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

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Version 5.0, dated 12 July 2018
DAIDS Study ID #11773
IND #110,847

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Information/Instruction to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT P1093 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 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 IRB/EC and regulatory entity requirements must be followed.

Before this LoA can be implemented at each site:

• All IRB/EC approvals and any other applicable regulatory entity approvals must be obtained

AND

• 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

Before the above two requirements are met, study implementation will continue under the previously-approved version of the protocol. Once the above two requirements are met, study sites should immediately begin implementing this amendment, using the Version 5.0 ICFs. Site-specific Version 5.0 ICFs should be used when obtaining informed consent for all participants enrolled under protocol Version 5.0. In addition, for previously enrolled participants, re-consent for study participation should be obtained at the next study visit using site-specific Version 5.0 ICFs.

Upon receiving IRB/EC approvals and any other applicable regulatory entity approvals, all sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS
PRO) at the Regulatory Support center. Sites will then receive a registration notification for the amendment 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 amendment. Modifications that are generally applicable to the study overall, across all sites, will be implemented immediately upon issuance of this amendment; these include designation of $C_{24h}$ as a primary endpoint and $\text{AUC}_{0-24}$ as a secondary endpoint; updates of PK exposure targets and ranges; and evaluation of PK exposures by weight band.

Please file this Summary of Changes, Version 5.0 of the protocol, corresponding site-specific ICFs, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for IMPAACT P1093.
Summary of Revisions

The primary goals of this protocol amendment were to increase the target 24-hour trough (C_{24h}) geometric mean (GM), to elevate the C_{24h} to be the primary outcome measure, to include an analysis by weight-band group in addition to age cohorts and to address emergent safety findings on dolutegravir (DTG) use at the time of conception from another study.

A list of revisions follows:

— Expansion of and updates to the relevant protocol sections and informed consent forms to include current data from P1093 and other adult studies on the safety and PK of DTG.
— Inclusion of updates to the relevant protocol sections and informed consent forms summarizing the interim analysis of an observational study from Botswana (Tsepamo) of women receiving DTG at the time of contraception.
— Inclusion of updates and clarifications to the relevant protocol sections and Schedules of Evaluations to ensure adequate and documented contraception use for female participants of child bearing potential.
— Inclusion of updates to the relevant protocol sections on the modeling and simulation of pharmacokinetic (PK) parameters to inform DTG dosing.
— Modification of the study design to include evaluation of dosing by weight band in addition to age cohort, as weight-band based dosing is increasingly being recommended by WHO and other entities.
— Modification of the intensive PK sampling procedures to include analysis of intensive PK in a non-fasting state – if determined necessary – in addition to a fasting state as previously specified.
— Promotion of C_{24h} to the primary PK parameter endpoint.
— Revision of the C_{24h} and AUC_{0-24} targets for evaluation of PK as follows: For C_{24h}, geometric mean (GM) target value of 995 ng/mL (changed from 750 ng/mL) with a range of 697 to 2260 ng/mL (changed from 500 – 2600 ng/mL). For AUC_{0-24}, the GM target of 46 ug.h/mL remains unchanged and the range is modified to 37 to 134 ug.h/mL (changed from 37 – 86 ug.h/mL).
— Increase in the overall sample size to “up to 300” participants (from “up to 160”) to ensure adequate numbers of participants for assessment of weight-band based dosing in addition to assessment within age cohorts.
— Broaden eligibility criteria to include treatment-naïve participants of any age (rather than only treatment-naïve participants under two years of age). The inclusion of treatment-naïve children at any age is based on cumulative safety data, and the rationale that it is likely to be used and recommended as first-line therapy in children.
— Inclusion of updated toxicity management guidelines and supplemental parameters for psychiatric events consistent with the current Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.
— Inclusion of updates to the protocol to reflect closure of Cohorts III and IV to further enrollment and removal of Cohort V which never opened to accrual; these three cohorts included the pediatric granule for suspension formulation which will not move forward for licensure. Evaluation of the film-coated tablets and dispersible tablets will continue under protocol Version 5.0.
— Inclusion of updates in the protocol and sample informed consent forms regarding entities who may access participant records.
— Modification of the sample informed consent forms to reflect all other protocol modifications, as needed.
— Incorporation of modifications included in prior clarification memoranda and letters of amendment associated with protocol Version 4.0.
— Other administrative corrections, clarifications and updates.
— Inclusion of a Protocol Signature Page.
Implementation of Changes and Rationale

The changes in the protocol text and informed consent forms are summarized below, generally in order of first appearance in the protocol.

- The protocol team and site investigator rosters were updated to reflect current membership and contact details; the abbreviations and definitions page was also updated.
- The background, rationale and attendant references were updated to include additional information on the safety, efficacy and PK of DTG including updates from PK and safety data from P1093 available as of 14 December 2017 (Sections 1.1, 1.2, 1.3, 1.4, and 1.5).
- Interim analysis of an observational study in Botswana (Tsepamo) revealed that 4 of 426 women receiving DTG at the time they became pregnant gave birth to infants with neural tube defects (NTDs); this rate of NTD was higher than that in women receiving other ARVs at the time of conception. No elevated risk of NTD was identified among infants of women who initiated DTG later in pregnancy. A mechanism for DTG to cause NTD has not been identified, and the potential association will be investigated further with data from the same ongoing study and other settings. However, the finding raises concern that DTG might affect the embryo in the first few weeks of pregnancy when the neural tube is formed. Version 4.0 of the protocol required that female participants of child-bearing age use at least two forms of contraception to prevent pregnancy; this was specified in the inclusion criteria (Section 4.1.8), section about pregnancy testing (Section 6.7.1), and in the informed consent forms (Appendices II and III). In addition, female participants who become pregnant should discontinue study drug immediately (Section 6.7.2). To further address participant safety, the following updates have been made:
  — Section 1.5 (Summary of Safety in Clinical Trials) and the informed consent forms (Appendices II and III) were updated to include pregnancy risk information on the Tsepamo findings.
  — Section 4.1.8 was re-worded for clarity; no operational changes were made.
  — Section 6.2 (Screening) was updated for consistency with the entry criteria and the requirement that participants must agree to use two forms of contraception if they are of reproductive potential and sexually active.
  — Section 6.7 (Pregnancy and Contraception) was updated to indicate that female participants aged 9 years and older will be asked during follow-up if they have reached menarche; if so, these participants will be asked if they are sexually active. For compliance with the protocol, sexually active participants are required to use two forms of birth control (acceptable methods are specified in Section 6.7). Instructions were also added for sites to contact the protocol team if a participant is unable or unwilling to use contraception.
  — Footnote 2 in Appendices IA and IB (Cohorts I, IIA, IIB, III and III-DT) was modified to include menarche status (females 9 years and older) and, for participants who have reached menarche, contraceptive use has been added to the history and physical exam requirements.
- A primary objective of P1093 is to characterize the PK of DTG in pediatric participants and compare the levels to those in adult participants to enable adequate dose selection in pediatric participants. In Version 4.0, both steady state AUC_{0-24} and C_{24h} were primary PK parameters with AUC_{0-24} designated as the primary endpoint for comparison. Recently, regulators have suggested that C_{24h} be elevated to a primary endpoint. Therefore, in protocol Version 5.0, C_{24h} is designated as a primary endpoint for PK comparison in parallel with AUC_{0-24} as a secondary endpoint. To ensure participant safety, the PK exposure targets and ranges for C_{24h} and AUC_{0-24} and acceptable individual minimal and maximal exposures have been updated based on available data in adults receiving 50 mg once daily and data collected in P1093.
  — Sections 1.6 and 1.6.1 were updated to include a rationale for this modification as well as the target PK exposures and ranges.
  — Schema, Section 2.1 (Primary objective #3), and Section 9.1 Clinical Pharmacology objective #1 were modified to indicate C_{24h} as the primary endpoint.
• Emerging data from Cohort IIA through V-DT showed that $C_{24h}$ (primary PK endpoint) was not comparable to the predefined target in pediatric participants weighing <30kg. Higher doses were selected to achieve a predefined $C_{24h}$ target based on modeling and simulation. Simulations from the interim population PK model showed that the proposed doses will provide trough concentrations in the target range.
  — The rationale for selection of higher doses to achieve higher $C_{24h}$ concentrations was added to Section 1.6.2.
  — A new section, Section 9.3 entitled “Evaluation of PK Exposures for Cohorts and Weight Bands” was added and includes information regarding analyses by weight band groups as well as information that was moved from Section 9.0.

• The fundamental P1093 study design remains unchanged and is designed to enroll participants and analyze data based on age cohorts. Since the study was first initiated, the WHO and other groups around the world have advocated moving away from age-based dosing and for consistent weight band based dosing. Regulatory agencies increasingly expect and analyze pediatric data by weight band to facilitate weight-based dosing recommendations in product labelling. Rather than modifying the P1093 study design from age-based enrollment to weight-based enrollment, analysis of WHO-recommended weight bands is included as a key secondary consideration in Version 5.0. Enrollment will be monitored to ensure that minimum numbers of participants are accrued both into each age cohort and into each relevant WHO weight band to facilitate robust weight-based data.
  — Section 1.6.5 was added to provide a rationale for adding dose analysis by weight band.
  — Section 3.1 were streamlined to provide an overview of the study design only and to introduce weight band analysis; language related to participant management was moved to Section 6.0
  — Section 3.4 was added to provide an overview of analysis by weight band.
  — Schema and Section 2.2, secondary objective #7 was modified to include analysis by weight band.
  — Figure 2 was updated to include weight band analysis and modifications to the study design described in Section 3.1.
  — Section 3.4 was added to describe evaluation by weight band.
  — Section 8.1 was expanded to include evaluation by weight band and an updated definition of evaluable participants.

• The eligibility criteria were modified to allow enrollment of ARV treatment-naive participants at any age, defined as not having initiated ARVs for treatment but could have received ARVs for prophylaxis. In Version 4.0, only ARV-naive participants < 2 years old were eligible for enrollment. This expansion is based on cumulative safety data in P1093 with the rationale that it is likely to be used and recommended as first line therapy in children.
  — Section 1.6.4 was added with rationale and justification for enrollment of naive participants at any age.
  — Entry criterion 4.1.3.2 was modified to allow ARV-naive participants of any age to enroll.
  — Entry criterion 4.1.10 was modified to allow enrollment of participants ≥ 2 years of age and ARV naïve with genotype results pending. This is consistent with enrollment requirements for participants < 2 years of age and ARV naïve.
  — Section 6.3 was updated with instructions for initiation of DTG and optimization of OBT in ARV participants ≥ 2 years of age and ARV naïve with genotypes pending.

• Schema and Section 2.2 – Secondary Objective #5 was clarified to include efficacy in addition to tolerability and safety as parameters for long-term follow-up. No procedural or statistical changes were modified; the protocol intent has not changed.

• Sections 3.3 and 5.0 were updated to reflect the closing of Cohorts III and IV to further enrollments and removal of Cohort V which never opened; these cohorts included the granules for suspension formulation which will not move forward for licensure. Evaluation of the film-coated tablets and dispersible tablets will continue under protocol Version 5.0.

• Section 4.3.1 – The examples of products of products containing divalent cations has been updated.
• Section 4.3.2 – Recently approved Bictegravir and other INSTI drugs were added to the list of disallowed medications.
• Section 5.1 – Instructions for redosing were added.
• Section 5.2.1 – Dolutegravir Film-coated Tablets – has been modified to indicate that the desiccant may not be provided.
• Section 5.2.3 – Administration procedures for dispersible tablets were updated and now include the option for placing the tablet directly on the tongue for Stage I participants after intensive PK and for all Stage II participants.
• Sections 6.1.1 through 6.1.8 were modified for consistency and clarity and table 12 was added to provide further clarification. The procedures remain the same.
• Section 6.4, entitled “Dose Adjustments” was added. Information regarding individual dose modifications from Sections 3.0, 8.0 and 9.0 were consolidated and moved to this section. No operational changes were made; individual dose modifications were allowed under previous protocol versions under the same circumstances.
• Section 6.5 and the Schedules of Evaluation (SoEs) in Appendices IA- IE and IG – Clarified that the date the specimen was collected for RNA testing is the date from which the 4-week visit for confirmation should be targeted.
• Section 6.6 and throughout the protocol – The overall study duration was clarified to indicate that participants are followed for about three years in long-term follow-up after completing 48 weeks of the study. The total follow-up period is 192 weeks.
• Section 7.3 – A supplemental table for grading of psychiatric events consistent with the most recent version of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) was added. All other events will continue to be graded following the DAIDS AE grading table V1.0, December 2004, Clarification August 2009.
• Section 8.5.3 – Safety Guidelines for Minimum Eight Participants Started at a Given Dose Level in Each Weight Band – was added.
• The total sample size was modified from up to 160 to up to 300 to allow for additional enrollments to complete weight band group analyses as well as age cohorts. The target number of evaluable participants at the accepted dose across all cohorts remains unchanged at 120. The Schema, Section 8.4 and sample informed consent forms were updated to reflect this change.
• The safety guidelines for weight band group were added in Section 8.5.3.
• The “Secondary Objective Analyses” were updated to describe data by weight band in addition to age cohorts. The Safety Guidelines for the Total Group, with a Minimum of Ten Participants Started at a Given Dose Level in Each Stage I Cohort, was updated in Section 8.6.2.2.
• Section 9.2.1 – Intensive PKs (Stage I) – Guidelines and procedures for intensive PK sampling while fasting in Stage I were made more concise; information from Sections 9.2.1.1 and 9.2.1.2 was moved to this section.
• A new section, Section 9.2.1.3 entitled “Sampling Non-Fasting (All Cohorts)” was added to provide instructions and guidance for intensive PK sampling in Stage I with feeding. These instructions will be followed if - upon review of PK data obtained with fasting - the Protocol Team determines that an additional PK evaluation should be performed in a non-fasting state to obtain the targeted levels. PK sampling collection and processing procedures are the same as for fasting.
• Information and instructions regarding consent for participants who reach the legal age of consent while in follow-up was added in Section 10.3.
• A new section, Section 10.4 entitled “Essential and Source Documents and Access to Source Data” was added.
• Updated language regarding regulatory entities that may review study records: Per ICH GCP E6 4.8.10(n) and DAIDS requirements, indicating that it is mandatory that all DAIDS-sponsored and/or supported trials include language that informs participants that other U.S., local, and international
regulatory entities may also review study records. This information in Section 10.4 and the sample informed consent forms has been updated accordingly.

- Section 10.5 was clarified to better reflect current IMPAACT guidelines.
- Sections 10.8 (Reimbursement/Compensation) and 10.9 (Management of New Information Pertinent to Study) are added.
- The target exposure for C24h was increased and remains unchanged for AUC0-24; however, the ranges of acceptable variability around both of these targets have been expanded based on safety data generated from P1093 and the study of DTG 50 mg PO BID. Sections 1.6.1 and 9.3 were updated accordingly.
- Entry criteria 4.2.3 and 4.2.4 were corrected – the intent is the same, and the entry criteria were not modified.
- Four Clarification Memoranda (CM) to Version 4.0: CM #1 (dated 8 December 2016); CM#2 (dated 7 April 2017); CM#3 (dated 11 July 2017); and CM#4 (dated 30 January 2018) were incorporated.
- Modifications to the Schedules of Evaluations (Appendices IA – IG and II) follow:
  - Appendices IA – IE and IG – columns entitled ‘Dose Adjustment PK Visit’ and ‘Dose Adjustment Safety Visit’ were added to include procedures specified when a participant’s dose is adjusted, per Section 6.4.
  - Appendices IA – IE and IG – a column entitled ‘Confirmed Suspected Virologic Failure’ was added for the visit completed to collect a second sample for HIV-1 RNA testing to confirm virologic failure. In addition, the footnotes for RNA PCR testing for this visit were clarified to ensure consistent terminology throughout the protocol and define the 4-week sampling timepoint for this visit as four weeks after collection of the same for the initial RNA PCR test. No change in procedures was made.
  - Appendices IA and IC – The language in the footnotes for intensive PK sampling was reorganized and new language was added to indicate that sampling may be done in a non-fasting state, per the Protocol Team’s request. No procedures were modified for intensive PK sampling with fasting.
- Modifications to Sample Informed Consent Forms follow:
  - Appendix II: Information was added to indicate that intensive PK sampling may be done in a non-fasting state.
  - Appendices II and III:
    - The Study Risks section was updated to include information from recent DTG clinical trials, the Tsepamo study (see above) and for consistency with the updated Investigator Brochure, V11.
    - The number of people who will take part in the study was revised to up to 300.
    - The What About Confidentiality Sections have been updated to include ‘other U.S., local and international regulatory entities’ as entities that may review research records.
    - The Long-Term Follow-Up section has been revised to indicate that contraception use will be assessed during follow-up.
    - Clarifications were made to the language regarding contraception use; no operational changes were made.