Site-Specific Letter of Amendment #1 for
Chiang Mai University (CRS 31784) and Shandukani Research (CRS 8051)

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 4.0 dated 13 April 2016

DAIDS ES # 11773
IND# 110,847

Letter of Amendment Date: 9 December 2016

Information/Instructions from the Division of AIDS

This Letter of Amendment (LoA) is specific to Chiang Mai University (CRS 31784) and Shandukani Research (CRS 8051). This LoA is not applicable to any other study sites.

This LoA must be submitted to the relevant Institutional Review Boards (IRBs)/Ethics Committees (ECs) as soon as possible for review and approval with the attendant revised site-specific informed consent form. IRB/EC approval is required prior to implementation of this LoA. Approval must also be obtained from other site regulatory entities if applicable per their policies and procedures. All IRB/EC and regulatory entity requirements must be followed.

Upon receiving IRB/EC approval and approval of any other applicable regulatory entities, this LoA is to be implemented immediately; updated informed consents should be used only for participants in which this LoA is applicable. The site is still required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The site will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. The site should not await this notification before implementing this LoA.

This LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO should be retained in the site’s essential documents files for IMPAACT P1093.

Summary of Revision and Implementation

Protocol Section 6.3 and the Informed Consent Templates indicate that the study drug (dolutegravir (DTG)) is to be provided by the pharmaceutical partner to participants who are deriving benefit from it after their study completion through a mechanism outside of the study, until one or more specified conditions are met (protocol Section 10.6). This original intention remains unchanged. However, to ensure that there is no gap between the time a participant completes the protocol-specified three-year safety follow-up period and when the drug is available outside of the study, it is clarified that participants at the Chiang Mai University Site (CRS 31784) and the Shandukani Research Site (CRS 8051) may remain on study for up to an additional 108 weeks (Week 300) with visits every 12 weeks (effectively extending the safety follow-up period for these participants) with DTG provided and safety visits and
laboratory monitoring continued at the same frequency specified in the Schedule of Evaluations in Appendix IE. This LoA is specific to these two sites because it is expected that participants may be coming off study at these sites before DTG is available through a mechanism outside of the study.

To implement this change, Section 6.3 and the Appendix Informed Consent templates have been modified as follows with additions to the text indicated in bold and deletions in strikethrough.

- **Section 6.3 Long Term Safety Follow-up**

  Subjects who successfully complete 48 weeks of DTG treatment will continue to receive DTG as part of long term safety follow-up and will be seen in clinic every 12 weeks for safety visits, see Appendix IE for details. Study drug will be provided for the duration of the study, including the three-year safety follow-up period **(Week 192)** defined in the protocol. Thereafter, subjects will be transitioned into care and treatment outside of the study, see Section 10.6. **Long-term follow-up for participants at Chiang Mai University (CRS 31784) and Shandukani Research (CRS 8051) sites may be extended up to an additional 108 weeks, to Week 300, with visits every 12 weeks at weeks 204, 216, 228, 240, 252, 264, 276, 288, and 300, per Appendix 1E.**

- **Appendix II and Appendix III, Informed Consent Templates for Subjects Enrolling in STAGE ONE and STAGE TWO**

*Long Term Follow-Up, 1st paragraph*

After you have been on study drug for approximately 48 weeks, you will enter the long term follow-up phase of the study. You will be asked to come back into clinic every 12 weeks (every 3 months) for 3 years. If the drug is not commercially available in your country after three years and your clinician determines that you/your child are deriving benefit from DTG, it will continue to be provided to you/your child but will no longer be provided through the study. *To be included at the Chiang Mai University (CRS 31784) and Shandukani Research (CRS 8051) sites only: However, if the drug cannot be provided outside of the study when you/your child complete the 3-year long term follow-up phase, you may stay in the study for up to approximately two additional years and continue receiving DTG and coming for study visits every 12 weeks as before until DTG is made available outside of the study.* Most visits will last about 30 minutes...