SUMMARY OF CHANGES

INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

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

(DAIDS Document ID 11773)

IND # 110,847 Held by NIAID

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Version 4.0, Dated 13 April 2016

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT P1093 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for review and approval. This amendment impacts the study informed consent forms (ICFs); all study sites must prepare updated ICFs and obtain IRB/EC approval of the updated forms. Approval must also be obtained from other 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, all sites should immediately begin implementing this amendment and using the updated ICFs. After all required approvals are obtained; updated ICFs should be used for all new participants. In addition, previously enrolled participants, at the next study visit, must be re-consented using the updated ICFs unless otherwise directed by the IRB/EC.

All study sites must submit an amendment registration packet to the DAIDS Protocol Registration Office (PRO); however, approval from the DAIDS PRO is not required prior to implementing the amendment.

This Summary of Changes, Version 4.0 of the protocol, corresponding site-specific ICFs, and all associated IRB/EC and regulatory entity correspondence should be retained in each site’s essential document files for IMPAACT P1093.
Summary of Revisions and Rationale

This protocol amendment addresses the following:

- Expansion and updating of the relevant protocol sections to include current data on the safety and PK of dolutegravir.
- Modification of the study design to include evaluation of dolutegravir dispersible tablets.
- Operational complexities and challenges.
- Broadening and clarification of eligibility criteria for both treatment naïve and treatment experienced participants.
- Incorporation of prior protocol clarifications memoranda and letters of amendment.
- Other administrative corrections, clarifications and updates.
- Modification of the sample informed consent forms (as needed) to reflect all other protocol modifications.

The changes and rationale are summarized briefly below, generally in order of first appearance in the protocol.

- Throughout the protocol, the version number was updated to Version 4.0 and the version date was updated to 13 April 2016; and ‘GSK1349572’ was replaced with ‘dolutegravir.’
- The protocol team and site investigator rosters were updated to reflect current membership and contact details; the glossary was also updated.
- The background, rationale and attendant references were updated to include additional information on the safety, efficacy and pharmacokinetics of dolutegravir, Sections 1.1, 1.2, 1.3, 1.5 and 5.2. Section 1.4 was added and summarizes the pharmacokinetic data from P1093 Cohorts I and IIA.
- The eligibility criteria was modified to allow enrollment of ARV treatment naïve participants less than 2 years old, defined as not having initiated ARVs for treatment but could have received ARVS for prophylaxis. In prior protocol versions only treatment experienced children were eligible for enrollment. In Version 4.0, enrollment has been expanded to include treatment-naïve infants and children. This expansion is based on information obtained from children and adolescents enrolled into Cohorts I and IIA of the study, establishment of the DTG doses for those age ranges, regulatory approval of dolutegravir for children > 12 years of age, and inclusion of DTG as a recommended first line therapy for adolescents and adults in U.S. Public Health guidelines.

The enrollment criteria was also broadened to include participants who are receiving ARVs for treatment and have been on a failing regimen for 4 to 12 weeks prior to enrollment (modified from 8 to 12 weeks) OR for participants < 2 years of age and have initiated ARVs for treatment < 4 weeks prior to screening (Section 4.1.3). Unchanged are the requirements to have HIV-1 RNA viral load greater than 1,000 copies/mL of plasma at screening and if not currently receiving ARV the participant must have been off ARVs for ≥ 4 weeks. In addition, the eligibility criteria were clarified to indicate that infants who received ARVs for PMTCT are eligible for enrollment.

- Justification for the changes in eligibility criteria and guidelines for initiation of ART and DTG to ensure that treatment initiation remains in accordance with current guidelines and standard of care has been added. (Sections 1.5, 1.6, 1.6.3, 3.1 and 6.2.3.) Section 4.2.16 (ARV treatment naïve exclusionary criterion) was removed and inclusion criterion Section 4.1.3.2 was added. In addition the third primary objective was modified to include evaluation...
of steady-state pharmacokinetics in infants who are treatment naïve in addition to treatment experienced infants. (Schema, Section 2.1)

- The procedure for optimizing background therapy relative to the PK studies was clarified to accommodate the diversity in ARV status now possible. For those enrolling in Stage I, dolutegravir is initiated on enrollment in all subjects, intensive PK occurs on day 5-10, and then background therapy is optimized immediately after completion of the PK visit, based upon genotype testing results, with permission of the team. If the participant is <2 yrs of age (cohort IV and V) and the genotype results are not available after the PK visit is complete, the background regimen should be modified immediately when the genotype results are available, with permission of the team. For those enrolling in Stage II, background therapy is optimized immediately upon enrollment, and first population PK study is performed at study week 4. (Sections 3.1 and 6.2.3)

- NVP, which was disallowed for participants enrolled in Stage I (Version 3.0) is now considered a disallowed medication for Stage II too. (Sections 4.1.4 and 4.3.1) due to uncertainty about its effect on dolutegravir metabolism. Prior exposure to NVP is permitted however participants must not have received NVP (prophylaxis or treatment) for 14 days prior to initiation of dolutegravir treatment; potential participants may be screened during this period of time though. Sections 4.1.4 and 4.3.2 and Table 11.

- The protocol has been modified throughout to include evaluation of a new pediatric formulation - dolutegravir dispersible tablets (DT) - for the younger age cohorts which is expected to replace the granule suspension preparation. This modification was included and planned for in Version 3.0. Cohorts III-DT (≥ 2 to < 6 years of age), IV-DT (≥ 6 months < 2 years of age, and V-DT (infant ≥ 4 weeks to < 6 months of age) were added to evaluate the dispersible tablet formulation. The dolutegravir dispersible tablets are expected to become available in 2nd quarter 2016. Enrollment to the granule formulation will continue until the dispersible tablets are available at the participating clinical trial unit, unless notified to the contrary by the P1093 Team. Specifically the following sections are added/modified:
  - Background Section 1.3 was updated to include additional information on the dolutegravir dispersible tablet formulation.
  - The sample size for evaluable subjects has been increased to 120 from 100 subjects. The sample size for Stage I remains unchanged with ten subjects targeted for enrollment. (Schema, Sections 3.0, 8.1, 8.4, 8.6.2.1 (Table 15)). The sample size for Stage II may include both participants receiving either granule suspension or DT although a minimum of 6 participants for these Stage II age cohorts must be initially assigned to receive the DT formulation (Section 3.2). The overall estimated sample size of 160 remains unchanged.
  - The study design was updated to include the evaluation of dispersible tablets and the new cohorts. (Section 3.3 was added and the Schema, Sections 3.0, 3.1, 3.2, 3.3 and 8.1 were updated.)
- The protocol has been modified to allow cohorts III-DT, IV-DT and V-DT to open as soon as a dose for granules in suspension has been determined for their respective cohorts. This change could mean that cohorts III-DT, IV-DT and V-DT would open simultaneously as opposed to sequentially, as in Version 3.0. The rationale for this is that dispersible tablets resulted in PK exposure that, on an mg to mg basis is bioequivalent to granules in a relative bioavailability study in adults. Therefore, the team expects that the initial dose to be studied in DT-mini cohorts would be more appropriately approximated based upon a dose generated from an age matched, granule mini-cohort that has already been completed as opposed to extrapolating from data generated from the next older DT-mini cohort. (Sections 3.3 and 8.1)

- Throughout the protocol ‘granules in sachets’ and other references to sachets were removed. This formulation was used in Version 3.0 as a place holder for the new pediatric formulation.

- Instructions and information regarding switching to dispersible tablets from granule suspension were added. (Sections 3.1, 3.2, 3.3.1, 5.0, 5.1.3 and 8.1)

- The Study Treatment Section was updated throughout to add information for the dispersible tablet formulation. (Sections 5.0, 5.1, 5.2, and 5.3)

- Preparations and dosing instructions for the granule suspension was removed from the protocol (Appendix IV). This information will be included in the study-specific Manual of Procedures (MOP) along with instructions for dispersible tablets.

- The target exposure for AUC_{0-24} and C_{24h} remain unchanged however the range of acceptable variability around these targets has been expanded based upon safety data generated from the study of dolutegravir 50 mg PO BID. Sections 1.6 and 9.0 are updated.

- For Cohorts III, IV and V (granule suspension Cohorts) – participants who switch from granule suspension to dispersible tablets and have completed 24 weeks of follow-up (note: population PK is already scheduled at 4, 12 and 24 weeks of follow-up) will have population PK blood samples collected at the ‘2-week switch visit’ and the next scheduled visit. (Section 9.2.2 and Appendices IA, IB, IC, ID and IE)

- The frequency of study visits for participants in long term follow-up on the granule formulation was modified from 8 weeks to 12 weeks due to the demonstration of an increased shelf-life of the granule formulation since finalization of protocol Version 3.0, requiring less frequent visits to refill medication. This change will harmonize the follow-up visits for participants on the granule formulation with participants on the tablet formulations, Section 6.3 and Schedule of Evaluations.

- The protocol was clarified to indicate that in addition to collection of samples for HIV genotypic and phenotypic resistance who experience virologic failure during the first 48 weeks of follow-up collection for HIV genotypic and phenotypic drug resistance and plasma/PBMC should continue for participants who experience virologic failure beyond week 48 (participants in long-term follow-up). (Section 6.2.5 and Appendix IE)

- The inclusion criterion for confirmation of HIV infection prior to study entry was updated to reflect current IMPAACT network policies and to allow enrollment of participants < 18 months of age with one positive result. (Sections 4.1.2, 6.6.6 and 6.2.1)
• To allow rapid enrollment to the younger cohorts subjects < 2 years old are not required to have the genotype testing results available at screening prior to enrollment. These subjects can enroll and if found to have no active drugs per genotype will discontinue study drug unless they have a > 1 log decrease in HIV RNA by 4 weeks post initiation of DTG. (Sections 4.1.10, 6.2.1, 6.2.3.3, 6.6.8).

• Subjects < 2 years old are not required to have the HIV-1 RNA result from screening available prior to enrollment. These subjects can enroll and if found to have a screening HIV-1 RNA of \( \leq 1000 \text{ c/ml} \) the subject will discontinue study drug. (Sections 4.1.5 and 6.6.7)

• An exclusion criterion for infants < 3 kgs at enrollment was added. (Section 4.2.2)

• The dosing regimens for the three different dolutegravir formulations being evaluated 10, 25 and 50 mg tablets, granules in suspension and the dispersible tablets was updated based on results from protocol Version 3.0 and other studies. (Sections 1.6.2, 5.1)

• Guidance for subjects to continue dosing at their given cohort dose throughout their participation in P1093 even as grow into an older cohort dose has been added to Section 5.1.

• A hypothesis section was added. (Schema and Section 1.7)

• Instructions for documentation of subjects from whom informed consent is obtained, but who are deemed ineligible or who do not enroll into the protocol for any reason has been provided Section 4.4

• References for participants who have completed follow-up to enroll in P1074 have been removed as that study has ended. Section 6.2.5

• Instructions to allow subjects enrolled in the mini-cohort who did not meet PK targets to switch to the new approved dose upon approval from the Protocol Team has been added to Section 6.2.4, Stage I 4th paragraph.

• The algorithm for resistance testing has been clarified to indicate that testing should be done in participants with virologic failure for subjects who continue on study after confirmation of virologic failure if HIV RNA is >400 copies/mL, Section 6.2.7 and Appendix IE.

• Throughout Section 8, the term SADR has been replaced with ‘drug-related adverse event.’

• Instructions for provision of dolutegravir at sites where dolutegravir is not available through standard of care, after a participant completes follow-up have been clarified. Section 10.6 is added and Section 6.3 is modified.

• A new criterion for study discontinuation has been added. Section 6.5.6.

• The viral load secondary outcomes classifications for virologic failure has been updated. Section 8.6.2.2 bullet c.

• The guidelines for dosing and drinking/eating around intensive PK sampling timepoints have been updated. Section 9.2.1.2.

• Appendix II (Dosing Tables) was removed. The dosing tables will be provided outside of the protocol on an open-access website. Subsequent appendices have been re-numbered.

• Appendix VII and VIII were removed and Appendix IV ‘Sample Informed Consent Form for Specimen Storage and Future Use’ for both NICHD and NIAID sites was added.
• Three Letters of Amendment (LoA): LOA #1 (dated 8 March 2013); LOA #2 (dated 15 November 2013); and site-specific LOA #3 (dated 18 September 2015) and three Clarification Memoranda (CM): CM #1 (dated 6 May 2013); CM #2 (dated 3 December 2014); and CM#3 (dated 8 September 2015) were incorporated.

• Other modifications to the Schedules of Evaluations Appendices IA – IG and II follow:
  - Appendices IA – ID and IG – the off treatment column has been renamed to Premature DC of Study Drug/On Study
  - Appendix IA – ID - samples storage for integrase resistance testing has been added to the Enrollment visit and genotyping and phenotyping has been added to the premature DC of Study Drug/On study visit (only if not done at failure).
  - Appendix IF was removed and subsequent appendices re-numbered. The procedures for participants in long-term follow-up who receive study provided dolutegravir or locally provided dolutegravir have been combined Appendices IA – ID and IG –
  - Appendices IA – IE - procedures for shipment of specimens for genotypic failure have been clarified
  - Appendices IC, ID and IG – guidelines for dosing and drinking/eating around intensive PK sampling timepoints have been updated.
  - Appendices IA – IE for participants who switch from granules to dispersible tablets a 2 week post switch visit has been added for a palatability assessment, HIV-1 RNA PCR and population PK sampling. In addition at the next scheduled visit these participants will have population PK sampling done.
  - Appendices IA – ID – The blood volume amounts for PK samples was reduced to 0.5 ml/sample and the blood volume amount for phenotyping was reduced to 2.0 ml. The blood amount for hematology for Cohorts IV and V was reduced to 0.5 ml.
  - Appendices IA- AD the following note is added under population PK sampling: For subjects on BID dosing refer to the study MOP for sampling time points.
  - Appendix IE includes the long term follow-up schedule for all formulations/cohorts.
  - Appendices IA – IE - an additional visit after participants switch from granule suspension to dispersible tablets and instructions for collecting PK specimens at this visit as well as at the next scheduled visit were added.
  - Appendices IE and IF – visit windows are added.
  - Appendix IE – genotyping is added every 48 weeks, as required and a virologic failure visit are added

• Modifications to Appendices II and III - Sample Consent Forms follow:
  - A statement has been added that dolutegravir is FDA-approved for use in children 12 years and older.
  - The frequency of study visits for participants in long-term follow-up was modified from 8 weeks for participants receiving granule suspension to 12 weeks.
- Information related to the available formulations of DTG has been updated to include dispersible tablets (referred to as dissolvable tablets throughout the consent). Specifically:

- Children older than 4 weeks of age - < 12 will receive dispersible tablets and acknowledgement that children between 6 to < 12 years of age may be allowed to switch to the film-coated tablet formulation at the discretion of the study team,

- Information regarding switching participants from DTG granule suspension to dissolvable tablets has been included. Notably, participants will be asked to return to clinic for a “2 Weeks Post-Switch” Visit in which they will complete a palatability assessment and a have an additional blood draw (for Population PK) at this visit and the next scheduled visit.

- Blood volumes have been updated throughout

- Guidelines for eating and drinking around the time of the Intensive PK Visit have been modified.

- The Study Risks section has been updated to include information from recent adult Phase I and Phase II B clinical trials.

- The benefit sections have been modified to indicate that while the team will work to provide post-trial access there is a possibility that drug may not be able to be provided.

- The On study Section, the specific timing of the collection of PK samples has been removed to allow for variability with BID dosing. The number of samples and volume collected remains the same.

- The purposes and Procedures section under ‘What do I/does my child have to do if I am/he/she becomes infected with tuberculosis while on this study?’ the timing of sample collection and blood volumes for the population PK samples has been corrected and is now consistent with Appendix IG.

- The language regarding storage and future use of samples has been removed for both NICHD and NIAID and a separate consent for storage of samples (Appendix IV) has been added for all sites.