Letter of Amendment #1 for:

IMPAACT P1093
Phase I/II, Multi-Center, Open-Label Pharmacokinetic Safety, Tolerability and Antiviral Activity of Dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

Version 5.0, dated 12 July 2018

DAIDS Study ID #11773
IND #110,847

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 P1093 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 P1093. If the IMPAACT P1093 protocol is amended in the future, applicable 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 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 and to incorporate the contents of previously-issued protocol Clarification Memoranda (CM).

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

Section B of this LoA includes the corrections and clarifications of protocol text that were included in corrected CM #1 (dated 26 September 2018) and CM #2 (dated 6 January 2019).

Section C of this LoA incorporates the contents of CM #3, 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 #3 provided operational flexibility for conducting study visits and procedures when needed for participant safety monitoring and to prioritize ongoing access and adherence to the study drug regimen. Per the study Sponsor, sites were instructed to implement the guidance provided in CM #3 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 #3, 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 P1093 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 membership, the protocol team roster is updated as follows:

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B. Clarifications and Corrections of Protocol Text from Corrected CM #1, dated 26 September 2018, and CM #2, dated 6 January 2019

1. In Sections 2.2, 8.2, and 8.6, the following updates are incorporated to correct inconsistencies in the specified timing of safety and tolerability analyses:

   Section 2.2, Secondary Objective 5
   To determine the extended long term (≥ **>** 48 weeks) safety, tolerability and efficacy of DTG in HIV-1 infected infants, children and adolescents.

   Section 8.2.1.1 (section heading)
   Toxicity through Week**s** 24 **and 48**

Section 8.2.3.1 (section heading)
Toxicity ~~through week 48 and~~ beyond **Week 48**

Section 8.6.2.1 (section heading)
Primary Analyses (performed on data through the Week 24 **and 48** visit**s**)

Section 8.6.2.2, Key Secondary Analyses, Safety
Safety assessments will be performed on ~~data collected through Week 48 and~~ long term data. These analyses will be similar to the ~~Weeks 24~~ analyses described in Section 8.6.2.**1** above. In addition, these analyses will also be performed with participants classified by weight band.

2. In Section 3.1, the following updates are incorporated to clarify screening and enrollment procedures for weight-band groups:

   - Stage 1 Full Cohort and Weight-band Analysis

     The study aims to ensure that adequate numbers of participants are enrolled into each of the age-defined cohorts as well as each of the weight-band groups. To this end, once 10 participants with evaluable data are enrolled into a cohort, additional enrollments into that cohort are only permitted if a participant will be contributing to achieve the minimum enrollment of 8 evaluable in a weight-band group. To ensure continuous enrollment into cohorts during Stage 1, enrollment does not close until it has been confirmed that 8 participants with evaluable data have been enrolled and completed PK and safety assessments into a weight band. ~~Up to~~ A maximum of an additional 2 participants **can be enrolled** while waiting for **determination that the data from the minimum of 8 participants in a given weight-band group are evaluable.** ~~these results to become available.~~

     Participants are enrolled into Stage I weight-band groups based on their weight at enrollment. However, if a participant is eligible for a given weight-band group by weight at screening but then has a different weight on the day of enrollment that places him/her into a different weight-band group, he/she will be allowed to enroll in Stage I, even if the minimum accrual targets for that weight-band group have been met. In this case, the participant will contribute to the Stage I full cohort and weight-band analysis based on weight at enrollment.

3. In Section 6.1.8 and Appendix IG, the following updates are incorporated to clarify the timeline for resuming once daily dosing of dolutegravir after discontinuation of rifampin-containing tuberculosis treatment:

   Section 6.1.8, Management of Participants Co-infected with TB, last bullet, second sentence:
   Approximately two weeks after ~~Upon~~ discontinuation of the rifampin containing anti-TB therapy, the participant's DTG dose will revert back to once daily administration unless on EFV, FPV/r, or TPV/r.

   Appendix IG, note directly following Schedule of Evaluations, third sentence:
   Approximately two weeks after ~~Upon~~ discontinuation of the rifampin containing anti-TB therapy, the participant's DTG dose will revert back to once daily administration.

4. In Section 5.2.3, second paragraph and first and second bullets, the following updates are incorporated to correct an inconsistency in dispensing procedures for dolutegravir dispersible tablets:

   ~~In Stage I and~~ Prior to intensive PK sampling **in Stage I,** each tablet is to be dispersed using ~~2 to 5 mL of~~ water. There are two options for dispensing described below.

   - Option 1: for older children, pour drinking water into the dosing cup. ~~For 1-2 tablets use 5mL of water. For 3-4 tablets use 10mL of water and for 5-6 tablets use 15 of water~~. **For 1-3 tablets use 5mL of water, for 4-6 tablets use 10mL of water.** Add the prescribed number of tablets to the water. Swirl the cup gently for 1-2 minutes to fully disperse the tablets. The medicine will be cloudy. If any lumps of tablet remain, swirl the cup gently until they are gone. ~~Give~~ **Administer** the prepared dose to the child. ~~Rinse the dosing cup before next use.~~ **Pour an additional 5 mL of water in the dosing cup, swirl the cup gently for approximately 15 seconds and administer the entire volume to the participant. Wash the dosing cup immediately after administration, allow to dry and store for the next use.**

   - Option 2: for infants and younger children, prepare medicine in dosing cup as directed in Option 1. Draw up all the medicine into the syringe. Place the tip of the syringe against the inside of the infant's cheek **and administer** ~~to give~~ the dose slowly**.** ~~Swirl~~ **Pour an additional** ~~a further~~ 2mL of water into the dosing cup, draw it into the syringe, and **administer the remaining volume** ~~give it all~~ to the infant. ~~Wash cup and syringe thoroughly~~. **Wash the dosing cup immediately after administration, allow to dry and store for the next use**

     After intensive PK sampling **in Stage I** and in Stage II each tablet can ~~continue to~~ be dispersed as described above or each tablet can be placed directly on the tongue and directly swallowed. Dispersible tablets may be given as multiples (up to a maximum of 6 tablets), depending on the weight of the child. Once dispersed, the medication should be ~~consumed from~~ **administered using** the supplied dosing cup or syringe, **as soon as possible, preferably** within **5** ~~five~~ minutes **but no longer than 30 minutes after preparation.**

5. In Appendices IA, IB, IC, ID, and IG, footnote for chemistries, the following updates are incorporated to clarifies guidelines for establishing a laboratory normal value for indirect bilirubin:

   Electrolytes (sodium, potassium, and HCO3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented. **The following formula can be utilized: indirect bilirubin = total bilirubin – direct (or "conjugated") bilirubin.**

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. "ULN" values routinely used/established by the site or
   c. 'ULN" values as per the **most current** Harriet Lane Handbook ~~(e.g. the current "ULN" for indirect bilirubin as per Harriet Lane Handbook is 0.4~~**) (In the 2018 version of the Harriet Lane Handbook, for a full term infant, the ULN for total bilirubin is 1.2 mg/dL (21µmol/L) and for direct bilirubin is 0.2 mg/dL (3.4 µmol/L); thus the ULN for indirect bilirubin would be 1.0 mg/dL (17.6 µmol/L)).**

C. Operational Guidance from Protocol CM #3, dated 31 March 2020

This CM provides operational guidance to study sites from the IMPAACT P1093 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 should contact the team (impaact.teamp1093@fstrf.org) with any questions or concerns regarding this CM or management of study participants.

Visit Scheduling

- 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.
- 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 missing a visit.
- Effective with the issuance of this CM, allowable windows are broadened as follows:

  Appendices IA, IB, IC and ID (All Cohorts, Stage I and Stage II)
  - Weeks 4, 8, 12 and 16 Visits: ±2 weeks
  - Week 24 Visit -6 to +4 weeks
  - Weeks 32 and 40 Visits: ±4 weeks
  - Week 48 Visit -4 to +6 weeks

  Appendix IE (Long-Term Follow-up)
  - Week 60 through Week 180 ±6 weeks
  - Week 192 Visit -6 to +12 weeks

  Appendix IF (Premature Discontinuation of Dolutegravir)
  - Week 4 Follow-Up Visit: -2 to +4 weeks
  - Every three months until resolved (if applicable): ±6 weeks

  Appendix IG (Participants who Start Rifampin)
  - Week 2 Visit ±2 weeks
  - Week 4 Visit -2 to +4 weeks
  - Week 12 and Every 8 weeks until end of rifampin therapy Visits: ±4 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 the parent/legal guardians 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 scheduled study visits should prioritize monitoring for adverse events and provision of study drug. With respect to specimen testing and storage, sites should follow the priority listing in the relevant Schedules of Evaluations. At sites where specimen collection and processing can be performed per the Laboratory Processing Chart, but HIV-1 RNA testing cannot be performed in real time, sites may collect, process, and store specimens for later testing (alternate laboratories must adhere to local regulations for clinical laboratory testing).
- Sites with no capacity to conduct in-person visits, either on-site or off-site, should consider whether any study procedures (e.g., history taking, adherence assessment) can be performed remotely (e.g., by telephone). If adverse events requiring further evaluation or management are identified during a remote contact, staff conducting the contact should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.

Study Drug Supply

- To avoid gaps in drug supply between visits, sites may dispense up to three months' supply of study drug, ensuring safety monitoring and addressing potential needs for dose modification due to weight gain. Further considerations are as follows:
  - Participants who have been dispensed an extra supply of study drug should still come for their scheduled visits, if possible.
  - If a participant is expected to grow into a higher weight band requiring a dose increase soon, sites should ensure accurate contact information with the family; if an in-person visit is not possible, study drug dose modifications may be implemented with dosing instructions provided to the participant's caregiver by telephone based on weight reported by the caregiver. Any such instruction should be source documented in the participant's study chart.
  - Sites should also make every effort to ensure adequate supplies of the other antiretroviral agents that comprise participants' optimized background treatment regimens.
- 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).

Documentation

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT P1093.
- 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
  - Dose modifications implemented remotely
- 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.