

Letter of Amendment #2 for:

IMPAACT P1101

Phase I/II Dose-finding, Safety, Tolerance and Pharmacokinetics Study of a Raltegravir-Containing Antiretroviral Therapy (ART) Regimen in HIV-infected and TB Co-infected Infants and Children

A Multicenter, International Trial of the
International Maternal Pediatric Adolescent AIDS
Clinical Trials Network (IMPAACT)

Protocol: Version 3.0, dated 24 April 2017

Letter of Amendment Date: 21 June 2018

NCT 01751568

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Version 3.0, dated 24 April 2017

DAIDS Document ID #11831

IND #77,787 Held By DAIDS

Letter of Amendment Date: 21 June 2018

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1101 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 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 receiving IRB/EC approval and any other applicable regulatory entity approvals, all sites should immediately begin implementing this LoA. Sites are required to submit a 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.

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 P1101. If the P1101 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

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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

The following modifications are included in this LoA:

1. Sections 6.5, 6.7, and 9.2 are modified to clarify the pharmacokinetic (PK) criteria for early study drug discontinuation for participants with $AUC_{0-12hr} \geq 63 \mu Mxhr$.
2. Section 7.2 is updated to clarify that confirmed Grade 3 and 4 adverse events are required to be reported as expedited adverse events.

Implementation

Detailed modifications of the protocol text included in this LoA are listed below. Additions to the text are indicated in **bold**; deletions are indicated by ~~strike through~~.

1. Pharmacokinetic criteria for early study drug discontinuation

a. Section 6.5, Pharmacokinetic Endpoint, second paragraph:

~~RAL will be stopped in any individual that has an $AUC_{0-12hr} \geq 63 \mu Mxhr$, per Section 9.0. Per~~
Section 9.0, if any individual has an $AUC_{0-12hr} \geq 63 \mu Mxhr$, the Protocol Team will review all available clinical, safety, PK, immunologic, and virologic data for the participant and determine if discontinuation of RAL is indicated. For participants that permanently discontinue RAL, evaluable PK and safety data will be used in the assessment of the dose for that cohort.

b. Section 6.7, Criteria for Early Treatment Discontinuation, fifth bullet:

- Participant has an $AUC_{0-12hr} \geq 63 \mu Mxhr$, **and the protocol team determines that RAL should be permanently discontinued**, per Section 9.0.

c. Section 9.2, Study Design, Modeling and Data Analysis, Pharmacokinetic Guidelines, sixth paragraph:

If any individual has an $AUC_{0-12hr} \geq 63 \mu Mxhr$ **, **the Protocol Team will review all available clinical, safety, PK, immunologic, and virologic data for the participant and determine if discontinuation of RAL is indicated** ~~participant will stop taking RAL. However, their~~ **For participants that permanently discontinue RAL, evaluable PK and safety data will be used in the assessment of the dose for that cohort.**

2. Expedited Adverse Event Reporting Requirements

Section 7.2, Reporting Requirements for this Study, second bullet:

- Other medically significant events for which expedited reporting is required include all cancers and pregnancies, fetal losses, IRIS events that qualify as serious adverse events, Hy's Law liver toxicities, and all **confirmed** Grade 3 and 4 toxicities.