Letter of Amendment #1 for:

IMPAACT P1108
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) Given in Combination with an Individualized Rifampin-Resistant Tuberculosis (RR-TB) Therapy in Infants, Children, and Adolescents with RR-TB Disease, Living with or without HIV

Version 2.0, dated 21 September 2022

DAIDS Study ID #11884
IND #131,832 Held By DAIDS

Letter of Amendment Date: 2 May 2023

Table of Contents

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT P1108 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 and regulatory entity approvals, each site should 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 (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 document files for IMPAACT P1108. If the IMPAACT P1108 protocol is amended in the future, applicable contents of this LoA will be incorporated into the next version of the protocol.

IMPAACT P1108
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) Given in Combination with an Individualized Rifampin-Resistant Tuberculosis (RR-TB) Therapy in Infants, Children, and Adolescents with RR-TB Disease, Living with or without HIV

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Version 2.0, Letter of Amendment #1
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 Harmonisation 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 primary purpose of this LoA is to remove accrual requirements for participants living with HIV in each cohort to minimize delays in study completion due to a general decline in potential participants living with HIV presenting for RR-TB treatment. This LoA also incorporates the contents of protocol Version 2.0 Clarification Memorandum #1, dated 29 March 2023; clarifies expectations for confirming BDQ adherence prior to the Week 2 visit; and updates the protocol team and study site rosters to reflect current membership.

Implementation

Modifications of protocol text are presented below. Where applicable, modified text is shown using strikethrough for deletions and bold type for additions.

1. *Schema, Sample Size:*

   Up to 84 participants total (24 for Cohort 1; 30 for Cohort 2; 30 for Cohort 3) to achieve 54 evaluable participants (18 per age cohort):

   Cohort 1: Age ≥ 6 to < 18 years
   Cohort 2: Age ≥ 2 to < 6 years
   Cohort 3: Age ≥ 0 to < 2 years

   ~~In each cohort, at least three participants living with HIV will be enrolled.~~

2. *Section 3.1, Cohort Approach, second paragraph:*

   Up to 24 participants in Cohort 1, up to 30 participants in Cohort 2, and up to 30 participants in Cohort 3 will be enrolled to achieve at least 18 evaluable participants in each cohort. In Cohort 1, up to 12 participants will be enrolled in each of the two weight bands (15 to < 30 kg and ≥30 kg) to achieve approximately nine evaluable participants in each weight band. ~~In each cohort, at least three participants living with HIV will be enrolled.~~ See Section 9.4 for further details on participant evaluability and replacement of non-evaluable participants.

3. *Section 4.3, Determination of HIV Status, the first paragraph is removed:*

   ~~At least nine participants living with HIV (at least three per cohort) will be enrolled in the study. In consultation with the DAIDS and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Medical Officers, if there is agreement regarding the need for additional data in participants living with HIV (e.g., possible differences are observed in BDQ exposure related to drug-drug interactions) additional participants living with HIV (e.g., up to 5-10) may be enrolled across all cohorts, unless the maximum cohort sample size has been reached.~~

4. *Section 6.3, Week 1 Visit, Participants who received non-study BDQ doses prior to Entry and will have intensive PK sampling at the Week 1 visit, last paragraph:*

   BDQ TIW dosing will be initiated after the intensive PK sampling is completed (see Section 5.3). At the Week 1 visit, applicable reminders should be provided for the scheduled Week 2 visit (see Section 6.4). **The date, time, and dose amount administered for the two BDQ daily doses preceding the Week 2 visit should be confirmed prior to the visit. If this dosing information is not confirmed for the last BDQ dose taken prior to the Week 2 visit, the visit should be rescheduled within the allowable visit window, with adherence support provided to help ensure appropriate dose administration on days preceding the rescheduled visit date.** The participant and/or caregiver/guardian should be reminded not to administer BDQ at home on the day of sparse PK sampling at the Week 2 visit.

5. *Section 9.4, Sample Size and Accrual, second paragraph:*

   Total accrual will depend on the number of participants who must be enrolled to achieve a minimum of 18 participants in each of the three age cohorts with evaluable PK data, including approximately nine participants with evaluable PK data in each weight band in Cohort 1. ~~At least three participants living with HIV will be enrolled in each cohort.~~

6. *Section 9.6.1, Primary Safety Analyses, first paragraph:*

   The primary safety analyses will focus on the 24-week time period during BDQ treatment and will include only participants whose total exposure to BDQ ~~has been~~ **was** at the final ~~BDQ dose recommended~~ **implemented dose** for their cohort for the protocol-specified period of BDQ administration. Participants who have been removed from treatment, or who have had their doses reduced as part of cohort management due to toxicities, will be included and treated as safety failures in the primary safety analysis (note that such participants may have to be excluded from any secondary analyses which require complete follow-up at the optimal dose). Participants whose doses have been adjusted on the basis of PK results will be excluded from these primary analyses, regardless if the participant initiated BDQ at the final ~~recommended~~ **implemented** dose, and sensitivity analyses performed in an attempt to determine whether the exclusion of these participants creates a selection bias which impacts upon any results. These primary analyses will be performed after the last participant of the last cohort has completed the study drug regimen over the 24-week dosing period.

7. *Section 9.6.1, Primary Safety Analyses, fourth paragraph:*

   In addition, if possible, a primary evaluation of safety across the 24 weeks of study treatment will be performed on the data from participants who have been started at the final recommended dose for a given cohort and have remained on that dose for the 24-week period or have left the study or had a dose modification due to safety failure prior to 24 weeks of exposure (in which case the participant will be analyzed as a failure). Note that such an analysis may not be possible, since the PK modeling procedure which will determine the final recommended dose will not guarantee that an adequate number of participants be on that dose. However, secondary safety analyses will include all safety data collected from first participant exposure to the end of the study, with results broken down by dose. This will include data representing the final **implemented** dose for each cohort, as well as data gathered during the dose finding stage, which may represent exposure to doses which have failed.

8. *Section 9.6.2.1, Safety, first paragraph:*

   The 24-week analyses described above for the primary analysis will be repeated as secondary analyses at 72 weeks after BDQ discontinuation and by HIV status. Of note, precision may be limited for participants living with HIV, **and for cohorts with few participants living with HIV (e.g., one or two participants), estimation with confidence limits will not be feasible** ~~particularly if only the required minimum number of participants living with HIV are enrolled~~. In addition, descriptive and exposure-related analyses will present safety data from participants whose doses have undergone individual adjustment or who were treated on doses other than the final ~~recommended~~ **implemented** dose for their cohorts.

9. *Section 9.6.2.2, TB Treatment Outcomes:*

   This Phase I/II study will only be able to describe treatment response in participants; this is not an efficacy trial. The proportions of participants classified at the end of their RR-TB treatment regimen as having exhibited bacteriological cure (defined under Section 8.5), and clinical (probable) cure, will be presented, bounded with 95% CIs. The proportions of participants classified at the end of study (Week 96/End of Study or Early Study D/C visits) as having exhibited bacteriological cure with no TB recurrence (defined under Section 8.5), and clinical (probable) cure with no TB recurrence, will be presented, bounded with 95% CIs. Participants who were classified as lost to follow-up will be excluded from the analysis set used to compute these proportions and CIs. The time to culture-conversion (in weeks, months) in participants with bacteriological confirmation will be presented. Descriptive analyses will compare those who convert their bacteriology with those who fail to do so over pre-specified time periods with respect to overall exposure to study drug as estimated by PK modeling. Similar analyses will also be performed by HIV status, as data allow. Of note, precision may be limited for participants living with HIV, **and for cohorts with few participants living with HIV (e.g., one or two participants), estimation with confidence limits will not be feasible** ~~particularly if only the required minimum number of participants living with HIV are enrolled~~.

10. *Section 10.2.1, Number of Participants:*

    Each cohort will enroll a minimum of 18 participants. Based on existing information on the dose-exposure relationship for BDQ in adults (58) and a simulation study to evaluate the expected power and parameter precision with the suggested sampling schedule and number of participants (see Appendix X), this number is expected to be sufficient to estimate the main PK parameter, clearance (CL), with acceptable precision (85). The simulation study also showed that this sample size, including six participants living with HIV in each age group of 18, will have almost 90% power to detect a 30% difference between participants living with and without HIV in either CL or bioavailability (F) with the selected design. ~~A minimum of three participants living with HIV will be enrolled in each cohort.~~ If less than six participants living with HIV are enrolled in a cohort, then the power will be reduced.

11. *To reflect current protocol team membership, Sarah Buisson, Madison Cooper, and Mats Karlsson are removed from the protocol team roster (deletions not shown). Andrea McMunn is added, and Kelly Dooley's contact information is updated as shown below.*

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12. *To reflect current membership at site 31441, Uday Rajput and Nishi Suryavanshi are removed from the study site roster (deletions not shown) and Aarti Kinikar and Mandar Paradkar have been added.*

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