IMPAACT 2014

PHASE I/II STUDY OF THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF DORAVIRINE (MK-1439) AND DORAVIRINE/LAMIVUDINE/TENOFOVIR DISOPROXIL FUMARATE (MK-1439A) IN HIV-1-INFECTED CHILDREN AND ADOLESCENTS
(Protocol Version 1.0)

Pharmaceutical Support Provided by: Merck & Company Inc.

NCT03332095
DAIDS Study ID #34150
IND #137,041 Held by NIAID/DAIDS

Primary Statistical Analysis Plan
Version 1.0

This is IMPAACT 2014 SAP Version 1.0 with names of authors and names of publication writing team members redacted.

June 4, 2020

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Version History

Version	Changes Made	Date Finalized
1.0	Original Version per Protocol Version 1.0	06/04/2020

1. Introduction

This Primary Statistical Analysis Plan (SAP) describes the proposed content for the primary statistical analysis of IMPAACT 2014, focusing on analyses that address the primary and secondary objectives for key pharmacokinetics (PK), safety, tolerability and efficacy outcome measures. These key analyses are intended to form the core of any presentation or publication used to disseminate the primary conclusions of the study.

This document has been developed to facilitate the discussion between the statisticians, study team, and industry sponsors regarding the statistical analyses to be performed and presented in the Primary Analysis Report. It also describes the timeline for reporting the results of the primary and secondary outcome measures that will be posted on ClinicalTrials.gov. More detailed specifications of the planned analyses, such as data sources, table/figure specifications, definitions of data-driven coding, and validation requirements, are presented in a separate document called, Analysis Implementation Plan (AIP). All PK analyses will be performed by the study pharmacologist who will draft a separate PK analysis plan. Also, a separate SAP for other objectives and outcome measures will be developed once results for the primary and secondary objectives are known, and the corresponding analyses will be presented in a separate report.

It is recognized that the primary SAP may be modified by the study team as new information becomes available or to reflect recommendations made by the SMC, if there are any.

All tables, figures and listings created based on the analyses described in this document will be shared with the industry sponsors.

2. Key SAP Updates

N/A

3. Study Overview

3.1 Study Design

IMPAACT 2014 is a Phase I/II study whose primary objectives are to evaluate the PK, safety, and tolerability of a single dose of 100 mg doravirine (DOR, MK-1439) and once daily regimen of doravirine (100 mg)/lamivudine (300 mg)/tenofovir disoproxil fumarate (300 mg) (DOR/3TC/TDF, MK-1439A) in HIV-1-infected children and adolescents 12 years to less than 18 years of age who weigh at least 35 kg. Participants will be enrolled into two sequential cohorts, Cohort 1 and Cohort 2. Participants will first be enrolled into Cohort 1 to evaluate the PK and safety of the 100 mg single dose of DOR, with intensive PK evaluations completed at entry and followed through two weeks on study to assess safety. Upon enrollment of a minimum of 12 evaluable participants (with a minimum of four participants between 35 and ≤45 kg), enrollment will be paused while the Cohort 1 PK and safety data are reviewed by the protocol team and the SMC. If results from Cohort 1 are supportive, Cohort 2 will open to enrollment to evaluate the safety and tolerability of the once daily fixed-dose combination regimen (DOR/3TC/TDF). The group of participants in Cohort 1 who meet the PK targets with no safety concerns will establish the weight threshold for enrollment into Cohort 2.

Note: Since identification of participants in the 35-≤45 kg weight group for enrollment into Cohort 1 turned out to be challenging, the protocol team and SMC reviewed the Cohort 1 safety and PK data for the >45 kg participants and determined that Cohort 2 can be opened to accrual for this weight group, while Cohort 1 remained open. The protocol was modified via Letter of Amendment (LoA) #2 to allow enrollment of participants >45 kg into Cohort 2, while attempting, but not requiring, to enroll at least four participants between 35 and ≤45 kg in Cohort 1.

A minimum of 40 evaluable participants will be accrued to Cohort 2. The first 10 participants will have intensive PK evaluations at Week 1 to evaluate the pharmacokinetics of 3TC and tenofovir (PK samples for DOR will also be collected at a subset of intensive time points). Sparse PK samples for DOR, 3TC, and tenofovir will be collected through Week 48 for all participants and they will be followed on treatment/study for 96 weeks. Safety, virologic, and immunologic outcomes will be collected longitudinally and analyzed at Weeks 24, 48 and 96.

3.2 Study Monitoring

PARTICIPANT SAFETY: On behalf of the Protocol Team, the Clinical Management Committee (CMC) will closely monitor participant safety. An independent IMPAACT Study Monitoring Committee (SMC) will also review this study regularly. SMC reviews will occur at least annually and may also occur on a more frequent or *ad hoc* basis if any issues or concerns arise, or if requested by the SMC or CMC. Please refer to section 9.6.2 of the protocol for details regarding safety-related events that would trigger an *ad hoc* SMC review.

DOSE EVALUATION: During the dose evaluation stage of this study (Cohort 1), the CMC will review the pharmacokinetic data, with the aim of confirming the dose for Cohort 2 while protecting participant safety. Prior to opening Cohort 2 to accrual, the CMC and SMC will review all PK and safety data from Cohort 1. If Cohort 1 fails the PK targets or there are safety concerns, an SMC review will be convened to determine under what conditions Cohort 2 may open to accrual.

As this is a small Phase I/II study there will be no use of formal interim statistical stopping rules.

3.3 Hypothesis

This is an estimation study; thus, there is no hypothesis testing.

3.4 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.

3.4.1 Primary Objectives and Outcome Measures

Primary Objectives for Cohort 1

- Evaluate the pharmacokinetics of a single dose of DOR in HIV-1-infected children and adolescents, when added to a stable ART regimen comprised of an InSTI plus two NRTIs, using intensive PK sampling at Entry for identification of minimum weight threshold for doravirine 100 mg dose.
- Evaluate the 2-week safety and tolerability of a single dose of DOR in HIV-1-infected children and adolescents, when added to a stable ART regimen comprised of an InSTI plus two NRTIs.

Primary Outcome Measures for Cohort 1

Pharmacokinetics

- Single-dose $AUC_{0-\infty}$, C_{max}, and C_{24hr} of DOR

Safety and Tolerability through Week 2

- Safety Outcome: All adverse events, regardless of severity grade
- Toxicity Endpoints Related to Study Drug: ≥ Grade 3, serious, discontinuation of study drug
- Death regardless of relationship to study drug

Primary Objective for Cohort 2

- Evaluate the 24-week safety and tolerability of DOR/3TC/TDF in HIV-1-infected children and adolescents.

Primary Outcome Measures for Cohort 2

Safety and Tolerability through Week 24

- Safety Outcome: All adverse events, regardless of severity grade
- Toxicity Endpoints Related to Study Drug: ≥ Grade 3, serious, discontinuation of study drug
- Death regardless of relationship to study drug

3.4.2 Secondary Objectives and Outcome Measures

Secondary Objectives for Cohort 2

- Evaluate the pharmacokinetics of DOR, 3TC, and tenofovir in HIV-1-infected children and adolescents receiving DOR/3TC/TDF, using intensive (tenofovir and 3TC) and semi-intensive (DOR) PK sampling at Week 1.
- Evaluate the 24-, 48-, and 96-week virologic efficacy of DOR/3TC/TDF in HIV-1-infected children and adolescents.
- Evaluate the 24-, 48-, and 96-week immunologic response (CD4 cell count and percentage change from baseline) of HIV-1-infected children and adolescents.
- Evaluate the 48- and 96-week safety and tolerability of DOR/3TC/TDF administered in HIV-1-infected children and adolescents.

Secondary Outcome Measures for Cohort 2

Pharmacokinetics through Week 1

- AUC_{0-24hr}, C_{max}, and C_{24hr} of DOR, 3TC, and tenofovir

Virologic Efficacy at Weeks 24, 48, and 96

- Plasma HIV-1 RNA<200 copies/mL
- Plasma HIV-1 RNA<50 copies/mL
- Plasma HIV-1 RNA<40 copies/mL
- Log10 drop from baseline in plasma HIV-1 RNA (ART-naïve participants)

Immunologic Response at Weeks 24, 48, and 96

- Change in CD4 count and percent from baseline

Safety and Tolerability through Weeks 48 and 96

- Safety Outcome: All adverse events, regardless of severity grade
- Toxicity Endpoints Related to Study Drug: ≥ Grade 3, serious, discontinuation of study drug
- Death regardless of relationship to study drug

Note: Results for the primary outcome measures are required to be submitted to ClinicalTrials.gov within one year of the Primary Completion Date (PCD) which, for this study, is the date when the Week 24 data has been collected for the last participant enrolled in Cohort 2. Data for evaluating virologic efficacy and immunologic response through Week 24 will be evaluated concurrently with the data for the primary objective for Cohort 2 (i.e., 24-week safety and tolerability of DOR/3TC/TDF). Longer-term secondary objectives such as safety, virologic efficacy, and immunologic response of DOR/3TC/TDF through Weeks 48 and 96 will be evaluated as outcome measures become available. The results for these longer-term secondary objectives will be posted to ClinicalTrials.Gov no later than one year after the last participant enrolled in Cohort 2 has reached Week 96.

4. Statistical Principles

4.1 General Considerations

- Information regarding analysis populations are provided below:

  - All Treated Population: Participants who have taken at least one dose of study drug.

4.2 Visit Schedule and Analysis Windows

For Cohort 1 and Cohort 2, study entry occurs within 30 days of screening. For analysis purposes, the day the participant takes the first dose of the study drug (*First Dose Date*), and not the study entry date, will be used as the reference for calculating the *Study Day of Assessment*.

Pre study entry, *Study Day of Assessment* will be calculated as:

Study Day of Assessment = (Assessment Date – First Dose Date)

Post study entry, *Study Day of Assessment* will be calculated as:

Study Day of Assessment = (Assessment Date – First Dose Date) + 1

This value will be used to determine the study visit associated with the assessment. In order to include assessments collected outside the visit windows defined in the protocol, wider *Analysis Windows* will be formed around each study visit using the midpoints between adjacent weeks as cutoffs. If there are multiple assessments within the *Analysis Window* for a given study week, the assessment closest to the *Target Study Day* will be used.

BASELINE: For all endpoints and outcome measures, the value used for baseline (Week 0) will be the latest measurement taken anytime from thirty days before *First Dose Date* through *First Dose Date*. Unless otherwise stated, if baseline values are missing, no derivation will be performed and baseline will be set to missing.

TREATMENT DISCONTINUATION: For Cohort 2 participants who discontinue the study treatment, safety data will be restricted through four weeks after last-dose-date. For efficacy and immunologic response analyses, data will be restricted to specimens collected through one day after last-dose-date.

Cohort 1 (All Participants):
Intensive PK samples will be collected around the single dose of DOR, ideally on the day of study entry, and will continue up to approximately 72 hours post-dose. Participants will have one scheduled visit at Week 2. The *Analysis Window* and *Target Study Day* for these scheduled study visits will be defined as follows:

Analysis Window (Based on Study Day of Assessment)	Study Week	Target Study Day
-30 to 1	Week 0	1
2 to 28	Week 2	15

Cohort 2 (Participants <u>Selected</u> for Intensive PK Evaluations):
Once enrolled into Cohort 2, the first 10 participants will have an extra study visit at Week 1, for intensive PK evaluation. Blood samples for measuring HIV-1 RNA and CD4 cell count will not be collected on this extra visit. Thereafter, participants will have scheduled visits at Weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 16 weeks through Week 96. The *Analysis Window* and *Target Study Day* for these scheduled study visits will be defined as follows:

Analysis Window (Based on Study Day of Assessment)	Study Week	Target Study Day
-30 to 1	Week 0	1
2 to 11	Week 1	8
12 to 21	Week 2	15
22 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 210	Week 24	169
211 to 294	Week 36	253
295 to 392	Week 48	337
393 to 504	Week 64	449
505 to 616	Week 80	561
≥ 617	Week 96	673

> (Last Dose Date – First Dose Date) +1	Follow-up (due to early treatment discontinuation)	(Last Dose Date – First Dose Date) + 29

Cohort 2 (Participants <u>not Selected</u> for Intensive PK Evaluations):
Since these participants are not selected to have intensive PK evaluations, they will not have a Week 1 visit and will only have scheduled visits at Weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 16 weeks through Week 96. Also, since blood samples for measuring HIV-1 RNA will not be collected on the Week 1 visit for participants who are selected to have intensive PK evaluations, the following table will apply to the scheduled visits for measuring HIV-1 RNA for all Cohort 2 participants. The *Analysis Window* and *Target Study Day* for these scheduled study visits will be defined as follows:

Analysis Window (Based on Study Day of Assessment)	Study Week	Target Study Day
-30 to 1	Week 0	1
2 to 21	Week 2	15
22 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 210	Week 24	169
211 to 294	Week 36	253
295 to 392	Week 48	337
393 to 504	Week 64	449
505 to 616	Week 80	561
≥ 617	Week 96	673
> (Last Dose Date – First Dose Date) +1	Follow-up (due to early treatment discontinuation)	(Last Dose Date – First Dose Date) + 29

Cohort 2-CD4 Cell Count and Percent Schedule (All Participants):
Since blood collection for measuring CD4 cell count occurs on a less frequent schedule than other outcome measures, a different set of *Analysis Windows* will need to be defined for each scheduled study visit. For measuring CD4 count, participants will have scheduled visits at Weeks 4, 12, 24, 48, and every 16 weeks through Week 96. The *Analysis Window* and *Target Study Day* for these scheduled study visits will be defined as follows:

Analysis Window (based on Study Day of Assessment)	Study Week	Target Study Day
-30 to 1	Week 0	1
2 to 56	Week 4	29
57 to 126	Week 12	85
127 to 252	Week 24	169
253 to 392	Week 48	337
393 to 504	Week 64	449
505 to 616	Week 80	561
≥ 617	Week 96	673
> (Last Dose Date – First Dose Date) +1	Follow-up (due to early treatment discontinuation)	(Last Dose Date – First Dose Date) + 29

4.3 Analyses of Outcome Measures

All analyses described below will be performed after the last participant enrolled in Cohort 2 has reached Week 24.

4.3.1 Primary Outcome Measures

Safety

The primary safety analyses will include all participants who were exposed to the study drug and will be restricted to data through Week 2 for Cohort 1 and Week 24 for Cohort 2. For Cohort 2 participants who discontinued the study drug prior to reaching Week 24, safety data will be restricted through four weeks after last dose date.

An overall summary of all AEs will be presented by cohort and, for Cohort 2, the summary will be broken down by ART status at entry (i.e., ART-naïve versus ART-experienced). In addition, 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 related to study drug.

Frequency distributions of the four toxicity endpoints listed in Section 3.4.1 will be presented by cohort and by ART status at entry (Cohort 2). Proportion of participants (bounded by exact 95% confidence intervals) and the listing of the participants experiencing any of these four toxicity endpoints will also be presented by cohort and by ART status at entry (Cohort 2).

Proportion of participants experiencing Grade 3 or higher AEs and those experiencing Grade 3 or higher AEs assessed as related to study drug, bounded by exact 95% confidence intervals, will be presented by cohort and by ART status at entry (Cohort 2).

4.3.2 Secondary Outcome Measures (Cohort 2)

Safety

Safety assessments will be performed on long-term data collected through Week 96. These analyses will be similar to Week 24 (Cohort 2) analyses described above and will be performed after the last participant enrolled in Cohort 2 has reached Week 96, or earlier if the study team decides to do so based on accrual or retention issues.

Virologic Efficacy

Virologic responses for Cohort 2 participants, based on plasma HIV-1 RNA (copies/mL), will be assessed at Week 24. Virologic outcomes at additional time points might also be evaluated. Virologic failure will be defined as HIV-1 RNA >200 copies/mL, >50 copies/mL, and >40 copies/mL, in three separate analyses. In addition, the log drop from baseline in plasma HIV-1 RNA will be calculated and summarized for ART-naïve participants. The proportion of participants with plasma HIV-1 RNA <200 copies/mL, <50 copies/mL, and <40 copies/mL, bounded by 95% confidence intervals, will be presented separately for all Cohort 2 participants, both in the aggregate and broken down by ART status at entry (i.e., ART-naïve versus ART-experienced).

MISSING HIV-1 RNA DATA: The Observed Failure Approach, which is a conservative approach to handle missing data, will be used. Based on this approach, missing values are considered as failures for participants missing data due to discontinuation of study drug as a result of virologic failure or for non-treatment related reasons with last available RNA >200/50/40 copies/mL; otherwise participants with missing values are excluded.

For regulatory submission purposes, 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. Participants will be classified as non-responders if they have missing HIV-1 RNA data throughout the analysis window surrounding the time point of interest; which has been defined in section 4.2. If participants discontinue the study drug prior to the time point of interest, virological failure will be determined by the HIV-1 RNA measurement at the time of discontinuation, if discontinuation occurred for reasons other than AE or death. For participants who have data collected within the analysis window of interest, virologic success or failure will be determined by the last available HIV-1 RNA measurement within that analysis window.

Immunologic Response

Mean changes in CD4 count and percent from baseline to Week 24 will be presented, both in the aggregate and broken down by ART status at entry (i.e., ART-naïve versus ART-experienced), bounded by 95% confidence intervals. Based on the Observed Failure Approach, missing CD4 values for participants who discontinued the study drug due to virologic failure or for non-treatment related reasons with last available RNA >200/50/40 copies/mL will be replaced with their baseline value; otherwise participants with missing values are excluded.

Note: Since the missing HIV-1 RNA and CD4 values for Cohort 2 participants will be imputed using a conservative approach, sensitivity analyses will be performed to assess the effects of these data imputations on the final results.

5. Report Contents

The following are the main planned sections of the Primary Analysis Report. Detailed descriptions of the content of each of these sections are provided in the AIP. Data for the Primary Analysis Report will be downloaded once the last participant in Cohort 2 has completed the Week 24 study visit, all queries have been resolved, and the database has been locked for analysis.

1. Accrual
2. Protocol Deviations
3. Study Status and Study Treatment Status
4. Selected Characteristics at Baseline
5. Medical History
6. Summary of Clinical Events
7. Summary of Laboratory Events
8. Analysis of Primary Outcome Measures
9. Analysis of Secondary Outcome Measures