting dose within each cohort, every adverse event of grade 3 or higher will be listed, along with patient demographics, the dose prescribed to the patient at the time of the event and the protocol team's assessment of the probability that this event was due to the study treatment.

- Analysis of Data Representing Exposure to the Doses Judged to be Optimal for Each Cohort

  Primary Analysis of Safety: consists of data from "evaluable" patients only, performed on data through the weeks 24 and 48 visit at the final dose.

  Each patient's safety data will be summarized as: the worst grade of adverse event experienced while on the first 24 and 48 weeks on the optimal dose of the study treatment and the worst grade of adverse event judged to be at least possibly due to study treatment during this time

period. Frequency distributions of these safety outcomes will be presented in the aggregate and broken down by cohort. Listings of all Grade 3+ events will be provided, broken down by type of toxicity (hepatic, hematologic, etc.).

The proportions of subjects experiencing grade 3+ adverse events will be presented in aggregate and broken down by Cohort, with these proportions bounded by exact 95% confidence intervals. Similar analyses will present the proportions of subjects exhibiting grade 3+ events which have been judged to be at least possibly related to study medication, again bounded by exact 95% confidence intervals.

NOTE: Given that the small sample sizes within cohorts will provide limited power for statistical tests of differences across age cohorts, interpretation of the results will depend upon whether differences across cohorts are great enough to be considered to be clinically significant. If no such differences are observed, then the clearest interpretation of the findings will come from the aggregated data, where analyses will have the greatest statistical precision. However, if results vary across cohorts to a clinically important extent, interpretation of results should take into account the issues represented by the stratification factor.

Key Secondary Safety Analysis

Safety assessments will be performed on long term data collected until the final patient reaches 5 years of follow-up. The key analyses will be similar to the Weeks 24 and 48 analyses described above, which will be performed on the data for all subjects through 5 years of follow-up.

6.3 Pharmacokinetics (this will come from the protocol pharmacologist)

6.4 Viral Load at Weeks 24 and 48:

Virologic outcomes, based on HIV-1 RNA (copies/ml), will be assessed at weeks 8, 12, 24 and 48. The criteria for success are: at least a 0.5 log10 reduction in HIV-1 RNA (copies/ml) at week 8, at least a 1 log10 reduction in HIV-1 RNA (copies/ml) at week 12 and either HIV-1RNA <400 copies/ml or at least a 2 log reduction in HIV-1 RNA at weeks 24 and 48.

At each of these time points the primary definition of virologic outcome will be calculated according to a Missing, Switch or Discontinuation = Failure (MSDF) algorithm – as codified by the FDA's snapshot algorithm. Subjects will be classified as virologic failures if they have missing HIV-1 RNA data throughout the window surrounding the time point of interest.

In addition subjects will be classified as virologic failures at any of these time points if they meet any of the following conditions prior to that time point:

a) Discontinuation of study treatment (except as allowed in protocol for Cohort IIIB subjects whose screening resistance data is not available at time of treatment initiation, but indicates lack of sensitivity to ETR when it becomes available);
b) Change in background therapy not allowed in the protocol;
c) Change in background ART substitutions permitted per protocol but prescribed while HIV-1 RNA ≥400 copies/mL, unless the decision to switch is documented as being before or at the first on-treatment visit where HIV-1 RNA is assessed (Week 4).

6.5 Immunologic Response: CD4 Count and Percentages at Weeks 24 and 48:

Change from baseline to weeks 24 and 48 in CD4 count, CD4 percent and CD4/CD8 ratio will be bounded by 95% confidence intervals and presented both in the aggregate and by age cohort. In addition, the proportions of subjects exhibiting an absolute drop of >5% in CD4 percent from baseline to weeks 12, 24 and 48 will be presented, bounded by 95% confidence intervals. Subjects who meet any of the conditions (a) to (c) of Section 8.6321 or who have absolute drop of >5% in their CD4% will be considered as treatment failures in these analyses.

6.6 *HIV Drug Resistance*

Correlations between baseline HIV genotypic and phenotypic drug resistance and any subsequent virologic failure will be evaluated. Subjects will be assessed for HIV genotypic and phenotypic drug resistance to the OBT and etravirine at screening, at the time of virologic failure (if this occurs) and at early discontinuation.

7 Week Windows for Analyses:

The week windows for all analyses will be as follows:

Study Day of Assessment	Assessment Window	Target Study Day of Window
-3 to 1	Week 0	1
2 to 42	Week 4	29
43 to 70	Week 8	57
71 to 98	Week 12	85
99 to 140	Week 16	113
141 to 196	Week 24	169
197 to 252	Week 32	225
253 to 308	Week 40	281
309 to 378	Week 48	337
379 to 462	Week 60	421
463 to 546	Week 72	505
547 to 630	Week 84	589
631 to 714	Week 96	673
715 to 798	Week 108	757
799 to 882	Week 120	841
883 to 966	Week 132	925
967 to 1050	Week 144	1009
1051 to 1134	Week 156	1093
1135 to 1218	Week 168	1177
1219 to 1302	Week 180	1261
1303 to 1386	Week 192	1345

1387 to 1470	Week 204	1429
1471 to 1554	Week 216	1513
Study Day of Assessment	Assessment Window	Target Study Day of Window
1555 to 1638	Week 228	1597
1639 to 1722	Week 240	1681
1723 to 1806	Week 252	1765
1807 to 1890	Week 264	1849
1891 to 1974	Week 276	1933
1975 to 2030	Week 288	2017
> (Study Day of last dose + 1)	Follow-up	Study Day of last dose + 14