IMPAACT
International Maternal Pediatric Adolescent
AIDS Clinical Trials Network

# 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

## IND#: 137,041
## DAIDS Study ID 34150

This file contains the current IMPAACT 2014 protocol comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #3, dated 28 April 2021
- Letter of Amendment #3, dated 10 June 2020
- Clarification Memorandum #2, dated 31 March 2020
- Letter of Amendment #2, dated 26 April 2019
- Corrected Clarification Memorandum #1, dated 13 February 2019
- Letter of Amendment #1, dated 7 May 2018
- Protocol Version 1.0, dated 7 September 2017

**Clarification Memorandum #3 for:**

**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

**Version 1.0, dated 7 September 2017**

**IND# 137,041**
**DAIDS Study ID 34150**

**Clarification Memorandum Date: 28 April 2021**

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## Summary of Clarifications and Rationale

This Clarification Memorandum (CM) updates protocol specifications to reflect current policies of the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), and National Institutes of Health (NIH). It also updates wording related to the IMPAACT Network Certificate of Confidentiality and updates the protocol team and site representative rosters. These updates do not impact the study design or study-specific procedures.

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## Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

IRBs/ECs may have acknowledged and/or approved remote site monitoring strategies prior to the issuance of this CM. If so, documentation of the acknowledgement and/or approval should be filed in your essential document files for IMPAACT 2014. This CM and any applicable IRB/EC correspondence should also be filed in your essential document files for IMPAACT 2014.

The information included in this memorandum will be incorporated into the next protocol amendment.

## A. DAIDS Policy Updates

1. Protocol Section 12 is updated to reflect current DAIDS policies for clinical site monitoring, which allow for on-site and remote monitoring. The prior contents of this section are replaced with the following:

   **Under contract to DAIDS or NICHD, site monitors will inspect study site facilities and review participant study records — including informed consent and assent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records — to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. Monitors also will review essential document files to ensure**

**compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by monitors.**

**Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by DAIDS or NICHD. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity (1). Site investigators will make study documents available for site monitors to review utilizing a secure platform that is 21 CFR Part 11 and HIPAA compliant. Potential platform options include: Veeva SiteVault, Medidata Rave Imaging Solution, Medidata Remote Source Review, site-controlled SharePoint or cloud-based portal, and direct access to electronic medical records. Other secure platforms that are 21 CFR Part 11 and HIPAA compliant may be utilized, as allowed by DAIDS Office of Clinical Site Oversight (OCSO) or NICHD.**

**Reference:**


1. **FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, Updated on January 27, 2021. Accessed at: https://www.fda.gov/media/136238/download**


2. Protocol Section 14.5 refers to the DAIDS policy on identification and classification of critical events. This policy has been retired. Section 14.5 is removed from the protocol and Section 13.1 has been updated to refer to the reporting requirements that still apply for sites conducting this study. The prior contents of the first paragraph in Section 13.1 are replaced with the following:

   **Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific informed consent and assent forms in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must promptly report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.**

3. Protocol Section 14.6 (now re-numbered as Section 14.5) refers to requirements for entry of study results into ClinicalTrials.gov. To reflect current NIH and regulatory requirements, the prior contents of this section are replaced with the following:

   **The NIH Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that clinical trials funded in whole or in part by the NIH will be registered and have summary results information submitted to ClinicalTrials.gov for public posting. The protocol team will comply with this policy as well as the requirements of 42 CFR 11.**

4. Protocol Sections 11.1, 11.2, 11.3, 13.2, 13.3, 13.7, 14.3, and 14.4 refer to the following DAIDS policies:

   - Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials
   - Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials
   - Requirements for Clinical Quality Management Plans

- Requirements for Manual of Operational Procedures
- Enrolling Children (including Adolescents) in Clinical Research: Clinical Site Requirements

These policies have been retired and replaced with instructions for sites that are now contained in the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual. Throughout the protocol, references to the above-listed policies are replaced with requirements specified in the DAIDS SCORE Manual (edits not shown here). The SCORE Manual is available at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

### B. Certificate of Confidentiality

The Certificate of Confidentiality described in protocol Section 13.7 has been deemed issued to the IMPAACT Network effective with the start date of the current Network funding cycle (1 December 2020). The first sentence in the last paragraph of this section is replaced with the following:

**In addition to the above, a Certificate of Confidentiality has been deemed issued for the IMPAACT Network by the US Department of Health and Human Services.**

### C. Protocol Team Roster Updates

To reflect current protocol team membership, Mona Farhad, Sarah Pasyar, Hedy Teppler, Rebecca LeBlanc, Scott Watson, and Yvonne Woolwine-Cunningham are removed from the protocol team roster (deletions not shown) and the team members shown below are added. Adeola Adeyeye is also added as a NIAID Medical Officer on the protocol cover page.

NIAID Medical Officers
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Protocol Laboratory Data Managers
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Westat Clinical Research Associate
**Chanell Wilkins**
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**Rockville, MD 20850, USA**
**Phone: (301) 610-5548**
**Email: chanellwilkins@westat.com**

### D. Site Representative Roster Updates

The following sites, which did not enroll any participants, are removed from the site representative roster: CRS 5051 (Mobeen Rathore, Saniyyah Mahmoudi); CRS 5092 (Allison Agwu, Aleisha Collinson-Streng, Thuy Anderson); CRS 6601 (Irma Febo, Ruth Santos); and CRS 8051 (Lee Fairlie, Hermien Gous). To reflect current site representatives, Amanda Robson (CRS 5017) and Nasreen Abrahams (CRS 8052) are removed (deletions not shown) and the representatives shown below are added:

University of Washington Children's Hospital
Seattle NICHD, CRS 5017
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# Letter of Amendment #3 for:

# 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

## Version 1.0, dated 7 September 2017

## DAIDS Study ID #34150
## IND #137,041

## Letter of Amendment Date: 10 June 2020

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### Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT 2014 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All applicable IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for IMPAACT 2014. If the IMPAACT 2014 protocol is amended in the future, applicable contents of this LoA will be incorporated into the next version of the protocol.

**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**

**DAIDS Study ID #34150**

## Version 1.0, Letter of Amendment #3
## Letter of Amendment Signature Page

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Council on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

| | |
|---|---|
| Signature of Investigator of Record | Date |

Name of Investigator of Record
(printed)

## Summary of Modifications and Rationale

The purpose of this LoA is to update the protocol team roster to reflect current membership, clarify and correct certain procedural specifications in the protocol, and incorporate the contents of protocol Clarification Memorandum (CM) #2.

Section A of this LoA includes the protocol team roster updates.

Section B of this LoA includes the procedural clarifications and corrections, which serve to:

- Clarify the requirement for sites to notify the IMPAACT 2014 Clinical Management Committee (CMC) of adverse events that are life-threatening or result in death
- Correct an inconsistency in clinical management requirements for participants experiencing decreased estimated glomerular filtration rate (eGFR)

Section C of this LoA incorporates the contents of CM #2, which was issued on 31 March 2020 to safeguard the health and well-being of study participants in the context of circulating SARS-CoV-2 and the associated COVID-19 pandemic. CM #2 provided operational flexibility for conducting study visits and procedures when needed to ensure ongoing access to study drug and to prioritize the conduct of clinically and scientifically important laboratory evaluations when possible. Per the study Sponsor, sites were instructed to implement the guidance provided in CM #2 immediately. All sites should continue to follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures during the COVID-19 pandemic, with utmost importance placed on the health and well-being of study participants and study staff. Consistent with the instructions provided in CM #2, implementation of Section C of this LoA is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with IMPAACT Network leadership and the study Sponsor, the IMPAACT 2014 Protocol Team will determine when, in the future, the guidance in Section C is no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform IRBs/ECs and other applicable regulatory entities.

## Implementation

Modifications of protocol text are shown in Sections A and B of this LoA, using strikethrough for deletions and bold type for additions where appropriate. Within these sections, modifications are generally shown in order of appearance in the protocol. Operational guidance for conducting study visits and procedures during the COVID-19 pandemic is provided in Section C of this LoA; conventions for use of strikethrough and bolding do not apply in this section.

### *A. Protocol Team Roster Updates*

To reflect current protocol team membership, Andee Fox and Hye Cho are removed from the protocol team roster (deletion not shown). Sarah Pasyar and Lina de Montigny are added.

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### *B. Procedural Clarifications and Corrections*

1. Protocol Section 8.1, Management of Adverse Events, fifth paragraph:

   Refer to Sections 8.2-8.6 for further guidance on management of adverse events, including general adverse events, liver toxicities, decline in renal function, non-study drug ARV-related toxicities, and monitoring and management of virologic failure. When management of an adverse event requires consultation with the CMC, the CMC should be contacted as soon as possible and within three business days of site awareness of the event. **In the event of any adverse event that is life-threatening or results in death, the CMC should be contacted as soon as possible and within three business days of site awareness, consistent with the potential triggers for SMC review described in Section 9.6.2.**

2. Protocol Section 8.4, Management of Decline in Renal Function (Cohort 2), third paragraph:

   Participants who experience progression to ~~a grade 3 or higher~~ **an** estimated GFR (calculated by the Schwartz formula; see Section 4.1.8) of <60 mL/min (1.73 $m^2$) must return for a confirmatory creatinine assessment within two to four weeks. If an estimated GFR of <60 mL/min (1.73 $m^2$) is confirmed, then DOR/3TC/TDF should be held and the investigator should contact the CMC to discuss the rationale for restarting study drugs (if appropriate).

### *C. Operational Guidance from Protocol CM #2, dated 31 March 2020*

This CM provides operational guidance to study sites from the IMPAACT 2014 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Clinical Management Committee and should contact the Clinical Management Committee (impaact.2014cmc@fstrf.org) with any questions or concerns regarding this CM or management of study participants.

#### Visit Scheduling

- Sites should implement safety checks by telephone (as available) prior to in-person visits to assess participant/parent/guardian willingness and ability to attend in-person visits, as well as assess the onset of any adverse events, including but not limited to signs and symptoms potentially consistent with COVID-19.
- Sites should prioritize completion of the Week 24 visit.
- Sites that anticipate operational disruptions or closures in the near future are advised to conduct study visits early in the allowable visit window. Visits conducted prior to opening of the allowable window would also be preferred to completely missing a visit at a later date.
- Sites that are currently experiencing operational disruptions or closures are advised to conduct study visits late in the allowable visit window. Visits conducted after closing of the allowable window would also be preferred to completely missed visits.
- Effective with the issuance of this CM, the allowable window for the Weeks 24, 36, and 48 visits is broadened to ±6 weeks.

**Prioritization of Study Visit Procedures**

- Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in full compliance with the protocol.
- Sites may also conduct study visits — in full or in part — off-site if permitted by applicable government, health authority, and institutional policies. Where this option is permitted, site staff should communicate with parents, guardians, and participants to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Off-site visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.
- Sites with limited capacity to conduct in-person study visits should prioritize provision of study drug (see below) and conduct of safety-related laboratory evaluations, specifically, chemistries, CBC, and, if applicable, pregnancy testing. In addition, at Week 24, HIV-1 RNA viral load and CD4 cell count should also be prioritized. If it is not possible to perform these tests consistent with the site's Protocol Analyte List (PAL), tests may be performed in alternate settings using alternate laboratory methods (alternate laboratories must adhere to local regulations for clinical laboratory testing). Sites should carefully consider how to maintain privacy and confidentiality when discussing sexual activity and pregnancy testing. Prioritization of other laboratory evaluations may depend on whether local processing is available, though the recommended prioritization is as follows: (1) HIV-1 RNA viral load; (2) CD4 cell counts; (3) PK; (4) Lipid profiles; (5) Stored samples for resistance testing.
- Sites with no ability to conduct in-person study visits, either at the study clinic or off-site, should consider whether any study procedures can be conducted remotely (e.g., by telephone). Evaluations should be prioritized as follows (as applicable for the individual participant and scheduled study visit in question):
  - Medical history taking and symptom-directed physical exam, noting assessment of vitals, height, and weight may be skipped
  - Adherence assessments and counseling, while maintaining privacy/confidentiality

**Study Drug Supply**

- Sites may dispense up to six months of study drug supplies to avoid gaps in ARV coverage. This should be done even if study visits or procedures cannot be performed for any reason.
- Where feasible, sites are encouraged to implement study drug delivery options involving outdoor pick-up or drop-off. Where outdoor pick-up or drop-off is not feasible, the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* permit shipment or courier of study drug from the site directly to participants. This method should only be used in the short-term and if permissible per local institutional and IRB/EC policies. Refer to the *Guidelines* for additional details on this method.
- Sites are encouraged to provide adherence assessment, counseling, and support remotely (e.g., by telephone).
- Sites are permitted to utilize rapid urine pregnancy test kits (either performed by study staff or given to and performed by participants themselves) in the context of these study drug pick-up or drop-off options. Sites should carefully consider how to maintain privacy and confidentiality of discussions related to sexual activity and the need for and results of pregnancy testing.

**Documentation**

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2014.
- Documentation should be entered in participant study charts in real-time should any of the following occur:
  - Missed visits
  - Out-of-window visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed and which were not)
  - Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays
  - Alternate provision of study drug
- In consultation with the Division of AIDS, the IMPAACT Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Similar guidance will be provided for documentation of use of alternate laboratories or alternate laboratory assays. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.

# Clarification Memorandum #2 for:

# 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

## Version 1.0, dated 7 September 2017

## IND# 137,041
## DAIDS Study ID 34150

## Clarification Memorandum Date: 31 March 2020

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### Summary of Clarifications

This Clarification Memorandum (CM) is being issued to safeguard the health and well-being of IMPAACT 2014 study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) pandemic.

As the study Sponsor, the Division of AIDS (DAIDS) has determined that this CM should be implemented immediately upon issuance. Consistent with United States Food and Drug Administration guidance, institutional review board/ethics committee (IRB/EC) approval of this CM is not required by the Division of AIDS prior to implementation. However, given the context of the COVID-19 pandemic and the importance of the guidance provided in this CM, sites should submit this CM to IRBs/ECs for their information or, if required by the IRBs/ECs, for their review and approval.

The purpose of this CM is to provide operational flexibility for conducting study visits and procedures when needed to ensure ongoing access to study drug and to prioritize the conduct of clinically and scientifically important laboratory evaluations when possible.

Implementation of this CM is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with IMPAACT Network leadership and the study Sponsor, the IMPAACT 2014 Protocol Team will determine when, in the future, the guidance provided in this CM is no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform their IRBs/ECs.

Please file this CM and any applicable IRB/EC correspondence in your essential document files for IMPAACT 2014.

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## Implementation

This CM provides operational guidance to study sites from the IMPAACT 2014 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Clinical Management Committee and should contact the Clinical Management Committee (impaact.2014cmc@fstrf.org) with any questions or concerns regarding this CM or management of study participants.

### Visit Scheduling

- Sites should implement safety checks by telephone (as available) prior to in-person visits to assess participant/parent/guardian willingness and ability to attend in-person visits, as well as assess the onset of any adverse events, including but not limited to signs and symptoms potentially consistent with COVID-19.
- Sites should prioritize completion of the Week 24 visit.
- Sites that anticipate operational disruptions or closures in the near future are advised to conduct study visits early in the allowable visit window. Visits conducted prior to opening of the allowable window would also be preferred to completely missing a visit at a later date.
- Sites that are currently experiencing operational disruptions or closures are advised to conduct study visits late in the allowable visit window. Visits conducted after closing of the allowable window would also be preferred to completely missed visits.
- Effective with the issuance of this CM, the allowable window for the Weeks 24, 36, and 48 visits is broadened to ±6 weeks.

### Prioritization of Study Visit Procedures

- Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in full compliance with the protocol.
- Sites may also conduct study visits — in full or in part — off-site if permitted by applicable government, health authority, and institutional policies. Where this option is permitted, site staff should communicate with parents, guardians, and participants to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Off-site visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.
- Sites with limited capacity to conduct in-person study visits should prioritize provision of study drug (see below) and conduct of safety-related laboratory evaluations, specifically, chemistries, CBC, and, if applicable, pregnancy testing. In addition, at Week 24, HIV-1 RNA viral load and CD4 cell count should also be prioritized. If it is not possible to perform these tests consistent with the site's Protocol Analyte List (PAL), tests may be performed in alternate settings using alternate laboratory methods (alternate laboratories must adhere to local regulations for clinical laboratory testing). Sites should carefully consider how to maintain privacy and confidentiality when discussing sexual activity and pregnancy testing. Prioritization of other laboratory evaluations may depend on whether local

processing is available, though the recommended prioritization is as follows: (1) HIV-1 RNA viral load; (2) CD4 cell counts; (3) PK; (4) Lipid profiles; (5) Stored samples for resistance testing.

- Sites with no ability to conduct in-person study visits, either at the study clinic or off-site, should consider whether any study procedures can be conducted remotely (e.g., by telephone). Evaluations should be prioritized as follows (as applicable for the individual participant and scheduled study visit in question):
  - Medical history taking and symptom-directed physical exam, noting assessment of vitals, height, and weight may be skipped
  - Adherence assessments and counseling, while maintaining privacy/confidentiality

**Study Drug Supply**

- Sites may dispense up to six months of study drug supplies to avoid gaps in ARV coverage. This should be done even if study visits or procedures cannot be performed for any reason.
- Where feasible, sites are encouraged to implement study drug delivery options involving outdoor pick-up or drop-off. Where outdoor pick-up or drop-off is not feasible, the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* permit shipment or courier of study drug from the site directly to participants. This method should only be used in the short-term and if permissible per local institutional and IRB/EC policies. Refer to the *Guidelines* for additional details on this method.
- Sites are encouraged to provide adherence assessment, counseling, and support remotely (e.g., by telephone).
- Sites are permitted to utilize rapid urine pregnancy test kits (either performed by study staff or given to and performed by participants themselves) in the context of these study drug pick-up or drop-off options. Sites should carefully consider how to maintain privacy and confidentiality of discussions related to sexual activity and the need for and results of pregnancy testing.

**Documentation**

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2014.
- Documentation should be entered in participant study charts in real-time should any of the following occur:
  - Missed visits
  - Out-of-window visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed and which were not)
  - Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays
  - Alternate provision of study drug
- In consultation with the Division of AIDS, the IMPAACT Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Similar guidance will be provided for documentation of use of alternate laboratories or alternate laboratory assays. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.

# Letter of Amendment #2 for:

# 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

## Version 1.0, dated 7 September 2017

## IND#: 137,041
## DAIDS Study ID 34150

## Letter of Amendment Date: 26 April 2019

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### Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT 2014 study, including the study informed consent forms (ICFs), and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All applicable IRB/EC and regulatory entity requirements must be followed.

Before this LoA can be implemented at any site, an "Implementation Notice" for the LoA must be issued by the IMPAACT Operations Center confirming that all operational requirements for implementing the LoA at the network level have been completed. Sites should also follow the instructions below regarding site-specific timing of implementation of the LoA.

For sites that were activated to initiate the study prior to issuance of this LoA, upon obtaining all required IRB/EC and regulatory entity approvals, each site should immediately begin implementing this LoA. Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA. For participants enrolled prior to implementation of this LoA and still on-study, re-consent for study participation should be obtained at the next scheduled study visit, using the revised site-specific ICFs corresponding to this LoA.

For sites that were not activated to initiate the study prior to issuance of this LoA, upon obtaining all required IRB/EC and regulatory entity approvals, sites are required to submit an LoA registration packet to the DAIDS PRO at the RSC. Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Activation will occur following receipt of all required IRB/EC and regulatory entity approvals for protocol Version 1.0 and this LoA; receipt of a protocol registration notification for protocol Version 1.0; receipt of the protocol registration notification for this LoA; completion of all other study activation requirements; and receipt of a site-specific study activation notice from the IMPAACT Operations Center.

Please file this LoA, corresponding site-specific informed consent forms, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT 2014. If the IMPAACT 2014 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

**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**
**Version 1.0, dated 7 September 2017**

**DAIDS Study ID #34150**

## Version 1.0, Letter of Amendment #2

### Letter of Amendment Signature Page

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

| | |
|---|---|
| Signature of Investigator of Record | Date |

Name of Investigator of Record
(printed)

## Summary of Modifications and Rationale

1. As identification of participants in the 35-≤45 kg weight group in Cohort 1 has been challenging, the protocol is modified to allow enrollment into Cohort 2 for children in the >45kg weight group, while attempting, but not requiring, to enroll at least four participants with weight between 35 kg and ≤45 kg into Cohort 1. Of note, in February 2019, the IMPAACT Study Monitoring Committee (SMC) conducted a safety and pharmacokinetic (PK) review of data for nine evaluable Cohort 1 participants. Based on review of all available data, the SMC agreed that the 100 mg once daily dose of doravirine met protocol-specified safety and PK guidelines. The SMC also agreed that currently available data are sufficient to support opening Cohort 2 to accrual of participants weighing more than 45 kg. The requirement to enroll a minimum of five participants in the 35-≤45 kg weight group into Cohort 2 was also revised to attempt to enroll this number but not require a minimum number of participants.
2. Update description of the presentation of oral granules of study drug and instructions on how to administer.
3. As documented in Clarification Memorandum #1, the protocol criteria to allow enrollment of ART-experienced, virologically suppressed was met, based on review of data from adult studies switching participants from a stable antiretroviral regimen to a once-daily single tablet regimen of doravirine 100 mg, lamivudine 300 mg, and tenofovir disoproxil fumarate 300 mg (DOR/3TC/TDF).
4. The protocol team and site investigator rosters have been updated to reflect current membership.
5. The sample informed consent forms for participation in Cohort 1 and in Cohort 2 (Appendices II and III) have been modified in accordance with updated risk language provided by Merck for DOR (MK-1439, Cohort 1) and DOR/3TC/TDF (MK-1439A, Cohort 2); other minor updates were incorporated based on additional changes included in this LoA.

## Implementation

The modifications included in this LoA are listed by modification and will be incorporated into the next protocol amendment as specified below. Changes to the study sample informed consent forms are grouped at the end of the document. Additions to the text are indicated in **bold**; deletions are indicated by ~~strikethrough~~.

1. *Updates to allow Cohort 2 to open for children >45kg while Cohort 1 continues enrolling participants 35kg-≤45kg*

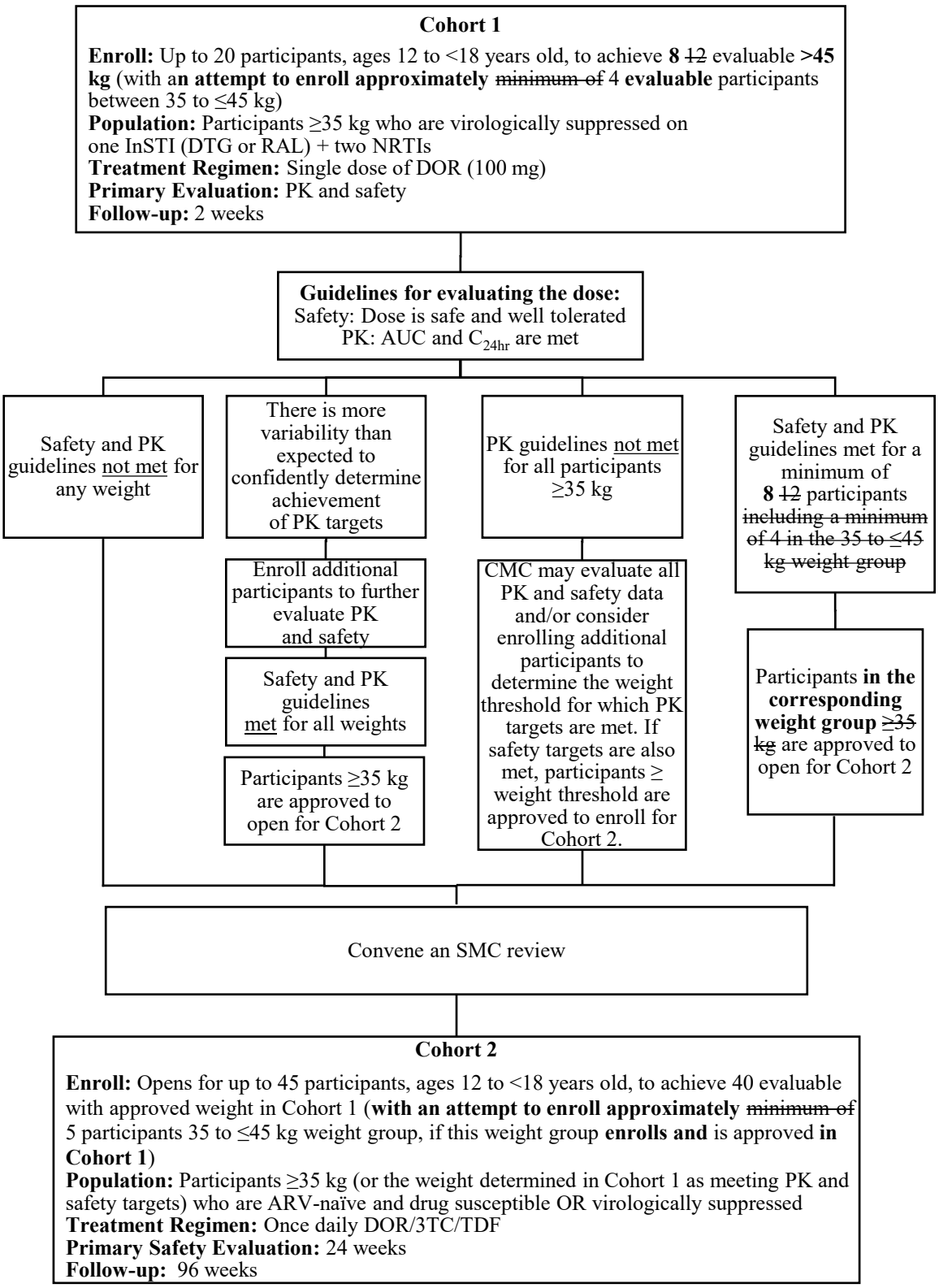
   a. *Schema, Study Population:*

      HIV-1-infected children and adolescents, from 12 years to less than 18 years of age who weigh at least 35 kg. Cohort 1 and 2 will enroll **concurrently** ~~sequentially~~:

   b. *Schema, Study Duration:*

      Approximately four years total from the date the first participant is enrolled. Accrual into Cohort 1 is expected to require approximately three to six months and participants in this cohort will be followed for two weeks. It is expected that Cohort 2 will open ~~three months after Cohort 1 is completed (~~following review of data from **the >45 kg weight group participants** in Cohort 1~~)~~. Accrual into Cohort 2 is expected to require approximately six to twelve months and participants in this cohort will be followed for 96 weeks.

*c. Figure 1, IMPAACT 2014 Overview of Study Design:*



*d. Section 1.4.1, Rationale for Dose Selection, fourth paragraph:*

To move forward the development of DOR and DOR/3TC/TDF for use in children and adolescents, children and adolescents for whom the full adult dose FDC is appropriate will be enrolled for the long-term portion of study (Cohort 2)**; enrollment into Cohort 1 will concurrently remain open until a minimum of 4 evaluable participants between 35 to ≤45 kg are enrolled or until Cohort 2 is fully enrolled. Even if Cohort 1 is not fully enrolled by the time Cohort 2 is enrolled, both cohorts will close for enrollment at that time.** The expectation is that **the adult dose will be appropriate for** ~~this will be~~ all children and adolescents with weight ≥35 kg. If this expectation is not borne out based on the results of Cohort 1, only children and adolescents in the weight range for which the 100 mg **doravirine dose** is appropriate will be enrolled into Cohort 2 and followed long-term. If, after the dose evaluation stage, it appears that lower-weight children and adolescents (for example, 35 – 40 kg) may require a dose less than 100 mg DOR, an age appropriate formulation that is currently in development and is intended to deliver a dose below 100 mg**,** will be employed to study safety and PK in such participants in a separate study.

*e. Section 1.4.2, Rationale for Study Design and Cohort Selection, third paragraph:*

Once the PK and safety targets for Cohort 1 are confirmed for the 100 mg DOR dose, DOR/3TC/TDF will be studied in Cohort 2 in HIV-1-infected children and adolescents **of the weight group(s) supported by results from Cohort 1**. While it is anticipated that the 100 mg DOR dose will meet PK targets for all participants with weights down to 35 kg, in the unlikely event that the dose is determined to be too high for lower weight participants, Cohort 2 will only open for those participants whose weight meet the PK and safety targets based on data from Cohort 1. If the 35 to ≤45 kg weight group **in Cohort 1 fully enrolls and** shows acceptable PK and safety, **Cohort 2 will open for the 35 to ≤45 kg weight group and the study will attempt to enroll approximately** ~~a minimum of~~ five participants in this weight group ~~will be enrolled~~ to Cohort 2.

*f. Section 3, Study Design, second and third paragraphs:*

The protocol will enroll two ~~sequential~~ cohorts, Cohorts 1 and Cohort 2, as described in Sections 3.1 and 3.2, respectively. In summary, participants will first be enrolled into Cohort 1 to evaluate the PK and safety of the 100 mg DOR dose, with intensive PK evaluation completed at entry and followed through two weeks on study to assess safety. Specimens will be shipped in real time with ongoing testing, with team review of PK and safety data as available. Upon enrollment of a minimum of **eight** ~~12~~ evaluable participants **with weight greater than 45 kg**, enrollment will be paused while the Cohort 1 PK and safety data are reviewed by the protocol team and the SMC. Data will be evaluated based on the algorithm in Section 9.2, with options of resuming enrollment into Cohort 1, proceeding with Cohort 2 enrollment, or assessing next steps for the study.

If results from Cohort 1 are supportive, **participants in the supported weight group(s)** will be enrolled into Cohort 2 to evaluate the safety and tolerability of a fixed-dose combination regimen, including DOR, 3TC, and TDF. A subset of participants will have intensive PK evaluations at Week 1 and all participants will have population PK evaluations through Week 48; the PK specimens will be shipped in batches with testing when sample collection is complete for all relevant participants (see Section 6.11.2). Participants will be followed through 96 weeks on study to assess long-term safety, virologic efficacy, and immunologic response, among other objectives as in Sections 2.3 and 2.4.

g. *Section 9.1, General Design Issues, first paragraph, last sentence, and second paragraph, first sentence:*

Participants will be enrolled into two ~~sequential~~ cohorts, as described in Section 3.

A minimum of **eight** ~~12~~ PK evaluable in Cohort 1 and 40 evaluable participants in Cohort 2 will be accrued to the study.

h. *Section 9.2, Dose Evaluation Algorithm, Cohort 1, first paragraph and first bullet:*

The study will implement a dose-evaluation algorithm of the 100 mg DOR based on PK data around the single-dose and safety data through Week 2. Cohort 1 will enroll an initial group of ~~12~~ evaluable participants **(at least eight in the >45 kg weight group)** and their PK and safety data will be evaluated as follows:

- If these ~~12~~ participants meet the PK guidelines (see Section 10.3.1) and there are no safety concerns (see Section 9.6.2, Participant Safety), then the DOR dose for Cohort 2 will be established and Cohort 2 will begin to accrue **participants of the supported weight group**, following an SMC review (see Section 9.6.2, Dose Evaluation). **Enrollment into Cohort 1 will concurrently remain open until a minimum of 4 evaluable participants between 35 to ≤45 kg are enrolled or until Cohort 2 is fully enrolled; even if Cohort 1 is not fully enrolled by the time Cohort 2 is enrolled, both cohorts will close for enrollment at that time**.

i. *Section 9.2, Dose Evaluation Algorithm, Cohort 2, first paragraph, first sentence:*

This cohort will begin to enroll once the PK and safety of the 100 mg DOR dose have been established from Cohort 1, as described above, and once the SMC has reviewed **applicable** ~~all~~ Cohort 1 data and approved enrollment into Cohort 2 (see Section 9.6.2, *Dose Evaluation*).

j. *Section 9.5, Sample Size and Accrual, Cohort 1, first paragraph:*

At least **eight** ~~12~~ evaluable participants **>45 kg** will be enrolled in Cohort 1 with **an attempt to enroll approximately** ~~a minimum of~~ four **evaluable** participants between 35 kg and 45 kg. Depending on the PK results, additional participants may be enrolled. **Even if Cohort 1 is not fully enrolled by the time Cohort 2 is enrolled, both cohorts will close for enrollment at that time**.

k. *Section 9.7.1, Primary Safety Analyses (on data through Week 2 for Cohort 1 and Week 24 for Cohort 2), third paragraph and Table 19:*

The proportions of participants experiencing Grade 3 or higher adverse events, bounded by exact 95% confidence intervals, will be presented by cohort and population classification at entry (Cohort 2). Similar analyses will present the proportions of participants with Grade 3 or higher events assessed as related to study drug, again bounded by exact 95% confidence intervals. Table 19 presents the upper and lower limits of confidence intervals around potential results observed in the groups of **n=8,** n=12, ~~n=15,~~ and n=40, and the combined groups of **n=48 and** n=52 ~~and n=55~~.

Table 19. Percent of Participants Experiencing ⩾Grade 3 Adverse Events (or ≥Grade 3 Adverse Events Attributed to the Study Medication) with Exact 95% Confidence Intervals

| N | n (%) With ⩾Grade 3 Adverse Events | 95% CI |
|---|---|---|
| **8** | **0 (0%)** | **0% - 37%** |
| 12 | 0 (0%) | 0% - 26% |
| ~~15~~ | ~~0 (0%)~~ | ~~0% - 22%~~ |
| 40 | 0 (0%) | 0% - 9% |
| **48** | **0 (0%)** | **0% - 7%** |
| 52 | 0 (0%) | 0% - 7% |
| ~~55~~ | ~~0 (0%)~~ | ~~0% - 6%~~ |
| | | |
| **8** | **1 (12%)** | **0% - 53%** |
| 12 | 1 (8%) | 0% - 38% |
| ~~15~~ | ~~2 (13%)~~ | ~~2% - 40%~~ |
| 40 | 4 (10%) | 3% - 24% |
| **48** | **5 (10%)** | **3% - 23%** |
| 52 | 5 (10%) | 3% - 21% |
| ~~55~~ | ~~6 (11%)~~ | ~~4% - 22%~~ |
| | | |
| **8** | **2 (25%)** | **3% - 65%** |
| 12 | 4 (33%) | 10% - 65% |
| ~~15~~ | ~~5 (33%)~~ | ~~12% - 62%~~ |
| 40 | 12 (30%) | 17% - 47% |
| **48** | **14 (29%)** | **17% - 44%** |
| 52 | 15 (29%) | 17% - 43% |
| ~~55~~ | ~~16 (29%)~~ | ~~18% - 43%~~ |

*l. Section 10.1, Pharmacology Overview and Objectives, Cohort 1, first paragraph:*

Cohort 1 will assess the single dose pharmacokinetics of a 100 mg dose of doravirine in **at least eight** ~~12~~ evaluable children and adolescents ≥35kg (with **an attempt to enroll approximately** ~~a minimum of~~ four **additional evaluable** participants between 35 to ≤45 kg).

*m. Section 10.1, Pharmacology Overview and Objectives, Cohort 1, second paragraph:*

If Cohort 1 pharmacokinetic results confirm this initial model **in participants >45 kg,** then Cohort 2 will open to participants weighing **>45 kg** ~~≥35 kg~~. **If Cohort 1 PK and safety results also confirm this initial model in participants 35 to ≤45 kg, then Cohort 2 will open to participants weighing ≥35 kg.** If exposure is deemed too high (i.e., exceeds that observed in adults at a 200 mg daily dose) in children or adolescents weighing closer to 35 kg, then Cohort 2 will open with a 100 mg daily dose only in children and adolescents above the weight determined to yield appropriate exposure from the Cohort 1 results.

*n. Section 10.3.2, Timing of Interim Analyses, first paragraph:*

Cohort 1 DOR pharmacokinetics will be summarized once **at least eight** ~~12~~ participants of **>45 kg** have completed the pharmacokinetic visit to confirm the dose for **this weight group in** Cohort 2. **Cohort 1 DOR pharmacokinetics will again be summarized if at least four participants 35 to**

**≤45 kg have completed the pharmacokinetic visit; if Cohort 2 has not yet fully enrolled, these data will be used to confirm the dose for this weight group in Cohort 2**. Samples from Cohort 1 participants should be shipped as soon as the 72-hour post-dose draw is completed and tested on an ongoing basis.

2. *Update description of the presentation of oral granules of study drug and instructions on how to administer*

   a. *Section 1.4.4, Rationale for Use of Tablets and Granules, second paragraph, first paragraph:*

   The age appropriate formulation may be administered **on** ~~in liquid or~~ soft food, as described further in Section **5.3** ~~5.2.2~~.

   b. *Section 5.2.2, Cohort 2, second paragraph:*

   Doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF): fixed-dose combination oral granules**, provided in capsules to be opened for administration. Each capsule contains 33.6 mg of DOR, 100 mg of 3TC, and 100 mg of TDF. The contents of three capsules is equivalent to the adult dose.** ~~The formulation is comprised of 100.6 mg of DOR, 300 mg 3TC, and 300 mg TDF, divided between three capsules of oral granules.~~ The **capsules** ~~individual components~~ may be stored **refrigerated at the site pharmacy** ~~separately~~ between 2°C and **8** ~~30~~°C (36°-**46** ~~86~~°F), protected from **moisture and** light with a desiccant. **Do not freeze. Study drug does not need to be refrigerated after being dispensed to the participant.** ~~The stability of the combination product is to be determined.~~

   c. *Section 5.3, Study Drug Administration, Cohort 2:*

   Cohort 2 — Doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) will be administered orally as a fixed-dose combination once daily.

   The fixed-dose combination DOR/3TC/TDF capsules **are not to be swallowed whole. They must** ~~may~~ be opened and the oral granules sprinkled on the tongue then swallowed (followed with water) **or**~~;~~ sprinkled onto ~~1-2 teaspoons of~~ soft food then swallowed~~; or dispersed in 5-10 mL liquid then swallowed~~. ~~In any case, administration must occur within 15 minutes of mixing.~~

3. *Update to allow the enrollment of ART-experienced, virologically suppressed participants in Cohort 2, as specified in Clarification Memo #1.*

***Review of Adult Switch Data Prior to Allowing ART-experienced, virologically suppressed participants into Cohort 2 of IMPAACT 2014***

**When the IMPAACT 2014 protocol was finalized in September 2017, data were not available on switching participants from their current regimen to a once-daily regimen including DOR/3TC/TDF but were anticipated to become available during the course of the IMPAACT 2014 study. The IMPAACT 2014 protocol therefore specified that inclusion of participants who are ART-experienced, virologically suppressed will be dependent on supportive results from at least one of the ongoing adult switch studies (PN024, PN028).**

**Specifically, Section 1.4.2 of the IMPAACT 2014 protocol specified that data from one of the adult switch studies would need to be available from the 24-week time point and reviewed by the**

**IMPAACT 2014 Clinical Management Committee (CMC) and the IMPAACT Study Monitoring Committee (SMC) to confirm that the data were supportive of enrolling ART-experience, virologically suppressed participants; as noted in the protocol, data would be considered supportive if 90% or more of the participants maintain virologic suppression for at least 24 weeks after switching.**

**The 24-week data are now available from the DRIVE-SHIFT study and were reviewed by the CMC in October and November 2018 and by the SMC in January 2019; following review of the data, the CMC and SMC agreed that the protocol-specified criteria were met, as follows. At week 24, the data showed that 93.7% (419/447) of the immediate switch group and 94.6% (211/223) of the delayed switch group had HIV-1 RNA <50 copies/mL (1). As 90% or more of the participants maintained virologic suppression for at least 24 weeks after switching, the protocol-specified criteria for allowing enrollment of ART-experienced, virologically suppressed participants into Cohort 2 of IMPAACT 2014 have been met. Once Cohort 2 is open to accrual, participants who meet the eligibility criteria as ART-naïve or ART-experienced will be allowed to enroll.**

**Reference:**


1. **Kumar P, Johnson M, Molina J, Rizzardini G, Cahn P, Bickel M, Mallolas J, Zhou Y, Morais C, Kumar S, Sklar P. LB2.. Switch to Doravirine/ Lamivudine/ Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. InOpen Forum Infectious Diseases 2018 Nov (Vol. 5, No. Suppl 1, ppS759-60**


4. *Updates to protocol team and site representatives rosters*

*To reflect current protocol team membership, Patricia Morgan, Carmelita Alvero, Linda Marillo, William Murtaugh, Andrea Kehler, Xia Xu, Sushma Kumar, and Jontraye Davis are removed from the protocol team roster; Rachel Scheckter, Yvonne Woolwine-Cunningham, Frances Whalen, Havilland Campbell, Hye Cho, Anthony Rodgers, and Marcus Bolton are added:*

Clinical Trials Specialists
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**Email: mbolton@fhi360.org**

*To reflect current site representative membership, Sandra Jones and Sylvia Dittmer are removed from the site representative roster; Jill Utech and Avy Violari are added:*

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**Email: violari@mweb.co.za**

5. *Updates to Appendices II and III, Sample Informed Consent Forms for Study Participation*

   a. *Appendix II: Sample Informed Consent Form for Participation in Cohort 1, item 15, table following first paragraph:*

| | |
|---|---|
| Overall Body Effects<br>~~• Overall weakness~~<br>• Headache<br>~~• Back pain~~<br>~~• Stuff, runny or uncomfortable nose~~<br>~~• Fever~~ | Effects on the Stomach<br>• Pain or upset stomach<br>• Loose or watery stools<br>• Vomiting |
| ~~Effects on Muscle and Bones~~<br>~~• Aches and pains~~ | Effects on Activity<br>• **Trouble sleeping**<br>• Drowsiness and tiredness<br>• Dizziness |

   b. *Appendix II: Sample Informed Consent Form for Participation in Cohort 1, item 1, third paragraph:*

   The two groups of the study are called Cohort 1 and Cohort 2. Cohort 1 ~~will be done~~ **began** first. This part will include up to 20 children and adolescents. Cohort 2 will be done after **part of** Cohort 1 is completed. Cohort 2 will include up to 45 children and adolescents. We will tell you about Cohort 1 first. This is a consent form for Cohort 1.

c. *Appendix III: Sample Informed Consent Form for Participation in Cohort 2, item 1, fifth paragraph:*

The two groups of the study are called Cohort 1 and Cohort 2. Cohort 1 ~~was done~~ **began** first. This part **will include** ~~included~~ up to 20 children and adolescents. Cohort 2 will be done after **part of** Cohort 1 is completed. Cohort 2 will include up to 45 children and adolescents. We will tell you about Cohort 1 first. This is a consent form for Cohort 2.

d. *Appendix III: Sample Informed Consent Form for Participation in Cohort 2, item 2, third paragraph:*

Another way to take DOR/3TC/TDF is as oral granules. Granules are kept in larger capsules or containers *[sites may use any locally understandable term to describe the granules]*. The **capsules should not be swallowed whole. The capsules should be opened to sprinkle the granules directly into the mouth or to mix the** granules ~~can be sprinkled or mixed~~ with soft food ~~or liquid~~.

e. *Appendix III: Sample Informed Consent Form for Participation in Cohort 2, item 19, table following first paragraph, boxes for Overall Body Effects and Effects on Stomach:*

Overall Body Effects
- Changes in the placement of body fat (increasing around the stomach, neck, or breast or decreasing in the arms, legs, or cheeks)
- Overall weakness
- Headache
- Back pain
- ~~Stuff, runny, or uncomfortable nose~~
- Allergic reaction
- Numbing, tingling, or pain in the hands and feet
- Fever

Effects on Stomach
- Pain or upset stomach
- Loose or watery stools
- Vomiting
- Gas
- **Dry mouth**
- **Change in your sense of taste**

# Corrected Clarification Memorandum #1 for:

# 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

## Version 1.0, dated 7 September 2017

## IND# 137,041
## DAIDS Study ID 34150

## Corrected Clarification Memorandum Date: 13 February 2019

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### Summary of Clarifications and Rationale

This Clarification Memorandum (CM) documents the protocol-specified review of data from adult studies switching participants from a stable antiretroviral regimen to a once-daily single tablet regimen of doravirine 100 mg, lamivudine 300 mg, and tenofovir disoproxil fumarate 300 mg (DOR/3TC/TDF). Based on this review, protocol criteria to allow enrollment of ART-experienced, virologically suppressed participants into Cohort 2 of IMPAACT 2014 have been met; once Cohort 2 is open to accrual, participants who meet the eligibility criteria as ART-naïve or ART-experienced will be allowed to enroll.

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### Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. The information included in this memorandum will be incorporated into the next full protocol amendment.

#### *Review of Adult Switch Data Prior to Allowing ART-experienced, virologically suppressed participants into Cohort 2 of IMPAACT 2014*

When the IMPAACT 2014 protocol was finalized in September 2017, data were not available on switching participants from their current regimen to a once-daily regimen including DOR/3TC/TDF but were anticipated to become available during the course of the IMPAACT 2014 study. The IMPAACT 2014 protocol therefore specified that inclusion of participants who are ART-experienced, virologically suppressed will be dependent on supportive results from at least one of the ongoing adult switch studies (PN024, PN028).

Specifically, Section 1.4.2 of the IMPAACT 2014 protocol specified that data from one of the adult switch studies would need to be available from the 24-week time point and reviewed by the IMPAACT 2014 Clinical Management Committee (CMC) and the IMPAACT Study Monitoring Committee (SMC) to confirm that the data were supportive of enrolling ART-experience, virologically suppressed

participants; as noted in the protocol, data would be considered supportive if 90% or more of the participants maintain virologic suppression for at least 24 weeks after switching.

The 24-week data are now available from the DRIVE-SHIFT study and were reviewed by the CMC in October and November 2018 and by the SMC in January 2019; following review of the data, the CMC and SMC agreed that the protocol-specified criteria were met, as follows. At week 24, the data showed that 93.7% (419/447) of the immediate switch group and 94.6% (211/223) of the delayed switch group had HIV-1 RNA <50 copies/mL (1). As 90% or more of the participants maintained virologic suppression for at least 24 weeks after switching, the protocol-specified criteria for allowing enrollment of ART-experienced, virologically suppressed participants into Cohort 2 of IMPAACT 2014 have been met. Once Cohort 2 is open to accrual, participants who meet the eligibility criteria as ART-naïve or ART-experienced will be allowed to enroll.

Reference:

1. Kumar P, Johnson M, Molina J, Rizzardini G, Cahn P, Bickel M, Mallolas J, Zhou Y, Morais C, Kumar S, Sklar P. LB2.. Switch to Doravirine/ Lamivudine/ Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. InOpen Forum Infectious Diseases 2018 Nov (Vol. 5, No. Suppl 1, ppS759-60

# Letter of Amendment #1 for:

# 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

## Version 1.0, dated 7 September 2017

## IND#: 137,041
## DAIDS Study ID 34150

## Letter of Amendment Date: 7 May 2018

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## Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT 2014 study, including the study informed consent forms (ICFs), and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining IRB/EC approval and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA and using the updated ICFs. After all required approvals are obtained, the updated ICFs should be used for all new participants. In addition, all previously enrolled participants must reconsent to ongoing study participation using the updated site-specific ICF. Re-consenting should take place at each enrolled participant's next study visit after all required approvals are obtained.

Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT 2014. If the IMPAACT 2014 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

**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**
**Version 1.0, dated 7 September 2017**

**DAIDS Study ID #34150**

## Version 1.0, Letter of Amendment #1

### Letter of Amendment Signature Page

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

_____ _____

Signature of Investigator of Record Date

_____

Name of Investigator of Record
(printed)

## Summary of Modifications and Rationale

1. Per ICH GCP E6 4.8.10(n) and DAIDS requirements, it is mandatory that all DAIDS-sponsored and/or supported trials include language that informs participants that other US, local, and international regulatory entities may also review study records. Section 11.2 and the sample ICFs in Appendices II and III have been updated accordingly.
2. As recommended by the United States Food and Drug Administration, the target steady-state $C_{24hr}$ for Cohort 1 has been updated to be consistent with the steady-state $C_{24hr}$ obtained in adults at the proposed dose. The protocol had originally targeted the value equivalent to over six times the $IC_{50}$ for DOR against wild type virus in the presence of 100% normal human serum. This has been updated in Sections 10.1 and 10.3.1.
3. The protocol team had originally anticipated that up to 2.5 mL blood would be required to assay lamivudine and tenofovir for the Cohort 2 intensive PK; however, EDTA blood collection tubes are only available in 2.0 mL and 3.5 mL sizes. In consultation with the testing laboratories, the blood volume has been changed to required collection of 2.0 mL.
4. A secondary study objective related to immunologic response includes assessment at Weeks 24, 48 and 96 for participants in Cohort 2; inclusion of testing of CD4 cell count at Week 96 was inadvertently left out of the protocol requirements and has been added. In addition, more frequent testing of CD4 cell count was recommended by the United States Food and Drug Administration; this testing has been added to Weeks 64 and 80.
5. Consistent with Section 4.1.5.1, corrections have been incorporated into Section 4.1.5.3 related to requirements for virologic suppression.
6. Consistent with Sections 6.4 and 8.6, corrections have been incorporated into Appendix III to indicate that ART-naïve participants should be recalled for confirmatory HIV-1 RNA testing if they have an HIV-1 RNA level ≥200 copies/mL after about six months on study.
7. The additional guidance for sequencing of procedures at the Cohort 1 Entry Visit inadvertently included the selection and confirmation of formulation; as only one formulation will be available for participants in Cohort 1, this procedural sequence has been removed.
8. Other minor updates and clarifications, including inclusion of the IND number and updates to the protocol team roster, have been incorporated for accuracy and clarity.

## Implementation

The modifications included in this LoA are listed by modification and will be incorporated into the next protocol amendment as specified below. Additions to the text are indicated in **bold**; deletions are indicated by ~~strikethrough~~.

*1. Update to regulatory entities that may review study records*

*a. Section 11.2, Essential and Source Documents and Access to Source Data, fourth paragraph, first sentence:*

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, Merck & Company, the FDA, site drug regulatory authorities, site IRBs/ECs, OHRP, and other **US, local, and international** ~~applicable~~ regulatory entities.

b. *Appendix II: Sample Informed Consent Form for Participation in Cohort 1, item 20, and Appendix III: Sample Informed Consent Form for Participation in Cohort 2, item 24, bullet added to listing of groups that oversee the study:*

Groups that oversee the study include:

- **Other United States, local, and international regulatory entities**

2. *Align the target steady-state $C_{24hr}$ to be consistent with that obtained in adults*

a. *Section 10.1, Pharmacology Overview and Objectives, first paragraph, last sentence*

Based on simulations of ten participants (four from the 35 to ≤45kg group and six from the >45 kg group) with these geometric mean exposures and $C_{24hr}$ and variability, the AUC criterion (i.e., geometric mean steady state $AUC_{0\text{-}24hr}$ does not exceed 64.5 μM*hr) and the $C_{24hr}$ criterion (i.e., **the geometric mean $C_{24hr}$ in participants is greater than 560 nM** ~~at least 90% of participants achieving at least 78 nM~~**)** are achieved with high probability **(~90**% ~~>99%~~).

b. *Section 10.3.1, PK Guidelines for Cohort 1 to Confirm the Dose for Cohort 2, second bullet defining acceptable PK for Cohort 1 participants*

- Steady state $C_{24hr}$ values for participants in Cohort 1 will be projected from the single dose PK profiles. **The geometric mean $C_{24hr}$** ~~At least 90%~~ of Cohort 1 participants should **exceed the proposed lower bound associated with efficacy: 60% of the steady state $C_{24hr}$ achieved at the 100 mg QD dose in adults, corresponding to 560 nM** ~~have $C_{24hr}$ values that exceed the PK target for suppression of wild type virus, currently estimated as 78 nM (equivalent to over six times the $IC_{50}$ for DOR against wild type virus in the presence of 100% normal human serum)~~.

3. *Update blood volume requirements for Cohort 2 Week 1 PK evaluations*

a. *Section 6.3.2, Table 15. Cohort 2 Week 1 PK Evaluation Sampling Time Points, volume required at 1 hr post-dose and 8 hrs post-dose*

| Time Points | 1 hr post-dose | 8 hrs post-dose |
|---|---|---|
| Volume | **2.0 mL** ~~2.5 mL~~ | **2.0 mL** ~~2.5 mL~~ |

hr(s)=hour(s); mins=minutes

b. *Appendix I-B, Schedule of Evaluation for Cohort 2, volume required at Week 1 for intensive PK sampling and total maximum blood volume*

| *Study Visit* | Weeks on Study |
|---|---|
| | 1[1] |
| ***Pharmacology*** | |
| Intensive PK sampling[1] | **21.5 mL** ~~22.5 mL~~ |
| **Total maximum blood volume** | **21.5 mL** ~~22.5 mL~~ |

c. *Appendix I-B, Schedule of Evaluation for Cohort 2, update to second bullet of footnote 1*

- **2.0 mL** ~~2.5 mL~~ should be collected at 1 hour post-dose and 8 hours post-dose

d. *Appendix III, Sample Informed Consent Form for Participation in Cohort 2, item 10, sixth paragraph*

We will draw about **2.0** ~~2.5~~ – 3.5 mL (less than 1 teaspoon) of blood at six different time points during the first day for the PK test and at one time point during the second day of the PK test (a total of about **21.5 mL** ~~22.5 mL~~ or less than 5 teaspoons). We will look at the amount of ARVs in your [child's] blood at each of these times.

4. *Add blood collection and testing for CD4 cell count for participants in Cohort 2 at Weeks 64, 80 and 96*

a. *Section 6.3.7, Table for Cohort 2 Q16 Week Visits (Weeks 64, 80, and 96)*

| | | |
|---|---|---|
| **Laboratory** | **Blood** | Collect blood for:<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>o Electrolytes (sodium, potassium, and $HCO_3$)<br>o Glucose<br>o Creatinine<br>o Lipase<br>o Phosphorus<br>o LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin)<br>• HIV-1 RNA<br>• **CD4 cell count**<br>• *At Week 96,* lipid profile |

b. *Appendix I-B, Schedule of Evaluation for Cohort 2, volume required at Q16 week visits and total maximum blood volume*

| ***Study Visit*** | **Weeks on Study** |
|---|---|
| | **Q16**[3] |
| ***Laboratory Evaluations*** | |
| CD4 cell counts | **2 mL** |
| **Total maximum blood volume** | **15 mL** ~~13 mL~~ |

5. *Corrections to Section 4.1.5.3, Cohort 2 ART-experienced*

a. *Section 4.1.5.3, Cohort 2 ART-experienced, Virologic suppression, first sub-bullet:*

- One or more HIV RNA PCR result below level of quantification (BLLQ) within **15 months** ~~6 months~~ prior to enrollment, AND

*b. Section 4.1.5.3, Cohort 2 ART-experienced, second note added following criterion:*

**Note: A single, unconfirmed HIV-1 RNA result greater than or equal to the level of quantification but less than 500 copies/mL, between 3 and 15 months, prior to enrollment is not exclusionary as long as the other criteria for documentation of virologic suppression are met.**

6. *Correction to Appendix III: Sample Informed Consent Form for Participation in Cohort 2, item 11, first paragraph, second and third sentences*

If the study ARVs are your [child's] first anti-HIV medicine, your [child's] viral load should be very low after about **six months** ~~four months~~. If tests show that the viral load is higher than expected after **six months** ~~four months~~, [you/your child] will have an extra visit.

7. *Correction of procedural sequencing in Section 6.2.1, Cohort 1 Entry Visit, second paragraph, second bullet*

- ~~Selection and confirmation of formulation must precede enrollment~~

8. *Other minor updates and clarifications*

*a. Following finalization of protocol Version 1.0, the United States Food and Drug Administration issued the Investigational New Drug (IND) application number under which this study will be conducted. The IND number is added to the protocol title page:*

IND #**137,041** ~~XX,XXXX~~ Held by NIAID/DAIDS

*b. Updates to protocol team roster: Justine Beck is added and Jenna Kearly is removed:*

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**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

**A Multisite Study of the**
**International Maternal Pediatric Adolescent**
**AIDS Clinical Trials Network**


**Sponsored by:**
National Institute of Allergy and Infectious Diseases
*Eunice Kennedy Shriver*
National Institute of Child Health and Human Development
National Institute of Mental Health

**Pharmaceutical Support Provided by:**
Merck & Company Inc.

**DAIDS Study ID #34150**
**IND #XX,XXXX Held by NIAID/DAIDS**



| | |
|---|---|
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| **Protocol Vice-Chair:** | Brookie Best, PharmD, MAS |
| **NIAID Medical Officer:** | Ellen Townley, MSN, FNP |
| **NICHD Medical Officer:** | Bill Kapogiannis, MD |
| **Clinical Trials Specialist:** | Patricia Morgan, PA, MSc<br>Katie McCarthy, MPH |



**Final Version 1.0**
**7 September 2017**

**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**

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**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**

**DAIDS Study ID #34150**

**Version 1.0**
**PROTOCOL SIGNATURE PAGE**

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS, and institutional policies).

| | |
|---|---|
| Signature of Investigator of Record | Date |

Name of Investigator of Record
(printed)

## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| 3TC | lamivudine |
| ABC | abacavir |
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ALT | alanine transaminase |
| ARV | antiretroviral |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BLLQ | below the level of quantification |
| $C_{24hr}$ | plasma drug concentration, 24 hours post dose |
| $C_{max}$ | maximum serum concentration |
| cART | combination antiretroviral therapy |
| CBC | complete blood count |
| CFR | (US) Code of Federal Regulations |
| CI | confidence interval |
| CLIA | Clinical Laboratory Improvement Amendments |
| CMC | Clinical Management Committee |
| CNS | central nervous system |
| CRF | case report form |
| CRPMC | Clinical Research Products Management Center |
| CV | coefficient of variation |
| DAIDS | Division of AIDS |
| DAIDS PRO | DAIDS Protocol Registration Office |
| DAERS | DAIDS Adverse Experience Reporting System |
| DMC | Data Management Center |
| DNA | deoxyribonucleic acid |
| DOR | doravirine (MK-1439) |
| DRV | darunavir |
| DTG | dolutegravir |
| EAE | expedited adverse event |
| EC | Ethics Committee |
| eCRF | electronic case report form |
| EFV | efavirenz |
| EIA | enzyme immunoassay |
| FDA | (US) Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDC | fixed-dose combination |
| FTC | Emtricitabine |
| FSTRF | Frontier Science and Technology Research Foundation |
| GCLP | Good Clinical Laboratory Practice |
| GFR | glomerular filtration rate |
| GM | geometric least-square mean |
| GMR | geometric mean ratio |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HPMC | hydroxypropylmethyl cellulose |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| IMPAACT | International Maternal Pediatric Adolescent AIDS Clinical Trials Network |
| IND | Investigational New Drug |
| INR | international normalized ratio |
| InSTI | integrase strand transfer inhibitor |
| IoR | Investigator of Record |
| IRB | Institutional Review Board |
| IRIS | immune reconstitution inflammatory syndrome |
| LDL | low-density lipoprotein |
| LDMS | Laboratory Data Management System |
| LPC | Laboratory Processing Chart |
| MK-1439 | doravirine |
| MK-1439A | doravirine/lamivudine/tenofovir disoproxil fumarate |
| MOP | Manual of Procedures |
| MSDF | "Missing, Switch or Discontinuation = Failure" analysis |
| NIAID | (US) National Institute of Allergy and Infectious Diseases |
| NICHD | (US) National Institute of Child Health and Human Development |
| NIH | (US) National Institutes of Health |

| | | | |
|---|---|---|---|
| NIMH | (US) National Institute of Mental Health | RSC | (DAIDS) Regulatory Support Center |
| NRTI | nucleoside reverse transcriptase inhibitor | SAE | Serious Adverse Event |
| | | SDMC | Statistical and Data Management Center |
| NNRTI | non-nucleoside reverse transcriptase inhibitor | SES | Subject Enrollment System |
| NVP | nevirapine | SID | study identification number |
| OHRP | (US) Office for Human Research Protections | SMC | Study Monitoring Committee |
| | | SMR | sexual maturity rating |
| PCR | polymerase chain reaction | SOP | Standard Operating Procedure |
| PI | protease inhibitor | SUSAR | Suspected Unexpected Serious Adverse Reaction |
| PID | participant identification number | | |
| PK | pharmacokinetics | TDF | tenofovir disoproxil fumarate |
| PoR | Pharmacist of Record | TFV | tenofovir |
| PRO | (DAIDS) Protocol Registration Office | $T_{max}$ | time to reach maximum concentration |
| | | ULN | upper limit of normal |
| QD | per day | UN | United Nations |
| RAL | raltegravir | US | United States |
| RNA | ribonucleic acid | VQA | Virology Quality Assurance |
| RPV | rilpivirine | WHO | World Health Organization |

# 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

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**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**

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# 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

## SCHEMA

**Purpose:** To evaluate the pharmacokinetics, safety, and tolerability of doravirine (DOR) and of doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) in HIV-1-infected children and adolescents

**Design:** Phase I/II, multi-site, open-label, non-comparative pharmacokinetic (PK) and safety study

**Study Population:** HIV-1-infected children and adolescents, from 12 years to less than 18 years of age who weigh at least 35 kg. Cohort 1 and 2 will enroll sequentially:

Cohort 1: Virologically suppressed on a combination of dolutegravir (DTG) or raltegravir (RAL) plus two nucleoside reverse transcriptase inhibitors (NRTIs)

Cohort 2: Antiretroviral treatment naïve or virologically suppressed

**Sample Size:** Cohort 1: Up to 20 participants to achieve at least 12 evaluable participants

Cohort 2: Up to 45 participants to achieve at least 40 evaluable participants

**Study Drugs:** Doravirine (DOR also referred to as MK-1439) – 100 mg oral tablet; and doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF also referred to as MK-1439A) – 100 mg/300 mg/300 mg oral tablet or, as available, oral granules

Cohort 1: A single dose of DOR (100 mg) added to current regimen of DTG or RAL plus two NRTIs

Cohort 2: Once daily DOR/3TC/TDF (100 mg/300 mg/300 mg)

**Study Duration:** Approximately four years total from the date the first participant is enrolled. Accrual into Cohort 1 is expected to require approximately three to six months and participants in this cohort will be followed for two weeks. It is expected that Cohort 2 will open three months after Cohort 1 is completed (following review of data from Cohort 1). Accrual into Cohort 2 is expected to require approximately six to twelve months and participants in this cohort will be followed for 96 weeks.

### Primary Objectives

**The primary objectives for Cohort 1 are to:**

- Evaluate the pharmacokinetics of a single-dose of DOR in HIV-1-infected children and adolescents, when added to a stable antiretroviral therapy (ART) regimen comprised of an integrase strand transfer inhibitor (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.

**The primary objective for Cohort 2 is to:**

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

### Secondary Objectives

**The secondary objectives of Cohort 2 are to:**

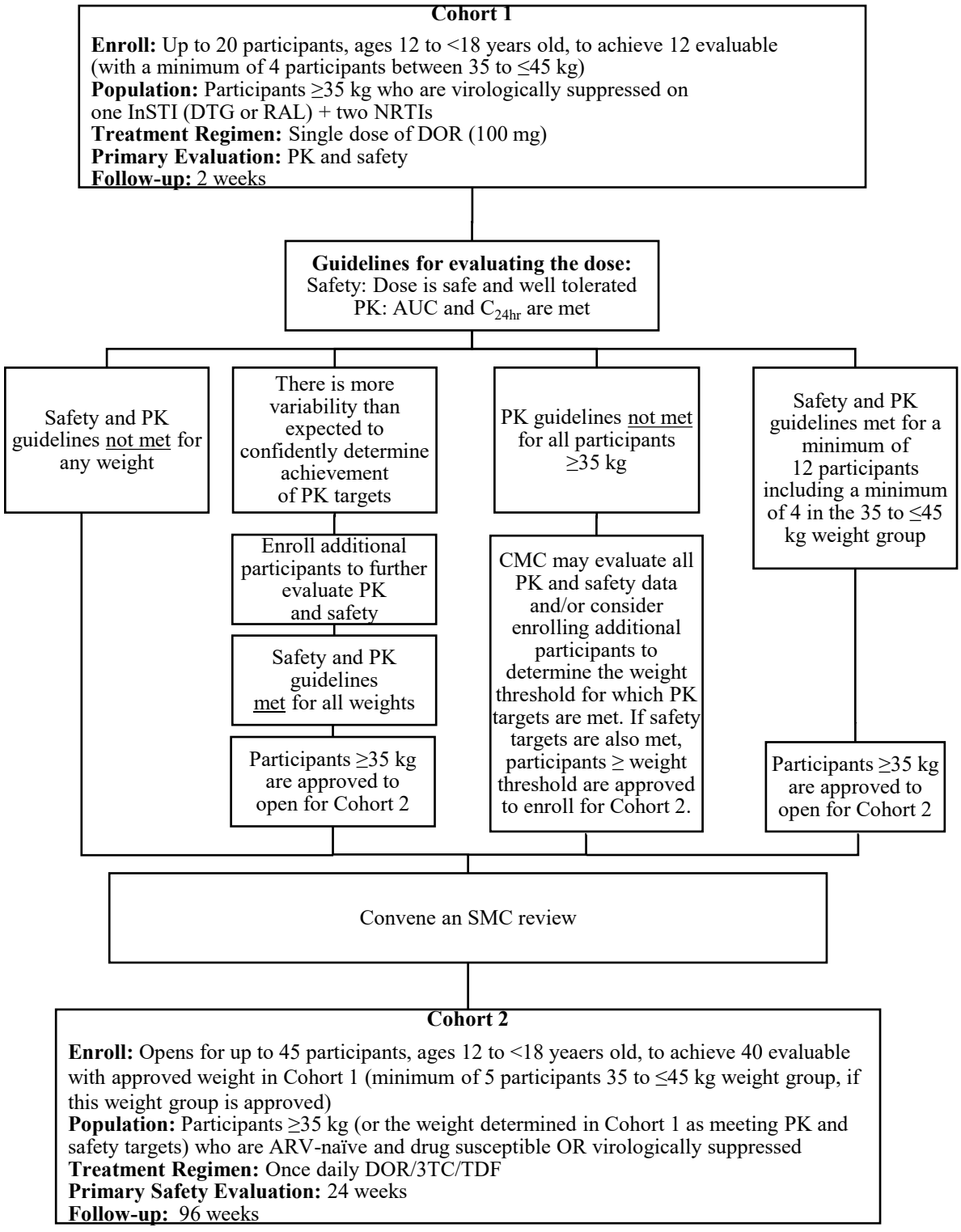
- Evaluate the pharmacokinetics of DOR, 3TC, and tenofovir in HIV-1-infected children and adolescents receiving DOR/3TC/TDF, using intensive (tenofovir and 3TC) and semi-intensive (DOR) PK sampling at Week 1.
- Evaluate the 24-, 48-, and 96-week virologic efficacy of DOR/3TC/TDF in HIV-1-infected children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

### Other Objectives

**The other objectives of Cohort 2 are to:**

- Evaluate the pharmacokinetics of DOR, 3TC, and tenofovir in HIV-1-infected children and adolescents receiving DOR/3TC/TDF, using sparse PK sampling through Week 48.
- Assess changes in HIV-1 genotype and phenotype to DOR and other components of the regimen in HIV-1-infected children and adolescents experiencing virologic failure.
- Evaluate acceptability, palatability, and adherence to DOR/3TC/TDF in HIV-1-infected children and adolescents through Week 96.

**Figure 1. IMPAACT 2014 Overview of Study Design**



# 1 INTRODUCTION

## 1.1 Background

Human immunodeficiency virus (HIV) infection, which causes acquired immunodeficiency syndrome (AIDS) and for many years was associated with substantial morbidity and mortality, has now become a chronic disease that can be controlled through life-long combination antiretroviral (ARV) therapy (cART) (1-4). Currently, there are more than 30 individual drugs and fixed-dose combinations available for the treatment of HIV-1 infection. These agents belong to five distinct mechanistic classes known as reverse transcriptase inhibitors [nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)], protease inhibitors (PIs), fusion inhibitors, entry inhibitors (CCR5 co–receptor antagonists), and integrase strand transfer inhibitors (InSTI). Successful combinations of antiretroviral medications generally utilize three agents from at least two different mechanistic classes. The goal of cART is to suppress HIV to undetectable levels so that immune function is preserved or restored. Yet, while cART can delay disease progression and death, as well as reduce the risk of HIV transmission, it does not cure the infection. As a result, lifelong treatment must be maintained, which may lead to therapy fatigue and to noncompliance if the treatment regimen is difficult to adhere to (e.g., pill burden, frequency of treatment) and associated with intolerable side-effects (5-7). This can potentially lead to treatment failures with possible development of resistant virus. Additionally, there is currently still significant concern regarding toxicities of some widely-used antiretroviral agents, including neuropsychiatric toxicities associated with efavirenz (EFV, an NNRTI), gastrointestinal toxicities such as diarrhea associated with multiple PIs, and serum lipid abnormalities associated with multiple mechanistic classes. Thus, potent treatment regimens that have an excellent safety and tolerability profile and are convenient are still highly desirable.

For initiation of combination antiretroviral therapy for HIV infection, currently available NNRTIs have constituted an important option for use as anchor agents, along with two NRTIs; however, each has limitations, and at present are on the preferred list for first line therapy in World Health Organization (WHO) but not U.S. treatment guidelines (8, 9). For example, while efavirenz has shown excellent efficacy over many years of use, it is associated with substantial neuropsychiatric intolerance and skin rash, as well as lipid abnormalities. In addition, EFV can be a perpetrator of drug-drug interactions as a mixed inducer or inhibitor of CYP3A and CYP2B6 enzymes. Rilpivirine (RPV) has shown suboptimal efficacy in patients with high viral load or low baseline CD4 cells, and thus is not indicated in patients with baseline viral load above 100,000 copies/mL or CD4 count below 200 cells/mL. In addition, RPV requires dosing with food and can lead to a prolonged QT interval at supratherapeutic doses (10). Importantly, high level resistance may occur in response to a single mutation for all currently available NNRTIs except etravirine, which must be dosed twice daily. Therefore, new agents of the NNRTI class that offer high potency, a distinct resistance profile, dosing convenience and a favorable safety and tolerability profile are needed.

Doravirine (DOR, MK-1439) is a novel NNRTI being studied for the treatment of HIV-1 infection in antiretroviral-naïve HIV-infected participants. Doravirine is a potent inhibitor of HIV-1 replication in vitro and is active against both wild type virus and the most common NNRTI resistant variants at concentrations achieved with once daily dosing. Doravirine displays excellent potency against wild type virus with an $IC_{50}$ of 12 nM in the presence of 100% normal human serum. Preclinical studies also indicate a favorable in vitro resistance profile that is distinct from other NNRTIs, with $IC_{50}$'s of 21, 31, and 55 nM against HIV-1 mutants containing the most frequently transmitted NNRTI mutations, K103N, Y181C and G190A, respectively,

under the same conditions (11). The $IC_{50}$ against viruses containing the double mutant K103N + Y181C is 33 nM. The preclinical toxicity profile of doravirine is favorable in rats up to six months in duration at 3, 30, and 450 mg/kg/day, and in dogs up to nine months in duration at 1, 10, and 1000 mg/kg/day. Juvenile toxicity studies have been conducted in 14 day old rats and indicate no DOR related toxicity; the no-observed-effect level was >300 mg/kg/day, suggesting the compound is safe in adolescents and children (12).

DOR can be dosed once daily, without regard to food. Metabolism of DOR is primarily by CYP3A, and it is subject to induction/inhibition of this enzyme by other agents. However, DOR is neither a metabolic inducer nor inhibitor, and thus is unlikely to be the cause of significant drug-drug interactions. The available data from Protocol 007 (PN007), a Phase 2 study in treatment-naive HIV-infected patients, demonstrate that DOR at a dose of 100mg daily in combination with tenofovir disoproxil fumarate (TDF)/emtricitabine has favorable safety and tolerability profile and potent efficacy, with ~78% of patients receiving DOR achieving undetectable viral load (<40 copies/mL) at week 48, as compared to ~78 % in participants receiving efavirenz with TDF/emtricitabine (13) (Section 1.2.2). In this study, DOR was generally well tolerated and demonstrated significantly less CNS toxicity than efavirenz (Section 1.2.3). Furthermore, DOR at a dose of 100 mg daily plus two NRTIs was shown to be non-inferior to darunavir 800mg/ritonavir 100mg plus two NRTIs in ART-naïve adults, with 83% of participants achieving a viral load <50 copies/mL at 48 weeks in PN018 (Section 1.2.3).

Doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF, MK-1439A) is a single-tablet fixed-dose combination (FDC) regimen that combines DOR with lamivudine (3TC) and TDF, two approved and commercially available NRTIs. A single tablet of DOR/3TC/TDF contains a full daily HIV treatment regimen of DOR 100 mg + 3TC 300 mg + TDF 300 mg. This FDC has been evaluated in Phase 1 studies, which showed comparable pharmacokinetics to the component agents. DOR/3TC/TDF is being studied in several ongoing Phase 2 and 3 studies.

These preclinical and clinical data provide key support for the initiation of clinical trials in adolescents and children, which includes the evaluation of both DOR as a single agent and DOR/3TC/TDF as a single-tablet fixed-dose combination regimen.

Development of DOR and DOR/3TC/TDF has included multiple Phase 1 studies, investigating safety, pharmacokinetics, and virologic efficacy. Phase 2 and 3 studies are on-going, investigating safety and efficacy of DOR and DOR/3TC/TDF. Table 1, below, summarizes selected studies, which are discussed in more detail in Sections 1.2-1.3.

**Table 1. Selected Adult Studies Using DOR or DOR/3TC/TDF**

| Phase | Study | N |
|---|---|---|
| 1 | PN001-01: Study of single and multiple doses of DOR with and without midazolam in healthy adults | 58* |
| | PN002: Study of effect of ritonavir on DOR PK in healthy adults | 8* |
| | PN005: Study of multiple dose of DOR in ART-naïve HIV-1 infected patients | 18* |
| | PN009: Study of relative bioavailability of DOR by age and gender | 36* |
| | PN026: Study of bioavailability of DOR/3TC/TDF in fasted conditions in healthy adults | 24* |
| | PN029: Study of bioavailability of DOR/3TC/TDF in fed and fasted conditions in healthy adults | 14* |
| 2b | PN007: Study of DOR plus TDF/FTC versus EFV plus TDF/FTC in treatment-naïve patients | 208* (Part 1)<br>132* (Part 2) |
| 2 | PN028: Study of DOR/3TC/TDF in patients switching from EFV for CNS intolerance | 84 |
| | PN030: Study of DOR/3TC/TDF in treatment-naïve patients with transmitted resistance to NNRTIs | 10** |
| 3 | PN018: Study of DOR versus boosted-darunavir in treatment-naïve patients | 769* |
| | PN021: Study of DOR/3TC/TDF versus EFV/FTC/TDF in treatment-naïve patients | 734* |
| | PN024: Study of DOR/3TC/TDF in patients switching from a PI or NNRTI-based regimen | 673* |

*=fully enrolled

**= screening halted due to enrollment challenges

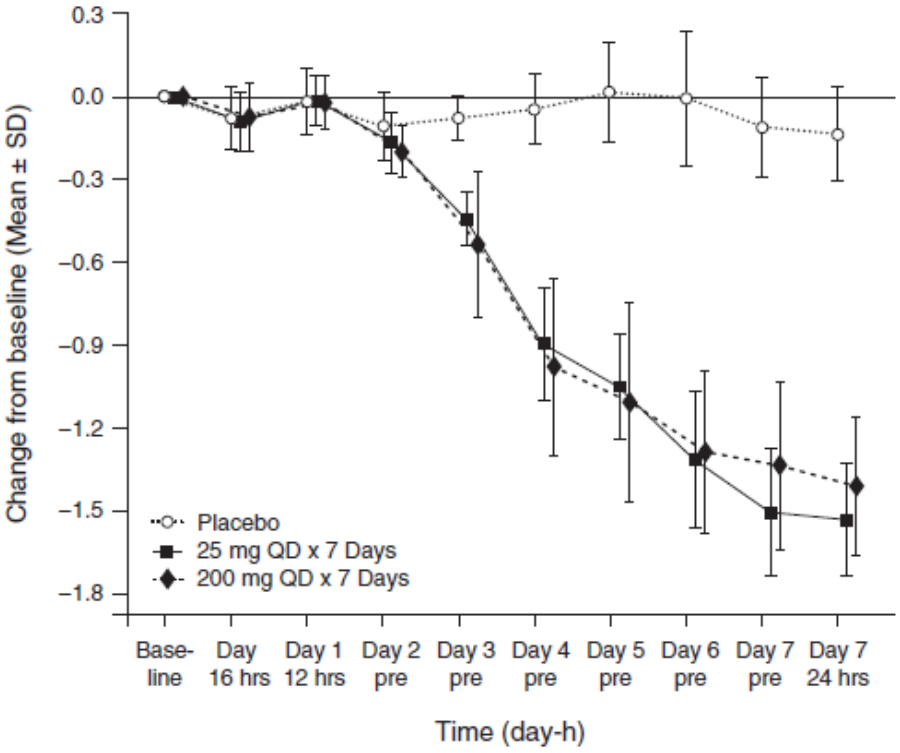
## 1.2 Clinical Efficacy

Evidence for clinical efficacy of DOR was established in two Merck-sponsored protocols, PN005 and PN007 (14, 15) and confirmed by the primary end point analysis at Week 48 from two Phase III studies in ART-naïve adults, PN018 and PN021 (16).

### 1.2.1 PN005

In PN005 eighteen HIV-infected, ART-naïve, adults received 25 mg DOR (n=6), 200 mg DOR (n=6) or placebo (n=6) for seven days and with daily HIV RNA concentrations and viral resistance determinations (14). The mean change from baseline in HIV RNA at 24 hours after the day 7 dose was –1.52 $\log_{10}$ copies/mL in the DOR 25-mg group and –1.41 $\log_{10}$ copies/mL in the DOR 200-mg group, versus –0.15 $\log_{10}$ copies/mL in the placebo group. Viral load reductions over time were similar for the two DOR groups (Figure 2). No participant showed evidence of viral breakthrough or development of NNRTI-resistance mutations.

**Figure 2. Mean Change from Baseline in Plasma HIV RNA ($log_{10}$ copies/mL) after Once-daily Administration of Doravirine (25 or 200 mg) or Placebo for 7 days**




### 1.2.2 PN007, PN018, and PN021

PN007 was a Phase 2b double-blind, randomized, dose-ranging study to compare the safety and antiretroviral activity of DOR plus TDF/FTC (Truvada®) versus efavirenz combined with TDF/FTC which was conducted in two parts (15). In part 1, participants were randomized to 25 mg (n=40), 50 mg (n=43), 100 mg (n=42) and 200 mg (n=41) of DOR versus 600 mg efavirenz (n=42) combined with TDF/FTC. All DOR doses showed numerically higher response rates compared to efavirenz (80.0%, 76.2%, 71.4%, 78.0% versus 64.3% of patients with <40 copies/mL for DOR 25 mg, 50 mg, 100 mg, 200 mg versus efavirenz arms, respectively). The treatment differences (DOR minus EFV) were not significant, and there was no dose-response for efficacy observed. Overall 76.4% of patients receiving DOR (at any dose) achieved <40 copies/mL compared with 64.3% for EFV. In addition, approximately 30% of participants in the study had baseline HIV RNA above 100,000 copies/mL, and, in this subgroup, DOR at all dosing levels showed virologic responses comparable to efavirenz. These efficacy data strongly support that the dose range studied (25-200 mg daily) was on the plateau of the dose response curve. The data from Protocol 007 showed an overall favorable safety and tolerability profile for DOR compared with EFV, with no differentiation among DOR doses (25 mg – 200 mg daily) with regard to safety. Based upon the 24-week results of Protocol 007, DOR at doses ranging from 25-200 mg was generally well-tolerated, with no apparent dose related toxicity. Fewer drug related adverse events (AEs) were observed for DOR than for EFV (34.9% for DOR overall versus 57.1% for EFV), and fewer CNS AEs were reported both at Week 8 and Week 24 (20.5% for DOR overall versus 33.3% for EFV at Week 8 and 23.4% for DOR overall versus 33.3% for EFV at Week 24). After the 24-week analysis, the 100 mg dose of DOR was selected for further study in Part 2 (see below for rationale) and at a subsequent visit (mostly by Week 48), the

participants randomized to other doses of DOR continued the study on 100mg of DOR plus TDF/FTC (13).

Part 2 of PN007 then opened, in which additional patients were randomized in a 1:1 ratio to the selected 100 mg dose of DOR (Total N = 108) or EFV (600 mg q.h.s.) (Total N = 108), each in combination with TDF/FTC for 96 weeks of blinded treatment. Evaluation of the 216 adults from Part 1 and 2 provided key long-term safety and efficacy data for DOR 100 mg daily (Table 2 through Table 4) as well as an assessment of CNS events (Table 5).

Results from combined Parts 1 and 2 of the above study after 48 weeks on DOR at the selected 100 mg dose (n=108) versus EFV (n=108) both with TDF/FTC are shown in Table 2 below.

**Table 2. PN007 Parts 1 and 2 (15)**

| | DOR 100 mg (N=108) | | EFV 600 mg (N=108) | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **Success (HIV RNA <40 copies/mL) at week 48*** | 84 | (77.8) | 85 | (78.7) |
| **Non-success at week 48** | 24 | (22.2) | 23 | (21.3) |
| **HIV RNA ≥40 copies/mL** | 18 | (16.7) | 14 | (13.0) |
| ≥40 and <200 copies/mL | 8 | (7.4) | 6 | (5.6) |
| ≥200 copies/mL | 3 | (2.8) | 2 | (1.9) |
| discontinued study due to lack of efficacy, or discontinued for other reasons with last HIV RNA ≥40 copies/mL† | 7 | (6.5) | 6 | (5.6) |
| **No virologic data at week 48 window** | 6 | (5.6) | 9 | (8.3) |
| discontinued study due to AE or death | 3 | (2.8) | 6 | (5.6) |
| discontinued study for other reasons with last HIV RNA <40 copies/mL | 3 | (2.8) | 2 | (1.9) |
| on study but missing data in week 48 window | 0 | (0.0) | 1 | (0.9) |

* Overall success/non-success rates are identical for Non-completer = Failure (NC=F) and the US Food and Drug Administration (FDA) snapshot approach. All patients also received TDF/FTC.
† Majority of patients in this category (5 of 7 in DOR group; 4 of 6 in EFV group) had last HIV RNA ≥200 c/mL. No treatment-emergent resistance mutations were detected in the 4 patients (3 DOR, 1 EFV) who had HIV RNA >500 c/mL at the time of virologic failure. Another patient who failed on DOR had a sample tested for resistance 1 month later: new NNRTI mutations (E138E/G + V179D) were present, with no change in phenotypic sensitivity (0.75-fold change) to DOR and 7.14-fold decreased susceptibility to EFV.

Similar results were noted at Week 96, with the proportion of participants achieving HIV-1 RNA <40 copies/mL (for Part I/II combined) being comparable between those participants who received DOR 100 mg (75.0%) and those who received EFV 600 mg (75.9%). (17)

The CD4 cell increase from baseline to Week 96 was 259.2 cells/mm$^3$ versus 263.6 for 100 mg DOR versus EFV.

In addition, the Merck adult clinical development program also includes five ongoing studies using DOR as single-tablet FDC or single agent in combination with TDF/FTC, as shown in Table 1.

Because the safety and efficacy data from Protocol 007 did not distinguish among the doses tested, the selection of DOR100 mg daily dose for study in Part 2 of Protocol 007 and in the Phase 3 studies has taken into consideration a number of additional factors. Firstly, DOR is a substrate of CYP3A metabolism and is subject to induction and inhibition of CYP3A by other

concomitant medications. Consequently, the 100 mg dose is more likely than the lower doses to provide adequate DOR exposures even in the setting of moderate metabolic inducers, and it allows for a safety margin in the setting of moderate metabolic inhibitors (since acceptable safety and tolerability were seen at the 200 mg dose in the Phase 2 study as well as at multiple doses and single doses as high as 750 mg and 1200 mg, respectively, in Phase 1 studies). Secondly, the 100-mg dose may provide forgiveness in the setting of the occasional missed dose. Thirdly, based on modeling and simulation, the 100-mg dose is predicted to provide adequate exposures and $C_{trough}$ concentrations in the setting of certain common NNRTI resistance mutations against which DOR is considered to be active in vitro, including the K103N, Y181C, and G190A mutations, as well as the dual K103N/Y181C mutation.

PN018 is an ongoing Phase 3, multicenter, double blind, randomized, active comparator-controlled clinical trial to evaluate the safety and efficacy of doravirine 100 mg once-daily versus darunavir 800 mg once-daily plus ritonavir 100 mg once-daily (DRV/r), each in combination with FTC/TDF or abacavir/lamivudine (ABC/3TC), in treatment naïve HIV-1 infected participants. Results from the primary efficacy endpoint analysis (the proportion of participants achieving HIV-1 RNA <50 copies/mL) after all participants completed 48 weeks of treatment demonstrated DOR had antiretroviral efficacy that was high and non-inferior compared to that of DRV/r. Specifically, 84% (321/383) of participants randomized to DOR 100 mg and 80% (306/383) of participants randomized to DRV/r achieved HIV-1 RNA <50 copies/mL (difference [95% CI]: +3.9% [-1.6, 9.4]) by the FDA Snapshot approach.

PN021 is an ongoing Phase 3, multicenter, randomized, double-blind trial designed to evaluate the safety and efficacy of once-daily DOR/3TC/TDF compared with once-daily EFV/FTC/TDF (administered as Atripla®) in treatment naïve participants with HIV-1 infection. The proportion of participants achieving HIV-1 RNA <50 copies/mL at Week 48 (FDA Snapshot) was 84% (307/364) in the DOR/3TC/TDF group and 81% (294/364) in the EFV/FTC/TDF group. The treatment difference (DOR/3TC/TDF – EFV/FTC/TDF) was 3.5% with an associated 95% CI of (-2.0, 9.0), demonstrating non-inferiority of DOR/3TC/TDF as compared to EFV/FTC/TDF.

### 1.2.3 Doravirine and Doravirine/Lamivudine/Tenofovir disoproxil fumarate Safety in Clinical Trials

DOR and DOR/3TC/TDF have been studied in 35 Phase 1 trials and in one completed Phase 2b trial (using DOR as single agent). Three Phase 3 (one with DOR and two with DOR/3TC/TDF) and two Phase 2 trials with DOR/3TC/TDF are in progress. All Phase 3 trials have completed enrollment; 48-week data are available for two Phase 3 studies (PN018 and PN021).

Across all Phase 1 studies, approximately 650 adult participants received at least one dose of DOR (including participants enrolled in DOC/3TC/TDF studies), including 372 healthy male participants, 206 healthy female participants, 12 healthy elderly female participants, 12 healthy elderly male participants, 12 male HIV-1 infected participants, eight participants with hepatic impairment, and eight participants with severe renal impairment. Across the Phase I program, approximately 522 participants have received a single-dose of DOR; of these participants, 500 have received a dose of ≥100 mg. Approximately 191 participants have received consecutive multiple doses of DOR; of these participants, 173 participants have received doses ≥100 mg (note: 67 participants are counted in both the single-dose group and multiple-dose group).

While the planned clinical dose in adults is 100 mg administered once-daily, the safety and tolerability of DOR have been investigated at single doses up to 1200 mg and multiple doses up to 750 mg for 10 days in healthy volunteers. These doses provide exposure multiples approximately 4.4-fold the steady-state exposure anticipated at the 100 mg dose. In addition, 12

adult male HIV-1 infected participants have received seven days of dosing with DOR 200 mg. Overall, DOR was found to be generally well-tolerated with no dose-dependent increases in specific AE. The majority of AEs were mild and moderate in severity. Only one AE (syncope) was of severe intensity; the AE was not considered related to DOR. Two serious adverse events (SAEs) have been reported (elevated liver enzymes in setting of new hepatitis C (HCV) infection and new onset sarcoidosis) in the Phase I program; both were not considered to be related to DOR.

A QTc study evaluating the effect of a supratherapeutic dose (1200 mg, corresponding to 3.3-fold the anticipated steady state $C_{max}$ at 100 mg) of DOR on QTc and other cardiac parameters has been completed. Data from this study demonstrated that DOR does not prolong the QTc interval to a clinically relevant degree.

To date, four Phase 1 studies (Protocols 014, 015, 026, and 029) have been conducted with DOR/3TC/TDF. The first two assessed prototype FDC formulations in healthy adults. Two additional studies evaluated the PK of the final adult FDC formulation compared to co-administration of individual components and the effect of food on the FDC formulation in healthy adults. The adverse events in these studies were all mild. No trends were identified in adverse events that differed from the labels of the marketed drugs or the Phase 2 data for DOR.

PN 007 Part 1 and 2

Safety data are available from the 108 adults receiving DOR at the 100 mg dose for 48 weeks in the combined Parts 1 and 2 of PN007. The clinical adverse events and laboratory abnormalities are summarized in Table 3 and Table 4 below.

**Table 3. Clinical Adverse Events (%) DOR + TDF/FTC versus EFV + TDF/FTC at 96 Weeks (17)**

| Clinical Adverse Events | DOR 100 mg (N=108) | EFV 600 mg (N=108) |
|---|---|---|
| Discontinued due to AE | 4.6 | 10.2 |
| Drug-related AE | 35.2 | 58.3 |
| Drug-related serious AE | 0 | 2.8 |
| Death | 0 | 0 |
| Diarrhea | 0.9 | 6.5 |
| Nausea | 7.4 | 6.5 |
| Fatigue | 3.7 | 4.6 |
| Dizziness | 7.4 | 26.9 |
| Headache | 2.8 | 5.6 |
| Abnormal dreams | 5.6 | 14.8 |
| Insomnia | 6.5 | 2.8 |
| Nightmares | 5.6 | 8.3 |
| Sleep disorder | 4.6 | 6.5 |

**Table 4. Laboratory Abnormalities ≥Grade 2 (%)**
**DOR + TDF/FTC versus EFV + TDF/FTC at 48 Weeks (15)**

| Laboratory Test | Grade (criteria) | DOR 100 mg (N=108) | EFV 600 mg (N=108) |
|---|---|---|---|
| Absolute neutrophil count | 2 (0.75-0.999 x $10^3$/µL) | 1.9 | 1.9 |
| | 4 (<0.50 x $10^3$/µL) | 0 | 0.9 |
| Platelet count | 2 (50 – 99.9 x $10^3$/µL) | 0.9 | 0.9 |
| LDL-cholesterol, fasting | 2 (160 – 189 mg/dL) | 2.0 | 3.9 |
| | 3 (≥190 mg/dL) | 0 | 1.9 |
| Total cholesterol, fasting | 2 (240 – 300 mg/dL) | 0 | 6.7 |
| | 3 (>300 mg/dL) | 0 | 1.9 |
| Triglycerides, fasting | 2 (500 – 750 mg/dL) | 0 | 1.9 |
| Glucose, fasting | 2 (126 – 250 mg/dL) | 3.2 | 1.1 |
| Aspartate aminotransferase | 2 (2.6 – 5.0 x ULN) | 0.9 | 3.7 |
| | 3 (5.1 – 10.0 x ULN) | 0.9 | 0 |
| | 4 (>10.0 x ULN) | 0 | 0.9 |
| Alanine aminotransferase | 2 (2.6 – 5.0 x ULN) | 0.9 | 0 |
| | 3 (5.1 – 10.0 x ULN) | 0.9 | 1.9 |
| Lipase | 2 (1.6–3.0 x ULN) | 4.7 | 7.4 |
| | 3 (3.1 – 5.0 x ULN) | 3.7 | 4.6 |
| | 4 (>5.0 x ULN) | 0.9 | 1.9 |

Data on CNS adverse events from the 108 participants in Parts 1 and 2 of the Phase 2 study who continued on the 100 mg DOR dose are available through Weeks 8 and 24 (Table 5). Overall, CNS AEs were more frequently reported in the EFV group than in the DOR group. The treatment difference was statistically significant at Weeks 8 and 24 ($p < 0.001$).

**Table 5. Proportion of Patients with Central Nervous System Adverse Events (CNS Events) by Week 8 and by Week 24 Part I/II Combined All Patients as Treated**

| Treatment | Percent of Patients with One or More Selected Adverse Events | | Doravirine minus Efavirenz ‡ | |
|---|---|---|---|---|
| | n/N | %(95% CI) | Difference (95% CI) | P-Value |
| **CNS Events† by Week 8** | | | | |
| Doravirine 100 mg | 26/108 | 24.1 (16.4, 33.3) | -20.4 (-32.4, -7.8) | 0.002 |
| Efavirenz 600 mg | 48/108 | 44.4 (34.9, 54.3) | | |
| **CNS Events† by Week 24** | | | | |
| Doravirine 100 mg | 29/108 | 26.9 (18.8, 36.2) | -20.4 (-32.6, -7.5) | 0.002 |
| Efavirenz 600 mg | 51/108 | 47.2 (37.5, 57.1) | | |

† Selected adverse events are from MedDRA terms of depression, nightmare, confusional state, suicidal ideation, nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, hallucination auditory, hallucination visual, completed suicide, suicidal behavior, major depression, depressed mood, depressive symptom, insomnia, disturbance in attention, somnolence, dizziness, concentration impaired.
‡ A negative value favors doravirine over efavirenz. The 95% CIs and p-values were calculated using Miettinen and Nurminen's method. Participants are counted once for each unique adverse event and may have had more than one unique adverse event.
n/N = Number of patients included in a given category / number of patients in each treatment group.
Note: Both doravirine and efavirenz were administered with Truvada®.

PN018

Safety data at 48 weeks are also available from PN018, the DOR versus DRV/r randomized trial in ART-naïve adults described above. Adverse event rates (overall, serious, drug-related, and leading to treatment discontinuation) were similar across treatment groups. The most common drug-related AEs (>10% in one or more treatment groups) were diarrhea (14%, 22%), nausea (11%, 12%), and headache (14%, 11%) for DOR and DRV/r, respectively (Table 6). Grade 3 or 4 laboratory changes occurred in ≤2% of participants in the DOR group and were similar between groups. Fasting LDL-C and non-HDL-C were reduced by DOR and increased by DRV/r with statistically significant treatment differences ($p<0.0001$).

**Table 6. PN018 Week 48 Summary of Clinical Adverse Events (16)**

| Clinical AE | DOR (N=383) | | DRV+r (N=383) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| One or more AE | 307 | (80%) | 300 | (78%) |
| Drug-related AE | 117 | (31%) | 123 | (32%) |
| Serious AE | 19 | (5%) | 23 | (6%) |
| Discontinued due to AE | 6 | (2%) | 12 | (3%) |
| **Most common AEs (≥ 10% in either group)** | | | | |
| Diarrhea | 54 | (14%) | 86 | (22%) |
| Nausea | 41 | (11%) | 46 | (12%) |
| Nasopharyngitis | 30 | (8%) | 39 | (10%) |
| Headache | 53 | (14%) | 41 | (11%) |
| **AEs of clinical interest** | | | | |
| Rash† | 28 | (7%) | 32 | (8%) |
| Neuropsychiatric‡ | 44 | (11%) | 50 | (13%) |

† Only 2 DOR participants and 1 DRV+r participant discontinued due to rash

‡ Includes disturbance in attention, dizziness, somnolence, abnormal dreams, confusional state, depressed mood, depression, insomnia, major depression, nightmare and psychotic disorder. No participants discontinued due to neuropsychiatric AEs

PN021

Week 48 safety data including neuropsychiatric AE results (Table 7 and Table 8) are available from PN021, the DOR/3TC/TDF versus EFV/3TC/TDF randomized trial in treatment-naïve adults described above.

**Table 7. PN021: Analysis of Participants with Neuropsychiatric Adverse Events by Week 48 (17)**

| | DOR/3TC/TDF Per Day (QD) (N=364) | | EFV/FTC/TDF QD (N=364) | | Treatment Differences (DOR/3TC/TDF - EFV/FTC/TDF), Estimate (95% CI)† | Two-Sided P-Value‡ |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | | |
| Participants in population | 364 | | 364 | | | |
| With one or more neuropsychiatric adverse event | 86 | (23.6) | 207 | (56.9) | -33.2 (-39.8, -26.4) | |
| With no neuropsychiatric adverse events | 278 | (76.4) | 157 | (43.1) | 33.2 (26.4, 39.8) | |
| Dizziness | 32 | (8.8) | 135 | (37.1) | -28.3 (-34.0, -22.5) | <0.001 |
| Sleep disorders and disturbances | 44 | (12.1) | 93 | (25.5) | -13.5 (-19.1, -7.9) | <0.001 |
| Altered sensorium | 16 | (4.4) | 30 | (8.2) | -3.8 (-7.6, -0.3) | 0.033 |
| Depression and suicide/self-injury | 15 | (4.1) | 24 | (6.6) | -2.5 (-5.9, 0.8) | nps* |
| Psychosis and psychotic disorders | 1 | (0.3) | 4 | (1.1) | -0.8 (-2.5, 0.5) | nps* |

The five categories of neuropsychiatric adverse event were predefined. Specific terms included for each category were based on MedDRA 19.1. Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a category is counted a single time for that category.

† The 95% Cis were calculated using Meittinen and Nurminen's method.

‡ Superiority is tested sequentially for dizziness, sleep disorders and disturbances, and altered sensorium.

*Not pre-specified for statistical testing.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

**Table 8. PN021 Week 48 Summary of Clinical Adverse Events (18)**

| Clinical AE | DOR/3TC/TDF (N=364) | | EFV/FTC/TDF (N=364) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| One or more AE | 301 | (83%) | 330 | (91%) |
| Drug-related AE | 113 | (31%) | 229 | (63%) |
| Serious AE | 13 | (4%) | 21 | (6%) |
| Discontinued due to AE | 11 | (3%) | 24 | (7%) |
| **Most common AEs (≥ 10% in either group)** | | | | |
| Headache | 47 | (13%) | 45 | (12%) |
| Diarrhea | 39 | (11%) | 49 | (14%) |
| Nasopharyngitis | 39 | (11%) | 31 | (9%) |
| Dizziness | 32 | (9%) | 135 | (37%) |
| Nausea | 28 | (8%) | 39 | (11%) |
| Abnormal dreams | 17 | (5%) | 42 | (12%) |
| Rash | 17 | (5%) | 44 | (12%) |

## 1.3 Doravirine Clinical Pharmacokinetics in Adults

### 1.3.1 Absorption and Pharmacokinetics of Single and Multiple Doses

PK data for single dose oral administration of the DOR tablet from up to 450 mg to healthy male participants demonstrated DOR was rapidly absorbed (PN001-01). DOR plasma concentrations declined in a monoexponential manner, with mean terminal elimination half-life values ranging from 12 to 16 hours. In single dose administration over the range 6 to 450 mg, DOR AUC and $C_{max}$ values were slightly less than dose proportional with corresponding $AUC_{0-24hr}$ exposures ranging from 2.02 to 82.4 µM.hr, $AUC_{0-\infty}$ ranging from 2.88 to 127 µM.hr, and $C_{max}$ ranging from 156 to 6010 nM (Table 9). $C_{24hr}$ values were 44 to 2070 nM over this dose range. (12)

**Table 9. Single Dose DOR PK Parameters with Dose Range from 6 mg to 450 mg**

| Pharmacokinetic Parameters | Panel A 6 mg | | | Panel B 12 mg | | | Panel A 25 mg | | | Panel B 50 mg | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | GM | 95% CI | N | GM | 95% CI | N | GM | 95% CI | N | GM | 95% CI |
| $AUC_{0-\infty}$ (µM*hr)† | 6 | 2.88 | (2.35, 3.52) | 6 | 4.88 | (3.98, 5.98) | 6 | 11.5 | (9.17, 13.7) | 6 | 17.6 | (14.4, 21.6) |
| $AUC_{0-24hr}$ (µM*hr)† | 6 | 2.02 | (1.70, 2.41) | 6 | 3.66 | (3.07, 4.35) | 6 | 7.03 | (5.91, 8.36) | 6 | 12.7 | (10.6, 15.1) |
| $C_{max}$ (nM)† | 6 | 156 | (126, 193) | 6 | 297 | (240, 367) | 6 | 460 | (372, 569) | 6 | 1070 | (860, 1320) |
| $C_{24hr}$ (nM)† | 6 | 43.9 | (35.1, 54.8) | 6 | 73.0 | (58.2, 91.4) | 6 | 194 | (155, 243) | 6 | 269 | (215, 338) |
| $T_{max}$ (hr)‡ | 6 | 1.00 | (1.00, 4.00) | 6 | 1.00 | (1.00, 3.00) | 6 | 5.00 | (1.00, 6.00) | 6 | 1.00 | (1.00, 4.00) |
| Apparent $t_{1/2}$ (hr)§ | 6 | 11.68 | 9.95 | 6 | 11.67 | 15.70 | 6 | 15.67 | 20.42 | 6 | 13.29 | 10.59 |
| **Pharmacokinetic Parameters** | **Panel A 100 mg** | | | **Panel B 150 mg** | | | **Panel A 300 mg** | | | **Panel B 450 mg** | | |
| | N | GM | 95% CI | N | GM | 95% CI | N | GM | 95% CI | N | GM | 95% CI |
| $AUC_{0-\infty}$ (µM*hr)† | 6 | 38.3 | (31.3, 46.8) | 6 | 49.9 | (40.7, 61.2) | 6 | 92.6 | (75.7, 113) | 6 | 127 | (104, 155) |
| $AUC_{0-24hr}$ (µM*hr)† | 6 | 22.8 | (19.2, 27.1) | 6 | 34.0 | (28.6, 40.5) | 6 | 58.9 | (49.5, 70.1) | 6 | 82.4 | (69.3, 98.0) |
| $C_{max}$ (nM)† | 6 | 1720 | (1390, 2120) | 6 | 2680 | (2170, 3320) | 6 | 3810 | (3090, 4710) | 6 | 6010 | (4870, 7430) |
| $C_{24hr}$ (nM)† | 6 | 593 | (475, 741) | 6 | 750 | (599, 940) | 6 | 1490 | (1190, 1870) | 6 | 2070 | (1660, 2580) |
| $T_{max}$ (hr)‡ | 6 | 1.50 | (1.00, 5.00) | 6 | 1.50 | (1.00, 4.00) | 6 | 3.50 | (2.00, 5.00) | 6 | 2.00 | (1.00, 5.00) |
| Apparent $t_{1/2}$ (hr) § | 6 | 15.26 | 43.98 | 6 | 13.84 | 27.65 | 6 | 15.62 | 27.08 | 6 | 14.80 | 34.52 |

† Back-transformed least squares mean and confidence interval from linear mixed effects model performed on natural log-transformed fasted values.

‡ Median (min, max) reported for $T_{max}$.

§ Geometric mean and percent geometric coefficient of variation (CV) reported for apparent $t_{1/2}$.

Square root of conditional mean squared error (residual error) from the linear mixed effects model = 0.178 for $AUC_{0-\infty}$, 0.195 for $C_{max}$, and 0.207 for $C_{24hr}$. When multiplied by 100, provides estimate of the pooled within-participant coefficient of variation.

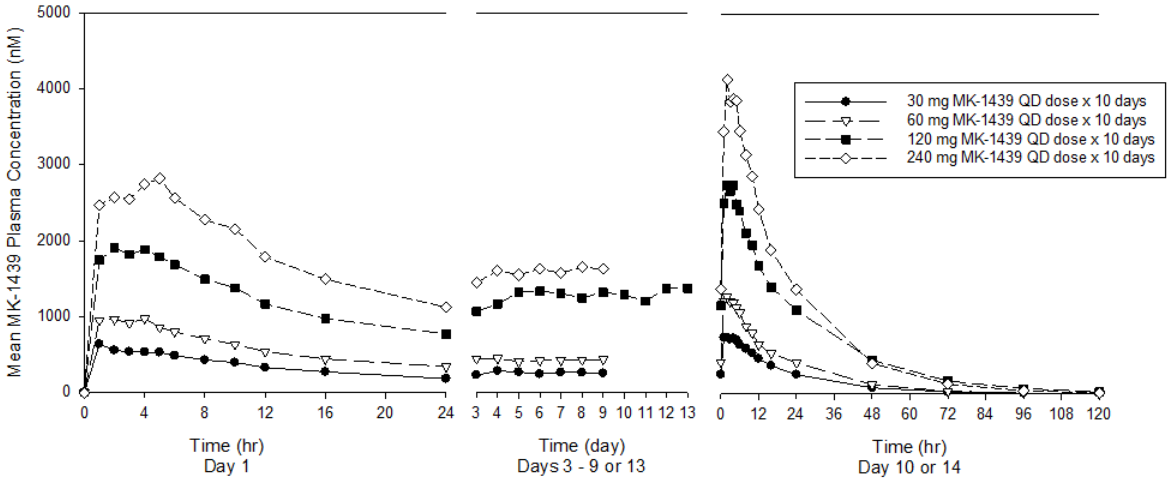
GM = Geometric least-squares mean; CI = Confidence interval.

Multiple dose pharmacokinetics are consistent with the single-dose data (Figure 3) with rapid absorption and monoexponential plasma level decline with mean terminal elimination half-life values ranging from 13 to 15 hrs. Mean observed exposures ($AUC_{0-24hr}$) on the last day of dosing ranged from 11.5 to 60.6 µM·hr over the 30 to 240 mg per day (QD) dose range. Mean $C_{max}$ and $C_{24hr}$ values on the last day of dosing ranged from 796 to 4470 nM and 246 to 1340 nM, respectively, over the 30 to 240 mg QD dose range. After multiple days of QD dosing, steady

state was achieved by approximately Day 2. At steady state, the mean $AUC_{0\text{-}24hr}$, $C_{max}$, and $C_{24hr}$ accumulation ratios, expressed as either the Day 10/Day 1 geometric mean ratios (GMRs) (30, 60, and 240 mg QD doses) or the Day 14/Day 1 GMRs (120 mg QD dose) were 1.2-1.4, consistent with predictions from single dose data (19). These data support QD dosing for DOR.

Doravirine pharmacokinetics is similar in healthy participants and HIV-1 infected patients. Based on a preliminary population pharmacokinetic analysis conducted with pooled data from the Phase 2 trial, where sparse PK samples were collected, and selected Phase 1 trials, the 100 mg dose is associated with steady state $AUC_{0\text{-}24hr}$, $C_{24hr}$, and $C_{max}$ values of 35.7 µM*hr, 831 nM, and 2.79 µM, respectively. Median doravirine steady state $AUC_{0\text{-}24hr}$ for 200 mg, the highest dose studied in Phase 2, is 64.5 µM*hr.

**Figure 3. Mean Plasma Concentration Profiles of DOR Following Administration of Multiple Oral Doses Once Daily to Health Fasted Male Participants (N=6-8)**




### 1.3.2 Effect of Food

Administration of the 100 mg DOR tablet to fourteen adults fasted and with a high fat meal demonstrated minimal effect on DOR pharmacokinetics when given with a high fat meal (PN029). The fed/fasted geometric mean ratios (GMRs) and 90% CIs of DOR $AUC_{0\text{-}\infty}$, $C_{max}$ and $C_{24hr}$ were 1.16 (1.06, 1.26), 1.03 (0.89, 1.19), and 1.36 (1.19, 1.55), respectively, while $T_{max}$ was delayed. Such an effect is not considered to be clinically meaningful based on the tolerability data in humans and toxicity data in animals to date. DOR can be administered without regard to food.

### 1.3.3 Effect of Gender

The effect of gender on the PK of DOR was assessed in a clinical trial among elderly men and women and non-elderly women (PN009). There was no clinically meaningful effect of gender on the PK of DOR. GMRs (female/male) and 90% CIs for $AUC_{0\text{-}\infty}$, $C_{max}$ and $C_{24hr}$ for DOR are 119.95%, (102.86, 139.88), 141.84%, (122.76, 163.87) and 101.72%, (83.63, 123.72), respectively.

### 1.3.4 Metabolism

DOR is metabolized in vitro by CYP3A and clinical drug-drug interaction studies are consistent with this being the major pathway of elimination.

### 1.3.5 Drug Interaction

DOR is not anticipated to perpetrate clinically meaningful drug interactions via major drug metabolizing enzymes or transporters. A clinical study with midazolam indicated that DOR is not a strong inhibitor or inducer of CYP3A metabolism (PN001-01).

Consistent with metabolism primarily via CYP3A, co-administration of DOR on Day 14 of ritonavir multiple dosing increased DOR exposure and $C_{max}$. The GMR (DOR + ritonavir/DOR alone) and 90% CI for DOR $AUC_{0-\infty}$ was 3.54 (3.05, 4.12). Doravirine $C_{max}$ and $T_{max}$ were only slightly increased after co-administration with ritonavir compared to DOR administered alone, but the mean apparent terminal $t_{1/2}$ of DOR was significantly increased from 13.9 to 34.9 hours (PN002). Ritonavir has a significant effect on the clearance of DOR due to inhibition of CYP3A, consistent with in vitro data indicating the predominant role of CYP3A in DOR metabolism. Additionally, co-administration of DOR on Day 14 of once daily rifampin resulted in significantly decreased levels of DOR due to induction of CYP3A metabolism by rifampin.

### 1.3.6 DOR/3TC/TDF Pharmacokinetics of the Tablet Formulation

A single tablet of DOR/3TC/TDF contains a full daily HIV treatment regimen of DOR 100 mg + 3TC 300 mg + TDF 300 mg. Pharmacokinetic studies conducted in adults have demonstrated similar levels of DOR when given as DOR or DOR/3TC/TDF). The pharmacokinetics of 3TC and TDF were also generally similar when administered as DOR/3TC/TDF or the individual components. While tenofovir $C_{max}$ was slightly decreased after administration of DOR/3TC/TDF compared to administration as TDF (Viread®), this decrease is not expected to be clinically meaningful (Table 10).

**Table 10. Pharmacokinetics of Doravirine, Lamivudine, Tenofovir Disoproxil Fumarate Administered as DOR/3TC/TDF or as Individual Components**

| Parameters | | GMRs (90% CIs) (DOR/3TC/TDF versus DOR 100 mg tablet, 3TC 300 mg tablet and TDF 245 mg tablet) |
|---|---|---|
| Doravirine | $AUC_{0-\infty}$ | 1.01 (0.94, 1.08) |
| | $AUC_{0\text{-last}}$ | 1.02 (0.95, 1.09) |
| | $C_{max}$ | 0.99 (0.91, 1.09) |
| | $C_{24hr}$ | 1.02 (0.94, 1.12) |
| Lamivudine | $AUC_{0-\infty}$ | 1.04 (1.00,1.09) |
| | $AUC_{0\text{-last}}$ | 1.04 (1.00, 1.08) |
| | $C_{max}$ | 1.00 (0.91,1.09) |
| Tenofovir | $AUC_{0-\infty}$ | 0.98 (0.93,1.03) |
| | $AUC_{0\text{-last}}$ | 0.99 (0.94, 1.04) |
| | $C_{max}$ | 0.87 (0.78,0.97) |

### 1.3.7 DOR Pharmacokinetics of the Oral Granule Formulation

The pharmacokinetics of the DOR coated oral granules planned to be used in this trial were evaluated in healthy adult participants (P052). As the oral granules are intended to be administered in soft food, the pharmacokinetics were evaluated following administration alone or with pudding or apple sauce. Following administration of 100 mg of DOR coated granules without food, there was no clinically meaningful difference in DOR $AUC_{0-\infty}$, $C_{max}$, or $C_{24}$ compared to the adult tablet without food. Administration of 100 mg of DOR coated granules in vanilla pudding also did not meaningfully impact DOR $AUC_{0-\infty}$, $C_{max}$, and $C_{24}$ compared to administration of coated granules without food. While administration of 100 mg of DOR coated granules in apple sauce increased DOR $AUC_{0-\infty}$, $C_{max}$, and $C_{24}$, these increases are not considered clinically meaningful (Table 11).

**Table 11. Pharmacokinetics of DOR Following Administration of Coated Oral Granules Compared to Administration of the Adult DOR Tablet**

| DOR PK parameter | GMR (90% CIs) | | |
|---|---|---|---|
| | 100 mg DOR coated granule (fasted) / 100 mg DOR adult tablet (fasted) | 100 mg DOR coated granule with vanilla pudding / 100 mg DOR coated granule (fasted) | 100 mg DOR coated granule with applesauce / 100 mg DOR coated granule (fasted) |
| $AUC_{0-\infty}$ | 0.89 (0.85, 0.94) | 0.99 (0.91, 1.07) | 1.26 (1.18, 1.34) |
| $C_{max}$ | 0.77 (0.70, 0.84) | 0.90 (0.79, 1.03) | 1.59 (1.47, 1.73) |
| $C_{24hr}$ | 0.95 (0.89, 1.01) | 0.96 (0.88, 1.04) | 1.21 (1.12, 1.30) |

The pharmacokinetics of the 3TC and TDF coated oral granules to be used in this trial were also evaluated in healthy adult participants (P054). Following fasted administration of 300 mg coated granules of lamivudine, lamivudine $AUC_{0-\infty}$ and $C_{max}$ were similar to administration of the 300 mg Epivir® adult tablet. Following administration of 300 mg of lamivudine coated granules in vanilla pudding or applesauce, lamivudine $AUC_{0-\infty}$ and $C_{max}$ were slightly, but not meaningfully, decreased relative to administration of the coated granules without food. The impact of administration of pudding or applesauce is not anticipated to be clinically meaningful (Table 12).

**Table 12. Pharmacokinetics of 3TC Following Administration of Coated Oral Granules Compared to Administration of the Adult 3TC Tablet**

| 3TC PK parameter | GMR (90% CIs) | | |
|---|---|---|---|
| | 300 mg 3TC coated granule (fasted) / 300 mg 3TC adult tablet (fasted) | 300 mg 3TC coated granule with vanilla pudding / 300 mg 3TC coated granule (fasted) | 300 mg 3TC coated granule with applesauce / 300 mg 3TC coated granule (fasted) |
| $AUC_{0-\infty}$ | 1.00 (0.96, 1.03) | 0.84 (0.78, 0.92) | 0.86 (0.83, 0.91) |
| $C_{max}$ | 0.99 (0.91, 1.08) | 0.84 (0.75, 0.95) | 0.84 (0.74, 0.96) |

Similarly, the pharmacokinetics of tenofovir following fasted administration of 300 mg coated granules of TDF were generally similar to administration of the 300 mg Viread® adult tablet. Following administration of 300 mg of TDF coated granules in vanilla pudding or applesauce, tenofovir $AUC_{0-\infty}$ and $C_{max}$ were slightly increased relative to administration of coated granules without food. The impact of administration of pudding or applesauce is not anticipated to be clinically meaningful (Table 13).

**Table 13. Pharmacokinetics of Tenofovir Following Administration of TDF Coated Oral Granules Compared to Administration of the Adult TDF Tablet**

| Tenofovir PK parameter | GMR (90% CIs) | | |
|---|---|---|---|
| | 300 mg TDF coated granule (fasted) / 300 mg TDF adult tablet (fasted) | 300 mg TDF coated granule with vanilla pudding / 300 mg TDF coated granule (fasted) | 300 mg TDF coated granule with applesauce / 300 mg TDF coated granule (fasted) |
| $AUC_{0-\infty}$ | 1.04 (0.96, 1.13) | 1.18 (1.11, 1.25) | 1.15 (1.08, 1.23) |
| $C_{max}$ | 1.03 (0.94, 1.14) | 1.23 (1.12, 1.35) | 1.20 (1.08, 1.33) |

## 1.4 Rationale for the Study

Development of tolerable, potent, once-daily dose ARV for use in children and adolescents remains a significant priority. First-line therapy with non-nucleoside reverse transcriptase inhibitors (NNRTIs) has proven to be effective for HIV-1 infected infants, children, and adolescents (20, 21). As described in the background above, each of the currently available NNRTIs have characteristics that make them less than optimal for preferred first-line treatment in HIV-1-infected children and adolescents.

Based on the preclinical and clinical data to date, DOR is an excellent candidate for further development in the pediatric population. The lack of evidence for reproductive toxicity, decreased CNS adverse events compared to EFV, wide therapeutic margin, and once-daily dosing provide advantages to DOR as treatment for HIV-1-infected children and adolescents. In addition, if the in vitro activity of DOR against several HIV-1 strains with common NNRTI resistance mutations (11) is confirmed in PN030, DOR will likely be a better switch option than nevirapine (NVP) (22, 23) or EFV for young children previously exposed to NVP and now suppressed on lopinavir/ritonavir. The proposed development plan to include an appropriate FDC formulation for younger age groups is also an advantage for DOR as future therapy for younger children.

This protocol is planned to be the first in a series of protocols to evaluate DOR and DOR/3TC/TDF in the pediatric population. The goal of this study is to obtain PK and safety data in participants from 12 years to less than 18 years who weigh ≥35 kg as a first step in the development of DOR for the treatment of HIV-1-infected pediatric patients.

It is anticipated that the safety and PK data from this study will inform the development of DOR and DOR/3TC/TDF in younger children.

### 1.4.1 Rationale for Dose Selection

The 100 mg QD dose of DOR was selected for the Phase 3 studies in adults based on considerations detailed in Section 1.2.2, above.

It is anticipated that the 100 mg QD adult dose will be appropriate for most, if not all, children and adolescents who weigh ≥35 kg; therefore, the 100 mg dose will be studied in this protocol (Cohort 1). Based on modeling and simulation, the 100 mg QD dose in children and adolescents ≥35 kg is projected to achieve steady state $C_{24hr}$ values similar to or greater than those achieved in adults at the 100 mg QD dose where efficacy was observed in the Phase 2b trial. In addition, steady state exposures in children and adolescents are not expected to exceed those corresponding to adults at the 200 mg QD dose (median steady state $AUC_{0\text{-}24hr}$ of ~64.5 μM*hr), the highest dose studied in the Phase 2b trial. Simulations using the 100 mg QD dose were run for children and adolescents with weights ranging from 31-85 kg. Projected exposures for the 100 mg QD dose in children at the lower end of this weight range are at the high end of the projected distribution of values but are not expected to exceed the range of exposures experienced by adults at the 200 mg QD dose. Thus, in this study, a weight threshold of 35 kg will be used until there is a better understanding of DOR PK in children, in order to minimize risk of exceeding the exposure observed for 200 mg in adults.

Based on the US Prescribing Information for lamivudine (3TC) (24), a total daily dose of 300 mg is appropriate for children that weigh ≥25 kg. The US Prescribing Information for TDF (25) indicates that a dose of 300 mg is appropriate for children 12 years of age and older who weigh 35 kg or more. The doses of 3TC (300 mg) and TDF (300 mg) used in the DOR/3TC/TDF tablet are thus approved for use in children and adolescents in this weight range (≥35 kg).

To move forward the development of DOR and DOR/3TC/TDF for use in children and adolescents, children and adolescents for whom the full adult dose FDC is appropriate will be enrolled for the long-term portion of study (Cohort 2). The expectation is that this will be all children and adolescents with weight ≥35 kg. If this expectation is not borne out based on the results of Cohort 1, only children and adolescents in the weight range for which the 100 mg is appropriate will be enrolled into Cohort 2 and followed long-term. If, after the dose evaluation stage, it appears that lower-weight children and adolescents (for example, 35 – 40 kg) may require a dose less than 100 mg DOR, an age appropriate formulation that is currently in development and is intended to deliver a dose below 100 mg will be employed to study safety and PK in such participants in a separate study.

### 1.4.2 Rationale for Study Design and Cohort Selection

Virologically suppressed children and adolescents on a stable integrase inhibitor-based ART regimen have been selected for participation in Cohort 1 for the following reasons. While there is enough efficacy data in adults and confidence in the model-based projected PK for the 100 mg DOR tablet to justify initiating the DOR PK analysis in HIV-infected children and adolescents who are treatment naive, verifying the DOR pharmacokinetics prior to initiating DOR/3TC/TDF as first-line therapy in ART-naïve children and adolescents provides additional safety. Being on a suppressive ART regimen while taking DOR will prevent the development of resistance should there be an unexpected deviation from the modeling such that the 100 mg dose would provide inadequate drug levels. Children and adolescents need to be stable on an integrase-based regimen rather than a PI-based regimen to minimize drug interactions with DOR that may affect the PK analysis. As there are no drug interactions between DOR and integrase inhibitors, a single dose of DOR will also not affect the efficacy of the participants' ARV regimen.

Doravirine multiple dose pharmacokinetics were consistent with predictions from single-dose data in the adult studies and there was no evidence of time-dependent changes in PK after multiple dosing. Thus, $AUC_{0-\infty}$ following a single dose is equivalent to a projected steady state $AUC_{0-24hr}$. Therefore, PK data can be obtained from a single-dose of DOR to project the steady state PK of DOR and verify the appropriateness of the 100 mg dose in children and adolescents 35 kg or greater (see Section 10.3.1 for additional details). Cohort 1 will include participants with weights down to 35 kg, who are more likely to deviate from the projected pediatric exposures at the 100 mg QD dose. As such, adequate representation of children and younger adolescents in Cohort 1 to enable characterization of DOR PK and its relationship with weight across the entire range intended for this study (≥35 kg) will be important for further development of DOR and DOR/3TC/TDF for younger children. Requirements to enroll a minimum of four participants between 35 to ≤45 kg were thus included for Cohort 1.

Once the PK and safety targets for Cohort 1 are confirmed for the 100 mg DOR dose, DOR/3TC/TDF will be studied in Cohort 2 in HIV-1-infected children and adolescents. While it is anticipated that the 100 mg DOR dose will meet PK targets for all participants with weights down to 35 kg, in the unlikely event that the dose is determined to be too high for lower weight participants, Cohort 2 will only open for those participants whose weight meet the PK and safety targets based on data from Cohort 1. If the 35 to ≤45 kg weight group shows acceptable PK and safety, a minimum of five participants in this weight group will be enrolled to Cohort 2.

Cohort 2 will enroll participants who are ART-naïve as well as ART-experienced, virologically suppressed. However, inclusion of participants who are ART-experienced, virologically suppressed will be dependent on results from one of the adult switch studies (PN024, PN028). The primary objectives of these studies are maintenance of virologic suppression for at least 24 weeks after switching. The adult switch studies are ongoing and include a Phase 2 study of switch from an EFV-based regimen for CNS toxicity (PN028) and a Phase 3 study of switch from a stable antiretroviral regimen of a ritonavir- or cobicistat-boosted protease inhibitor (PI) (specifically, atazanavir, darunavir, or lopinavir), or cobicistat-boosted elvitegravir (an InSTI), or a NNRTI (specifically, EFV, NVP, or RPV), each administered with two NRTIs (PN024). In both of these adult switch studies, inclusion is limited to individuals who are virologically suppressed with no prior virologic failure and participants switch to DOR/3TC/TDF without any wash-out from their prior ART regimen. Once the 24-week data are available from one of the adult switch studies, the data will be reviewed by the Clinical Management Committee (CMC) and IMPAACT Study Monitoring Committee (SMC) prior to opening Cohort 2 for the ART-experienced, virologically suppressed participants (see Section 9.6.2). Data from the adult switch studies will be considered supportive if 90% or more of the participants maintain virologic suppression for at least 24 weeks after switching.

It is not anticipated that the ART-experienced, virologically suppressed participants entering Cohort 2 would be included in the subset of participants selected for intensive PK studies, as the results from the switch studies, if they become available during the study, are not expected until Cohort 2 is close to full accrual. However, this option is included in the protocol to allow flexibility and to facilitate improved accrual if any challenges arise.

If the data from the switch studies are not supportive, Cohort 2 will only enroll HIV-1-infected, ART-naïve participants.

### 1.4.3 Rationale for Pharmacokinetic Studies of Doravirine, Lamivudine, and Tenofovir in Cohort 2

The tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) components in DOR/3TC/TDF are new generic formulations. Intensive pharmacokinetic sampling for tenofovir and 3TC is planned in a subset of Cohort 2 participants to obtain data on these generic agents in children and adolescents. These data will be necessary to support further development of the DOR/TDF/3TC FDC for younger children. New doses of TDF and 3TC have been proposed for use in the age appropriate FDC for children aged 2 – 11 years and a population PK approach will be used to support characterization of the PK to confirm the appropriateness of the proposed new doses in a separate study.

Pharmacokinetic samples for DOR will also be collected at a subset of the times when intensive PK samples are drawn for tenofovir and 3TC. The DOR samples will be used to further characterize PK in the population enrolled in this study and will support the development of the pediatric population PK model for DOR. Sparse PK samples will also be obtained for DOR, 3TC, and TDF in Cohort 2 to further characterize the PK of DOR, 3TC, and tenofovir over 48 weeks.

### 1.4.4 Rationale for Use of Tablets and Granules

The adult film-coated tablet will be available for participants in Cohort 1 and Cohort 2. However, an age appropriate formulation of DOR/3TC/TDF consisting of oral granules is being developed. If an age appropriate formulation is available, both the adult film-coated tablet and the granule formulations will be an option for participants in Cohort 2.

The age appropriate formulation may be administered in liquid or soft food, as described further in Section 5.2.2. This will provide flexibility for participants who cannot or prefer not to swallow the film-coated tablet. This will also allow obtaining preliminary data on the palatability and acceptability of the granule formulation to inform the development of future protocols for younger children.

## 1.5 Hypotheses

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

# 2 OBJECTIVES

## 2.1 Primary Objectives for Cohort 1

The primary objectives of Cohort 1 are to:

2.1.1 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.

2.1.2 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.

## 2.2 Primary Objective for Cohort 2

The primary objective of Cohort 2 is to:

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

## 2.3 Secondary Objectives for Cohort 2

The secondary objectives of Cohort 2 are to:

2.3.1 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.
2.3.2 Evaluate the 24-, 48-, and 96-week virologic efficacy of DOR/3TC/TDF in HIV-1-infected children and adolescents.
2.3.3 Evaluate the 24-, 48-, and 96-week immunologic response (CD4 cell count and percentage change from baseline) of HIV-1-infected children and adolescents.
2.3.4 Evaluate the 48- and 96-week safety and tolerability of DOR/3TC/TDF administered in HIV-1-infected children and adolescents.

Objectives through Week 24 will be evaluated approximately concurrently with the primary objective for Cohort 2; additional longer-term secondary objectives for Cohort 2 will be evaluated as outcomes are available.

## 2.4 Other Objectives for Cohort 2

2.4.1 Evaluate the pharmacokinetics of DOR, 3TC, and tenofovir in HIV-1-infected children and adolescents receiving DOR/3TC/TDF, using sparse PK sampling through Week 48.
2.4.2 Assess changes in HIV-1 genotype and phenotype to DOR and other components of the regimen in participants experiencing virologic failure.
2.4.3 Evaluate acceptability, palatability, and adherence of DOR/3TC/TDF in HIV-1-infected children and adolescents through Week 96.

# 3 STUDY DESIGN

This is a Phase I/II, multi-site, open-label, non-comparative PK, safety, and tolerability study of doravirine (DOR) and a fixed-dose combination of doravirine, lamivudine, and tenofovir disoproxil fumarate (DOR/3TC/TDF) in HIV-1-infected children and adolescents. Refer to Figure 1 for an overview of the study design, to Sections 4.1-4.2 for the study eligibility criteria, and to Section 4.4 for a description of the study recruitment, screening, and enrollment process. Participants are expected to be enrolled at study sites in South Africa, Thailand, and the United States.

The protocol will enroll two sequential cohorts, Cohorts 1 and Cohort 2, as described in Sections 3.1 and 3.2, respectively. In summary, participants will first be enrolled into Cohort 1 to evaluate the PK and safety of the 100 mg DOR dose, with intensive PK evaluation completed at entry and followed through two weeks on study to assess safety. Specimens will be shipped in real time with ongoing testing, with team review of PK and safety data as available. Upon enrollment of a

minimum of 12 evaluable participants, enrollment will be paused while the Cohort 1 PK and safety data are reviewed by the protocol team and the SMC. Data will be evaluated based on the algorithm in Section 9.2, with options of resuming enrollment into Cohort 1, proceeding with Cohort 2 enrollment, or assessing next steps for the study.

If results from Cohort 1 are supportive, participants will be enrolled into Cohort 2 to evaluate the safety and tolerability of a fixed-dose combination regimen, including DOR, 3TC, and TDF. A subset of participants will have intensive PK evaluations at Week 1 and all participants will have population PK evaluations through Week 48; the PK specimens will be shipped in batches with testing when sample collection is complete for all relevant participants (see Section 6.11.2). Participants will be followed through 96 weeks on study to assess long-term safety, virologic efficacy, and immunologic response, among other objectives as in Sections 2.3 and 2.4.

## 3.1 Cohort 1

Up to 20 HIV-1-infected children and adolescents may be enrolled at study sites, to achieve at least 12 evaluable participants. Participants must be 35 kg or greater and 12 years to less than 18 years of age, receiving DTG or RAL plus two NRTIs, with virologic suppression. A minimum of four participants between 35 and ≤45 kg will be enrolled in this cohort. A single dose of DOR in a 100 mg tablet formulation (the adult dose) will be added, at entry, as a fourth agent (one time only) with intensive PK evaluations conducted around this single-dose. No additional doses of DOR will be taken; participants will continue their ARV regimen.

Participants will be followed for two weeks in Cohort 1 with clinical and laboratory evaluations as described in Section 6 and shown in the Schedule of Evaluations in Appendix I-A (Cohort 1). Safety outcomes will be assessed at two weeks.

Participants will be considered evaluable based on the criteria in Sections 9.1 and 10.3.1.

## 3.2 Cohort 2

Accrual into Cohort 2 will open following review of Cohort 1 PK and safety data by the CMC and SMC, as described in Section 9.6. Up to 45 HIV-1-infected children and adolescents may be enrolled at study sites, to achieve at least 40 evaluable participants. Participants must be 12 years to less than 18 years of age and will be either ART-naïve or ART-experienced and virologically suppressed. Participants who are ART-naïve should also have genotypic resistance testing results that indicate susceptibility to study drugs at screening; if results are available from medical records, participants who are ART-experienced should also have results that indicate susceptibility to study drugs. All participants will initiate DOR/3TC/TDF at entry. DOR/3TC/TDF will initially be provided in tablet formulation, as described in Section 5; if the age appropriate granule formulation becomes available during implementation of Cohort 2, this formulation will be provided as an option for participants. Participants may be allowed to switch formulations during the study, as described further in Section 6.9.

Enrollment to Cohort 2 is expected to open initially with only ART-naïve participants. It is anticipated that data from the Phase 2b or 3 switch studies in virologically suppressed adults (PN028 and PN024; see Table 1 and Section 1.2.3) may become available during the conduct of this study. If these adult data indicate virologic efficacy and safety, this study will allow enrollment of children and adolescents who are ART-experienced and virologically suppressed without evidence of prior virologic failure into Cohort 2 (see Section 1.4.2). If the data from the switch studies are not supportive, Cohort 2 will only enroll ART-naïve children and adolescents.

The minimum weight threshold for enrollment will be determined from Cohort 1 and, if Cohort 2 opens to participants in the 35 to ≤45 kg weight group, a minimum of five participants in this weight group will be enrolled. The first 10 participants enrolled into Cohort 2 will also have intensive PK sampling to evaluate the pharmacokinetics of DOR, 3TC, and tenofovir.

Participants will be followed for 96 weeks in Cohort 2 with clinical and laboratory evaluations performed as described in Section 6 and shown in the Schedule of Evaluations in Appendix I-B (Cohort 2). Every attempt will be made to retain participants for the duration of the study, unless they meet the criteria for early discontinuation, which include but are not limited to discontinuation of study drug, as listed in Section 4.6. Safety outcomes will be assessed throughout follow-up, with standard evaluations performed at all sites; complete physical exams will be done annually. Secondary virologic efficacy outcomes will be assessed throughout follow-up, using a single HIV-1 RNA testing platform, at all sites in real time.

Participants will be considered evaluable based on the criteria in Section 9.1.

# 4 STUDY POPULATION

This study will be conducted in HIV-1-infected children and adolescents 12 years to less than 18 years of age weighing at least 35 kg. There is no specified route of HIV transmission. Children and adolescents will be selected for the study according to the criteria in Sections 4.1 and 4.2 and the guidelines in Section 4.3. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.4. Considerations related to participant retention and withdrawal/termination from the study are provided in Sections 4.5 and 4.6, respectively. Details regarding genotyping are provided in Section 4.7.

*Note:* Participants who have completed follow-up in Cohort 1 are eligible for enrollment in Cohort 2 as ART-experienced, virologically suppressed children and adolescents; previous exposure to DOR is not exclusionary.

## 4.1 Inclusion Criteria

All the following criteria must be met in order for individuals to be enrolled in this study:

4.1.1 Age 12 years to less than 18 years at entry

4.1.2 Weight greater than or equal 35 kg at entry

4.1.3 *If not of legal age to provide independent informed consent:* Parent or guardian is willing and able to provide written informed consent for study participation; in addition, when applicable per local Institutional Review Board / Ethics Committee (IRB/EC) policies and procedures, potential participant is willing and able to provide written informed assent for study participation

*If of legal age to provide independent informed consent as determined by site Standard Operating Procedures (SOPs) and consistent with site IRB/EC policies and procedures:* Potential participant is willing and able to provide written informed consent for study participation

4.1.4 Confirmed HIV-1-infection based on documented testing of two samples collected at different time points:

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One enzyme immunoassay (EIA) OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA polymerase chain reaction (PCR)
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

Sample #2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved, and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

All samples tested must be whole blood, serum, or plasma. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified (US sites) or Virology Quality Assurance (VQA)-approved (non-US sites) laboratory. For tests performed in other (non-GCLP-compliant or non-VQA-approved) settings, adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available.

4.1.5 ART exposure, virologic suppression, and resistance requirements, as follows:

4.1.5.1 Cohort 1

- ART exposure requirements, based on individual or parent/guardian's report and, if available, confirmed by medical records:
  - At entry, receiving combination ART with RAL or DTG plus 2 NRTIs; AND
  - At entry, has not received NNRTIs, PIs, or cobicistat within the previous 30 days;

AND

- Virologic suppression, as documented in medical records and as defined by:
  - One or more HIV RNA PCR result below the level of quantification (BLLQ) within 15 months prior to enrollment, AND
  - If any HIV RNA PCR tests have been done within 3 months prior to enrollment, all results are below the level of quantification, AND
  - HIV RNA PCR result less than 40 copies/mL at screening, performed as per Section 6.11.2

*Note: A single, unconfirmed HIV-1 RNA result greater than or equal to the level of quantification but less than 500 copies/mL, between 3 and 15 months, prior to enrollment is not exclusionary as long as the other criteria for documentation of virologic suppression are met.*

4.1.5.2 Cohort 2 ART-naïve

- ART exposure requirements, based on individual or parent/guardian's report and, if available, confirmed by medical records:
  - At entry, received no ARVs for treatment of HIV infection including investigational agents (prior receipt of ARVs for prevention of perinatal transmission is permitted);

AND

- Screening genotypic resistance test results indicate susceptibility to DOR, TDF, and 3TC (see Section 4.7; result must be available prior to enrollment), performed as per Section 6.11.2;

AND

- If available, as documented in medical records, any prior genotypic resistance test result indicates susceptibility to DOR, TDF, and 3TC (see Section 4.7)

*Note: For individuals that are re-screened, the genotypic resistance test does not need to be repeated.*

4.1.5.3 Cohort 2 ART-experienced

- ART exposure requirements, based on individual or parent/guardian's report and, if available, confirmed by medical records:
  - No previous history of change in ARVs due to clinical or virologic failure, in the opinion of the site investigator or designee;

AND

- Virologic suppression, as documented in medical record and as defined by:
  - One or more HIV RNA PCR result below level of quantification (BLLQ) within 6 months prior to enrollment, AND
  - If any HIV RNA PCR tests have been done within 3 months prior to enrollment, all results are below the level of quantification, AND
  - HIV RNA PCR result less than 40 copies/mL at screening, performed as per Section 6.11.2;

AND

- If available, as documented in medical records, any prior genotypic resistance test result indicates susceptibility to DOR, TDF, and 3TC (see Section 4.7)

*Note: This group of ARV-experienced, virologically suppressed participants will only enroll once there are data from the adult switch studies indicating virologic efficacy and safety (see Section 1.4.2). Sites will be informed via a Clarification Memorandum when ART-experienced participants can be enrolled.*

4.1.6 Grade 2 or lower hemoglobin, AST, ALT, alkaline phosphatase, and lipase on specimens obtained at screening

4.1.7 *For Cohort 2 only,* grade 2 or lower creatinine, proteinuria, and glycosuria on specimens obtained at screening

4.1.8 Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 $m^2$, on specimens obtained at screening, based on the Schwartz equation which is as follows:

Schwartz formula: GFR (mL/min/1.73 $m^2$) = K x Ht cm/Pcreat

| K=constant | Cr mg/mL |
|---|---|
| Children 2-12 years | 0.55 |
| Female 13-21 years | 0.55 |
| Males 13-21 years | 0.70 |

4.1.9 For females who have reached menarche or who are engaging in sexual activity (self-reported), negative pregnancy test at entry

4.1.10 For females engaging in sexual activity that could lead to pregnancy (self-reported), agrees to use two effective, medically accepted birth control methods while on study and for two weeks after permanently discontinuing study drug

4.1.11 For males engaging in sexual activity that could lead to pregnancy (self-reported), agrees to use condoms while on study and for two weeks after permanently discontinuing study drug

4.1.12 Able and willing to swallow available formulation(s) (tablet or, as available, oral granules)

*Note: The study is expected open to accrual with only the tablet formulation available. Sites will be informed when the oral granule formulation is available for participant use. Once the granule formulation is available, participants in Cohort 2 will be asked to choose which formulation they would like to take at Entry. Formulation switches during the study may be allowed, as described in Section 6.9.*

## 4.2 Exclusion Criteria

Participants must be excluded from the study if, at any time during the screening period, any of the following are identified:

4.2.1 Evidence of decompensated liver disease manifested by the presence of or a history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs or symptoms of advanced liver diseases

*Note: Individuals with chronic hepatitis B who have grade 2 or lower ALT and AST and have no significant impairment of hepatic synthetic function (significant impairment of hepatic synthetic function is defined as a serum albumin <2.8 mg/dL or an INR >1.7 in the absence of another explanation for the abnormal laboratory value) are eligible.*

4.2.2 *For Cohort 2 only,* detectable hepatitis C virus (HCV) by RNA PCR or current or planned treatment with direct antiviral agent for HCV

*Note: HCV antibody positivity but undetectable by HCV RNA PCR results are permitted.*

4.2.3 Presence of any active AIDS-defining opportunistic infection

4.2.4 History of malignancy (ever), with the exception of localized malignancies such as squamous cell or basal cell carcinoma of the skin

4.2.5 Clinical evidence of pancreatitis, as determined by the clinician (at entry)

4.2.6 Use of nafcillin, dicloxacillin, or any of the prohibited medications, within 30 days prior to study entry (see Section 5.8 for a complete list of prohibited medications)

4.2.7 For females, currently breastfeeding an infant at entry

4.2.8 Enrolled in another clinical trial of an investigational agent, device, or vaccine

4.2.9 Unlikely to adhere to the study procedures or keep appointments, in the opinion of the site investigator or designee

4.2.10 Used, or anticipates using, chronic systemic immunosuppressive agents or systemic interferon (e.g., for treatment of HCV infection) within 30 days prior to study entry

*Note: Systemic corticosteroids (e.g., prednisone or equivalent up to 2 mg/kg/day) for replacement therapy or short courses (≤30 days) are permitted. See Section 5.8 for a complete list of prohibited medications.*

4.2.11 Diagnosed with current active tuberculosis and/or is currently being treated with a rifampicin-containing regimen

4.2.12 Individual has any other condition, that in the opinion of the site investigator or designee, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving study objectives

## 4.3 Co-Enrollment Considerations

Co-enrollment in other studies (e.g., observational studies) is permitted with approval from the Protocol Chairs of both studies (excluding the clinical trials noted in 4.2.8, above). Requests for approval of co-enrollment should be emailed to the Clinical Management Committee (CMC; refer to Sections 7.1.2 and 9.6.1 for more information regarding the role of the CMC for this study).

## 4.4 Recruitment, Screening, and Enrollment Process

Recruitment methods for this study may vary across sites and will vary based on the expected enrollment cohort. All participants must be 12 years to less than 18 years of age at the time of enrollment and must be HIV-1-infected; participants may be perinatally or behaviorally infected.

Recruitment of participants for Cohort 1 is expected to rely on current patients being seen at a study clinic or from active identification and referral of HIV-1-infected children and adolescents who are ART-experienced and virologically suppressed. Recruitment of participants for Cohort 2 is expected to rely more on active identification and referral of newly diagnosed HIV-1-infected children and adolescents (i.e., Cohort 2 ART-naïve). In addition, if data from the adult switch studies indicate virologic efficacy and safety, participants who are ART-experienced and

virologically suppressed will be allowed to enroll (see Section 1.4.2); it is expected that recruitment methods for these participants will more closely mirror methods to recruit for Cohort 1.

Upon identification of a potentially eligible participant, study staff will provide information about the study to the parent or guardian and/or the potential participant (as applicable). Each parent or guardian and/or potential participant (as applicable) who expresses interest in learning more about the study will be provided additional information, education, and counseling as part of the study informed consent process. The process will include detailed review of the study informed consent and assent forms (as applicable), time to address any questions or concerns the potential participant, parent, or guardian may have, and an assessment of understanding, before proceeding to informed consent and assent decisions. Informed consent and assent processes will be fully documented, consistent with the Division of AIDS (DAIDS) policies referenced in Section 11.2. Refer to Section 13.3 for further information on informed consent procedures for this study.

Each site must establish SOPs for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of enrollment. Sites are encouraged to minimize the time from screening to enrollment; for Cohort 2, ART-naïve participants, in particular, the screening period should be as short as possible so that ART initiation is not unduly delayed.

Eligibility screening will be initiated after written informed consent is provided. Screening will include confirmatory HIV-1 testing (if needed) and assessment of other entry criteria. If at any time, it is determined that an individual is not eligible for the study, or that study participation may not be feasible or in the participant's best interest, the eligibility screening process will be discontinued; these individuals should be actively referred to non-study sources of care. Screening assessments, unless otherwise noted (see Section 6.1), should be completed within 30 days prior to entry. Re-screening is permitted one time within a six-month period, as further described in Section 6.1.

Individuals who are found to meet the study eligibility criteria will be enrolled and ideally will receive their first dose of study drug at study entry. Screening procedures may be performed on the day of enrollment; however, individual's HIV test results and hematology and chemistry test results must be available for eligibility determination prior to enrollment.

Participants in Cohort 1 will undergo intensive pharmacokinetic evaluations ideally beginning on the day of entry through approximately 72 hours post-study drug ingestion. As described further in Section 6.2.1, participants may stay at the clinical research facility overnight for the PK evaluations, depending on site capacity.

The IMPAACT Data Management Center (DMC) Subject Enrollment System (SES) will be used to assist with tracking the screening and enrollment process. When informed consent is obtained, participant identification numbers (PIDs) will be assigned and a study-specific screening number will be obtained through the SES. For individuals found to be eligible, enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID) and prescribing information for the cohort in which the participant has been enrolled. For individuals who are screened and found to be ineligible for the study, or who do not enroll in the study for any reason, an eCRF will be entered to record the

screening outcome. Refer to Section 9.6 for more information on monitoring participant accrual in this study.

## 4.5 Participant Retention

Once a participant is enrolled in this study, study staff will make every effort to retain the participant for the protocol-specified duration of follow-up and thereby minimize potential biases associated with loss-to-follow-up. Refer to Section 9.6 for more information on monitoring participant retention in this study.

## 4.6 Participant Withdrawal or Termination from the Study

Regardless of the participant retention procedures referenced above, participants may voluntarily withdraw from the study at any time. Participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Participant re-locates away from the study site and cannot be transferred to another site or is otherwise determined to be lost-to-follow-up
- Participant or parent/guardian refuses further treatment and/or follow-up evaluations
- Participant is permanently discontinued from study drug for any reason (see Section 8.7; participants in Cohort 2 will be asked to continue on study for at least 4 weeks after they discontinue study drugs or until resolution [return to baseline] or stabilization of any adverse events with the frequency of visits determined by the site investigator)
- Site investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant, after consultation with the CMC
- The study is stopped or canceled by the sponsors, government or regulatory entities, or site IRBs/ECs

Should the consenting parent (or guardian) of a participant die or no longer be available for any reason, sites should follow the guidelines and procedures as directed by their IRBs/ECs. In general, if participants in Cohort 2 are doing well on the study drug, it is expected that they will stay on study drug and will have safety assessments performed per the local standard of care while continued study participation is being determined. Study sites may continue to provide care for the participant as needed and appropriate (outside of the study), consistent with the local standard of care. If a guardian cannot be identified, or if the guardian does not consent to continued study participation, the participant must be withdrawn from the study. Refer to Section 13.3 for further guidance on parent/guardian consent for study participation.

For any participant who is withdrawn or terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and, for participants in Cohort 2, will make every effort to complete final evaluations as described in Section 6.5. In the event that the circumstances that led to a participant's withdrawal or termination change (e.g., the family returns to the study site area after having re-located previously), the site investigator or designee should contact the CMC to discuss options for resumption of follow-up.

### 4.7 Genotyping

A list of genotypes will be posted on the study-specific website:

http://impaactnetwork.org/studies/IMPAACT2014.asp

Participants who are re-screened do not need to repeat genotype testing.

## 5 STUDY DRUG CONSIDERATIONS

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations. Refer to Figure 1 for an overview of the study design and to the Investigator's Brochures (IBs) for further information about the study drugs.

### 5.1 Study Drug Regimens

**Cohort 1** Participants enrolled in Cohort 1 will receive doravirine (DOR, MK-1439) once on the day of intensive PK evaluations.

**Cohort 2** Participants enrolled in Cohort 2 will receive a fixed-dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF, MK-1439A) once daily for 96 weeks on study.

### 5.2 Study Drug Formulations

#### 5.2.1 Cohort 1

Doravirine (DOR): 100 mg oral tablets. The formulation is a film-coated, compressed tablet, comprised of 100 mg DOR. Store between 2°C and 30°C (36°-86°F), protected from light and moisture, in the original container, tightly closed. Tablets may not be crushed or split.

#### 5.2.2 Cohort 2

Doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF): fixed-dose combination oral tablets. The formulation is a film-coated, bilayer compressed tablet, comprised of 100 mg DOR, 300 mg 3TC, and 300 mg TDF. Store between 2°C and 25°C (36°-77°F), protected from moisture and freezing. Tablets may not be crushed or split.

Doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF): fixed-dose combination oral granules. The formulation is comprised of 100.6 mg of DOR, 300 mg 3TC, and 300 mg TDF, divided between three capsules of oral granules. The individual components may be stored separately between 2°C and 30°C (36°-86°F), protected from light with a desiccant. The stability of the combination product is to be determined.

## 5.3 Study Drug Administration

**Cohort 1** A single dose of doravirine (DOR) will be administered orally and directly observed in the clinic on the day of intensive PK. Administration will occur in the context of PK specimen collection as described in Section 6.

**Cohort 2** Doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) will be administered orally as a fixed-dose combination once daily.

The fixed-dose combination DOR/3TC/TDF capsules may be opened and the oral granules sprinkled on the tongue then swallowed (followed with water); sprinkled onto 1-2 teaspoons of soft food then swallowed; or dispersed in 5-10 mL liquid then swallowed. In any case, administration must occur within 15 minutes of mixing.

Doravirine tablets must be swallowed whole and may not be crushed or split. Participants and caregivers will be counseled as needed throughout the study to help ensure adherence. Refer to Section 6.10 for additional information on adherence counseling for participants in Cohort 2. Site staff will confirm full adherence with dosing three days prior to scheduling the intensive PK visit for the first 10 participants of Cohort 2.

## 5.4 Study Drug Supply

Doravirine and DOR/3TC/TDF will be supplied by Merck & Company and will be available through the Clinical Research Products Management Center (CRPMC).

The other components of the ARV regimen in Cohort 1 are not considered study product and will not be supplied by the study.

Upon successful completion of protocol registration procedures, the site pharmacist can obtain the study drug for this study by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

## 5.5 Study Drug Accountability

Site pharmacists must maintain complete records of all study drugs received from the CRPMC.

## 5.6 Final Disposition of Study Drug

Any unused study drug remaining at US sites after the study is completed or terminated must be returned to the CRPMC (unless otherwise directed by the sponsor). Any unused study drug remaining at non-US sites after the study is completed or terminated will be destroyed. Site pharmacists will follow the relevant instructions for return or destruction of unused study drug provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

## 5.7 Concomitant Medications

All concomitant medications received by enrolled participants will be source documented from 30 days prior to entry through study discontinuation as part of the medical and medications histories obtained at each study visit (see Section 6.7). This includes prescription and non-

prescription (over-the-counter) medications; vaccines and other preventive medications; contraceptives; antacids; vitamins and other nutritional supplements; and alternative, complementary, and traditional medications and preparations. Requirements for entering concomitant medications into eCRFs are specified in Section 6.7.

## 5.8 Prohibited Medications

Any participant who requires a medication considered prohibited while on the study drug must have the study drug permanently discontinued. A list of prohibited medications is provided below:

- Bosentan
- Carbamazepine
- Modafinil
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampicin
- St. John's Wort

In the event that a need for one or more of the above-listed medications is identified, the site investigator or designee should consult the CMC for further guidance on management.

Use of nafcillin or dicloxacillin within 30 days prior to study entry is prohibited (if needed after entry, see below in Section 5.9).

## 5.9 Precautionary Medications

The site investigator or designee should consult with the CMC for any participant who requires a medication considered precautionary while on the study drug, ideally in advance (or as soon as possible) of administration. A list of precautionary medications is provided below:

- Nafcillin and dicloxacillin (which induce CYP3A4 activity) – if treatment with more than 7 days of nafcillin or dicloxacillin is required while on the study drug, the study drug may need to be permanently discontinued; site investigators should consult with the CMC to determine study drug management. Alternative antibiotics, such as oxacillin, cefazolin, or clindamycin, should be selected when clinically appropriate.
- Herbal remedies

# 6 STUDY VISITS AND PROCEDURES

An overview of the schedule of study visits and evaluations is provided in Appendix I-A (Cohort 1) and Appendix I-B (Cohort 2); blood draw volumes for each visit are also detailed in these appendices. Information related to scheduled visits is presented in Sections 6.1-6.3; information related to an event driven visit for virologic failure is presented in Section 6.4; information related to an early discontinuation visit is presented in Section 6.5; information on post-study contacts is presented in Section 6.6; information on medical and medications history, physical examinations, assessment of palatability and acceptability, and assessment of adherence are presented in Sections 6.7-6.10. Additional considerations for laboratory procedures are provided in Section 6.11.

All visits and procedures must be performed at the approved clinical research site or approved associated facilities. All visits and procedures must be documented in accordance with the US National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) policies for source documentation; refer to Section 11 for more information on documentation requirements and completion of eCRFs. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up. All visits and procedures specified to be performed at scheduled visits should ideally be performed on the same day. However, if this is not possible (e.g., if a participant must leave the clinical research site before all procedures can be performed), visits may be split, with procedures performed on more than one day within the allowable visit window.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent; scheduling telephone contacts and visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be documented consistent with site SOPs. Study staff should inform parents/guardians (or participants, if applicable) of clinically meaningful physical exam findings and laboratory test results, when available.

## 6.1 Cohort 1 and Cohort 2 Screening Visit

Refer to Section 4.4 for a description of the study recruitment, screening, and enrollment process.

Screening may be initiated after written informed consent is obtained. All screening procedures are expected to be performed within 30 days prior to study entry. Multiple visits may be conducted within the 30-day time frame to complete all required procedures and to repeat laboratory tests, if necessary. For Cohort 1 and Cohort 2, creatinine testing is required in relation to the eligibility criterion in Section 4.1.8; as soon as the screening creatinine test result is obtained, the estimated GFR should be calculated using the Schwartz equation, and all results should be graded for severity as specified in Section 7.3.3. For Cohort 2, ART-naïve participants, the screening period should be as short as possible so that ART initiation is not unduly delayed.

For Cohort 1, participants will take the study drug as a tablet; for Cohort 2, participants may be offered the study drug as either a tablet or as oral granules. If both formulations are available, the site investigator or designee should explain the differences between formulations as part of the informed consent process and document the participant's decision prior to enrollment in the

study. Formulation switches may be allowed during the study, as described further in Section 6.9.

For potential participants who do not meet the eligibility criteria, screening should be discontinued once ineligibility is determined and these individuals should be actively referred to non-study sources of care.

| **Screening Visit Procedures (within 30 days prior to study entry)** | | |
|---|---|---|
| **Administrative and Regulatory** | | • Obtain written informed consent for IMPAACT 2014<br>• Assign PID to child or adolescent<br>• Obtain screening number from SES<br>• Obtain available documentation of participant's HIV status |
| **Clinical** | | • Obtain available medical records and medical and medications history<br>• Assess documentation of HIV infection in relation to study requirements<br>• Assess ARV history in relation to study requirements<br>• Perform complete physical exam, including body weight<br>• *For Cohort 2,* WHO staging |
| **Laboratory** | **Blood** | Collect blood for:<br>• Confirmatory HIV testing, *if needed per Section 4.1.4*<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>○ Creatinine<br>○ Lipase<br>○ LFTs (AST, ALT, and alkaline phosphatase)<br>• HIV-1 RNA<br>• *For Cohort 2,* Hepatitis C antibody; if Hepatitis C antibody positive, HCV RNA PCR<br>• *For Cohort 2,* Hepatitis B surface antigen<br>• *For Cohort 2, ART-naïve,* genotypic resistance testing (real-time) |
| | **Urine** | *For Cohort 2,* collect urine for:<br>• Dipstick urinalysis, including specific gravity, pH, blood, ketones, glucose, protein, and nitrite |

Participants can be re-screened once in a six-month period if determined to be ineligible on the initial screening process and, for Cohort 2, ART-naïve participants, if re-screening would not delay initiation of ART. If any participant is re-screened, all the screening procedures listed above must be repeated, with the exception that:

- A new PID should not be assigned
- Confirmatory HIV testing and genotype testing need not be repeated
- Previously documented medical and medications history information should be reviewed and updated through the date of re-screening (it is not necessary to re-record history information that was previously documented)
- Informed consent need not be repeated, if re-screening occurs less than 60 days after the initial consent

## 6.2 Cohort 1 Visits and Procedures

### 6.2.1 Cohort 1 Entry Visit

Refer to Section 4.4 for a description of the study recruitment, screening, and enrollment process. Procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination and enrollment. For eligible and enrolled participants, PK sampling should ideally begin on the day of entry. In the event that a participant is found to be ineligible on the day of enrollment, enrollment should not occur.

Additional guidance for sequencing of procedures at the Cohort 1 Entry Visit is as follows:

- Final eligibility determination and confirmation (medical history, complete physical exam, and, if needed, pregnancy testing) must precede enrollment; if pregnancy testing is required per Section 4.1.9, a blood or urine pregnancy test should be performed, with results available for eligibility determination prior to enrollment
- Selection and confirmation of formulation must precede enrollment
- Enrollment must precede prescribing of study drug
- Prescribing must precede dispensing of study drug
- Pre-dose PK blood sample must precede ingestion of the single dose of study drug
- Ingestion of study drug must precede palatability and acceptability assessment

Participants will be entered into the study on Day 0, with PK procedures continuing up to approximately 72 hours post-dose, as outlined below.

| Cohort 1 Entry Visit Procedures (Day 0) | | |
|---|---|---|
| **Administrative and Regulatory** | | • Complete final eligibility determination and confirmation*<br>• Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant and generate SID; print and file a copy of the confirmation file |
| **Clinical** | | • Update medical and medications history since last visit*<br>• Perform complete physical exam, including body weight* |
| **Laboratory** | **Blood** | Collect blood for:<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>o Electrolytes (sodium, potassium, and $HCO_3$)<br>o Glucose<br>o Creatinine<br>o Lipase<br>o Phosphorus<br>o LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin)<br>• CD4 cell counts<br>• HIV-1 RNA<br>• Intensive PK evaluation, per Table 14 below |
| | **Blood or Urine** | Collect blood or urine for:<br>• Pregnancy test, *if needed per Section 4.1.9* (see above for further guidance)* |
| **Study Drug** | | • Prescribe, dispense, and facilitate administration of the doravirine dose AFTER collection of pre-dose PK sample<br>• Administer palatability and acceptability assessment AFTER administration of the doravirine dose |

*Perform prior to enrollment

Assessment of creatinine is required at this visit. As soon as the creatinine result is obtained, the estimated GFR should be calculated using the Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

A single dose of doravirine will be observed in the clinic on the same day as the intensive PK evaluation and ideally on the day of entry. PK sampling will be conducted over the course of approximately 72 hours, with one sample collected pre-dose and eight samples collected post-dose, as shown in Table 14, below.

**Table 14. Cohort 1 Intensive PK Evaluation Sampling Time Points**

| Time Points | Pre-dose | 1 hr post-dose | 2 hrs post-dose | 4 hrs post-dose | 8 hrs post-dose | 12 hrs post-dose | 24 hrs post-dose | 48 hrs post-dose | 72 hrs post-dose |
|---|---|---|---|---|---|---|---|---|---|
| **Window** | No window | ± 15 mins | ± 15 mins | ± 1 hr | ± 1 hr | ± 1 hr | ± 2 hrs | ± 2 hrs | ± 2 hrs |

hr(s)=hour(s); mins=minutes

Depending on site capacity and participant preferences, participants and their parents or guardians may stay at the clinical research facility overnight for the PK sampling.

### 6.2.2 Cohort 1 Week 2 Visit

The Week 2 Visit is targeted to take place on Day 14, counted from the day of entry as Day 0, with an allowable window of ± 2 days. This visit is the final scheduled visit for participants in Cohort 1. There is no required sequencing of procedures at this visit.

| Cohort 1 Week 2 Visit (Day 14 ± 2 days) | | |
|---|---|---|
| **Clinical** | | • Update medical and medications history since last visit<br>• Perform symptom-directed physical exam<br>• Identify/review/update adverse events |
| **Laboratory** | **Blood** | Collect blood for:<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>○ Electrolytes (sodium, potassium, and $HCO_3$)<br>○ Glucose<br>○ Creatinine<br>○ Lipase<br>○ Phosphorus<br>○ LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin) |

Assessment of creatinine is required at this visit. As soon as the creatinine result is obtained, the estimated GFR should be calculated using the Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

At this visit, arrangements should be made to provide all clinically meaningful results to the participant's parent or guardian. The participant and parent or guardian should be informed of how to contact study staff with any post-study questions and how to learn about the results of the study when available.

## 6.3 Cohort 2 Visits and Procedures

### 6.3.1 Cohort 2 Entry Visit

Refer to Section 4.4 for a description of the study recruitment, screening, and enrollment process. The procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination and enrollment. In the event that a participant is found to be ineligible on the day of enrollment, enrollment should not occur.

Additional guidance for sequencing of procedures at the Cohort 2 Entry Visit is as follows:

- Final eligibility determination and confirmation (medical history, complete physical exam, and, if needed, pregnancy testing) must precede enrollment; if pregnancy testing is required per Section 4.1.9, a blood or urine pregnancy test should be performed, with results available for eligibility determination prior to enrollment
- Selection and confirmation of formulation must precede enrollment
- Enrollment must precede prescribing of study drug
- Prescribing must precede dispensing of study drug
- Pre-dose PK blood collection must precede ingestion of the first dose of study drug

ART-experienced, virologically suppressed participants will discontinue previous ARVs and start DOR/3TC/TDF on the day of enrollment.

| Cohort 2 Entry Visit Procedures (Day 0) | | |
|---|---|---|
| **Administrative and Regulatory** | | • Complete final eligibility determination and confirmation*<br>• Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant and generate SID; print and file a copy of the confirmation file |
| **Clinical** | | • Update medical and medications history since last visit*<br>• Perform complete physical exam, including body weight* |
| **Laboratory** | **Blood** | Collect blood for:<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>o Electrolytes (sodium, potassium, and $HCO_3$)<br>o Glucose<br>o Creatinine<br>o Lipase<br>o Phosphorus<br>o LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin)<br>• Lipid profiles<br>• HIV-1 RNA<br>• CD4 cell count<br>• Sparse PK evaluation (see Section 6.3.8)<br>• *Participants who are ART-naïve only*, store plasma for phenotypic resistance testing |
| | **Blood or Urine** | Collect blood or urine for:<br>• Pregnancy test, *if needed per Section 4.1.9* (see above for further guidance)* |
| **Study Drug** | | • If granule formulation is available, confirm selection of formulation*<br>• Prescribe, dispense, and facilitate administration of DOR/3TC/TDF AFTER collection of the pre-dose PK sample<br>• Provide instructions for DOR/3TC/TDF administration and adherence counseling to the participant, parent or guardian |

*Perform prior to enrollment

Assessment of creatinine is required at this visit. As soon as the creatinine result is obtained, the estimated GFR should be calculated using the Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

### 6.3.2 Cohort 2 Week 1 Visit: Participants Selected for Intensive PK Evaluations ONLY

For the first 10 participants enrolled in Cohort 2 only, intensive PK evaluations are targeted at Week 1. The Week 1 Visit is targeted to take place on Day 8, counted from the day of entry as Day 0, with an allowable window of + 5 days.

Additional guidelines and guidance for sequencing of procedures at the Cohort 2 Week 1 Visit is as follows:

- The intensive PK evaluation should be scheduled so that the observed dosing of study drug is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing.
- Prior to this visit, adherence to study drug should be emphasized and supported. Sites may use reminder calls or scheduling cards for participants and parents or guardians to reinforce adherence within the three days prior to the scheduled intensive PK evaluation. (For example, sites could call or visit the participant and/or parent/guardian prior to the scheduled PK evaluation to reinforce adherence.)
- Participants should take study drug for three days (i.e., be fully adherent) prior to the intensive PK visit; the study drug dose and time of the previous three study drug doses should be source documented and entered into eCRFs. If a missed dose is reported within this period, the intensive PK evaluation should be rescheduled. As described in Section 6.9, participants may change their formulation after entry if the granule formulation is available; however, they would need to be on the new formulation at least one day prior to the intensive PK at Week 1.
- Participants who report intercurrent illness immediately prior to or on the day of the scheduled PK visit that may have interfered with study drug administration or resulted in malabsorption of study drug (e.g., fever, vomiting, diarrhea), the intensive PK evaluation should be rescheduled.
- Depending on site capacity and participant preferences, participants and their parents or guardians may stay at the clinical research facility overnight for the PK sampling.

| Cohort 2 Week 1 Visit (Day 8 + 5 days) | | |
|---|---|---|
| **Clinical** | | • Obtain interval medical and medications history<br>• Perform symptom-directed physical exam<br>• Identify/review/update adverse events<br>• Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) |
| **Laboratory** | **Blood** | Collect blood for:<br>• Intensive PK evaluation, per Table 15 below |
| **Study Drug** | | • Prescribe and dispense study drug, as needed<br>• Provide instructions for DOR/3TC/TDF administration and adherence counseling to the participant, parent or guardian, as needed |

Samples will be collected per Table 15, below.

**Table 15. Cohort 2 Week 1 PK Evaluation Sampling Time Points**

| Time Points | Pre-dose | 1 hr post-dose | 2 hrs post-dose | 4 hrs post-dose | 8 hrs post-dose | 12 hrs post-dose | 24 hrs post-dose |
|---|---|---|---|---|---|---|---|
| **Window** | No window | ± 15 mins | ± 15 mins | ± 1 hr | ± 1 hr | ± 1 hr | ± 2 hrs |
| **Volume** | 3.5 mL | 2.5 mL | 3.5 mL | 3.5 mL | 2.5 mL | 3.5 mL | 3.5 mL |
| **Analyte** | DOR, 3TC, tenofovir | 3TC, tenofovir | DOR, 3TC, tenofovir | DOR, 3TC, tenofovir | 3TC, tenofovir | DOR, 3TC, tenofovir | DOR, 3TC, tenofovir |

hr(s)=hour(s); mins=minutes

### 6.3.3 Cohort 2 Week 2 Visit

The Week 2 Visit is targeted to take place on Day 14, counted from the day of entry as Day 0, with an allowable window of ± 1 week. There is no required sequencing of procedures at this visit. For the participants selected for intensive PK evaluations (i.e., the first 10 enrolled into Cohort 2), although the visit windows overlap, the Week 2 visit procedures may NOT be combined with Week 1 visit procedures and Week 2 visit procedures must be conducted after Week 1 visit procedures.

| **Cohort 2 Week 2 Visit (Day 14 ± 1 week)** | | |
|---|---|---|
| **Clinical** | | • Obtain interval medical and medications history<br>• Perform symptom-directed physical exam<br>• Identify/review/update adverse events<br>• Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) |
| **Laboratory** | **Blood** | Collect blood for:<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>o Electrolytes (sodium, potassium, and $HCO_3$)<br>o Glucose<br>o Creatinine<br>o Lipase<br>o Phosphorus<br>o LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin)<br>• HIV-1 RNA |
| | **Urine** | Collect urine for:<br>• Dipstick urinalysis, including specific gravity, pH, blood, ketones, glucose, protein, and nitrite |
| **Study Drug** | | • Prescribe and dispense study drug, as needed<br>• Provide instructions for DOR/3TC/TDF administration and adherence counseling to the participant, parent or guardian, as needed<br>• Administer palatability and acceptability assessment |

Assessment of creatinine is required at this visit. As soon as the creatinine result is obtained, the estimated GFR should be calculated using the Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

### 6.3.4 Cohort 2 Week 4 Visit

The Week 4 Visit is targeted to take place on Day 28, counted from the day of entry as Day 0, with an allowable window of - 1 week to + 2 weeks. If possible, pre-dose sparse PK blood collection should precede ingestion of the study drug (see Section 6.3.8). As described in Section 6.9, participants may change their formulation after entry if the granule formulation is available; however, they would need to be on the new formulation at least one day prior to the first sparse PK assessment visit at Week 4.

| Cohort 2 Week 4 Visit (Day 28, - 1 week / + 2 weeks) | | |
|---|---|---|
| **Clinical** | | • Obtain interval medical and medications history<br>• Perform symptom-directed physical exam<br>• Identify/review/update adverse events<br>• Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) |
| **Laboratory** | **Blood** | Collect blood for:<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>o Electrolytes (sodium, potassium, and $HCO_3$)<br>o Glucose<br>o Creatinine<br>o Lipase<br>o Phosphorus<br>o LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin)<br>• HIV-1 RNA<br>• CD4 cell count<br>• Sparse PK evaluation (see Section 6.3.8) |
| | **Blood or Urine** | Collect blood or urine for:<br>• Pregnancy test, *if needed per Section 8.8.1* |
| **Study Drug** | | • Administer adherence assessment<br>• Prescribe and dispense study drug, as needed (see Section 6.3.8 for additional detail regarding timing on study drug administration during the sparse PK evaluation)<br>• Provide instructions for DOR/3TC/TDF administration and adherence counseling to the participant, parent or guardian, as needed |

Assessment of creatinine is required at this visit. As soon as the creatinine result is obtained, the estimated GFR should be calculated using the Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

### 6.3.5 Cohort 2 Weeks 8, 12, and 16 Visits

After the Week 4 Visit, participants will attend follow-up visits every 4 weeks through Week 16, i.e., Week 8, Week 12, and Week 16. These visits will be counted from the day of entry as Day 0, with a targeted window of ± 2 weeks. There is no required sequencing of procedures at these visits.

| **Cohort 2 Follow-up Week 8 (Day 56 ± 2 weeks), Week 12 (Day 84 ± 2 weeks), and Week 16 (Day 112 ± 2 weeks)** | | |
|---|---|---|
| **Clinical** | | • Obtain interval medical and medications history<br>• Perform symptom-directed physical exam<br>• Identify/review/update adverse events<br>• Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) |
| **Laboratory** | **Blood** | Collect blood for:<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>o Electrolytes (sodium, potassium, and $HCO_3$)<br>o Glucose<br>o Creatinine<br>o Lipase<br>o Phosphorus<br>o LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin)<br>• HIV-1 RNA<br>• *At Weeks 8 and 12,* sparse PK evaluation (see Section 6.3.8)<br>• *At Week 12,* lipid profile<br>• *At Week 12,* CD4 cell count |
| | **Blood or Urine** | Collect blood or urine for:<br>• Pregnancy test, *if needed per Section 8.8.1* |
| | **Urine** | *At Weeks 12,* collect urine for:<br>• Dipstick urinalysis, including specific gravity, pH, blood, ketones, glucose, protein, and nitrite |
| **Study Drug** | | • Administer adherence assessment<br>• Prescribe and dispense study drug, as needed<br>• Provide instructions for DOR/3TC/TDF administration and adherence counseling to the participant, parent or guardian, as needed |

Assessment of creatinine is required at this visit. As soon as the creatinine result is obtained, the estimated GFR should be calculated using the Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

### 6.3.6 Cohort 2 Weeks 24, 36, and 48 Visits

After the Week 16 Visit, participants will attend follow-up visits at Weeks 24, 36, and 48. These visits will be counted from the day of entry as Day 0, with a targeted window of ± 2 weeks. In addition, for these visits, an allowable window of ± 4 weeks is specified. Every effort should be made to conduct all visits within the targeted window; however, visits are permitted to be conducted within the allowable window. If possible, at Weeks 24 and 48, pre-dose sparse PK blood collection should precede ingestion of the study drug (see Section 6.3.8). At Week 36, there is no required sequencing of procedures.

| **Cohort 2 Follow-up Week 24 (Day 168 ± 2 weeks), Week 36 (Day 252 ± 2 weeks), and Week 48 (Day 336 ± 2 weeks); *Allowable visit windows:* ± 4 weeks** | | |
|---|---|---|
| **Clinical** | | • Obtain interval medical and medications history<br>• *At Weeks 24 and 36,* perform symptom-directed physical exam<br>• *At Week 48,* perform complete physical exam<br>• Identify/review/update adverse events<br>• Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) |
| **Laboratory** | **Blood** | Collect blood for:<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>o Electrolytes (sodium, potassium, and $HCO_3$)<br>o Glucose<br>o Creatinine<br>o Lipase<br>o Phosphorus<br>o LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin)<br>• HIV-1 RNA<br>*At Weeks 24 and 48*, collect blood for:<br>• Lipid profile<br>• CD4 cell count<br>• Sparse PK evaluation (see Section 6.3.8) |
| | **Blood or Urine** | Collect blood or urine for:<br>• Pregnancy test, *if needed per Section 8.8.1* |
| | **Urine** | *At Weeks 24 and 48,* collect urine for:<br>• Dipstick urinalysis, including specific gravity, pH, blood, ketones, nitrite, glucose and protein |
| **Study Drug** | | • Administer adherence assessment<br>• Prescribe and dispense study drug, as needed (*at Weeks 24 and 48*, see Section 6.3.8 for additional detail regarding timing on study drug administration during the sparse PK evaluation)<br>• Provide instructions for DOR/3TC/TDF administration and adherence counseling to the participant, parent or guardian, as needed |

Assessment of creatinine is required at this visit. As soon as the creatinine result is obtained, the estimated GFR should be calculated using the Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

### 6.3.7 Cohort 2 Q16 Week Visits (Weeks 64, 80, and 96)

After the Week 48 Visit, participants will attend follow-up visits every 16 weeks through Week 96, i.e., Week 64, Week 80, and Week 96. These visits will be counted from the day of entry as Day 0, with a targeted window of ± 4 weeks. In addition, for these visits, an allowable window of ± 8 weeks is specified. Every effort should be made to conduct all visits within the targeted window; however, visits are permitted to be conducted within the allowable window. There is no required sequencing of procedures at these visits.

| **Cohort 2 Follow-up Week 64 (Day 448 ± 4 weeks), Week 80 (Day 560 ± 4 weeks), and Week 96 (Day 672 ± 4 weeks); *Allowable visit windows: ± 8 weeks*** | | |
|---|---|---|
| **Clinical** | | • Obtain interval medical and medications history<br>• *At Weeks 64 and 80,* perform symptom-directed physical exam<br>• *At Week 96,* perform complete physical exam<br>• Identify/review/update adverse events<br>• Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) |
| **Laboratory** | **Blood** | Collect blood for:<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>o Electrolytes (sodium, potassium, and $HCO_3$)<br>o Glucose<br>o Creatinine<br>o Lipase<br>o Phosphorus<br>o LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin)<br>• HIV-1 RNA<br>• *At Week 96,* lipid profile |
| | **Blood or Urine** | Collect blood or urine for:<br>• Pregnancy test, *if needed per Section 8.8.1* |
| | **Urine** | *At Weeks 64 and 96*, collect urine for:<br>• Dipstick urinalysis, including specific gravity, pH, blood, ketones, nitrite, glucose and protein |
| **Study Drug** | | • Administer adherence assessment<br>• Prescribe and dispense study drug, as needed<br>• Provide instructions for DOR/3TC/TDF and adherence counseling to the participant, parent or guardian, as needed<br>• *At Week 96,* collect any remaining study drug supplies |

Assessment of creatinine is required at this visit. As soon as the creatinine result is obtained, the estimated GFR should be calculated using the Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

At the Week 80 Visit, information and counseling should be provided to the participant (and parent or guardian) to begin to prepare for study exit at the Week 96 Visit. Referrals to non-study care and treatment should be discussed as needed, with emphasis on the importance of retention in care following study completion.

At the Week 96 Visit, prior discussions of transition to non-study care and treatment should be reviewed, with information, counseling, and/or referrals provided as needed. Study drug cannot be dispensed to participants at or after this visit; therefore, operational plans must be in place to

permit transition to non-study care and treatment at this visit. Arrangements should be made to provide all clinically meaningful results to the participant's parent or guardian. The participant and parent or guardian should be provided information on how to remain in contact with study staff (if desired) and how to learn about the results of the study when available. The participant's parent or guardian should also be provided information, counseling, and referrals to non-study sources of care and treatment for the participant, as applicable. See also Section 6.6.

### 6.3.8 Cohort 2 Sparse Pharmacokinetic Evaluations (Entry and Weeks 4, 8, 12, 24, and 48)

Sparse PK samples will be collected among all participants in Cohort 2, as detailed in Table 16, below. At all visits when a sparse PK sample is collected, source document prior study drug dose and time and enter into eCRFs.

**Table 16. Cohort 2 Sparse PK Evaluation Sampling Time Points**

| Visit Week | Entry | Week 4 | Week 8 | Week 12 | Week 24 | Week 48 |
|---|---|---|---|---|---|---|
| **Time Points** | Pre-dose | Pre-dose* | Random | Random | Pre-dose* and 0.5 – 2 hours post-dose | Pre-dose* and 0.5 – 2 hours post-dose |

Participants and parents/guardians should be reminded to record the time that the most recent study drug dose was given. Sites may use reminder calls or scheduling cards for participants and parents or guardians to reinforce these requirements.

***Special Notes for Sparse PK Evaluations at Weeks 4, 24, and 48***

If possible, at Weeks 4, 24, and 48, blood collection for the pre-dose PK evaluation should precede ingestion of the dose of study drug. Prior to this visit, participants and their parents/guardians should be reminded to hold the daily administration of study drug, so that the dose can be observed at the site.

If not possible to schedule the visits at the time of the participant's usual study drug dose, the PK draws can be done without regard to the timing of the study drug dose. At Weeks 24 and 48, the last two samples should be drawn 0.5 – 2 hours apart.

## 6.4 Cohort 2 Confirmation of Virologic Failure Visit

Refer to Section 8.6 for more information on monitoring HIV-1 viral load, definitions of virologic failure, and managing virologic failure.

Virologic failure is defined as two consecutive plasma HIV-1 RNA test results ≥200 copies/mL.

- For participants who were ART-naïve at enrollment, the first of the two consecutive results should be obtained from a specimen collected for the first test at or after Week 24, counted from the date of enrollment. For example, if an ART-naïve participant has a viral load ≥200 copies/mL at Week 16, no Confirmation of Virologic Failure Visit is needed. If the same participant has a viral load ≥200 copies/mL at Week 24, the result must be confirmed through a Confirmation of Virologic Failure Visit.
- For participants who were ART-experienced at enrollment, the consecutive results may be at any time after the date of enrollment. For example, if an ART-experienced participant has a

viral load ≥200 copies/mL at Week 12, the result must be confirmed through a Confirmation of Virologic Failure Visit.

Any participant with a plasma HIV-1 RNA level ≥200 copies/mL either 1) at or after Week 24 (ART-naïve) or 2) at any time after the date of enrollment (ART-experienced) should be recalled to the clinic for confirmatory testing within four weeks, and no more than six weeks, of the date of specimen collection for the initial test. Other procedures should be performed according to the "Confirmation of Virologic Failure" column of the Schedule of Evaluations for Cohort 2 (Appendix I-B). These procedures may be combined with regularly scheduled visit procedures if they are performed within the allowable window of a regularly scheduled visit.

The specimen collected for genotypic and phenotypic resistance testing should be stored for later testing (see the Laboratory Processing Chart, LPC).

The site staff should investigate potential causes for virologic failure such as inadequate adherence, interruptions due to toxicity management, or other extenuating circumstances. In addition to the protocol-specific procedures listed in this section, study staff may complete other tasks and assessments consistent with local standards of care and site SOPs, including separate, real-time resistance testing (an additional sample would need to be collected beyond the samples collected and stored for protocol-specific future genotypic and phenotypic resistance testing).

There is no required sequencing of procedures at this visit.

| **Confirmation of Virologic Failure Visit Procedures** | | |
|---|---|---|
| **Clinical** | | • Obtain interval medical and medications history<br>• Perform complete physical exam, including body weight<br>• Identify/review/update adverse events<br>• Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) |
| **Laboratory** | **Blood** | Collect blood for:<br>• HIV-1 RNA<br>• Store plasma for future genotypic and phenotypic resistance testing |
| | **Blood or Urine** | Collect blood or urine for:<br>• Pregnancy test, *if needed per Section 8.8.1* |
| **Study Drug** | | • Administer adherence assessment<br>• Prescribe and dispense study drug, as needed<br>• Provide instructions for ARV administration and adherence counseling to the participant, parent or guardian, as needed |

## 6.5 Cohort 2 Early Discontinuation Visit

Refer to Section 4.6 for criteria for participant withdrawal or termination from the study. For any participant who is withdrawn or terminated from the study prior to the scheduled study completion of follow-up at Week 96 (Cohort 2 participants), every effort should be made to perform a final series of study evaluations, if possible, according to the "Early D/C" column of AppendiAppendix I-B, Schedule of Evaluations for Cohort 2. However, any evaluations performed within the 28 days prior to the Early Discontinuation Visit need not be repeated at the visit.

| Early Discontinuation Visit Procedures | | |
|---|---|---|
| **Clinical** | | • Obtain interval medical and medications history<br>• Perform complete physical exam, including body weight<br>• Identify/review/update adverse events<br>• Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) |
| **Laboratory** | **Blood** | Collect blood for:<br>• Complete blood count with differentials and platelet count<br>• Chemistries:<br>o Electrolytes (sodium, potassium, and HCO3)<br>o Glucose<br>o Creatinine<br>o Lipase<br>o Phosphorus<br>o LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin)<br>• HIV-1 RNA<br>• CD4 cell count<br>• Store plasma for future genotypic and phenotypic resistance testing |
| | **Blood or Urine** | Collect blood or urine for:<br>• Pregnancy test, *if needed per Section 8.8.1* |
| **Study Drug** | | • Administer adherence assessment<br>• Collect any remaining study drug supplies |

Assessment of creatinine is required at this visit. As soon as the creatinine result is obtained, the estimated GFR should be calculated using the Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

The specimens collected for genotypic and phenotypic resistance testing should be stored for later testing at the end of the study (see the LPC).

At this visit, arrangements should be made to provide all clinically meaningful results to the participant's parent or guardian. The participant and parent or guardian should be provided information on how to remain in contact with study staff (if desired) and how to learn about the results of the study when available. The participant's parent or guardian should also be provided information, counseling, and referrals to non-study sources of care and treatment for the participant, as applicable.

## 6.6 Cohort 2 Post-Study Contacts

As indicated in Section 6.3.7, planning for transition to non-study care and treatment for participants in Cohort 2 should begin at the Week 80 visit, and the transition should be implemented at the Week 96 visit. Following the Week 96 Visit, study staff will complete a final study contact with each participant's parent or guardian to confirm the transition and, in particular, confirm access to non-study ARVs (or continued post-study access to study drug, see Section 13.11). This contact should take place within four weeks after the Week 96 visit and should be documented in each participant's study chart. These contacts are not expected to be entered into eCRFs. However, eCRF data collection is required after the Week 96 Visit in the following scenarios:

- If a participant becomes pregnant while on study: Refer to Section 8.8.2; in this scenario, the pregnancy outcome must be ascertained and the relevant eCRFs entered after the participant discontinues the study to record the pregnancy outcome. Relevant eCRFs will also be entered to capture any ARV changes during the pregnancy.

- If confirmation of virologic failure is pending after the Week 96 Visit: Refer to Section 6.4; in this scenario, the confirmatory HIV-1 RNA PCR assay must be performed and the relevant eCRFs entered to record the result of the assay.

- If the participant has any laboratory result grade 3 or higher at the Week 96 visit: participants should be asked to be continued on study for up to thirty days or until resolution (return to baseline) or stabilization (i.e. grade 2 or lower), whichever is sooner, with the frequency of visits determined by the site investigator.

## 6.7 Medical and Medications History

Collection of medical and medication history information is required at each scheduled visit. A baseline history is established at Screening and Entry, and interval (since the last visit) histories are obtained at subsequent follow-up visits. All history information may be obtained based on participant self-report or as reported by the parent or guardian but available medical records should be obtained when possible to supplement self-reported information.

Documented medical conditions will be assessed for severity as described in Section 7.3.3, and new conditions occurring during follow-up will also be assessed for relationship to study drug as described in Section 8.1. Relevant dates will be recorded for all conditions and medications; see Section 5.9 for more information on concomitant medications.

Table 17 specifies the baseline and interval medical and medications history elements that must be source documented for participants, as well as associated eCRF entry requirements.

**Table 17. Documentation Requirements for Medical and Medication Histories**

| Assess for and Source Document | Enter into eCRFs |
|---|---|
| ***Baseline Medical and Medication History Elements*** | |
| Age and other socio-demographics | Yes (all) |
| HIV diagnosis, Sexual Maturity Rating (SMR), WHO clinical staging (Cohort 2), and ARV treatment history (including all ARV use within the 30 days prior to enrollment) | Yes (all) |
| History of allergy and/or hypersensitivity (including to ARVs) | Yes (all) |
| Ongoing or clinically relevant medical conditions (including malignancies and sleep history) occurring during the 30 days prior to enrollment | Yes (all) |
| Medications (other than ARVs, see above) taken within the 30 days prior to enrollment and/or ongoing at enrollment | Yes (all) |
| Assessment of sexual activity and contraception | — |
| Any other information needed to determine eligibility for the study | — |
| ***Interval Medical and Medication History Elements*** | |
| Current status of conditions that were ongoing at the previous visit | Any updates of previous entries (e.g., resolution dates) |
| Occurrence of any new conditions since the last visit | Any newly identified adverse events that meet criteria in Section 7.2 |
| Current status of medications that were ongoing at the previous visit | Any updates of previous entries (e.g., stop dates) |
| Use of any new medications since the last visit (see Section 5.7 for more information on concomitant medications)<br><br>**Note:** For participants in Cohort 1, DOR would be considered study drug and all other ARVs would be considered concomitant medications. For participants in Cohort 2, DOR/3TC/TDF would be considered study drug and no other concomitant ARVs would be expected (unless the study drug is not tolerated or otherwise has to be changed). | • Study drug and formulation taken from time of enrollment through completion of follow-up, including timing of prior study drug dose at the sparse PK visits (see Section 6.3.8) and timing of last three study drug doses at the intensive PK visit (see Section 6.3.2)<br>• Any concomitant ARVs taken while on study drug<br>• Any new use of concomitant medications while on study drug<br>• All medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2<br>Note: eCRFs will also capture whether traditional medications were taken during follow-up. |
| Assessment of current sexual maturity, sexual activity, and contraception | — |

## 6.8 Physical Examinations

A physical examination is required at each scheduled visit. For Cohort 1, complete exams are required at the Screening and Entry Visits; a symptom-directed exam is required at Week 2. For Cohort 2, complete exams are required at the Screening and Entry visits, Weeks 48 and 96, and Confirmation of Virologic Failure and Early Discontinuation visits; symptom-directed exams are required at all other scheduled visits.

Complete exams should include the following:

- Height and weight
- Vital signs, including heart rate, temperature and blood pressure
- Examination of:
  - General appearance
  - Head
  - Eyes
  - Ears
  - Nose
  - Neck
  - Mouth and throat
  - Lymph nodes
  - Lungs
  - Heart
  - Abdomen
  - Musculoskeletal system
  - Skin
  - Neuro
  - Sexual Maturity Rating (SMR) (Entry only)

- Examination of other body systems driven by other identified signs or symptoms

Symptom-directed exam should include the following:

- Height and weight
- Vital signs, including heart rate, temperature and blood pressure
- Examination of body systems driven by identified signs or symptoms

At all visits, additional assessments may be performed at the discretion of the examining site investigator.

All exam findings should be source documented and entered into eCRFs. Abnormal findings identified prior to administration of first dose of study drug will be entered into eCRFs. Abnormal findings identified after administration of first dose of study drug will be entered into eCRFs as specified in Section 7.2.

## 6.9 Cohort 1 and Cohort 2 Study Drug Palatability and Acceptability

A study-specific form will document palatability and acceptability of 100 mg DOR in Cohort 1 and the fixed-dose combination DOR/3TC/TDF in Cohort 2. Assessment of participant palatability and acceptability will be assessed by questionnaire as indicated in the Schedule of Evaluations in Appendix I-A and Appendix I-B and may include participant or parent/guardian opinion on the size and shape of the tablets and, in Cohort 2, oral granules, required dosing frequency, or overall taste and ease of swallowing.

Participants in Cohort 2 may be offered the study drug as either a tablet or as oral granules; if both formulations are available, participants will be asked to confirm their selection prior to enrollment. Participants may change their formulation after entry; however, they would need to be on the new formulation at least one day prior to the intensive PK (if applicable) or the first sparse PK assessment visit (Week 4). Further formulation changes during the study are discouraged and every effort should be made to have participants remain on the same formulation. The formulation will be source documented and entered into eCRFs at Entry and whenever there is a change in formulation. If the formulation is changed after Entry, assessment of participant palatability and acceptability will be assessed by questionnaire at the time of the switch. The site investigator or designee may consult with the CMC for further guidance or recommendations if a participant wants to switch formulations; consultation and approval from the CMC are not required.

## 6.10 Cohort 2 Study Drug Adherence Assessment and Counseling

Study staff will provide adherence counseling to participants and parents/guardians throughout the period of study participation. Counseling may be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs. Counseling should be provided in a client-centered manner, tailored as needed to the information, skills building, and support needs of each participant. Information on correct use of study drugs will be provided, particularly at the time of enrollment and in the early stages of follow-up. Counseling will also address challenges to consistent use of study drug over time, with the aim of supporting participants in identifying strategies to address any such challenges.

Adherence to the study drug regimen will be assessed by questionnaire as indicated in the Schedule of Evaluations in Appendix I-B. These data will not be used as a basis for adherence counseling. The results of HIV-1 viral load testing performed throughout follow-up provide a biologic measure of adherence and may be used to guide feedback to participants and parents/guardians and associated adherence counseling. Refer to Section 8.6 for more information on virologic monitoring and management.

## 6.11 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at:

https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

### 6.11.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the LPC, which will be posted on the study-specific webpage:

http://impaactnetwork.org/studies/IMPAACT2014.asp

In accordance with US National Institutes of Health (NIH) recommendations, pediatric (less than 18 years) blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg over any eight-week period. Adult (18 years and older) blood collection will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

In the event that blood collection must be limited, available specimens will be prioritized for use in the following order: (1) confirmatory HIV testing (if needed at Screening Visit), (2) safety (chemistries, CBC, pregnancy testing), (3) genotypic resistance testing (if needed at Screening Visit); (4) PK, (5) HIV-1 viral load, (6) Hepatitis B surface antigen, Hepatitis C antibody, and Hepatitis C RNA PCR testing (as required at Screening Visit), (7) CD4 cell counts, (8) lipid profiles, and (9) stored samples for resistance testing.

### 6.11.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in Section 6.11, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by the Schedules of Evaluations in Appendix I-A and Appendix I-B and specifications for clinical management provided in Section 8. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in the LPC. Any specimens stored at the Screening Visit for participants who do not subsequently enroll in the study will be destroyed.

HIV-1 RNA assays must be performed in real time in a CLIA-certified (US sites) or VQA-approved (non-US sites) laboratory using the testing platform specified in the LPC. In Cohort 2, HIV genotypic resistance assays must also be performed in a CLIA-certified laboratory (US sites) and in a DAIDS-approved, GCLP-compliant laboratory that is VQA-certified (non-US sites); samples collected should be tested or stored as follows:

- Samples from the Screen visit will be run in real-time to inform eligibility.
- Samples from the Confirmation of Virologic Failure visit will be run in real-time, if the second consecutive test confirms the HIV-1 RNA level.
- Samples from the Early Discontinuation visit will be stored for later testing at the end of the study.

Specimens collected, processed, and stored at site laboratories for PK evaluations are expected to be shipped to the designated testing laboratory as follows:

- Cohort 1 intensive PK samples from the Entry visit must be shipped immediately after completion of the visit and will be run on an ongoing basis.
- Cohort 2 intensive PK samples will be batch shipped and will generally be run after all intensive PK samples have been collected.
- Cohort 2 sparse PK samples will be batch shipped and will generally be run after all sparse PK samples have been collected or on an ongoing basis if needed based on sample stability limits.

After all protocol-specified laboratory testing has been performed, residual specimens may be of interest for future research use. Participants' parents or guardians (or participants if applicable) will be asked to provide written informed consent for future research use of these specimens, if permitted by site IRBs/ECs and other applicable review bodies. Parents or guardians (or participants) may choose to provide or to decline informed consent for future research use of residual specimens with no impact on other aspects of participation in the study. If informed consent for future research use of residual specimens is initially provided but participants' parents or guardians (or participants) subsequently change their mind and withdraw that consent, all remaining residual samples will be destroyed.

### 6.11.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as currently recommended by the US Centers for Disease Control and Prevention, NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

# 7 SAFETY MONITORING, ASSESSMENT AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1-7.3 describe safety-related roles, responsibilities, and procedures. The safety monitoring roles of the CMC and the IMPAACT Study Monitoring Committee (SMC) are briefly referenced in Sections 7.1.2 and 7.1.3 and described in greater detail in Sections 9.6.1 and 9.6.2.

## 7.1 Safety-Related Roles and Responsibilities

### 7.1.1 Site Investigators

Site investigators are responsible for monitoring of all study participants and for alerting the CMC if unexpected concerns arise. Site investigators and their designees will enter safety-related data on eCRFs as indicated in Section 7.2 and complete expedited adverse event (EAE) reporting as indicated in Section 7.3. Site investigators are also responsible for prompt reporting to their IRBs/ECs and other applicable review bodies of any unanticipated problems involving risks to participants or others.

### 7.1.2 Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Protocol Chair and Vice Chairs, Medical Officers, Statisticians, Data Managers, Pharmacologists, Clinical Trials Specialists, selected Protocol Investigators, and representatives from Merck & Company. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility, study drug administration, and management of adverse events. Refer to Section 8 for more information on participant management.

On behalf of the full Protocol Team, the CMC will also monitor participant safety through routine review of study data reports as described in Section 9.6.

### 7.1.3 Study Monitoring Committee

An independent IMPAACT SMC will contribute to monitoring participant safety in this study. Refer to Section 9.6.2 for more information on the role of the SMC in monitoring this study.

## 7.2 Safety-Related Data Collection

*Note: This section describes eCRF data collection for pre-existing conditions and adverse events. As part of this description, reference is made to criteria for EAE reporting and severity grading; refer to Sections 7.3.2 and 7.3.3, respectively, for detailed information on these topics.*

The definition of the term adverse event provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. Adverse events apply to all participants from the time of initial study drug administration.

#### *Pre-Existing Conditions*

Any pre-existing conditions identified among enrolled participants during the 30 days prior to initial administration of study drug that are ongoing or clinically relevant will be entered into eCRFs.

#### *Adverse Events*

All adverse events – except as specified in the IMPAACT Do Not Report List – will be entered into eCRFs, regardless of severity grade and relationship to study drug.

#### *Laboratory Test Results*

In addition to the recording specified above, all protocol-specified laboratory test results will be entered into the relevant eCRFs. In addition, any abnormal results of laboratory tests ordered by the site investigator to evaluate adverse events considered related to study drug should be entered on eCRFs.

***Overdose***

For this study, an overdose is defined as more than twice the recommended daily dose in a calendar day. All study drug overdoses should be entered into the relevant eCRF and will be reported routinely to the pharmaceutical sponsor.

## 7.3 Expedited Adverse Event (EAE) Reporting

### 7.3.1 EAE Reporting to DAIDS

Requirements, definitions, and methods for expedited reporting of adverse events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the Regulatory Support Center (RSC) website at:

http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at:

http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting

For questions about DAERS, contact NIAID Clinical Research Management System at CRMSsupport@niaid.nih.gov. Questions may also be sent from within the DAERS application itself.

For questions about expedited reporting, contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.

### 7.3.2 EAE Reporting Requirements for this Study

The serious adverse event (SAE) Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agent for which expedited reporting is required is doravirine (DOR) for Cohort 1 and doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) for Cohort 2.

In addition to the above, the following must also be reported in an expedited manner (i.e., as EAE):

- All Grade 4 adverse events
- All pregnancy complications, including intrauterine fetal demise, spontaneous abortions, or therapeutic or otherwise medically indicated abortions
- All malignancies
- Any immune reconstitution inflammatory syndrome (IRIS) events

### 7.3.3 Grading Severity of Events (applies to EAEs and all other adverse events)

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, will be used in this study. This table is available on the RSC website:

http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables

### 7.3.4 EAE Reporting Period

For each enrolled participant, the EAE reporting period begins at the time of administering the first dose of study drug and continues through the protocol-specified end of follow-up for each cohort.

After the above specified period, only suspected, unexpected, serious adverse reactions (SUSAR) as defined in Version 2.0 of the EAE Manual will be reported if the study staff become aware of the events on a passive basis (e.g., from publicly available information).

# 8 PARTICIPANT MANAGEMENT

## 8.1 Management of Adverse Events

All adverse events identified in this study will be source documented in research records, consistent with the policies and procedures referenced in Section 7. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3) and relationship to study product, assessed by the site clinician according to the following categories and definitions:

**Related** There is a reasonable possibility that the adverse event may be related to study drug.

**Not related** There is not a reasonable possibility that the adverse event may be related to study drug.

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual, referenced in Section 7.3.1 above.

As described in greater detail below, adverse events identified in participants will be managed based on their severity and assessed relationship to study drug.

All adverse events must be followed to resolution (return to baseline) or stabilization, with the frequency of repeat evaluations determined by the clinical significance of each event. Additional evaluations beyond those listed in Appendix I-A and Appendix I-B may be performed at the discretion of the site investigator to determine the etiology of a given event and/or further assess its severity or relationship to study product. Clinical management of all adverse events should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards.

Refer to Sections 8.2-8.6 for further guidance on management of adverse events, including general adverse events, liver toxicities, decline in renal function, non-study drug ARV-related toxicities, and monitoring and management of virologic failure. When management of an adverse event requires consultation with the CMC, the CMC should be contacted as soon as possible and within three business days of site awareness of the event.

Criteria for premature discontinuation of study drug are presented in Section 8.7 and guidance and requirements for contraception, pregnancy testing, and management of participants who become pregnant are presented in Section 8.8.

## 8.2 General Management (Cohort 2)

The general guidelines (by grade, Table 18) apply to management of study drug in response to toxicities other than hepatic and renal events, for which guidelines are provided in Sections 8.3 and 8.4, respectively.

Any interruption of DOR/3TC/TDF of more than seven days should be discussed with the CMC prior to restarting.

Any participant who permanently discontinues study drug will be transitioned to the local standard of care to receive an alternative, locally-available ARV treatment regimen. To the extent possible and as medically indicated, site staff should work to ensure any ART interruptions are as short as possible. Participants should be transitioned to non-study care and treatment should be reviewed, with information, counseling, and/or referrals provided as needed. Participants will be asked to continue on study for at least four weeks after they discontinue study drugs or until resolution (return to baseline) or stabilization of any adverse events with the frequency of visits determined by the site investigator. All procedures will be done with the expectation that no further PK sampling will be done.

**Table 18. General Guidelines for Management of Participants in Cohort 2**

| | |
|---|---|
| **Grade 1** | Continue study drug and perform routine monitoring. |
| **Grade 2** | Continue study drug; monitor closely as per site investigator and work-up to exclude other causes. |
| **Grade 3** | Upon initial identification of a Grade 3 event, the CMC should be notified (within three business days) and non-study drug explanations for the event should be considered. The participant should be re-evaluated weekly until improvement to Grade 2 or lower or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.<br><br>If the initial Grade 3 event is a laboratory abnormality, the test should be repeated as soon as possible (within three business days of site's awareness). If the initial event is assessed as not related to study drug, study drug may be continued while awaiting the repeat test result; otherwise study drug should be held. If the repeat test does not yield a Grade 3 result, the event should be managed according to the grade of the repeat result.<br><br>For Grade 3 clinical events and confirmed a Grade 3 laboratory events:<br>• If the event is assessed as **not related** to study drug, study drug should be continued (or resumed if previously held).<br>• If the event is assessed as **related** to study drug, the CMC should be notified AND study drug should be held unless the site investigator feels that continuation of the study drug is in the participant's best interest. In this case, the decision whether to hold study drug should be made in consultation with the CMC.<br>If study drug is held, resumption may be considered in consultation with the CMC once the event has improved to Grade 2 or lower. If study drug is resumed and the Grade 3 event recurs (confirmed), study drug must be permanently discontinued. |
| **Grade 4** | Upon initial identification of a Grade 4 event, the CMC should be notified (within three business days of site awareness) AND study drug should be held unless the site investigator feels that continuation of the study drug is in the participant's best interest. In this case, the decision whether to hold study drug should be made in consultation with the CMC. Non-study drug explanations for the event should be considered. The participant should be re-evaluated weekly until improvement to Grade 2 or lower or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.<br><br>If the Grade 4 event is a laboratory abnormality, the test should be repeated as soon as possible (within 3 business days). If the repeat test does not yield a Grade 4 result, the event should be managed according to the grade of the repeat result.<br><br>For Grade 4 clinical events and confirmed Grade 4 laboratory events:<br>• If the event is assessed as **not related** to study drug, study drug may be resumed only with approval from the CMC.<br>• If the event is assessed as **related** to study drug, study drug must be permanently discontinued. |

## 8.3 Management of Liver Toxicities (Cohort 2)

Study drug will be held if any of the following liver chemistry criteria are confirmed:

- Grade 2 or higher AST or ALT AND Grade 2 or higher total bilirubin AND, at the same time, alkaline phosphatase less than Grade 2 (Hy's Law)
- Grade 4 ALT; if another cause of ALT elevation is identified, the participant may be re-challenged after receiving the approval of the CMC.
- Grade 2 or higher ALT with symptoms of hepatitis or hypersensitivity (e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash or eosinophilia). If another cause of ALT elevation is identified, the participant may be re-challenged after receiving the approval of the CMC.

If any of the above liver chemistry hold criteria are met, sites must:

- Repeat laboratory testing as soon as possible (within three business days of site awareness)
- Report the event to the CMC within 24 hours of site awareness

## 8.4 Management of Decline in Renal Function (Cohort 2)

Participants who experience an increase in serum creatinine to a grade 2 or above or from grade 2 (baseline) to grade 3 or above must return for a confirmatory creatinine assessment within two to four weeks. If the creatinine elevation is confirmed, the investigator should contact the CMC to discuss additional follow-up and medical management.

Participants who experience an increase in proteinuria or glycosuria to a grade 2 or above or from grade 2 (baseline) to grade 3 or above must return for a confirmatory urinalysis within two to four weeks. If the increased proteinuria or glycosuria is confirmed, the investigator should contact the CMC to discuss additional follow-up and medical management.

Participants who experience progression to a grade 3 or higher estimated GFR (calculated by the Schwartz formula; see Section 4.1.8) of <60 mL/min (1.73 $m^2$) must return for a confirmatory creatinine assessment within two to four weeks. If an estimated GFR of <60 mL/min (1.73 $m^2$) is confirmed, then DOR/3TC/TDF should be held and the investigator should contact the CMC to discuss the rationale for restarting study drugs (if appropriate).

Consideration for confounding factors (e.g., other medications; dehydration and concurrent conditions) should be taken into account, and a nephrology consult may be obtained.

## 8.5 Non-Study Drug Antiretroviral Drug-Related Toxicity

Toxicities resulting from components of a standard of care ART in Cohort 1 will be managed by the site investigator, according to best clinical practice; consultation with the CMC is available but not required.

## 8.6 Monitoring and Management of Virologic Failure (Cohort 2)

### *Monitoring*

HIV-1 RNA (viral load) will be monitored closely with frequent testing as specified in the Schedule of Evaluations, Appendix I-B. All HIV-1 RNA assays must be performed in a CLIA-certified (US) or VQA-approved (non-US) laboratory using the testing platform specified in the LPC. Site investigators should review the results of each test as well as trends over time and consult with the CMC regarding any individual test results or trends of concern. As noted in Section 6.10, viral load results should be provided to participants' parents or guardians (and/or participants, if applicable) and may be used to guide adherence counseling.

### *Definition of Virologic Failure*

Virologic failure is defined as two consecutive plasma HIV-1 RNA test results ≥200 copies/mL. For participants who were ART-naïve at enrollment, the consecutive results should be from specimens collected for the first test at or after Week 24, counted from the date of enrollment. For participants who were ART-experienced at enrollment, the consecutive results may be at any time after the date of enrollment.

### *Confirmation of Virologic Failure*

Any participant with a plasma HIV-1 RNA level ≥200 copies/mL either 1) at or after Week 24 (ART-naïve) or 2) at any time after the date of enrollment (ART-experienced) should be recalled to the clinic for confirmatory testing ideally within four weeks, and no more than six weeks, of the date of specimen collection for the initial test. As indicated in Section 6.4, other evaluations – including specimen collection and storage for future genotypic and phenotypic resistance testing – will also be performed at the time of specimen collection for confirmatory HIV-1 RNA testing.

The stored specimen collected for genotypic and phenotypic resistance testing should be stored for later testing (see the LPC).

Participant should ideally be contacted prior to the confirmatory virologic failure visit to assess and address any issues with adherence, access, intercurrent illness or other situation which might have impacted the virologic response.

### *Management of Confirmed Virologic Failure*

The CMC should be consulted regarding management of all participants with confirmed virologic failure (or if the confirmatory sample cannot be collected within six weeks of the date of specimen collection for the initial test).

Participants with confirmed virologic failure due to remediable causes (e.g., non-adherence, intercurrent illness, or other factors not associated with DOR/3TC/TDF) may potentially remain on the study drug.

If the HIV-1 RNA test result is not confirmed (i.e., is less than 200 copies/mL), the participant should remain on DOR/3TC/TDF. Enhanced adherence support or other interventions to address the virologic increase should be provided, as applicable.

## 8.7 Criteria for Premature Discontinuation of Study Drug

Administration of study drug will be permanently discontinued in the following circumstances:

- Pregnancy (see Section 8.8.2)
- The participant experiences an adverse event that requires discontinuation as defined in Sections 8.2-8.4.
- The site investigator determines that further administration of study drug would be detrimental to the participant's health or well-being.
- Virologic failure as described in Section 8.6.
- New data become available that indicate study drug should be discontinued as determined by the CMC.

**NOTE:** In the event of discontinuation of study drug, participants will be asked to continue on study for at least four weeks after they discontinue study drugs or until resolution (return to baseline) or stabilization of any adverse events with the frequency of visits determined by the site investigator.

## 8.8 Contraception, Pregnancy Testing, and Management of Participants Who Become Pregnant on Study

### 8.8.1 Contraception and Pregnancy Testing

At the Entry visit but prior to enrollment, all participants must meet the contraception and pregnancy testing requirements as described in Sections 4.1.9-4.1.11.

During study participation, all participants should be provided with contraception counseling, as applicable, and consistent with requirements in Sections 4.1.10-4.1.11. Sites should reinforce directions related to use of effective, medically accepted contraception methods and all female participants who are engaging in sexual activity that could lead to pregnancy should be counseled about NOT becoming pregnant while in the study. For participants engaging in sexual activity that could lead to pregnancy, self-reported confirmation of contraception use should be obtained at every visit. These discussions should be source documented in research records. If participants engaging in sexual activity that could lead to pregnancy report discontinuation of contraception use, the site should consult the CMC on further management.

Counseling should be provided per site SOPs, which should reflect WHO guidelines for HIV-infected men and women as well as local standards of care. Counseling should reflect the ARVs that participants are currently taking and the potential interactions between these ARVs and available contraceptive methods. Study sites should ideally integrate provision of contraceptive methods with other services offered to study participants and should provide referrals to non-study sources of methods that cannot be provided at the study site. All participants will be counseled about use of condoms. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV-1 transmission.

Pregnancy testing will be conducted among female participants who have reached menarche or who are engaging in sexual activity that could lead to pregnancy at follow-up visits consistent with the Schedule of Evaluations (Appendix I-A and Appendix I-B). For both cohorts, pregnancy testing is required at the Entry visit, prior to enrollment to confirm eligibility. For Cohort 2, additional testing is required at follow-up visits consistent with the Schedule of Evaluations (Appendix I-B).

### 8.8.2 Management of Participants Who Become Pregnant on Study

Any participant who becomes pregnant (intrauterine) while on study drug should have study drug permanently discontinued as soon as an alternative, locally-available treatment regimen can be started (i.e., there should be no break or lapse in HIV treatment). Participants should be transitioned to non-study care and treatment, with information, counseling, and/or referrals provided as needed.

Participants who become pregnant will be permanently discontinued from study drug and permanently discontinued from the study, per Section 8.7. Any pregnancy that occurs during study participation must be reported to the CMC immediately (within 24 hours of site awareness). Pregnancy test results will be disclosed to participants and their parent/guardians consistent with local standards of care; local standard procedures will be noted in site-specific informed consent and assent forms. In settings where disclosure to parents/guardians will be at the choice of the participant, participants will be counseled that — because pregnancy will result in discontinuation of study drug and study participation — proactive (rather than potential inadvertent) disclosure to parents/guardians may be advised.

Participants or parents/guardians will be contacted following study discontinuation to ascertain the pregnancy outcome (completion/termination of the pregnancy) and any ARV changes during the pregnancy. Pregnancy complications, including intrauterine fetal demise, spontaneous abortions, or therapeutic or otherwise medically indicated abortions should be reported to the CMC immediately (within 24 hours of site awareness) and reported as an EAE (see Section 7.3.2). Additional post-study contacts should be completed to ascertain pregnancy outcomes (see Section 6.6). Outcomes may be ascertained based on maternal report but medical records should be obtained whenever possible to supplement maternal reports.

Study sites are encouraged to prospectively register pregnant participants in the Antiretroviral Pregnancy Registry (APR) prior to pregnancy outcome by calling the following number in the US: +1-800-258-4263. Outside of the US, see the APR website (www.apregistry.com) for additional toll-free numbers.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 General Design Issues

IMPAACT 2014 is a Phase I/II study whose primary objectives are to evaluate the PK, safety, and tolerability of a single dose of doravirine (DOR, MK-1439) and once daily regimen of doravirine/lamivudine/tenofovir disoproxil fumarate (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, as described in Section 3.

A minimum of 12 PK evaluable in Cohort 1 and 40 evaluable participants in Cohort 2 will be accrued to the study. Participants in Cohort 1 will be considered evaluable if they received the prescribed dose and had PK samples collected and assayed per protocol (PK evaluability defined in Section 10.3.1); participants in Cohort 2 will be considered evaluable if they either, 1) completed 24 weeks of study on the study drug, OR 2) were classified as a safety or virologic failure, due to

incurring a study drug related adverse event or meeting virologic failure criteria during the first 24 weeks of treatment.

If a participant in Cohort 1 is deemed PK unevaluable, then the participant will be replaced and will be excluded from the PK analysis during the dose evaluation. If there is some uncertainty about the participant's exposure to the correct dose of the study drug, then that participant may also be excluded from the safety analysis, in addition to the PK analysis.

If a participant in Cohort 2 is deemed unevaluable, then the participant will be replaced and may be excluded from the PK and safety analyses. In addition, if Cohort 2 opens enrollment to ART-experienced participants (see Section 3.2), enrollment into Cohort 2 of participants who have completed their two-week follow-up in Cohort 1 may introduce a selection bias. In such cases, it may be necessary to perform sensitivity analyses on the final data to test whether the results of the final safety analysis are consistent with and without such participants' data. In addition, since participants in Cohort 2 will only be followed while on study drug and some of their missing viral load and CD4 values will be imputed using a conservative approach, sensitivity analyses will be performed to assess the effects of these data imputations on the final results.

## 9.2 Dose Evaluation Algorithm

### *Cohort 1*

The study will implement a dose-evaluation algorithm of the 100 mg DOR based on PK data around the single-dose and safety data through Week 2. Cohort 1 will enroll an initial group of 12 evaluable participants and their PK and safety data will be evaluated as follows:

- If these 12 participants meet the PK guidelines (see Section 10.3.1) and there are no safety concerns (see Section 9.6.2, *Participant Safety*), then the DOR dose for Cohort 2 will be established and Cohort 2 will begin to accrue, following an SMC review (see Section 9.6.2, *Dose Evaluation*).
- If the DOR dose does not achieve the PK targets in the lower weight group of 35 to ≤45 kg, the following will be done:
  - If DOR exposure is considered too high for all participants in this weight group, no participants ≤45 kg will be enrolled in Cohort 2.
  - If DOR exposure is considered too low for all participants in this weight group, the CMC will evaluate all PK and safety data and consider enrolling additional participants in this weight group to reach a final decision regarding the lower weight cut-off for enrollment into Cohort 2.
  - If only a subset of participants in the lower weight group achieve the PK targets, the CMC may consider enrolling additional participants to confirm the weight determined to yield appropriate exposure to the DOR dose. Accrual into Cohort 2 will then be limited to participants above this weight cut-off, provided there were no safety concerns for this group based on results from Cohort 1.
- If there is more variability than expected in the PK results such that a confident determination regarding achievement of the PK targets cannot be made, additional participants may be enrolled into Cohort 1 to clarify the PK results as needed. 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.

The goal is to enroll 12 participants at a 100 mg DOR dose in Cohort 1 who meet the PK guidelines and have no drug-related grade 3 or higher AEs, providing adequate data to establish the 100 mg DOR dose, with the appropriate lower weight threshold, for Cohort 2.

#### *Cohort 2*

This cohort will begin to enroll once the PK and safety of the 100 mg DOR dose have been established from Cohort 1, as described above, and once the SMC has reviewed all Cohort 1 data and approved enrollment into Cohort 2 (see Section 9.6.2, *Dose Evaluation*). Participants will receive DOR/3TC/TDF. The first 10 participants will have intensive PK sampling to evaluate the pharmacokinetics of 3TC and tenofovir. PK samples for DOR will also be collected in these first 10 participants at a subset of intensive time points. Sparse PK samples for DOR, 3TC, and tenofovir will be collected through Week 48 to further describe the DOR, 3TC, and tenofovir exposure achieved with DOR/3TC/TDF (see Section 6.3.8). Safety, virologic, and immunologic outcomes will be collected longitudinally and analyzed at Weeks 24, 48 and 96.

The goal is to enroll 40 participants in Cohort 2 to evaluate the PK, safety, virologic efficacy and immunologic response of DOR/3TC/TDF.

## 9.3 Endpoints and Outcome Measures

In the following sections, the words "Endpoint" and "Outcome" refer to dependent variables on which objectives will be evaluated. "Endpoint" refers to whether a specific criterion has been met, while "Outcome" refers to a continuous or categorical variable, which is relevant to protocol objectives, but does not reflect a specific criterion. Each of the four listed toxicity endpoints will be analyzed separately.

*Note: The numbering of the outcome measures in this section corresponds to the numbering of the objectives in* Section 2.

The primary outcome measures listed in Sections 9.3.1 and 9.3.2 as well as secondary outcome measures in Sections 9.3.3.1-9.3.3.3 through Week 24 will be addressed in the study's primary statistical analysis plan, which will define the content of the primary analysis report. This report will form the basis for the primary study publication and results reporting to ClinicalTrials.gov. A secondary analysis report will address the secondary outcomes measures listed in Sections 9.3.3.2-9.3.3.4 at Weeks 48 and 96 and will form the basis for secondary publication(s) and additional results reporting to ClinicalTrials.gov. Outcomes of interest for other objectives (intended for subsequent publications) are listed in Section 9.3.4.

| | |
|---|---|
| **9.3.1** | **Primary Endpoints and Outcome Measures for Cohort 1** |
| **9.3.1.1** | Pharmacokinetics<br>• Single-dose $AUC_{0-\infty}$, $C_{max}$, and $C_{24hr}$ of DOR |
| **9.3.1.2** | Safety and Tolerability through Week 2<br>• Safety Outcome: All adverse events, regardless of severity grade<br>• Toxicity Endpoints:<br>– Grade 3 or higher adverse events assessed as related to study drug<br>– Serious adverse events assessed as related to study drug<br>– Permanent discontinuation of study drug due to adverse events assessed as related to study drug<br>– Grade 5 adverse events (death) regardless of relationship to study drug |
| **9.3.2** | **Primary Endpoints and Outcome Measures for Cohort 2** |
| **9.3.2.1** | Safety and Tolerability through Week 24<br>• Safety Outcome: All adverse events, regardless of severity grade<br>• Toxicity Endpoints:<br>– Grade 3 or higher adverse events assessed as related to study drug<br>– Serious adverse events assessed as related to study drug<br>– Permanent discontinuation of study drug due to adverse events assessed as related to study drug<br>– Grade 5 adverse events (death) regardless of relationship to study drug |
| **9.3.3** | **Secondary Endpoints and Outcome Measures for Cohort 2** |
| **9.3.3.1** | Pharmacokinetics through Week 1<br>• $AUC_{0-24hr}$, $C_{max}$, and $C_{24hr}$ of DOR, 3TC, and tenofovir |
| **9.3.3.2** | Virologic Efficacy at Weeks 24, 48, and 96<br>• Plasma HIV-1 RNA<200 copies/mL<br>• Plasma HIV-1 RNA<50 copies/mL<br>• Plasma HIV-1 RNA<40 copies/mL<br>• Log10 drop from baseline in plasma HIV-1 RNA (ART-naïve participants) |
| **9.3.3.3** | Immunologic Response at Weeks 24, 48, and 96<br>• Change in CD4 count and percent from baseline |
| **9.3.3.4** | Safety and Tolerability through Weeks 48 and 96<br>• Safety Outcome: All adverse events, regardless of severity grade<br>• Toxicity Endpoints:<br>– Grade 3 or higher adverse events assessed as related to study drug<br>– Serious adverse events assessed as related to study drug<br>– Permanent discontinuation of study drug due to adverse events assessed as related to study drug<br>– Grade 5 adverse events (death) regardless of relationship to study drug |
| **9.3.4** | **Other Endpoints and Outcome Measures for Cohort 2** |
| **9.3.4.1** | Pharmacokinetics through Week 48<br>• Plasma concentrations of DOR, 3TC, and tenofovir |
| **9.3.4.2** | Genotypic and Phenotypic<br>• Genotypic and phenotypic measures of resistance at baseline and at virologic failure |
| **9.3.4.3** | Acceptability, Palatability, and Adherence through Week 96<br>• Acceptability, palatability, and adherence measures |

## 9.4 Randomization and Stratification

There will be no randomization and no stratification. Participants will be enrolled into Cohort 1 and Cohort 2 as described below.

## 9.5 Sample Size and Accrual

Sample sizes and the expected accrual timeframes for each cohort are described below. See Section 9.1 for definitions of evaluability.

### *Cohort 1*

At least 12 evaluable participants will be enrolled in Cohort 1 with a minimum of four participants between 35 kg and 45 kg. Depending on the PK results, additional participants may be enrolled.

Accrual into Cohort 1 is expected to be completed within 3-6 months after the first participant is enrolled. However, if additional participants are required based on PK results, additional time may be needed to fully meet the accrual and PK targets.

### *Cohort 2*

Up to 45 participants will be enrolled in Cohort 2 to achieve at least 40 evaluable participants. Based on the PK and safety evaluations in Cohort 1, if 35 kg is established as the lower weight threshold, a minimum of five participants between 35 kg and 45 kg will be enrolled.

Accrual into Cohort 2 will begin following confirmation of the DOR dose in Cohort 1. Accrual is expected to be completed within 6-12 months after the first participant is enrolled in Cohort 2. However, if additional participants are required (e.g., some participants considered unevaluable), additional time may be needed to fully meet the accrual targets.

## 9.6 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard procedures described in the IMPAACT Manual of Procedures. Included in these standard procedures is monthly review of participant accrual and retention by the IMPAACT Management Oversight Group. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. Sections 11 and 12 provide more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

### 9.6.1 Monitoring by the Protocol Team

#### *Study Progress and Quality of Study Conduct*

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and the quality of study conduct.

The team will closely monitor participant accrual and retention based on reports that will be generated at least monthly by the SDMC. The team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections. The team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and accrual performance following activation. For any site that is delayed in completing the study activation process, or that falls short of its accrual projections, the team will communicate with the site to identify the barriers the site has encountered and the operational strategies and action plans to address these.

The Protocol Team will monitor participant retention in a manner similar to participant accrual. On behalf of the Protocol Team, the CMC will monitor other key indicators of the quality of study conduct (e.g., adherence to study drug regimen, data quality, and data and specimen completeness) based on reports generated by the SDMC and will take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

#### *Participant Safety*

On behalf of the Protocol Team, the CMC will closely monitor participant safety through routine review of safety reports generated by the SDMC. These reports will provide tabulations of adverse events specified for entry into eCRFs, as described in Section 7.2. The CMC will review these reports via conference call or other meeting at least monthly. At the time of each review, the DAIDS Medical Officer will also review any EAEs (defined in Section 7.3) reported to the DAIDS Safety Office that are not yet reflected in the data reports. The CMC will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern.

The CMC will also monitor whether any of the safety-related triggers specified in Section 9.6.2 are met. If so, the CMC will rapidly review the triggering events and notify the SMC that an ad hoc review is required. The CMC will likewise request SMC review of any other safety concerns that may be identified throughout the course of the study.

#### *Dose Evaluation*

During the dose evaluation stages of this study (Cohort 1), the CMC will also review the pharmacokinetic data, with the aim of confirming the dose for Cohort 2 while protecting participant safety. The CMC will review PK and safety data reports at least monthly and take action as needed according to the guidelines in Section 10.3.1 (PK) and Section 9.6.1, *Participant Safety*, above.

Following any pause, participant accrual may be resumed if resumption is recommended by the CMC or SMC.

### 9.6.2 Monitoring by the SMC

An independent IMPAACT SMC will review this study regularly, following policies described in the IMPAACT Network Manual of Procedures.

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. Reviews will focus on participant accrual, retention, study conduct, and safety. An SMC review of safety and PK data will also take place prior to opening Cohort 2 for accrual. Additional SMC reviews focused on safety may also occur as indicated below (*Participant Safety* and *Dose Evaluation*). Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges identified during their reviews.

#### *Study Progress and Quality of Study Conduct*

The SMC will monitor study progress and the quality of study conduct through review of the same types of data reports as the Protocol Team and CMC.

#### *Participant Safety*

The SMC will monitor participant safety through review of the same types of safety data reports as the CMC. For ad hoc or triggered safety reviews, more limited data may be provided, focusing on the events that triggered the reviews.

Triggered SMC reviews will occur in the following scenarios:

(1) In the event of **any adverse event that is life-threatening or results in death**, the CMC will review the event as soon as possible (ideally within three business days of site awareness) and assess its relationship to study drug:
   - If either the site investigator or the CMC assesses the event as related to study drug, participant accrual will immediately be paused. An ad hoc SMC review will be convened as soon as possible to discuss how the study should proceed.
   - If the site investigator and the CMC assess the event as not related to study drug, participant accrual will continue. The SMC will be informed of any of these events along with the CMC's assessment and decision-making.

(2) In the event of any unresolvable disagreement within the CMC on an issue that would impact decision making or if the CMC encounters any other event or trend of concern, an SMC review of the relevant data will be convened. The CMC may choose to pause participant accrual and/or administration of study drug, pending the outcome of the SMC review.

(3) For Cohort 1, if more than 20% of participants experience grade 3 or higher AEs determined to be related to study drug, an ad hoc SMC review will be convened as soon as possible. The SMC will review all the relevant safety and pharmacokinetic data, along with the recommendations of the CMC, and will determine whether and under what conditions (1) further dose-evaluation activities for this cohort may proceed, and (2) Cohort 2 may open for accrual.

***Dose Evaluation***

The team and the SMC will review all PK and safety data from Cohort 1 to determine if Cohort 2 will open to accrual. 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.

***Enrollment of ART-Experienced, Virologically Suppressed Participants in Cohort 2***

As noted in Section 1.4.2, once the 24-week data are available from one of the adult switch studies, the data will be reviewed by the CMC and SMC prior to opening Cohort 2 for the ART-experienced, virologically suppressed participants. If the CMC and SMC agree to open Cohort 2 for ART-experienced, virologically suppressed participants, sites will be informed via a Clarification Memorandum when ART-experienced participants can be enrolled (see Section 4.1.5.3).

## 9.7 Analyses

The safety analysis will consist of descriptive statistics summarizing outcomes by cohorts. See pharmacology Section 10 for description of PK analyses.

### 9.7.1 Primary Safety Analyses (on data through Week 2 for Cohort 1 and Week 24 for Cohort 2)

The primary analyses will include all participants exposed to the 100 mg DOR dose and will be restricted to data through Week 2 for Cohort 1 and Week 24 for Cohort 2. For participants who discontinued the study drug prematurely, safety data will be restricted through four weeks after last dose date (see Section 4.6). These analyses will be performed after the last participant enrolled in Cohort 2 has reached Week 24. For regulatory submission purposes, all safety outcomes will be presented in the aggregate as well as broken down by cohort.

An overall summary of all AEs will be presented by cohort and, for Cohort 2, the summary will be broken down by population classification at entry (i.e., ART-naïve versus ARV-experienced). In addition, each participant's safety data will be summarized as: the worst grade of adverse event experienced through these time points and the worst grade of adverse event assessed as related to study drug. Frequency distributions of the safety outcomes, which will include (1) grade 3 or higher adverse events assessed as related to study drug, (2) serious adverse events assessed as related to study drug, (3) permanent discontinuation of study drug due to adverse events assessed as related to study drug, and (4) death due to adverse events regardless of relationship to study drug, will be presented by cohort and by population classification at entry (Cohort 2). The proportions (bounded by exact 95% confidence intervals) and the listings of the participants experiencing these safety outcomes will also be presented by cohort and by population classification at entry (Cohort 2).

The proportions of participants experiencing Grade 3 or higher adverse events, bounded by exact 95% confidence intervals, will be presented by cohort and population classification at entry (Cohort 2). Similar analyses will present the proportions of participants with Grade 3 or higher events assessed as related to study drug, again bounded by exact 95% confidence intervals. Table 19 presents the upper and lower limits of confidence intervals around potential results observed in the groups of n=12, n=15, and n=40, and the combined groups of n=52 and n=55.

**Table 19. Percent of Participants Experiencing ≥Grade 3 Adverse Events (or ≥Grade 3 Adverse Events Attributed to the Study Medication) with Exact 95% Confidence Intervals**

| N | n (%) With ≥Grade 3 Adverse Events | 95% CI |
|---|---|---|
| 12 | 0 (0%) | 0% - 26% |
| 15 | 0 (0%) | 0% - 22% |
| 40 | 0 (0%) | 0% - 9% |
| 52 | 0 (0%) | 0% - 7% |
| 55 | 0 (0%) | 0% - 6% |
| | | |
| 12 | 1 (8%) | 0% - 38% |
| 15 | 2 (13%) | 2% - 40% |
| 40 | 4 (10%) | 3% - 24% |
| 52 | 5 (10%) | 3% - 21% |
| 55 | 6 (11%) | 4% - 22% |
| | | |
| 12 | 4 (33%) | 10% - 65% |
| 15 | 5 (33%) | 12% - 62% |
| 40 | 12 (30%) | 17% - 47% |
| 52 | 15 (29%) | 17% - 43% |
| 55 | 16 (29%) | 18% - 43% |

### 9.7.2 Key Secondary Analyses for Cohort 2

All secondary analyses 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.

***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 in Section 9.7.1 above. In addition, any participant who discontinued the study due to a study drug related adverse event or virologic failure will be classified as a safety failure through Week 96. For participants who discontinued the study due to other reasons, sensitivity analyses will be performed to see whether the final results will change by classifying these participants as safety failures versus excluding them from the long-term safety analyses.

***Viral Load***

Virologic responses for Cohort 2, based on plasma HIV-1 RNA (copies/mL), will be assessed at Weeks 24, 48, and 96. Virologic failure will be defined for the analyses as HIV-1 RNA >200 copies/mL, >50 copies/mL, and >40 copies/mL, in three separate analyses at Weeks 24, 48, and 96. For analysis purposes, the log drop from baseline in plasma HIV-1 RNA will be calculated and summarized for ART-naïve participants at Weeks 24, 48, and 96. The Observed Failure Approach, which is a conservative approach to handle missing data, will be used: 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. 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 participant population (i.e., ART-naïve versus ART-experienced).

For regulatory submission purposes**,** at all 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. Participants will be classified as virologic failures if they have missing HIV-1 RNA data throughout the window surrounding the time point of interest. (This window will be defined in the analysis plan.) In addition, participants will be classified as virologic failures at any of these time points if they discontinue study drug prior to that time point. Participants who switched or changed from the study drug to another regimen prior to the time points of interest, except for those who substituted single agents for the FDC, will be classified as virologic failures. Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the participant is on-treatment within the visit of interest window.

#### *CD4*

Median and the associated interquartile range for changes in CD4 count and percent from baseline to Weeks 24, 48, and 96 will be presented, both in the aggregate and broken down by population classification 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.

#### *HIV Drug Resistance*

Participants who meet the criteria for protocol-defined virologic failure (see Section 8.6) will be evaluated for HIV-1 drug resistance to DOR and other components of the regimen. For these participants, changes in the HIV-1 genotype and phenotype from baseline to the point of virologic failure will be presented descriptively.

#### *Acceptability, Palatability, and Adherence*

Acceptability, palatability, and adherence measures reported by the participant will be summarized, both in the aggregate and broken down by population classification at entry (i.e., ART-naïve versus ARV-experienced).

# 10 PHARMACOLOGY PLAN

The design and analysis plans for objectives 2.1.1, 2.3.1, and 2.4.1 are described in this section.

## 10.1 Pharmacology Overview and Objectives

### *Cohort 1*

Cohort 1 will assess the single dose pharmacokinetics of a 100 mg dose of doravirine in 12 evaluable children and adolescents ≥35kg (with a minimum of four participants between 35 to ≤45 kg). The goal of Cohort 1 is to confirm the weight range for which a 100 mg once daily dose of DOR is appropriate. Preliminary modeling suggests that a 100 mg daily dose of doravirine should be safe and effective for children or adolescents who weigh 35 kg or more. The projected geometric mean steady state $AUC_{0\text{-}24hr}$ in children weighing 35 to ≤45 kg is 50 µM*hr (%CV: 50.7%) and for children weighing >45 kg is 35.4 µM*hr (%CV: 61.1%). Similarly, projected geometric mean steady state $C_{24hr}$ in children weighing 35 to ≤45 kg is 935 nM (%CV: 105%) and for children weighing >45 kg is 740 nM (%CV: 120%). Based on simulations of ten participants (four from the 35 to ≤45kg group and six from the >45 kg group) with these geometric mean exposures and $C_{24hr}$ and variability, the AUC criterion (i.e., geometric mean steady state $AUC_{0\text{-}24hr}$ does not exceed 64.5 µM*hr) and the $C_{24hr}$ criterion (i.e., at least 90% of participants achieving at least 78 nM) are achieved with high probability (>99%).

If Cohort 1 pharmacokinetic results confirm this initial model, then Cohort 2 will open to participants weighing ≥35 kg. If exposure is deemed too high (i.e., exceeds that observed in adults at a 200 mg daily dose) in children or adolescents weighing closer to 35 kg, then Cohort 2 will open with a 100 mg daily dose only in children and adolescents above the weight determined to yield appropriate exposure from the Cohort 1 results.

The primary pharmacokinetic objective for Cohort 1 is to evaluate the single-dose pharmacokinetics of DOR in children and adolescents receiving DOR along with a stable ART regimen including an integrase inhibitor plus two NRTIs, using intensive PK sampling at Entry.

### *Cohort 2*

Cohort 2 will assess the steady-state sparse pharmacokinetics of DOR, 3TC, and tenofovir once daily in 40 evaluable participants weighing ≥35 kg (or the weight determined in Cohort 1), using intensive PK sampling at Week 1 and sparse PK sampling through 48 weeks. In addition, Cohort 2 will evaluate the steady-state intensive pharmacokinetics of TFV and 3TC given as the FDC to the first 10 participants enrolled into Cohort 2 (see Section 1.4.3 for rationale). PK samples for DOR will also be obtained at a subset of the intensive sampling time points. Pharmacokinetic data and models generated through this study will inform further development of the DOR/3TC/TDF FDC for treatment of HIV in younger children in future studies and inform the pediatric sparse PK model for DOR.

## 10.2 Methods and Timing for Collections, Processing, Handling, and Storage

PK sample collection methods, processing, storage and shipping instructions are detailed in the LPC.

Pharmacokinetic sampling will occur as detailed in Section 6 and as summarized below:

***Intensive PK collections***

- Cohort 1, Entry: Intensive PK samples should be collected around the single dose of DOR administered in addition to the standard ARV regimen as described in Section 6.2.1.
- Cohort 2, Week 1: Intensive PK samples for 3TC and tenofovir should be collected around a dose at steady state as per Section 6.3.2. PK samples for DOR will also be collected in a subset of time points.

***Sparse PK collections***

- Cohort 2, Entry, Weeks 4, 8, 12, 24, and 48: Sparse PK samples for DOR, 3TC, and tenofovir should be collected at each required study visit, as per Section 6.3.8.

## 10.3 PK Guidelines for Dose Confirmation and Timing of Interim Analyses

### 10.3.1 PK Guidelines for Cohort 1 to Confirm the Dose for Cohort 2

For Cohort 1 participants, acceptable PK is defined as follows:

- Exposure that does not exceed that observed at the 200 mg QD doravirine dose in adult HIV-infected patients (currently estimated to be 64.5 µM*hr; the target value may be updated as additional doravirine PK data in adult patients become available). Since $AUC_{0-\infty}$ following a single dose is equivalent to steady state $AUC_{0-24hr}$, the $AUC_{0-\infty}$ values for Cohort 1 should be generally similar to the corresponding steady state $AUC_{0-24hr}$ values in adult HIV-infected patients. A geometric mean steady state $AUC_{0-\infty}$ that does not exceed the steady state $AUC_{0-24hr}$ associated with the 200 mg QD dose in adults will be targeted, but additional considerations based on the observed PK in Cohort 1 relative to the total distribution of exposures at 200 mg QD may also be taken into account.
- Steady state $C_{24hr}$ values for participants in Cohort 1 will be projected from the single dose PK profiles. At least 90% of Cohort 1 participants should have $C_{24hr}$ values that exceed the PK target for suppression of wild type virus, currently estimated as 78 nM (equivalent to over six times the $IC_{50}$ for DOR against wild type virus in the presence of 100% normal human serum).

Cohort 1 participants will be evaluable for PK guidelines if the AUC and $C_{24hr}$ values can be calculated or estimated with the data available. If these PK parameters cannot be estimated, then the participant will be unevaluable for PK guidelines. An unevaluable participant will be replaced. All PK data (from unevaluable and evaluable participants and visits) will be reported at the end of the study. Only evaluable participant PK data will be used in the PK guidelines assessment.

As described in Sections 9.3.1.1 and 10.5, $C_{max}$ will be evaluated among participants in Cohort 1; however, $C_{max}$ will not be used in the evaluation to confirm the dose for Cohort 2.

### 10.3.2 Timing of Interim Analyses

Cohort 1 DOR pharmacokinetics will be summarized once 12 participants have completed the pharmacokinetic visit to confirm the dose for Cohort 2. Samples from Cohort 1 participants should be shipped as soon as the 72-hour post-dose draw is completed and tested on an ongoing basis.

Cohort 2 DOR, 3TC and TFV pharmacokinetics will be summarized after the first 10 participants have completed the PK evaluation at Week 1. These assays may be performed in batch once these visits have been completed. Cohort 2 DOR, 3TC, and tenofovir sparse pharmacokinetics will be summarized at the end of the study.

Additional interim pharmacokinetic analyses may be performed at any time the CMC deems it necessary to assess the exposure to the current dose.

## 10.4 Laboratory Performing the Assays

The laboratories performing the doravirine, tenofovir, and lamivudine assays will be detailed in the LPC.

## 10.5 Primary and Secondary Data Analysis Plan

The primary pharmacokinetic outcome variables for Cohort 1 participants are $AUC_{0-\infty}$, $C_{24hr}$, and $C_{max}$ of DOR. Other standard pharmacokinetic parameter estimates will also be calculated ($T_{max}$, apparent terminal half-life, apparent clearance [CL/F], and apparent volume of distribution [$V_z$/F]).

The pharmacokinetic outcome variables for Cohort 2 (intensive or sparse sampling only) for DOR, TFV, and 3TC are $AUC_{0-24hr}$, $C_{max}$, and $C_{24hr}$. Other standard pharmacokinetic parameter estimates may also be calculated (e.g., $T_{max}$).

For all intensive, semi-intensive, or sparse PK evaluations (Cohort 1: DOR and Cohort 2: DOR, 3TC, and TFV), non-compartmental analyses will be conducted. $C_{max}$, $T_{max}$, and $C_{24hr}$ will be observed from the concentration versus time curve for each participant. $AUC_{0-\infty\ predicted}$ will be estimated by the linear up/log down trapezoidal rule up to the last measurable concentration plus $C_{last\text{-}predicted}/\lambda_z$. $AUC_{0-24hr}$ will be estimated by the linear up/log down trapezoidal rule up to the last measurable concentration. Apparent clearance will be calculated as dose divided by AUC. The apparent $V_z$/F will be determined as CL/F divided by $\lambda_z$, where $\lambda_z$ is the terminal slope of the log concentration versus time curve. The half-life ($t_{1/2}$) is calculated as $0.693/\lambda_z$. Sparse PK samples will be included in population PK analyses.

## 10.6 Anticipated Outcomes

The goal of this study is to gain an understanding of DOR and FDC component pharmacokinetics in children and adolescents, and to define the dose(s) that achieve the desired systemic exposure in this population.

# 11 DATA HANDLING AND RECORD KEEPING

## 11.1 Data Management Responsibilities

As described in Section 4.4, data on screening and enrollment in this study will be collected using the DMC SES.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled individuals, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the website referenced in Section 11.2).

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFs, with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data (including pharmacokinetic data) are transferred electronically to the DMC through the LDMS or through other secure mechanisms.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the Subject Enrollment System is available on the DMC portal at www.frontierscience.org.

## 11.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at:

https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

Study sites must comply with DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study drugs for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, Merck & Company, the FDA, site drug regulatory authorities, site IRBs/ECs, OHRP, and other applicable regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

### 11.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at:

https://www.niaid.nih.gov/sites/default/files/qmppolicy.pdf

## 12 CLINICAL SITE MONITORING

Site monitors under contract to NIAID or NICHD will visit study sites to inspect study facilities and review participant study records including consent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records, to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. The monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by the monitors.

## 13 HUMAN SUBJECTS PROTECTIONS

### 13.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific ICFs in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRB/EC any changes in the study and any unanticipated problems involving risks to participants or others.

All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 14.2).

### 13.2 Vulnerable Participants

The NIH is mandated by law to ensure that children be included in clinical research when appropriate (26). This study responds to that mandate and will provide clinical research data to inform doravirine and DOR/3TC/TDF safety and dosing in children and adolescents. Nonetheless, the children and adolescents who take part in this study are considered vulnerable

participants per the US Code of Federal Regulations, and site IRBs/ECs must consider the potential risks and benefits to child and adolescent participants as described in 45 CFR 46 Subpart D (for children).

With respect to 45 CFR 46 Subpart D, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 14.2, and the risk category assigned by the IRB/EC further determines the parental informed consent requirements for the study at each site.

The specifications of 45 CFR 46.404 and 45 CRF 46.405 are generally expected to apply to Cohort 1 and Cohort 2, respectively; therefore, the consent of one parent is expected to be obtained for this study. Nonetheless, each site's IRBs/ECs must document their risk determination and the consent requirements associated with the IRB/EC determination must be followed; study sites should adapt the signature pages of their site-specific ICFs as needed to reflect the IRB/EC determination. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs must document their risk determination, and study sites should adapt the signature pages of their site-specific ICFs as needed to accommodate the parental consent requirements associated with the IRB/EC determination. However, it is generally expected that the consent of one parent is sufficient for this study.

Study sites must comply with all IRB/EC requirements and the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at:

https://www.niaid.nih.gov/sites/default/files/enrollingchildrenrequirements.pdf

## 13.3 Informed Consent

As indicated in Section 4.1.3, site investigators and their designees will be required to determine participant age and ability to provide independent informed consent for study participation consistent with IRB/EC policies and procedures. Each site must establish SOPs, roles, and responsibilities for completing these determinations, and study staff involved in completing these determinations must have documented training in the relevant policies and procedures prior to study initiation.

Written informed consent and written assent will be obtained for study participation as follows:

- *If the potential participant is not of legal age to provide independent informed consent*: Parent or legal guardian must provide written informed consent. Written informed assent from the potential participant will be conducted per site IRB/EC policies and will generally be obtained if the participant is able to understand the nature, significance, and risks of the study.

  *Note:* Refer to Section 13.2 for considerations related to parental consenting requirements; IRB/EC risk determinations will guide whether the consent of one or both parents may be required for this study. All IRB/EC requirements must be followed.

- *If the potential participant is of legal age and able to provide independent informed consent as determined by site SOPs*: The potential participant must provide written informed consent for study participation.

Written informed consent and assent (as applicable) for participation will be obtained before any study-specific procedures are performed (see Appendix II and Appendix III). The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will describe what is known about the safety and tolerability of the study drugs and participants and parents/guardians will be extensively counseled on the importance of adherence to the ARV regimen. The informed assent process will include a similar process, with the amount of information and level of detail provided as part of assent processes will be tailored to the age of the potential participant, guided by IRB/EC policies and procedures; the sample informed consent forms (Appendix II and Appendix III) can be modified to meet the requirements for assent.

As part of the informed consent and assent process, consenters will be asked whether they agree to storage and future research testing of biological specimens remaining after all protocol-specified testing has been performed (see Appendix IV). This storage and future use is optional and may be declined with no impact on other aspects of study participation. Likewise, genetic testing of residual specimens is optional and may be declined. As with the main study sample informed consent forms, the sample informed consent form for storage and future research testing (Appendix IV) can be modified to meet the requirements for assent.

If the participant, parent, or guardian (as applicable) is unable to read, the process for consenting illiterate participants, as defined or approved by the local IRB/EC, should be followed. Sites must also establish and maintain written procedures describing standards for obtaining informed assent, reflective of applicable IRB/EC guidance.

As indicated above, it is generally expected that only one parent or guardian will provide informed consent for the child's or adolescent's participation in the study. However, parental consenting requirements at each site will depend on the IRB/EC risk determination described in Section 13.2; all IRB/EC requirements will be followed. Participants will enroll in the study as minors and will generally require consent from a parent or guardian.

Should the consenting parent (or guardian) of a participant die or no longer be available for any reason, sites should follow the guidelines and procedures as described by their IRBs/ECs. In general, if participants are doing well on the study drug, it is expected that they will stay on study drug and will have safety assessments performed per the local standard of care while continued study participation is being determined. Study sites may continue to provide care for the participant as needed and appropriate (outside of the study), consistent with local standard of care. If a guardian cannot be identified, or if the guardian does not consent to continued study participation, the participant must be withdrawn from the study. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 13.2), all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled child or adolescent, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

The sample informed consent forms provided in Appendix II, Appendix III, and Appendix IV include signature pages to accommodate potential participants to provide both assent with parental/guardian consent (as would be expected for most participants) and consent (as would be expected for participants considered of legal age, such as emancipated minors). In the scenario of assent with parental consent, the participant would be expected to complete the participant's signature block on the form and the parent or guardian would be expected to complete the participant's parent/guardian signature block on the form. As such, the sample forms may be used for both assent and consent, with the appropriate signatures entered on the appropriate pages. Study sites are also permitted to develop separate assent and consent forms for this study, if required by site or IRB/EC policies and procedures; for example, sites may develop one assent form for children 12 to 15 years of age at lower reading and comprehension levels than another assent form for children 16 to less than 18 years of age.

Each participant is expected to take part in the informed consent process with his or her parent or legal guardian and, in general, both the assent of the participant and the consent of the parent or legal guardian will be required for all consent decisions. For example, if the participant does not provide assent, or the parent or legal guardian does not provide consent, the participant will not be enrolled in the study. The same approach will be taken for consent for storage and future research testing of biological specimens. Participants may also reach the legal age of consent during follow-up. In this case, written informed consent for continued participation (Appendix II and Appendix III) and specimen storage and future use (Appendix IV) will be obtained from participants once they reach legal age at their next study visit. If participants do not consent for continued study participation, they should be discontinued from the study; similarly, if they do not consent for specimen storage and future use, all specimens will be destroyed after all protocol-related testing is complete.

Refer to Section 4.4 for further information on informed consent procedures for this study.

## 13.4 Potential Benefits

There may be no direct benefit to participants who take part in this study. However, information learned in this study may be of benefit to participants and others in the future, particularly information that may lead to more treatment options for HIV-infected children and adolescents. Participants may also appreciate the opportunity for themselves to contribute to HIV-related research.

## 13.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures and risks associated with receipt of DOR and DOR/3TC/TDF.

Most study procedures are routine medical procedures that are associated with minimal to no risk in participants. Blood collection may cause pain, bruising, swelling, or fainting. There is a very small chance of infection where the needle is inserted.

Refer to Section 1.2.3 and the Investigator's Brochures for the study drugs for a complete description of the potential risks associated with the use of these drugs.

For virologically suppressed, ART-experienced participants enrolling into Cohort 2, there is the potential risk that the study drugs may not be as effective in maintaining viral suppression as participants' current regimen.

Refer to Section 13.7 for further information on privacy and confidentiality. Despite all efforts to maintain confidentiality, involvement in the study could become known to others, possibly leading to unfair treatment, discrimination, or other social impacts (e.g., because participants could become known as having HIV). For example, participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities.

## 13.6 Reimbursement/Compensation

Pending IRB/EC approval, participants will be reimbursed for costs associated with completing study visits (e.g., transport costs). Reimbursement amounts will be specified in site-specific ICFs or other materials if applicable per IRC/EC policies and procedures.

## 13.7 Privacy and Confidentiality

All study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Section 11.2.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms) will be identified by PID only. Likewise, communications between study staff and protocol team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

In addition to the above, a Certificate of Confidentiality has been obtained for this study from the US Department of Health and Human Services. This certificate protects study staff from being compelled to disclose study-related information by any US federal, state, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants. Because the certificate cannot be enforced outside of the US, however, it applies only to US sites and participants.

## 13.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including, HIV infection identified among study participants to health authorities. Participants will be made aware of all applicable reporting requirements as part of the study informed consent process.

### 13.9 Management of Incidental Findings

Site investigators will inform parents or guardians (or participants, if applicable) of all clinically meaningful physical exam findings and laboratory test results. PK test results in this study will not be routinely provided. When applicable, site investigators will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

### 13.10 Management of New Information Pertinent to Study Participation

Study staff will provide parents or guardians (or participants, if applicable) with any new information learned over the course of the study that may affect willingness to continue receiving study drug and/or remain in follow-up in the study.

### 13.11 Post-Study Access to Study Drug

Participants will be transitioned into care and treatment outside of the study at the end of their study participation as per local standards. If DOR/3TC/TDF is not locally available for a participant in Cohort 2 completing the study, then the pharmaceutical company or their partners will make every effort to provide DOR/3TC/TDF following the participant's completion of the study through a mechanism outside of the protocol, until one or more of the following events occur:

- DOR/3TC/TDF is available from another source (e.g., government programs, aid programs, assistance programs, etc.) to all participants in each specific country; OR
- Until participants are no longer deriving benefit; OR
- If development of DOR/3TC/TDF is terminated, if this occurs.

However, because in-country provision is not only dependent on the pharmaceutical company's willingness to provide DOR/3TC/TDF, but also on the country's importation requirements and other approvals and processes, the consent form acknowledges the possibility that DOR/3TC/TDF may not be available post-study, despite the company's efforts.

## 14 ADMINISTRATIVE PROCEDURES

### 14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). Merck & Company will provide study drugs for this study but is not involved in sponsorship or regulatory oversight of the study.

Within NIAID, DAIDS is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study drugs prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with independent clinical site monitors who will perform monitoring visits as described in Section 12. As part of these visits, monitors will inspect study-

related documentation to ensure compliance with all applicable US and local regulatory requirements.

## 14.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by their local IRBs/ECs and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICFs will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICFs will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available on the RSC website:

http://rsc.tech-res.com/clinical-research-sites/protocol-registration

## 14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US and local regulations. Study implementation will also be guided by the IMPAACT Manual of Procedures (MOP), LPC, and other study implementation materials, which will be available on the IMPAACT website: www.impaactnetwork.org.

Study implementation at each site will also be guided site-specific SOPs. The DAIDS policy on Requirements for Manual of Operational Procedures specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 11.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

### 14.4 Protocol Deviation Reporting

Per the policy for *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* (available at the website referenced in Section 11.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT MOP.

### 14.5 Critical Event Reporting

Per the DAIDS policy on *Identification and Classification of Critical Events*, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, which is available at:

https://www.niaid.nih.gov/sites/default/files/criticaleventsmanual.pdf

### 14.6 ClinicalTrials.gov

This protocol is not subject to the Food and Drug Administration Amendments Act of 2007 (FDAAA). However, it will be registered in ClinicalTrials.gov to meet International Committee of Medical Journal Editors requirements.

## 15 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Manual of Procedures.

# 16 REFERENCES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## Appendix I-A: Schedule of Evaluations for Cohort 1

| *Study Visit* | Screen | Entry | Week 2 |
|---|---|---|---|
| *Visit Window* | | Day 0 | ±2 days |
| **CLINICAL EVALUATIONS** | | | |
| Informed consent | X | | |
| Medical history | X | X | X |
| Complete physical exam | X | X | |
| Symptom-directed physical exam | | | X |
| Study drug administration | | X | |
| Palatability and acceptability assessment | | X | |
| **LABORATORY EVALUATIONS** | | | |
| Confirmatory HIV testing [if needed] | [0 – 6mL] | | |
| Pregnancy test[1] | | X | |
| CBC with differential and platelets | 1 mL | 1 mL | 1 mL |
| Chemistries | 3 mL | 3 mL | 3 mL |
| HIV-1 RNA | 6 mL | 6 mL | |
| CD4 cell count | | 2 mL | |
| Intensive PK sampling[2] | | 9 mL | |
| **Total maximum blood volume** | 16 mL | 22 mL | 4 mL |

[1]At entry, all females who have reached menarche or who are engaging in sexual activity that could lead to pregnancy must have a pregnancy test, with results available prior to enrollment. Urine (5 mL) or blood (1 mL) tests are acceptable. The total blood volume shown above accommodates collection of 1 mL of blood, if needed.

[2]Intensive PK sampling will be done as indicated in Section 6.2.1 from entry through 72 hours post-dose. The blood volume per sample is 1 mL.

## Appendix I-B: Schedule of Evaluations for Cohort 2

| *Study Visit* | Screen | Entry | Weeks on Study | | | | | | | | | | Confirmation of Virologic Failure | Early D/C |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1[1] | 2 | 4 | 8 | 12 | 16 | 24[2] | 36[2] | 48[2] | Q16[3] | | |
| *Visit Window* | | Day 0 | 8-13 d | ±1 wk | -1 wk-+2 wk | ±2 wk | ±2 wk | ±2 wk | ±2 wk | ±2 wk | ±2 wk | ±4 wk | | |
| **CLINICAL EVALUTIONS** | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | |
| Medical history | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete physical exam | X | X | | | | | | | | | X | Wk 96 | X | X |
| Symptom-directed physical exam | | | X | X | X | X | X | X | X | X | | Wks 64 & 80 | | |
| Adherence assessment | | | | | X | X | X | X | X | X | X | X | X | X |
| WHO staging | X | | | | | | | | | | | | | |
| Palatability and acceptability assessment | | | | X | | | | | | | | | | |
| **LABORATORY EVALUATIONS** | | | | | | | | | | | | | | |
| Confirmatory HIV testing [if needed] | [0-6 mL] | | | | | | | | | | | | | |
| CBC with differential and platelets | 1 mL | 1 mL | | 1 mL | 1 mL | 1 mL | 1 mL | 1 mL | 1 mL | 1 mL | 1 mL | 1 mL | | 1 mL |
| Chemistries | 3 mL | 3 mL | | 3 mL | 3 mL | 3 mL | 3 mL | 3 mL | 3 mL | 3 mL | 3 mL | 3 mL | | 3 mL |
| Lipid profiles | | 2 mL | | | | | 2 mL | | 2 mL | | 2 mL | 2 mL (Wk 96 only) | | |
| Urinalysis | X | | | X | | | X | | X | | X | Wks 64 & 96 | | |
| Hepatitis B and C | 4 mL | | | | | | | | | | | | | |
| Pregnancy test[4] | | X | | | X | X | X | X | X | X | X | X | X | X |
| HIV-1 RNA | 6 mL | 6 mL | | 6 mL | 6 mL | 6 mL | 6 mL | 6 mL | 6 mL | 6 mL | 6 mL | 6 mL | 6 mL | 6 mL |
| CD4 cell counts | | 2 mL | | | 2 mL | | 2 mL | | 2 mL | | 2 mL | | | 2 mL |
| Genotypic resistance test[5] | 2 mL[5] | | | | | | | | | | | | | |
| Store for resistance testing | | 4 mL[5] | | | | | | | | | | | 6 mL[6] | 6 mL[6] |
| ***Pharmacology*** | | | | | | | | | | | | | | |
| Intensive PK sampling[1] | | | 22.5 mL | | | | | | | | | | | |
| Sparse PK sampling[7] | | 3.5 mL | | | 3.5 mL | 3.5 mL | 3.5 mL | | 7 mL | | 7 mL | | | |
| **Total maximum blood volume** | 22 mL | 22.5 mL | 22.5 mL | 10 mL | 16.5 mL | 14.5 mL | 18.5 mL | 11 mL | 22 mL | 11 mL | 22 mL | 13 mL | 13 mL | 19 mL |

Appendix I-B Footnotes:

[1]Only for the first 10 participants enrolled, intensive PK sampling will be done as indicated in Section 6.3.2. Samples should be collected per Table 15 and as below:

- 3.5 mL should be collected at pre-dose, 2 hours post-dose, 4 hours post-dose, 12 hours post-dose, and 24 hours post-dose
- 2.5 mL should be collected at 1 hour post-dose and 8 hours post-dose

[2]The target visit window for Weeks 24, 36, and 48 is ± 2 weeks; however, the allowable visit window is ± 4 weeks.

[3]Refer to Section 6.3.7. After Week 48, participants will complete scheduled follow-up visits every 16 weeks (Q16) through Week 96. The target visit window for Q16 visits is ± 4 weeks; however, the allowable visit window is ± 8 weeks. Refer to Section 6.6 for potential post-study contacts after Week 96.

[4]At entry, all females who have reached menarche or who are engaging in sexual activity that could lead to pregnancy must have a pregnancy test, with results available prior to enrollment. During follow-up, all females who have reached menarche or who are engaging in sexual activity must have pregnancy testing performed. Pregnancy testing may also be performed if pregnancy is suspected. Urine (5 mL) or blood (1 mL) tests are acceptable. The total blood volume shown in the relevant columns above accommodates collection of 1 mL of blood, if needed.

[5]For ART-naïve participants only: a sample for genotypic resistance testing should be collected at Screening and tested prior to Entry; a sample for phenotypic resistance testing should be collected and stored at Entry.

[6]Specimens should be collected and stored for future genotypic and phenotypic resistance testing at the Confirmation of Virologic Failure Visit and the Early D/C Visit from all participants.

[7]Sparse PK sampling will be done as indicated in Section 6.3.8.

# Appendix II: Sample Informed Consent Form for Participation in Cohort 1

**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**

**Version 1.0, 7 September 2017**

***Introduction***

[You are/Your child is] being asked to take part in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide that [you/your child] will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

***About the study***

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]* are doing this study to test an anti-HIV medicine (ARV) called doravirine (DOR) for children who have HIV. HIV is the virus that causes AIDS.

The study will include up to 65 children and adolescents 12 years to less than 18 years of age who have HIV. The study will include children and adolescents from the United States, Thailand, and South Africa. There will be two groups of children in this study. [You/Your child] will be in a group of up to 20 children. Children and adolescents in this group will be in the study for about 2 weeks.

The person in charge of this study at this site is *[insert name of Principal Investigator]*. A company called Merck is providing the ARV, doravirine (DOR). The United States National Institutes of Health are sponsoring this study.

**1. The study is being done to test DOR in children and adolescents.**

Children and adolescents with HIV usually take a combination of three or more ARVs to stay healthy. There are not as many ARVs available for children and adolescents as for adults because many ARVs have not yet been tested in children.

DOR is a new ARV that is being tested in adults in the United States and other countries. DOR is not currently approved in the United States or Europe. DOR, either alone or in combination with other ARVs, has been studied closely in more than 700 adults. DOR has been shown to be safe and effective compared with other approved ARVs, like efavirenz and darunavir. This is the first study of DOR in children.

The two groups of the study are called Cohort 1 and Cohort 2. Cohort 1 will be done first. This part will include up to 20 children and adolescents. Cohort 2 will be done after Cohort 1 is completed. Cohort 2

will include up to 45 children and adolescents. We will tell you about Cohort 1 first. This is a consent form for Cohort 1.

In Cohort 1, DOR will be given at one time. [You/Your child] will continue to take [your/his or her] regular ARVs.

The study will look at whether DOR is safe or causes any bad side effects when given to children and adolescents who have HIV. The study will also look at the amount of DOR in blood. This is called an intensive pharmacokinetic (PK) evaluation. More information on this evaluation is in #8 below.

If the results from Cohort 1 show that DOR is safe and that the amount of DOR in the blood is correct, Cohort 2 will start. In Cohort 2, children and adolescents will take DOR once per day with other ARVs for about two years. We will look at whether this combination of ARVs is safe when given to children and adolescents. The study will also look at how the combination of ARVs control the virus for children and adolescents. For ARVs to be considered effective, they must be able to control the amount of HIV so that HIV cannot be found in the blood.

**2. We will give [you/your child] DOR as a tablet.**

There are different ways to take ARVs, for example, as tablets that are swallowed or chewed or as liquids. We will give [you/your child] DOR as a tablet. The tablet needs to be swallowed whole – it cannot be broken or crushed.

**3. It is your decision whether or not [you join/your child joins] the study.**

Deciding to join the study is voluntary. You may choose [to allow your child] to join or not join. If you choose [to allow your child] to join, you can change your mind and [stop the study/take your child out of the study] at any time. Your choices will have no effect on your [child's] medical care at this clinic. Access to services and the benefits and rights [you normally have/your child normally has] will not be affected.

We will tell you about new information from this or other studies that may affect your [child's] health, welfare, or willingness to stay in this study. If you want the results from this study, tell the study staff.

Take your time and consider your decision carefully. If you wish, you can talk to other people about [joining/allowing your child to join] the study. You can bring other people to the clinic with you to learn about the study.

***No matter what you decide about the study, it is important to receive care and treatment for HIV infection. [You/Your child] should continue taking the regular ARVs as usual.***

***Finding out if [you qualify/your child qualifies]***

**4. We will ask questions and discuss the study requirements with you.**

If you decide to [join/let your child join] the study, we will first do some tests to see if [you qualify/your child qualifies]. To find out, we will:

- Review medical records. We may also ask you questions about your [child's] health
- Ask about ARV use
- Talk with you about the study requirements and if [you are/your child is] able to meet these requirements
- Give a physical exam
- Draw blood for tests. We will take up to about 16 mL (about 3 teaspoons) of blood. These tests will look at your [child's] blood cells and how well the liver and kidneys are working. The tests will also:
  - Confirm that you [your] child has HIV. There are certain HIV tests that are required for this study. If the required tests are not in the medical records, we will do the tests that are needed.
  - Check the amount of HIV in the blood. This is called viral load.

These procedures will take about two hours *[here and throughout this form, sites may modify the expected visit duration as needed]*.

**5. For females, we may also do a test to check for pregnancy.**

If [you have/your daughter has] had her period or [you are/your daughter is] sexually active, we will collect urine or blood to test for pregnancy to see if [you/she] qualifies for the study at the Entry visit (see #7 below). The pregnancy test must show that [you/she] is not pregnant in order to qualify for the study.

*[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians:* We will talk over the test result as soon as it is available with [you/your child] in private without parents/guardians present. [You/Your child] must give us permission before we can share these results with parents/guardians. If the test shows that [you are/she is] pregnant, we will give [you/your child] information on where medical care and other services can be received.*]*

If [you/she] enter the study, [you/she] will be required to use two forms of birth control while in the study and for two weeks after stopping DOR. We will talk to [you/your child] about how to prevent pregnancy.

**6. We will tell you if [you/your child] qualifies.**

We will give you the results of all procedures and explain the results to you.

If these procedures show that [you do/your child does] <u>not</u> qualify for the study, we will tell you this and [you/your child] <u>will not</u> be entered into the study. We will give you information on where medical care and other needed services may be received.

If these procedures show that [you <u>do</u>/your child <u>does</u>] qualify for the study, [you/your child] <u>will</u> be entered into the study.

***Being in the study***

**7. If [you qualify/your child qualifies], [you/he or she] will have two additional study visits.**

[You/Your child] will have two visits about two weeks apart. At these visits, we will:

- Review medical records
- Ask about ARVs
- Ask how you/your child is feeling
- Do a physical exam. At the first visit, this exam will include examination of your [child's] genitals to see the stage of development.
- Draw blood for tests. We will take up to 12 mL of blood (about 2 ½ teaspoons) for these tests. These tests will check:
  - Blood cells
  - How well the liver and kidneys are working
  - At the first visit, how much HIV is in the blood
  - How many CD4 cells are in the blood. CD4 cells are cells that fight infections
- For females, we will also collect urine or blood to check for pregnancy at the first visit (see #5 above).

**8. At the first visit, we will give DOR to [you/your child]. We will also look very closely at the amount of DOR in your [child's] blood.**

This is called an intensive pharmacokinetic (PK) evaluation. This is to see how much of the medication is in the blood and how long it stays.

On the first day of this visit, we will give [you/your child] DOR while at the study clinic. This is so that we can note the time [you/your child] took DOR. We will ask [you/your child] how it felt to take the tablet (for example, how the tablet tasted or how easy or difficult it was to swallow the tablet). The procedures for this visit will happen over about 72 hours (about 3 days).

*[Sites may modify this paragraph to appropriately describe how the intensive PK evaluation will be conducted, including procedures for overnight stays:* In the first 24 hours after [you/your child] takes DOR, we will draw about 1 mL (about ¼ teaspoon) of blood at seven different times. We will draw about 1 mL after about two days and again after about three days. We will draw about 9 mL total (about 2 teaspoons). We will look at the amount of DOR in the blood at each of these times. We will help you remember this before and during the visit. [You/Your child] may be able to stay at the clinic or hospital during this visit*.]*

*[Sites: modify language as appropriate to indicate procedures for the intensive PK collection.* A small plastic tube (like a "drip") will be placed in your [child's] arm to draw blood samples. This tube is attached to a plastic needle so that we can draw blood several times. We will not need to stick [you/your child] with a needle each time. The plastic tube may stay in place for the blood draws in the first 24 hours.]

**9. The tests for the amount of DOR in your [child's] blood will be done at different laboratories.**

We will do most of the tests of blood or urine here at our laboratory. We will give you the results of most of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals as needed.

We will also draw blood to check the amount of DOR in your [child's] blood. The test will be done at laboratories in the United States or other countries. We will not give you the results of this test during the study.

All of the tests will be done while the study is ongoing.

**10. We may take [you/your child] off of the study.**

We may take [you/your child] off the study early if:
- The study is stopped for any reason.
- We determine that the study requirements cannot be met (for example, if [you/your child] cannot come to the clinic).
- We determine that staying in the study might cause harm.

**11. Please tell us if you want [your child] to leave the study.**

[You are/Your child is] free to leave the study at any time for any reason. The care at this clinic will not be affected, but it is important for us to know about your decision. We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

***Risks of the study***

**12. There is little risk from the study procedures.**

Most procedures done in this study are routine medical procedures, with little risk to [you/your child]. Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

**13. There are some risks of DOR.**

DOR may have side effects and some of the most common or most serious effects are listed below. There may also be unknown side effects because this is the first time DOR will be studied in children. The lists do not include all the possible side effects. If you have questions about side effects not included in these lists, you can ask us.

Some side effects are minor and some can be severe. Some are common and some are rare. Some people who take DOR have some of these effects. Some people have different side effects.

If [you join/your child joins] the study, we will tell you about the side effects of DOR. We will also check for any side effects during the visits and tell you what to do if [you have/your child has] any side effects.

**14. We will tell you about the most severe side effects first.**

First, you should know about the possible severe side effects that can be caused by DOR. These effects are rare, but they can cause serious health problems and can result in death:

- Liver problems. The liver is an organ near the stomach. If there are liver problems, [you/your child] might have yellowing of the skin or whites of the eyes; dark or tea-colored urine; pale colored stools; upset stomach or vomiting; loss of appetite; pain, aching or tenderness of the right side below the ribs; or itchy skin. This effect was seen in one adult who took DOR.

**15. There are also more common and not severe side effects from DOR.**

You should also know about the more common side effects. They were reported in two or more of 100 healthy adults who took DOR. These side effects are not severe. There are many possible mild and moderate side effects. The most common ones are listed below:

| | |
|---|---|
| **Overall Body Effects**<br>• Overall weakness<br>• Headache<br>• Back pain<br>• Stuff, runny or uncomfortable nose<br>• Fever | **Effects on the Stomach**<br>• Pain or upset stomach<br>• Loose or watery stools<br>• Vomiting |
| **Effects on Muscle and Bones**<br>• Aches and pains | **Effects on Activity**<br>• Drowsiness and tiredness<br>• Dizziness |

**16. There is a possible effect on pregnancy or unborn babies.**

HIV and ARVs may lead to some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some ARVs are more likely to cause these effects than others. We do not yet know if DOR is safe in pregnancy. There were no pregnancy complications seen when DOR was given in animals.

**17. There could be risks of disclosure of your [child's] information.**

We will make every effort to keep your [child's] information private and confidential. Study records and specimens will be kept in secure locations. All specimens and most records will be labeled only with a code number. However, your [and your child's] name[s] will be written on some records.

Despite our best efforts to keep your [child's] information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, [you/your child] could be treated badly or unfairly. You could feel stress or embarrassment.

*[To be included at US sites:* To help us protect your [child's] privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify [you/your child], such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify [you/your child]. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your [child's] participation in the study to others, if you wish.*]*

***Benefits of the study***

**18. There may be no benefit to [you/your child] from being in the study.**

By joining the study, [you/your child] will be part of the search for ARVs that may be better for children. We do not expect that being in the study will benefit [you/your child] in any way.

[You/Your child] will have health checks, including tests for amount of HIV in your [child's] blood, called viral load, and for the amount of cells that fight HIV, called CD4. Information learned from this study may help other children with HIV.

***Other information about the study***

**19. There are no costs from being in the study.**

There are no costs to you for study visits, DOR, or procedures.

*[Insert information about compensation/reimbursement here, e.g.,* You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).*]*

**20. Study records may be reviewed by study staff and groups that oversee the study.**

Groups that oversee the study include:
- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site regulatory entities]*
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- The IMPAACT Network that is coordinating the study
- Merck Ltd. (the company that makes DOR)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your [child's] name or identify [you/your child] personally.

A description of this study will be available on ClinicalTrials.gov. This website will not include information that can identify you or your child. At most, the website will include a summary of the results. You can search this website at any time.

Your [child's] study information may be disclosed to other authorities if required by law.

**21. If [you get/your child gets] sick or injured, contact us immediately.**

Your [child's] health is important to us. We will make every effort to protect your [child's] well-being and minimize risks. It is possible, however, that [you/your child] could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

*[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.]* If a study-related illness or injury occurs, we will treat [you/your child] or tell you were you can get treatment. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through *[site name or]* the U.S. National Institutes of Health.

***Whom to contact***

**22. If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about the study:
  *[insert name and telephone number of investigator or other study staff]*

- If you have questions about your [child's] rights as research participants or concerns about how [you are/your child is] being treated in the study:
  *[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]*

- If [you have/your child has] any health or other problems that may be related to study participation:
  *[insert name and telephone number of investigator or other study staff]*

- If you want [your child] to leave the study:
  *[insert name and telephone number of investigator or other study staff]*

***Signatures***

**If you agree to [let your child] participate in this study, please sign or make your mark below.**

Before deciding whether to [let your child] participate in this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you [and your child] if you decide [to allow your child] to join.

If you decide [to allow your child] to join, we will tell you any new information from this study or other studies that may affect your willingness [for your child] to stay in the study. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

*[Insert signature blocks as required by site IRB/EC policies.]*

**Signature blocks for participants <u>below</u> legal age to provide independent informed consent**

***Participant Assent***

| | |
|---|---|
| _____ | _____ |
| Participant's Name (print) | Participant's Signature and Date |

***Parent/Legal Guardian Consent***

| | |
|---|---|
| _____ | _____ |
| Parent/Guardian Name (print) | Parent/Guardian Signature and Date |
| _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature and Date |
| _____ | _____ |
| Witness's Name (print) (As appropriate) | Witness's Signature and Date |

**Signature blocks for participants of legal age to provide independent informed consent**

| | |
|---|---|
| _____ | _____ |
| Participant's Name (print) | Participant's Signature and Date |
| _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature and Date |
| _____ | _____ |
| Witness's Name (print) (As appropriate) | Witness's Signature and Date |

# Appendix III: Sample Informed Consent Form for Participation in Cohort 2

**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**

**Version 1.0, 7 September 2017**

***Introduction***

[You are/Your child is] being asked to take part in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide that [you/your child] will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

***About the study***

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]* are doing this study to test an anti-HIV medicine (ARV) called doravirine (DOR) for children who have HIV. HIV is the virus that causes AIDS.

The study will include up to 65 children and adolescents 12 years to less than 18 years of age who have HIV. The study will include children and adolescents from the United States, Thailand, and South Africa. There will be two groups of children in this study. Your child will be in a group of up to 45 children. Children and adolescents in this group will be in the study for about 2 years.

The person in charge of this study at this site is *[insert name of Principal Investigator]*. A company called Merck is providing the ARVs, including DOR. The United States National Institutes of Health are sponsoring this study.

**1. The study is being done to test DOR as part of a combination medicine in children and adolescents.**

Children and adolescents with HIV usually take a combination of three or more ARVs to stay healthy. There are not as many ARVs available for children and adolescents as for adults because many ARVs have not yet been tested in children.

DOR is a new ARV that is being tested in adults in the United States and other countries. The combination of ARVs also includes two other ARVs called lamivudine (3TC) and tenofovir disoproxil fumarate (TDF). *[Sites: insert any locally appropriate names of combination drugs or individual drugs used at your site here and throughout the form.]*

TDF and 3TC are approved in the United States and Europe. Both of these ARVs are commonly used in adults and children. DOR is a newer ARV that is being studied in adults. DOR is not currently approved in the United States or Europe. *[Sites to modify as needed:* TDF and 3TC are approved in *[site country]]*.

This combination of DOR, TDF, and 3TC has been studied closely in 86 healthy adults. DOR, either alone or in combination with other ARVs, has been studied closely in more than 700 adults. DOR has been shown to be safe and effective when compared to the approved ARVs, like efavirenz and darunavir. This is the first study of DOR in combination with TDF and 3TC in children.

The two groups of the study are called Cohort 1 and Cohort 2. Cohort 1 was done first. This part included up to 20 children and adolescents. Cohort 2 will be done after Cohort 1 is completed. Cohort 2 will include up to 45 children and adolescents. We will tell you about Cohort 1 first. This is a consent form for Cohort 2.

In Cohort 1, DOR was given one time at one visit to children and adolescents. This group looked at whether DOR causes any bad side effects when given to children and adolescents. This group also looked at the amount of DOR in blood. This is called an intensive pharmacokinetic (PK) evaluation.

Because results from Cohort 1 show that DOR is safe and that the amount of DOR in the blood is correct, Cohort 2 will start. The children and adolescents in this group will either have never received ARVs for treatment or are currently receiving ARVs for treatment and doing well. This group will look at whether this new combination of ARVs is safe or causes any bad side effects when given to children and adolescents. The group will also look at how the combination of ARVs control the virus for children and adolescents. For ARVs to be considered effective, they must be able to control the amount of HIV so that HIV cannot be found in the blood.

Some children and adolescents may join the study who have never taken ARVs before. Some children and adolescents may join the study who are taking ARVs and are doing well on their ARVs. If [you are/your child is] taking ARVs for treatment before the study, we will ask your child to start taking the study ARVs on the same day that your child stops taking the ARVs from before the study (see #8 below).

**2. We may have two different ways to take DOR/3TC/TDF.**

There are different ways to take ARVs, for example, as tablets that are swallowed or chewed or as liquids. This study may have two different ways for children to take DOR/3TC/TDF. We will tell you if [you/your child] have different options.

One way to take DOR/3TC/TDF is as a tablet. The tablet needs to be swallowed whole – it cannot be broken or crushed.

Another way to take DOR/3TC/TDF is as oral granules. Granules are kept in larger capsules or containers *[sites may use any locally understandable term to describe the granules]*. The granules can be sprinkled or mixed with soft food or liquid.

*[Sites may adapt the following paragraphs, depending on availability of the granule formulation:*
You [and your child] may choose how to take the DOR/3TC/TDF. We will talk to you about the options and ask for your [your child's] decision. We will help [take/give] the DOR/3TF/TDF.

During the study, we would prefer that [you/your child] take the study ARV in the same way. However, [you/your child] may decide to take the study ARV the other way. For example, [you/your child] may start taking the DOR as oral granules and then decide to take the DOR as a tablet. If [you/your child] switch, we will also ask how it felt to take the tablet or granules (for example, how DOR tasted, how easy or difficult it was to swallow the tablet, how easy or difficult it was to mix the granules).*]*

**3. It is your decision whether or not [you join/your child joins] the study.**

Deciding to join the study is voluntary. You may choose [to allow your child] to join or not join. If you choose [to allow your child] to join, you can change your mind and [stop the study/take your child out of the study] at any time. Your choices will have no effect on your [child's] medical care at this clinic. Access to services and the benefits and rights [you/he or she] normally has will not be affected.

We will tell you about new information from this or other studies that may affect your [child's] health, welfare, or willingness to stay in this study. If you want the results from this study, tell the study staff.

Take your time and consider your decision carefully. If you wish, you can talk to other people about [joining/allowing your child to join] the study. You can bring other people here to learn about the study with you.

***No matter what you decide about the study, it is important to receive care and treatment for HIV infection. We will tell you about your options for obtaining care and treatment for your [child's] HIV.***

**4. Only children who qualify can participate in the study.**

If you decide to join the study, we will first do some tests to see if [you qualify/your child qualifies].

***Finding out if [you qualify/your child qualifies]***

**5. We will ask questions and discuss the study requirements with you.**

If you decide to [join/let your child join] the study, we will first do some tests to see if [you qualify/your child qualifies]. To find out, we will:

- Review medical records. We may also ask you questions about your [child's] health
- Ask about ARV use
- Talk with you about the study requirements and if [you are/your child is] able to meet these requirements
- Give a physical exam
- Draw blood for tests. We will take up to about 22 mL (less than 5 teaspoons) of blood. These tests will look at your [child's] blood cells and how well the liver and kidneys are working. The tests will also:
  - Confirm that you [your child] has HIV. There are certain HIV tests that are required for this study. If the required tests are not in the medical records, we will do the tests that are needed.
  - Check the amount of HIV in the blood. This is called viral load.
  - If [you have/your child has] never taken any ARVs for treatment, we will check whether [you are/your child is] resistant to certain ARV medications. Resistance means that an ARV may no longer work again HIV.
  - Check if [you have/your child has] Hepatitis B or Hepatitis C. Hepatitis B and Hepatitis C are diseases of the liver.
- Collect urine to check on how your [child's] kidneys are working
- For females, we may also collect urine or blood to check for pregnancy. More information is given in #6 below.

**6. For females, we may do a pregnancy test to see if [you/your daughter] qualifies for the study. We may also test for pregnancy during the study. Females who become pregnant will stop the study ARVs.**

If [you have/your daughter has] had her period or [you are/your daughter is] sexually active, we will collect urine or blood to test for pregnancy to see if [you/she] qualifies for the study. The pregnancy test must show that [you/she] is not pregnant to qualify for the study. If [you/she] enter the study, [you/she] will be required to use two forms of birth control while in the study. We will talk to [you/your child] about how to prevent pregnancy.

During the study, we will collect blood or urine to test for pregnancy. If [you/your child] becomes pregnant during the study, please let us know right away. If [you/your child] becomes pregnant, [you/your child] will stop taking the study ARVs and leave the study early.

*[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or legal guardians:* We will talk over the test result as soon as it is available with [you/your child] in private without parents/guardians present. [You/Your child] must give us permission before we can share these results with parents/guardians. If [you are/your child is] pregnant, we will take [you/your child] off the study early. This means that even if we did not tell your parent or guardian, they might find out you were pregnant. If the test shows that [you are/she is] pregnant, we will give [you/your child] information on where medical care and other services can be received.*]*

We will contact [you/your child] after [your/your child's] last study visit to find out the outcome of the pregnancy. We will also ask about any ARVs [you/your child] took during the pregnancy.

**7. We will tell you if [you/your child] qualifies.**

We will give you the results of all procedures and explain the results to you.

If these procedures show that [you do/your child does] <u>not</u> qualify for the study, we will tell you this and [you/your child] <u>will not</u> be entered into the study. We will give you information on where medical care and other needed services can be received.

If these procedures show that [you <u>do</u>/your child <u>does</u>] qualify for the study, [you/your child] <u>will</u> be entered into the study.

***Being in the study***

**8. If [you qualify/your child qualifies], [you/he or she] will enter the study. Participants will have about 12 scheduled visits over 2 years.**

Visits will be more frequent in the first year. During this time, visits will be at entry, 2, 4, 8, 12, 16, 24, 36, and 48 weeks. After the first year, there will be at least three more visits, each four months apart.

Some children and adolescents may need to stop the study early. More information about this is given in #14 below.

Each visit will take about 2 to 3 hours. At these visits, we will:
- Review medical records
- Ask about ARVs

- Do a physical exam. At the first visit, this exam will include examination of your [child's] genitals to see the stage of development.
- Draw blood for tests. We will take between 10 mL and 19 mL of blood at each visit (about 2 and less than 4 teaspoons). At some visits, we will only do some of the tests. At other visits, we will do all of the tests. These tests may check:
  - Blood cells and the amount of fat in the blood
  - How well the liver and kidneys are working
  - How much HIV is in the blood
  - How many CD4 cells are in the blood. CD4 cells are cells that fight infections
  - How much of the study ARVs are in the blood (see #9 below)
  - If [you have/your child has] never taken any ARVs for treatment, we will save some blood for later resistance testing
  - We will also save any extra blood for future testing after the study is over. We will not tell you the results of any future tests. We will ask you about saving these extra samples in a separate form.
- Collect urine to check on how the kidneys are working.
- We may also do a test to check if [you are/your child is] pregnant (see #6 above).

[You/Your child] will also receive study ARVs at the entry, or first, visit. We will show you [and your child] how to take the ARVs. It is very important that [you/your child] takes the ARVs as instructed. We will take as much time as needed for you [and your child] to understand the instructions and identify strategies that will help to take the ARVs are instructed. After [you/your] child has been taking the study ARVs for two weeks, we will also ask how it felt to take the tablet or oral granules (for example, how DOR tasted, how easy or difficult it was to swallow the tablet, how easy or difficult it was to mix the granules).

If [you were/your child was] taking ARVs for treatment before the study, we will ask [you/your child] to stop taking the ARVs from before the study and start taking the study ARVs on the same day.

**9. At some visits, we will look to see how much of the study ARVs are in your [child's] blood.**

[You/Your child] will also have blood drawn to measure the amount of study ARVs in the blood. This is called a pharmacokinetic evaluation, or PK evaluation.

At 6 visits, we will take about 3.5 – 7 mL of blood drawn (less than 2 teaspoons). This blood will be drawn in the same way that other blood for the study is drawn.

At 4, 24, and 48 weeks after [you start/your child starts] the study, we may ask [you/your child] to take the study ARVs while at the study clinic so we can note the time [you/your child] took the study ARVs. On the day of this visit, we may ask [you/your child] to **not** take the study ARVs at home. We will help you remember this before each visit.

At 24 weeks and 48 weeks after [you start/your child starts] the study, we will draw blood two times at least 30 minutes apart.

**10. For the first 10 participants in this part of the study: there will be an extra visit about one week after [you start/your child starts] the study where we will look very closely at the amount of study ARVs in the blood.**

About one week after [you start/your child starts] the study, [you/your child] will have blood drawn to very closely measure the amount of study ARVs in the blood and how long it stays. This is called an intensive pharmacokinetic (PK) evaluation.

At this visit, we will ask you [and your child] when she or he took the study ARVs in the past three days. For three days before this visit, you must be sure that the child takes the study ARVs on time. **This is very important.** We will help you remember this before the visit.

On the day of this visit, **do not [take/give]** the medicine [to your child] at home. [You/Your child] will take the study ARVs while at the study clinic so that we know the time [you/your child] took the study ARVs.

[You/Your child] will then stay at the clinic or hospital for up to 24 hours. *[sites: modify language as appropriate to indicate procedures for overnight stays* – If the study clinic is able, you and your child may be allowed to stay at the clinic the night before and during your first PK visit.*]*

*[Sites: modify language as appropriate to indicate procedures for the intensive PK collection.* A small plastic tube (like a "drip") will be placed in your [child's] arm to draw blood samples. This tube is attached to a plastic needle so that we can draw blood several times. We will not need to stick your child with a needle each time. The plastic tube may stay in place until all the blood samples are drawn.*]*

We will draw about 2.5 – 3.5 mL (less than 1 teaspoon) of blood at six different time points during the first day for the PK test and at one time point during the second day of the PK test (a total of about 22.5 mL or less than 5 teaspoons). We will look at the amount of ARVs in your [child's] blood at each of these times.

**11. Children and adolescents will have an extra visit if their HIV is not controlled.**

Participants will have viral load tests at all visits. If the study ARVs are your [child's] first anti-HIV medicine, your [child's] viral load should be very low after about four months. If tests show that the viral load is higher than expected after four months, [you/your child] will have an extra visit. If [you were/your child was] on other ARVs before starting the study, your [child's] viral load should stay very low during the study. If tests show that the viral load is higher than expected at any time during the study, [you/your child] will have an extra visit. If your [child's] viral load is high at the last study visit, we will ask you to come back to the clinic after that to have an extra visit.

These extra visits will take about one hour. At these visits we will:

- Review medical records
- Ask about your [child's] health, ARVs, and other medicines
- Do a physical exam
- Draw blood (up to 13 mL or less than 3 teaspoons) for tests. The tests will check the HIV viral load. We will save some blood for later resistance testing.
- Give you additional supplies of ARVs as needed

If the repeat test also shows the high numbers of HIV in your [child's] blood, we will talk with you about whether [you/your child] should stay on the study ARVs.

**12. The tests for the amount of ARVs in your [child's] blood will be done at different laboratories.**

We will do most of the blood tests here at our laboratory. Some of the blood tests will be done in the U.S. or other countries. We will give you the results of most of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals as needed.

We will also draw blood to check the amount of ARVs in your [child's] blood here in the clinic. The test will be done at laboratories in the U.S. or other countries.

Some tests may be done while the study is ongoing; others after the study is done. We will not give you the results of the pharmacokinetic tests during the study.

**13. We may stop your [child's] study ARVs or take [you/your child] off the study early.**

We may take your child off the study ARVs if:

- [You are/Your child is] not able to come to the study visits or we determine that [you/your child] cannot meet the study requirements.
- [You are/Your child is] not able to take the study ARVs.
- The study ARVs are not controlling the HIV in your [child's] blood.
- [You/Your child] becomes pregnant (see #6 above).
- Continuing the study ARVs may be harmful to [you/your child].
- You request to stop the study ARVs [for your child].

If [you stop/your child stops] the study ARVs, [you/your child] will stop the study early. We will ask you to come back to the clinic [with your child] about four weeks after [you stop/your child stops] the study ARVs. [You/Your child] will not have any other visits after this.

We may also take [you/your child] off the study early if the study is stopped for any reason.

The study cannot provide other types of ARVs, but we will give information, counseling, and referrals to where children can get care and treatment they need. We will help make sure [you/your child] can get ARVs from outside of the study. If the study stops early, every effort would be made to make certain that there is no interruption in your [child's] therapy.

**14. Please tell us if you want [your child] to leave the study.**

[You are/Your child is] free to leave the study at any time for any reason. The care that [you receive/your child receives] at this clinic will not be affected, but it is important for us to know about your decision. We will ask you to [come/bring your child] to the clinic for one last visit. At this visit, we will do the same types of procedures listed in #8 (see above). We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

*After the study*

**15. Receiving the study ARVs after the study is over.**

As [you come/your child comes] to the end of the study, we will work with you to plan for your [child's] care and treatment outside the study. It is important that we plan for this in advance, so that there is no gap in your [child's] taking ARVs as [you finish/he or she finishes] the study. Taking ARVs without interruption is the best-known way for [you/your child] to stay healthy.

We will tell you where [you/your child] can go to receive needed care and treatment after [you finish/he or she finishes] the study. If [you are/your child is] gaining benefit from the ARVs given in the study, the company that is providing these ARVs (Merck) will try to provide these ARVs to your child. They will be provided until they are otherwise available locally, until [you are/your child is] no longer gaining benefit, or if the company decides to stop studying the ARVs. However, there is no guarantee this will be possible. If this is <u>not</u> possible, [you/your child] will need to switch to other ARVs that are available locally. We will explain the options to you and help ensure your [child's] access to ARVs outside the study. We will also contact you again within the first four weeks after [you finish/your child finishes] the study to confirm that [you are/he or she is] receiving ARVs.

*Risks of the study*

**16. There is little risk from the study procedures.**

Most procedures done in this study are routine medical procedures, with little risk to [you/your child]. Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

**17. There are some risks from the study ARVs.**

All ARVs can cause side effects, whether taken along or when taken in combination. This includes any ARVs that you would receive outside the study. The study ARVs, doravirine, lamivudine, and tenofovir disoproxil fumarate, may have side effects. Some of the most common or most serious effects are listed below. There may also be unknown side effects because this is the first time DOR will be studied in children. The lists do not include all the possible side effects. If you have questions about side effects not included in these lists, you can ask us.

Each of the study ARVs can cause side effects, when taken alone or when taken in combination. Some side effects are minor; others can be severe. Some are common and some are rare. Some people who take the study ARVs have some of these effects. Some people have different side effects. We do not expect to see different side effects if the ARVs are combined or if they are given separately.

If [you join/your child joins] the study, we will tell you about the side effects of the study ARVs that [you/your child] will take. We will also check for any side effects during the visits and tell you what to do if [you have/your child has] any side effects.

**18. We will tell you about the most severe side effects first.**

First, you should know about the possible severe side effects. These effects are rare, but they can cause serious health problems and can result in death:

- Liver problems. The liver is an organ near the stomach. If there are liver problems, [you/your child] might have yellowing of the skin or whites of the eyes; dark or tea-colored urine; pale colored stools; upset stomach or vomiting; loss of appetite; pain, aching or tenderness of the right side below the ribs; or itchy skin. This can be caused by DOR, 3TC, and TDF.

- Build-up of acid in blood, called lactic acidosis, very enlarged liver, fatty liver, or death have been reported. If [you have/your child has] these problems, [you/your child] might have unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness, and shortness of breath. This can be caused by 3TC and TDF.

- Pancreas problems. The pancreas is an organ near the stomach. If your [child's] pancreas becomes inflamed, [you/your child] may have stomach pain, upset stomach or vomiting, or more fats in the blood. This can be caused by 3TC.

- Kidney problems. The kidneys are organs near the middle of the back (one on each side). Doctors usually find out about kidney problems from tests of the blood. These effects can be caused by TDF.

**19. There are also more common and not severe side effects from the study ARVs.**

You should also know about the more common side effects. These side effects are not severe. There are many possible mild and moderate side effects. The most common ones are listed below:

<table>
<tr>
<td>Overall Body Effects<br>• Changes in the placement of body fat (increasing around the stomach, neck, or breast or decreasing in the arms, legs, or cheeks)<br>• Overall weakness<br>• Headache<br>• Back pain<br>• Stuff, runny, or uncomfortable nose<br>• Allergic reaction<br>• Numbing, tingling, or pain in the hands and feet<br>• Fever</td>
<td>Effects on Blood<br>• Decrease in the blood cells that fight infection<br>• Other changes in the blood tests that may show problems with the liver or pancreas. The blood tests may show how well these organs are working, or they may look for substances made by the organs, or they may look for fats in the blood.<br><br>Effects on Skin<br>• Rash<br><br>Effects on the Chest<br>• Shortness of breath</td>
</tr>
<tr>
<td>Effects on Muscle and Bones<br>• Aches and pains<br>• Loss of muscle<br>• Bone thinning or softening (which could increase the chance of breaking a bone)<br><br>Effects on Stomach<br>• Pain or upset stomach<br>• Loose or watery stools<br>• Vomiting<br>• Gas</td>
<td>Effects on Activity<br>• Drowsiness and tiredness<br>• Trouble sleeping<br>• Dizziness<br>• Abnormal dreams, hallucinations and nightmares<br>• Clumsiness or lack of coordination<br>• Feeling of deep sadness or unworthiness (depression)</td>
</tr>
</table>

**20. There may be other possible risks from the study ARVs.**

*Possible effects on pregnancy or unborn babies*

HIV and ARVs may lead to some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some ARVs are more likely to cause these effects than others. We do not yet know if this combination of ARVs with DOR is safe in pregnancy. There were no pregnancy complications seen when DOR was given in animals.

If [you/your child] becomes pregnant during the study, please let us know right away.

*Immune reconstitution syndrome*

In some people with advanced HIV infection, signs and symptoms from other infections or certain diseases may occur soon after starting combination ARVs but can also occur later. Some of these symptoms may be life threatening. If [you start/your child starts] having new symptoms, or if you notice that any existing symptoms are getting worse after starting the ARVs, tell your doctor immediately.

*Hepatitis B*

Some ARVs are active against hepatitis B. For children who have hepatitis B, and take ARVs that are active against hepatitis B, stopping the ARVs could cause the hepatitis B to worsen. If this happens, most children get better quickly without treatment, but in rare cases this has resulted in death.

*Risk of resistance*

All ARVs can cause some resistance. Resistance means that the ARVs may not work against HIV if it is taken again in the future. To stop resistance, it is important that [you take/give your child] the ARVs as instructed, and do not miss any doses.

*Risk related to stopping study ARVs*

If the study is unexpectedly stopped early or if you reach the end of the study and it is not possible to continue the study ARVs and you therefore need to change to different anti-HIV medicines, there is a risk that the new ARVs would not work as well as the study ARVs.

*[Sites should include for participants who are ART-experienced: Risk of switching ARVs*

If [you are/your child is] switching to study ARVs from different anti-HIV medicines, there is a possibility that the study ARVs will not work as well as your [child's] current anti-HIV medicines. We will test the viral load during the study to check (see #8 above).*]*

**21. There could be risks of disclosure of your [child's] information.**

We will make every effort to keep your [child's] information private and confidential. Study records and specimens will be kept in secure locations. All specimens and most records will be labeled only with a code number. However, your [and your child's] names will be written on some records.

Despite our best efforts to keep your [child's] information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, [you/your child] could be treated badly or unfairly. You could feel stress or embarrassment.

*[To be included at US sites:]* To help us protect your [child's] privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify [you/your child], such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify [you/your child]. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your [child's] participation in the study to others, if you wish.

***Benefits of the study***

**22. There may be no benefit to [you/your child from being in the study.**

By joining the study, [you/your child] will be part of the search for ARVs that may be better for children. We do not know if being in the study will benefit [you/your child] in any way. There may be a direct benefit to [you/your child] by taking part in this study, but no guarantee can be made. For example, the study drugs may lower the amount of HIV in the blood. There may also be benefit if the results from this study lead to a safe and effective dose of the study drugs for children. It is also possible that [you/your child] may receive no direct benefit from this study. Information learned from this study may help other children who have HIV.

[You/Your child] will have regular visits here and frequent checks on your [child's] health, including tests for amount of HIV in your [child's] blood, called viral load, and for the amount of cells that fight HIV, called CD4. It is possible that the study ARVs will slow your [child's] HIV infection. Information learned from this study may help other children with HIV.

***Other information about the study***

**23. There are no costs to you from [you/your child] being in the study.**

There are no costs to you for study visits, study ARVs, or procedures.

*[Insert information about compensation/reimbursement here, e.g.,* You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).*]*

**24. Study records may be reviewed by study staff and groups that oversee the study.**

Groups that oversee the study include:
- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site regulatory entities]*
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- The IMPAACT Network that is coordinating the study
- Merck Ltd. (the company that makes the study ARVs)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will not use your [child's] name or identify [you/your child] personally.

A description of this study will be available on ClinicalTrials.gov. This website will not include information that can identify you or your child. At most, the website will include a summary of the results. You can search this website at any time.

Your [child's] study information may be disclosed to other authorities if required by law.

**25. If [you take/your child takes] any new medication or uses alcohol or recreational drugs, please inform your study doctor.**

Some medications, including herbal medications, may make the ARVs not work as well or be less safe. Please let the study doctor know if [you start/your child starts] any new medicines. Use of alcohol or intravenous drugs may increase the risk of side effects from the ARVs. [Please discuss with the study doctor if [you are/your child is] using intravenous drugs or drinking alcohol].

**26. If [you get/your child gets] sick or injured, contact us immediately.**

Your [child's] health is important to us. We will make every effort to protect your [child's] well-being and minimize risks to [you/your child]. It is possible, however, that [you/your child] could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

*[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.]* If a study-related illness or injury occurs, we will treat [you/your child] or tell you were you can get the treatment your child needs. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through *[site name or]* the National Institutes of Health.

***Whom to contact***

**27. If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about the study:
  *[insert name and telephone number of investigator or other study staff]*

- If you have questions about your [child's] rights as research participants or concerns about how [you are/your child is] being treated in the study:
  *[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]*

- If [you have/your child has] any health or other problems that may be related to study participation:
  *[insert name and telephone number of investigator or other study staff]*

- If you want [your child] to leave the study:
  *[insert name and telephone number of investigator or other study staff]*

***Signatures***

**If you agree to [let your child] participate in this study, please sign or make your mark below.**

Before deciding whether to [let your child] participate in this study, make sure you have read this form, or had it read to you, and that all your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you [and your child] if you decide [allow your child] to join.

If you decide to [allow your child to] join, we will tell you any new information from this study or other studies that may affect your willingness [for your child] to stay in the study. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

*[Insert signature blocks as required by site IRB/EC policies.]*

**Signature blocks for participants <u>below</u> legal age to provide independent informed consent**

***Participant Assent***

| | |
|---|---|
| _____ | _____ |
| Participant's Name (print) | Participant's Signature and Date |

***Parent/Guardian Consent***

| | |
|---|---|
| _____ | _____ |
| Parent/Guardian Name (print) | Parent/Guardian Signature and Date |
| _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature and Date |
| _____ | _____ |
| Witness's Name (print) (As appropriate) | Witness's Signature and Date |

**Signature page for participants of legal age to provide independent informed consent**

| | |
|---|---|
| _____ | _____ |
| Participant's Name (print) | Participant's Signature and Date |
| _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature and Date |
| _____ | _____ |
| Witness's Name (print) (As appropriate) | Witness's Signature and Date |

# Appendix IV: Sample Informed Consent Form for Specimen Storage and Future Use

## 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

## Version 1.0, 7 September 2017

You have decided [to allow your child] to join the study named above. As part of the study, [your/your child] will have blood and urine collected. After these samples are tested for the study, some samples may be left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future.

This form gives information about use of extra samples. Please read it, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of extra samples at the end of the form.

### 1. It is your decision whether or not to allow the extra samples to be used.

You are free to say yes or no, and to change your mind at any time. Your decision will not affect your [child's] participation in the study. If you say no, all extra samples will be destroyed.

### 2. If you agree, your [child's] extra samples will be kept in a repository.

*[Sites should insert one of the two options shown below. Choose/adapt the second option if local regulations do not permit storage of samples for future research use in the United States.]*

A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. If you agree to have extra samples stored, the samples will be kept in this repository. There is no limit on how long the samples will be kept *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

A repository is a secure facility that is used to store samples. The IMPAACT Network has a repository in the United States. However, our local regulations require that extra samples be stored in our country. Therefore, we will keep the samples here at our laboratory. There is no limit on how long the samples will be kept *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

### 3. Extra samples could be used for different types of research.

Extra samples may be used for research on HIV, the immune system, and other diseases. The research may be done in the United States or in other locations.

If you agree, the extra samples could also be used for research that looks at your [child's] genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your [child's] samples would only be used to look at genes related to HIV and the immune system.

Any research done with the extra samples must be reviewed and approved by the IMPAACT Network. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the people whose samples will be used.

The research done with extra samples is not expected to give any information relevant to your [child's] health. Therefore, the results will not be given to the study staff or to you. The results also will not be placed in your [child's] study records.

**4. There is little risk to your child.**

When extra samples are used for research, they are labeled with a code number only. To protect your [child's] privacy, no names are used. However, information such as age, gender, HIV status, and other health information may be linked to the samples. Information on the ARVs your child received in the study may also be linked to the samples.

There may be some risks from tests of your [child's] genes. If others found out the results of these tests, they could treat [you/your child] badly or unfairly. However, this is almost impossible because the results will not be given to the study staff, or to you, [or to your child] and will not be in your [child's] study records.

**5. There may be no benefit to [you/your child].**

By allowing extra samples to be used for research, [you/your child] will be part of the search for new information that may benefit people with HIV in the future. However, the research done with the extra samples is not expected to directly benefit [you/your child] in any way.

**6. You will not be paid for use of your [child's] samples.**

There is no cost to you for use of your [child's] extra samples. The samples will not be sold, and you will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with [you/your child].

**7. Information from research using extra samples may be reviewed by groups that oversee the research.**

These groups include:
- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research

The people who do research with the extra samples and the groups listed above are required to make efforts to keep information private and confidential.

The results of research done with the extra samples may be presented publicly or published. However, no presentation or publication will use your [child's] name or identify [you/your child] personally.

**8. If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about use of your [child's] extra samples:
  *[insert name and telephone number of investigator or other study staff]*.

- If you later change your mind about use of your [child's] extra samples:
  *[insert name and telephone number of investigator or other study staff]*.

- If you have questions about your [child's] rights as a research participant or concerns about how [you are/your child is] being treated in the study:
  *[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]*.

***Signatures***

Before deciding whether [your/to allow your child's] extra samples [can/to] be used for research, make sure you have read this form, or had it read to you. Make sure all your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

You do not give up any rights by signing this form.

*[Insert initial and signature blocks as required by site IRB/EC policies and the IRB/EC determination if the level of risk to children in the categories specified in 45 CFR 46.404-407. Separate consent decisions must be documented for genetic testing]*.

**For YOUR [CHILD's] extra samples, write your initials or make your mark next to your choice.**

_____ I allow my [child's] extra samples to be used for research on HIV, the immune system, ARVs, and other diseases. I also allow my [child's] samples to be used for tests of his or her genes.

_____ I allow my [child's] extra samples to be used for research on HIV, the immune system, ARVs, and other diseases. I do <u>not</u> allow my [child's] samples to be used for tests of his or her genes.

_____ I do <u>not</u> allow my [child's] extra samples to be used for any research.

**Signature blocks for participants <u>below</u> legal age to provide independent informed consent**

***Participant Assent***

| | |
|---|---|
| _____ | _____ |
| Participant's Name (print) | Participant's Signature and Date |

***Parent/Guardian Consent***

| | |
|---|---|
| _____ | _____ |
| Parent/Guardian Name (print) | Parent/Guardian Signature and Date |
| _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature and Date |
| _____ | _____ |
| Witness's Name (print) (As appropriate) | Witness's Signature and Date |

**Signature blocks for participants of legal age to provide independent informed consent**

| | |
|---|---|
| _____ | _____ |
| Participant's Name (print) | Participant's Signature and Date |
| _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature and Date |
| _____ | _____ |
| Witness's Name (print) (As appropriate) | Witness's Signature and Date |