Clarification Memorandum # 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

Clarification Memorandum Date: 29 March 2023

Summary of Clarifications and Rationale

This Clarification Memorandum (CM) serves to clarify terminology for the study analyses related to BDQ dosing.

Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. This CM and any applicable IRB/EC correspondence should be maintained in site essential document files for IMPAACT P1108. The clarifications included in this CM will be incorporated into any future amendment of the IMPAACT P1108 protocol.

As indicated in protocol Section 10.2, interim pharmacokinetic (PK) analyses will be performed during study implementation to select BDQ doses for each cohort. Thereafter, PK modeling will be used to determine a final recommended BDQ dose for each cohort. The final recommended BDQ dose may or may not have been selected for a given cohort. Regardless of the final recommended dose, primary safety data analyses will be based on the BDQ dose selected for each cohort during study implementation, which is referred to as the final implemented dose. Protocol Sections 9.6.1 and 9.6.2.1 are modified to clarify that primary safety data analyses will be based on implemented doses. Additions to the text are indicated in bold; deletions are indicated by strikethrough.

1. *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.

2. *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.

3. *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, 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.