IMPAACT P1108

A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

IND #: 131,832
DAIDS ES #11884

This file contains the current IMPAACT P1108 protocol comprised of the following documents, presented in reverse chronological order:

- Letter of Amendment #4, dated 10 June 2020
- Clarification Memorandum #6, dated 1 April 2020
- Clarification Memorandum #5, dated 14 February 2020
- Letter of Amendment #3, dated 17 October 2019
- Letter of Amendment #2, dated 28 February 2019
- Letter of Amendment #1, dated 8 August 2018
- IMPAACT P1108 Protocol Signature Page for protocol Version 1.0, with Clarification Memoranda #1-4
- Clarification Memorandum #4, dated 26 July 2018
- Clarification Memorandum #3, dated 8 March 2018
- Clarification Memorandum #2, dated 10 July 2017
- Clarification Memorandum #1, dated 1 May 2017
- Protocol Version 1.0, dated 3 March 2016
Letter of Amendment #4 for:

IMPAACT P1108
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016

DAIDS Study ID #11884
IND #131,832

Letter of Amendment Date: 10 June 2020

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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.

This LoA incorporates the contents of protocol Clarification Memorandum (CM) #6, which was issued on 1 April 2020 to safeguard the health and well-being of IMPAACT P1108 study participants in the context of circulating SARS-CoV-2 and the associated COVID-19 pandemic. Per the study Sponsor, sites were instructed to implement the guidance provided in CM #6 immediately.

Upon obtaining IRB/EC approvals and any other applicable regulatory entity approvals, sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. 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.
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 Harmonization 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, Rationale, and Implementation

This LoA incorporates the contents of protocol Clarification Memorandum (CM) #6, which was issued on 1 April 2020 to safeguard the health and well-being of study participants in the context of circulating SARS-CoV-2 and the associated COVID-19 pandemic. CM #6 provided operational flexibility for conducting study visits and procedures when needed and to prioritize the conduct of clinically and scientifically important evaluations when possible.

Consistent with the instructions provided in CM #6, implementation of this LoA is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with IMPAACT Network leadership and the study Sponsor, the IMPAACT P1108 Protocol Team will determine when, in the future, the specifications of this LoA are no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform IRBs/ECs and other applicable regulatory entities.

Operational Guidance from Protocol CM #6, dated 1 April 2020

This CM provides operational guidance to study sites from the IMPAACT P1108 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. All sites should follow applicable government, health authority, institutional policies with respect to conduct of study visits and procedures and adhere to international standards for infection prevention and control, with utmost importance placed on the health and well-being of study participants and study staff. Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Core Team and contact the P1108 Core Team (impaact.p1108core@fstrf.org) with any questions or concerns regarding this CM or management of study participants.

Visit Scheduling
- Sites that anticipate operational disruptions or closures in the near future are advised to conduct study visits early in the visit window. Sites that are currently experiencing operational disruptions or closures are advised to conduct study visits late in the visit window.

- Sites should utilize the protocol-specified visit windows to schedule study visits in-person, when possible, in full compliance with the protocol. Sites that anticipate a visit may need to be conducted prior to or after closing of the protocol-specified visit window, due to operational disruptions or closures, should notify the P1108 Core Team (impaact.p1108core@fstrf.org).

- Sites should implement safety checks over the telephone (as available) prior to in-person visits to assess the study participants and/or caregivers willingness to continue with in-person visits, as well as assess the onset of any new adverse events (AEs), including but not limited to signs and symptoms potentially consistent with COVID-19. Sites should also use the telephone contacts to communicate essential information regarding infection prevention and control to protect the health and well-being of study participant and site staff.

Prioritization of Study Visit Procedures
- Sites with limited capacity to conduct study visits in-person at the study clinic may conduct off-site visits and/or remote visits, in accordance with the guidance provided below. Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in compliance with the protocol, with consideration of the guidance below.
• The IMPAACT Network has requested that all specimens be held at sites until further notice. Pharmacokinetic (PK) samples should continue to be collected per the protocol, if possible, and stored on-site until instructed to ship by the protocol team and/or IMPAACT Network. Specimens for lactate/pyruvate (L/P) should not be collected or shipped during this time. As feasible, sites should continue to collect and test specimens for local lactate for participant safety monitoring.

• **In-person off-site visits:** Sites may conduct study visits — in full or in part — off-site if proper Personal Protective Equipment (PPE) is available for study personnel. Where this option is permitted, site staff should communicate with participants and/or their caregivers to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality.

Off-site visit procedures should be conducted by designated site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any AE(s) or social impacts that may occur during the visits. If AEs requiring further evaluation or management are identified during an off-site visit or remote visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.

Sites with limited ability to conduct all study procedures during an in-person visit should prioritize participant safety through clinical procedures and evaluations, followed by laboratory procedures and evaluations, and provide contraceptive counseling as applicable for each visit. Study procedures should be prioritized in the order outlined below as applicable per the scheduled study visit requirements:

1. Clinical procedures/evaluations:
   - Update medical and medications history since the last study visit, including new TB exposure history, AEs and all concomitant medications
   - Physical examination and vitals as per the protocol and clinically indicated
   - Assess TB treatment outcome (Week 120 only)
   - CXR (Week 120 only)

2. Laboratory procedures/evaluations (in order of prioritization). *Note: If it is not possible to perform these tests consistent with the site’s Protocol Analyte List, tests may be performed in alternate laboratories using alternate assays (alternate laboratories must adhere to local regulations for clinical laboratory testing).*
   - LFTs, Chemistries, Hematology
   - Local lactate (Week 96)
   - Pregnancy test
   - Urinalysis
   - Sparse PK
   - RNA PCR and lymphocyte subsets (HIV-infected only)
   - Serum and urine biomarkers collected only per site capacity

3. Provide contraceptive counseling, as applicable

At off-site visits when specimen collection is required, the procedures specified in protocol Section 6.14 must be followed. Blood and urine may be collected at off-site visits. Further invasive specimen collection, such as for sputum or gastric aspirate, should **NOT** be attempted in non-medical site settings due to infection control concerns.
• **Remote visits (e.g. via telephone):** Sites with no ability to conduct an in-person study visit (either at the clinic or off-site) may perform the following study procedures remotely, per the respective scheduled study visit, prioritized in the order outlined below:
  – Update medical and medications history since last visit, including new TB exposure history, AEs and all concomitant medications
  – Assess TB treatment outcome (Week 120 only)
  – Provide contraceptive counseling, as applicable

As above, staff conducting remote visits should be adequately qualified and trained to immediately assess and/or manage any AEs or social impacts that may occur during the visits. If AEs requiring further evaluation or management are identified during a remote visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.

**Documentation**

• Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT P1108.

• Documentation should be entered in participant study charts in real-time should any of the following occur:
  – Missed visits
  – Out-of-window visits
  – Off-site visits (document the location of the visit)
  – Incomplete or partial visits (document which procedures were performed, and which were not)
  – Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  – Any other participant contacts
  – Use of alternate laboratories or alternate laboratory assays

• In consultation with DAIDS, the IMPAACT Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Similar guidance will be provided for documentation of use of alternate laboratories or alternate laboratory assays. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.
Clarification Memorandum #6 for:

IMPAACT P1108
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016

DAIDS ES #11884
IND #131,832 Held by DAIDS

Clarification Memorandum Date: 1 April 2020

Summary of Clarifications

This Clarification Memorandum (CM) is being issued to safeguard the health and well-being of IMPAACT P1108 study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) pandemic.

As the study Sponsor, the Division of AIDS (DAIDS) has determined that this CM should be implemented immediately upon issuance. Consistent with United States Food and Drug Administration guidance, Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by DAIDS prior to implementation. However, given the context of the COVID-19 pandemic and the importance of the guidance provided in this CM, sites should submit this CM to IRBs/ECs for their information or, if required by the IRBs/ECs, for their review and approval.

The purpose of this CM is to provide operational flexibility for conducting study visits and procedures when needed and to prioritize the conduct of clinically and scientifically important participant evaluations when possible.

Implementation of this CM is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with IMPAACT Network leadership and the study Sponsor, the IMPAACT P1108 Protocol Team will determine when, in the future, the guidance provided in this CM is no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform their IRBs/ECs.

Please file this CM and any applicable IRB/EC correspondence in your essential document files for IMPAACT P1108.
Implementation

This CM provides operational guidance to study sites from the IMPAACT P1108 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. All sites should follow applicable government, health authority, institutional policies with respect to conduct of study visits and procedures and adhere to international standards for infection prevention and control, with utmost importance placed on the health and well-being of study participants and study staff. Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Core Team and contact the P1108 Core Team (impaact.p1108core@fstrf.org) with any questions or concerns regarding this CM or management of study participants.

Visit Scheduling

- Sites that anticipate operational disruptions or closures in the near future are advised to conduct study visits early in the visit window. Sites that are currently experiencing operational disruptions or closures are advised to conduct study visits late in the visit window.

- Sites should utilize the protocol-specified visit windows to schedule study visits in-person, when possible, in full compliance with the protocol. Sites that anticipate a visit may need to be conducted prior to or after closing of the protocol-specified visit window, due to operational disruptions or closures, should notify the P1108 Core Team (impaact.p1108core@fstrf.org).

- Sites should implement safety checks over the telephone (as available) prior to in-person visits to assess the study participants and/or caregivers willingness to continue with in-person visits, as well as assess the onset of any new adverse events (AEs), including but not limited to signs and symptoms potentially consistent with COVID-19. Sites should also use the telephone contacts to communicate essential information regarding infection prevention and control to protect the health and well-being of study participant and site staff.

Prioritization of Study Visit Procedures

- Sites with limited capacity to conduct study visits in-person at the study clinic may conduct off-site visits and/or remote visits, in accordance with the guidance provided below. Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in compliance with the protocol, with consideration of the guidance below.

- The IMPAACT Network has requested that all specimens be held at sites until further notice. Pharmacokinetic (PK) samples should continue to be collected per the protocol, if possible, and stored on-site until instructed to ship by the protocol team and/or IMPAACT Network. Specimens for lactate/pyruvate (L/P) should not be collected or shipped during this time. As feasible, sites should continue to collect and test specimens for local lactate for participant safety monitoring.

- In-person off-site visits: Sites may conduct study visits — in full or in part — off-site if proper Personal Protective Equipment (PPE) is available for study personnel. Where this option is permitted, site staff should communicate with participants and/or their caregivers to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality.

Off-site visit procedures should be conducted by designated site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody.
These staff should also be adequately qualified and trained to immediately assess and/or manage any AEs or social impacts that may occur during the visits. If AEs requiring further evaluation or management are identified during an off-site visit or remote visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.

Sites with limited ability to conduct all study procedures during an in-person visit should prioritize participant safety through clinical procedures and evaluations, followed by laboratory procedures and evaluations, and provide contraceptive counseling as applicable for each visit. Study procedures should be prioritized in the order outlined below as applicable per the scheduled study visit requirements:

1. Clinical procedures/evaluations:
   - Update medical and medications history since the last study visit, including new TB exposure history, AEs and all concomitant medications
   - Physical examination and vitals as per the protocol and clinically indicated
   - Assess TB treatment outcome (Week 120 only)
   - CXR (Week 120 only)
2. Laboratory procedures/evaluations (in order of prioritization). Note: If it is not possible to perform these tests consistent with the site’s Protocol Analyte List, tests may be performed in alternate laboratories using alternate assays (alternate laboratories must adhere to local regulations for clinical laboratory testing).
   - LFTs, Chemistries, Hematology
   - Local lactate (Week 96)
   - Pregnancy test
   - Urinalysis
   - Sparse PK
   - RNA PCR and lymphocyte subsets (HIV-infected only)
   - Serum and urine biomarkers collected only per site capacity
3. Provide contraceptive counseling, as applicable

At off-site visits when specimen collection is required, the procedures specified in protocol Section 6.14 must be followed. Blood and urine may be collected at off-site visits. Further invasive specimen collection, such as for sputum or gastric aspirate, should NOT be attempted in non-medical site settings due to infection control concerns.

- **Remote visits (e.g. via telephone):** Sites with no ability to conduct an in-person study visit (either at the clinic or off-site) may perform the following study procedures remotely, per the respective scheduled study visit, prioritized in the order outlined below:
  - Update medical and medications history since last visit, including new TB exposure history, AEs and all concomitant medications
  - Assess TB treatment outcome (Week 120 only)
  - Provide contraceptive counseling, as applicable

As above, staff conducting remote visits should be adequately qualified and trained to immediately assess and/or manage any AEs or social impacts that may occur during the visits. If AEs requiring further evaluation or management are identified during a remote visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.
**Documentation**

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT P1108.

- Documentation should be entered in participant study charts in real-time should any of the following occur:
  - Missed visits
  - Out-of-window visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed, and which were not)
  - Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays

- In consultation with DAIDS, the IMPAACT Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Similar guidance will be provided for documentation of use of alternate laboratories or alternate laboratory assays. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.
Clarification Memorandum #5 for:

IMPAACT P1108
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016
DAIDS ES #11884
IND #131,832 Held by DAIDS
Clarification Memorandum Date: 14 February 2020

Information/Instructions to Study Sites

This Clarification Memorandum (CM) has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the sponsor prior to implementation; however, sites may submit this CM to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The content of this CM does not impact the study sample informed consent forms or the benefit-to-risk ratio for study participants. This CM should be maintained in each site’s essential documents file for IMPAACT P1108. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of and follow this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT P1108 protocol.

Summary of Clarifications, Rationale, and Implementation

The purpose of this CM is to address an internal inconsistency in the IMPAACT P1108 protocol. Specifically, documentation of HIV status is not required per protocol at the early study discontinuation (D/C) visit following completion of study treatment (i.e., off treatment visits). Protocol Section 6, Study Visits and Procedures, and the sample informed consent and assents forms do not indicate that documentation of HIV status is required at the early study D/C visit, and this evaluation was inadvertently included in error in protocol Appendix I, Schedule of Evaluations. However, HIV testing may be performed at the early study D/C visit as per local standard of care.
Letter of Amendment #3 for:

IMPAACT P1108
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016

DAIDS Study ID #11884
IND# 131,832 held by DAIDS

Letter of Amendment Date: 17 October 2019

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1108 study, including the study sample informed consent form (ICF), 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 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 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 Notice for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete.

For sites that were activated to initiate the study for all or specific cohorts prior to issuance of this LoA: A Registration Notice for this LoA must be received prior to implementation of this LoA and enrolling additional participants in P1108. Once the Registration Notice is received, participant accrual may be resumed, using the updated revised site-specific ICFs corresponding to this LoA for all new participants. In addition, all previously enrolled participants must re-consent for ongoing study participation using the updated site-specific ICFs corresponding to this LoA. Re-consenting should take place at each participant’s next study visit after the Registration Notice for this LoA is received.

For sites that were not activated to initiate the study for all or specific cohorts prior to issuance of this LoA: A Registration Notice for this LoA must be received prior to activation. Activation will occur following receipt of the Registration Notice; completion of all other study activation requirements; and receipt of a site-specific study activation notice from the IMPAACT Operations Center.

Please file this LoA, corresponding site-specific ICFs, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1108. If the P1108 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.
I will conduct this study in accordance with the current version of this protocol, including this Letter of Amendment, and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (U.S.) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization 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., U.S. 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 purpose of this LoA is to update the study sample ICF and assent form to incorporate current information regarding the use of bedaquiline (BDQ) and its potential risks and benefits as well as updates to allow administration of lopinavir/ritonavir (LPV/r) with BDQ and after BDQ discontinuation based on current safety data. Appendix I, Schedule of Evaluations (SoE), is also updated to correct the total blood volumes for Cohort 3 and blood volume for IGRA testing for consistency with current testing requirements.

Implementation

Detailed modifications of the protocol text are shown below in general order of appearance in the protocol. Deletions in the protocol text are indicated by strikethrough, and additions are indicated in bold.

1. **Section 1.2, Prior Research, Use of BDQ in HIV-infected patients on ART:**
   a. **First paragraph, last sentence:**
      [...] However, LPV/r will not be used in children included in our study.
   b. **Third paragraph, last sentence:**
      [...] Children on P1108 will not be receiving LPV/r containing regimens.
   c. **Fourth paragraph, last sentence:**
      [...] The use of EFV and LPV/r will not be allowed.

2. **Section 5.7.1, Medications disallowed during administration of BDQ and for up to four weeks after the last dose of BDQ, third paragraph:**
   Efavirenz (EFV) and boosted protease inhibitors are is not allowed. **LPV/r may be administered.**

3. **Appendix I: Schedule of Evaluation for All Cohorts (1, 2 and 3):**
   Appendix I is modified to correct the total blood volumes for Cohort 3 at Weeks 4, 8, and 16 visits and the blood volume required for IGRA testing in footnote #2. For ease of reference, the full appendix is attached.

4. **Appendix XI: Sample Informed Consent Form:**
   a. **WHAT DOES MY CHILD/BABY HAVE TO DO IF /HE/SHE IS IN THIS STUDY?, Screening, sixth, eighth and ninth bullets:**
      - Study staff will check your child’s TB status with a TB skin test or take a small amount of blood (approximately 3-4 ml, less than 1 teaspoonful of blood) if the TB skin test is not locally available.
      - The study staff will review medical records to see whether your child is HIV exposed or HIV-infected. If the medical records are not clear, the study staff will test your child for HIV. **If the required tests are not in your child’s medical records, we will do the tests that are needed. We may need to take a little more than a teaspoon (6.0 mL) of blood for these tests based on your child’s age.**
      - If your child is HIV-infected, the study staff will also look for the amount of HIV in his/her blood and check the amount of cells that fight against HIV—your child’s immune status (CD4 count). **We would need to take less than a teaspoon (4.0 mL) of blood for these tests.**
b. WHAT ARE THE RISKS OF THE STUDY?:

What is known about using BDQ in adults?

[...]

From trials in 380 TB disease patients who received BDQ (312 of whom received BDQ for as long as six months i.e., as long as children in this trial), along with other TB drugs, BDQ seemed to be generally safe and well tolerated. The most commonly reported side effects in these trials were:

- Nausea
- Joint pain
- Headache
- Increase of a chemical called uric acid in the blood
- Vomiting

High levels of uric acid may be associated with an increased risk of joint pain or gout, a type of arthritis.

No serious side effects or significant changes to pulse rate, blood pressure, or breathing related to BDQ were seen.

In one of the trials of BDQ that compared the medication and a placebo, there was very little difference between the frequency of the side effects experienced by people taking the medication and people taking the placebo:

<table>
<thead>
<tr>
<th></th>
<th>BDQ/Background regimen</th>
<th>Placebo/Background regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>30 (less than half of the people)</td>
<td>26 (about a third of the people)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (about a quarter of the people)</td>
<td>21 (about a quarter of the people)</td>
</tr>
<tr>
<td>Joint pains</td>
<td>26 (about a third of the people)</td>
<td>18 (less than a quarter of the people)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (less than a quarter of the people)</td>
<td>10 (only an eighth of the people)</td>
</tr>
<tr>
<td>Increase of a chemical called uric acid in the blood</td>
<td>24 (about a third of the people)</td>
<td>28 (about a third of the people)</td>
</tr>
</tbody>
</table>

[...]

Deaths

In previous studies, no deaths have been reported in adults not infected with TB who received BDQ. In some studies in people being treated for TB, there were more deaths among the participants receiving BDQ compared to those not receiving the drug. However, after reviewing all of the information, study doctors concluded that the deaths were unlikely to be related to the BDQ. In a study of adults with TB, more deaths were seen in participants who received BDQ compared to participants who did not receive BDQ. The doctors working on that study could not find a reason for this difference. Most of the deaths occurred several months after the participants stopped taking BDQ. However, doctors are not able to determine if the deaths were related to BDQ or not.

This study is being done because information from research and routine care indicates that BDQ may reduce the risk of death in adults and adolescents with MDR-TB. If MDR-TB is not treated well, MDR-TB disease may worsen and cause death. One participant in this study has died. This participant was very sick from MDR-TB and other illnesses and was in the hospital for several weeks before entering this study. On the day of his death, the child came home for dinner after playing during the day. After dinner, the child was resting when he started having trouble breathing. The child then died before he could be seen by a doctor and the cause of his death is unknown. All available information about this child has been carefully reviewed and it seems most likely that his death was due to his health problems other than TB, which improved while in the study, and not due to BDQ.
As the study continues, the study doctors will continue to closely monitor all participants in the study and potential risks of any bad effects. This will be done while participants are taking BDQ and for about 2 years after stopping BDQ.

Approvals

As of 30 April 2014, BDQ, when taken together with other TB drugs, has been approved to treat difficult adult cases of MDR-TB in the United States and Europe and all adult cases of MDR-TB in Russia and South Korea. In October 2014, BDQ was approved for use in adult MDR-TB patients in South Africa. Since adults started taking BDQ for MDR-TB, the number of deaths due to MDR-TB in the world has decreased. BDQ is recommended by the World Health Organization (WHO) for adults and children six years of age and older with MDR-TB. BDQ is approved for use in adults in the US and many other countries. [Sites: add information on local approvals, if applicable]

5. Appendix XII: Sample Assent Form, WILL TAKING PART IN THE STUDY HURT ME?:

BDQ is being developed to treat MDR-TB. All drugs can cause unwanted effects called “side effects.” Not all potential side-effects of BDQ in humans are known. Based on studies that tested BDQ in adults, we learned that BDQ is generally safe and no serious side effects were seen.

This study is being done because research and regular TB care shows that BDQ can reduce death due to TB in adults and adolescents with MDR-TB. If MDR-TB is not treated well, MDR-TB disease may worsen and cause death.

In a study of adults with TB, more deaths were seen in participants who received BDQ compared to participants who did not receive BDQ. Most of the deaths occurred several months after the participants stopped taking BDQ. The doctors working on that study were not able to determine if the deaths were related to BDQ or not. This study is being done because research and routine care shows that BDQ may reduce the risk of death in adults and adolescents with MDR-TB. If MDR-TB is not treated well, MDR-TB disease may worsen and cause death. One child in this study has died. This child was very sick from MDR-TB and other serious health problems and was in the hospital for several weeks before starting the study. All available information about this child has been carefully reviewed. It seems likely that this child’s death was due to health problems other than TB, which improved while in the study, and not due to BDQ.

As the study continues, the study doctors will continue to closely monitor all participants in the study and potential risks of bad effects from BDQ. The most common side effects that adults in these studies had were:

- Headache
- Dizziness
- Diarrhea
- Nausea
- Joint pain
- Vomiting
## Appendix I: Schedule of Evaluation for All Cohorts (1, 2 and 3)

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>On treatment visits</th>
<th>Unscheduled Visit</th>
<th>Early RDQ D/C or Study D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entry/Day 0</td>
<td>Wk 1</td>
<td>Wk 2</td>
<td>Wk 4</td>
</tr>
<tr>
<td><strong>CLINICAL EVALUATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documentation of HIV status</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Physical exam</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Pill dispensing</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Adherence assessment</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>TB disease status and severity</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Tuberculin Skin Testing</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CXR</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audiology</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY EVALUATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Chemistries</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
</tr>
<tr>
<td>LFT</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>TSH (ft4 if TSH is elevated)</td>
<td>2.0 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum biomarkers (storage)</td>
<td>0.5-1 mL</td>
<td>0.5-1 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1: lactate to local lab</td>
<td>2.0 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1: lactate/pyruvate</td>
<td>2.0 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Specimens for TB micro lab</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Urine biomarker (storage)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Intensive PK</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sparse PK</td>
<td>0.5-1.0 mL</td>
<td>0.5-1.0 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-Infected only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA PCR (viral load)</td>
<td>3.0 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td>1.0 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL BLOOD VOLUMES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1</td>
<td>4.0 mL</td>
<td>10-14.0 mL</td>
<td>4.0 mL</td>
<td>8.0 mL</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>4.0 mL</td>
<td>6-10.0 mL</td>
<td>4.0 mL</td>
<td>8.0 mL</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>3.5 mL</td>
<td>5.5-9.5 mL</td>
<td>3.5 mL</td>
<td>5.5 mL</td>
</tr>
</tbody>
</table>

Letter of Amendment #3
IMPAACT P1108 Protocol Version 1.0

Page 6 of 7

17 October 2019
## Appendix I (cont.): Schedule of Evaluation for All Cohorts (1, 2 and 3)

<table>
<thead>
<tr>
<th>Off treatment visits</th>
<th>Unsched. Visit</th>
<th>Early Study D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 32</strong> (8 wks post BDQ)</td>
<td><strong>Week 40</strong> (16 wks post BDQ)</td>
<td><strong>Week 48</strong> (24 wks post BDQ)</td>
</tr>
<tr>
<td><strong>CLINICAL EVALUATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Documentation of HIV status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>TB treatment outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY EVALUATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Chemistries</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
</tr>
<tr>
<td>LFT</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>TSH (fT4 if TSH is elevated)</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
</tr>
<tr>
<td>Serum biomarkers (storage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1: lactate to local lab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1: lactate/ pyruvate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Specimens for TB micro lab</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Urine biomarkers (storage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sparse PK</td>
<td>0.5-1.0 mL</td>
<td>0.5-1.0 mL</td>
</tr>
<tr>
<td><strong>HIV-Infected only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
</tr>
<tr>
<td><strong>TOTAL BLOOD VOLUMES</strong> (higher volumes for HIV+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1</td>
<td>6-7.0 mL</td>
<td>4.0 mL</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>6-7.0 mL</td>
<td>4.0 mL</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>5.5-6.5 mL</td>
<td>3.5 mL</td>
</tr>
</tbody>
</table>

(1) Refer to protocol section 4.3 for acceptable documentation of HIV status at screening. In the absence of such documentation, HIV testing should be conducted as part of the screening process and may entail the collection of up to 6 mL depending on type of tests validated for use at the site. Documentation of HIV status of HIV-exposed participants in Cohort 3 is required at Week 48 (24 weeks post BDQ), Week 120/End of Study. If acceptable documentation is not available, additional blood may need to be collected.

(2) If TST is not available at the site, IGRA may be done. This would require that an additional 3-4.0 mL of blood be collected at these time points.

(3) If lactate is greater than or equal to 3 mmol/L, an additional 2.0 mL for repeat testing will be necessary; refer to LPC and Appendix IX: Toxicity Management of Specific Toxicities: Lactate.

(4) A blood (1 mL) or urine (5 mL) pregnancy test may be performed. The total blood volume for these time points may require an additional 1 mL of blood.

Letter of Amendment #3
IMPAACT P1108 Protocol Version 1.0
17 October 2019
Letter of Amendment #2 for:

IMPAACT P1108
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016

DAIDS Study ID #11884
IND# 131,832 held by DAIDS

Letter of Amendment Date: 28 February 2019

---

*Information/Instructions to Study Sites from the Division of AIDS*

The information contained in this Letter of Amendment (LoA) impacts 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 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, each site should immediately begin implementing this LoA. As this LoA specifies initial study drug dosing for Cohort 2 and Cohort 3, participants may not be enrolled in these cohorts until after all required approvals of this LoA have been obtained. Once all required approvals are obtained, accrual into Cohorts 2 and 3 may be initiated at each site.

Sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a Registration Notice 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 documents files for IMPAACT P1108. If the P1108 protocol is amended in the future, the 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) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016

DAIDS Study ID #11884
IND# 131,832

Letter of Amendment #2, dated 28 February 2019

Letter of Amendment Signature Page

I will conduct this study in accordance with the current version of this protocol, including this Letter of Amendment, and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (U.S.) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization 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., U.S. 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**

This LoA documents the completion of the protocol-specified pharmacokinetic (PK) modeling of the Cohort 1 PK data and initial bedaquiline (BDQ) dosing for Cohorts 2 and 3.

Participants enrolled in Cohorts 2 and 3 will receive BDQ according to the dosing schedule shown below in updates to protocol Section 5.2 and the Schema. The BDQ dosing schedule was determined by population PK modeling performed based on PK data for the first 12 evaluable participants in Cohort 1, consistent with protocol Sections 3.2 and 10.2.3.

**Implementation**

The modifications included in this LoA are listed below in general order of appearance in the protocol. Deletions in the protocol text are indicated by strikethrough, and additions are indicated in **bold**.

1. **Schema, Study Treatment:**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Age and Weight</th>
<th>BDQ Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to 24</td>
<td>≥ 6 to &lt; 18</td>
<td>400 mg once per day for two weeks</td>
</tr>
<tr>
<td>participants</td>
<td>≤ 18 years</td>
<td>then 200 mg three times per week on <strong>Monday, Wednesday, and Friday</strong> for 22 weeks</td>
</tr>
<tr>
<td>to achieve</td>
<td>≥ 30 kg</td>
<td></td>
</tr>
<tr>
<td>18 evaluable</td>
<td>≥ 6 to &lt; 18</td>
<td>200 mg once per day for two weeks</td>
</tr>
<tr>
<td>(nine in each</td>
<td>≤ 18 years</td>
<td>then 100 mg three times per week on <strong>Monday, Wednesday, and Friday</strong> for 22 weeks</td>
</tr>
<tr>
<td>weight band)</td>
<td>≥ 15 to &lt;30 kg</td>
<td></td>
</tr>
</tbody>
</table>

| **Cohort 2**    | 2 to < 6       | Calculated using model-based dose selection                                  |
| up to 24        | ≤ 6 years      |                                                                            |
| participants    | ≥ 7 kg         | **Participants > 7 to ≤ 30 kg:**                                             |
| to achieve      |                | 200 mg once per day for two weeks then 100 mg three times per week on **Monday, Wednesday, and Friday** for 22 weeks |
| 18 evaluable    |                | **Participants 7 kg:**                                                       |
|                 |                | 100 mg once per day for two weeks then 50 mg three times per week on **Monday, Wednesday, and Friday** for 22 weeks |

| **Cohort 3**    | 0 to < 2       | Calculated using model-based dose selection                                  |
| up to 24        | ≤ 2 years      |                                                                            |
| participants    | ≥ 3 kg         | **Participants > 7 to ≤ 30 kg:**                                             |
| to achieve      |                | 200 mg once per day for two weeks then 100 mg three times per week on **Monday, Wednesday, and Friday** for 22 weeks |
| 18 evaluable    |                | **Participants ≥ 3 to ≤ 7 kg:**                                             |
|                 |                | 100 mg once per day for two weeks then 50 mg three times per week on **Monday, Wednesday, and Friday** for 22 weeks |
2. **Section 5.2, second paragraph and Table 2B: Cohort 2 and Cohort 3 BDQ Dosing has been added following Table 2 (now titled Table 2A: Cohort 1 BDQ Dosing):**

For Cohorts 2 and 3, dosing will be determined using a model-based selection method and a weight banding approach, based on all available data from Cohort 1 as well as information from adult studies. Also refer to Sections 8.0 and 9.0. Specifications for weight banded dosing for Cohort 2 and Cohort 3 will be provided to sites in a protocol Clarification Memorandum (CM) Letter of Amendment (LoA). Refer to Section 10.0 for a detailed rationale for the modeled dose selection approach. For all cohorts, the maximum duration of study treatment is 24 weeks.

**Table 2A: Cohort 1 BDQ Dosing**

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Weeks 1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6 to &lt; 18 years</td>
<td>≥30 kg*</td>
<td>BDQ 400 mg once daily, every day Given as four of the 100 mg tablets to equal 400 mg per dose Total weekly dose of 2800 mg</td>
</tr>
<tr>
<td></td>
<td>≥15 kg to &lt; 30 kg</td>
<td>BDQ 200 mg once daily, every day Given as two of the 100 mg tablets to equal 200 mg per dose Total weekly dose of 1400 mg</td>
</tr>
</tbody>
</table>

**Table 2B: Cohort 2 and Cohort 3 BDQ Dosing**

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Weeks 1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0 to &lt; 6 years</td>
<td>&gt; 7 to ≤ 30 kg</td>
<td>BDQ 200 mg once daily, every day Given as two 100 mg tablets to equal 200 mg per dose Total weekly dose of 1400 mg</td>
</tr>
<tr>
<td></td>
<td>≥ 3 kg to ≤ 7 kg</td>
<td>BDQ 100 mg once daily, every day Given as one 100 mg tablet Total weekly dose of 700 mg</td>
</tr>
<tr>
<td></td>
<td>≥ 3 kg to ≤ 7 kg</td>
<td>BDQ 50 mg once a day only on Monday, Wednesday and Friday with at least 48 hours between doses Total weekly dose of 150 mg</td>
</tr>
</tbody>
</table>
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) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016

DAIDS Study ID #11884
IND# 131,832 held by DAIDS

Letter of Amendment Date: 8 August 2018

---

**Information/Instructions to Study Sites from the Division of AIDS**

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1108 study, including the sample informed consent form (ICF), 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 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 receiving IRB/EC approval and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA and using the updated ICFs. After all required approvals are obtained, the updated ICFs should be used for all new participants. In addition, all previously enrolled participants must reconsent to ongoing study participation using the updated site-specific ICF. Re-consenting should take place at each enrolled participant’s next study visit after all required approvals are obtained.

Sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a Registration Notice 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 documents files for IMPAACT P1108. If the P1108 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.
I will conduct this study in accordance with the current version of this protocol, including this Letter of Amendment, and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (U.S.) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization 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., U.S. 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 following modifications are included in this LoA:

1. Per ICH GCP E6 4.8.10(n) and DAIDS requirements, 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. Protocol Section 11.2 and the sample ICF are updated accordingly.

2. Study eligibility criteria are updated for clarity and precision as follows:
   a) The diagnosis of only extrathoracic MDR-TB is allowed for study participation
   b) Acceptable ART regimens for HIV-infected participants are further expanded based on current safety data

3. Sections 4.2.8 and 7.3.3 are updated from Clarification Memorandum (CM) #2, dated 10 July 2017, to specify use of the Corrected Version 2.1, dated July 2017, of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events in IMPAACT P1108.

4. The duration of an approved ART regimen for HIV-infected participants prior to BDQ initiation in Section 5.7.1 is modified for consistency with inclusion criterion 4.1.7.

5. Appendix I, Scheduled of Evaluation for All Cohorts (1, 2 and 3), is modified to reflect blood and urine volume collection for pregnancy testing.

Implementation

Detailed modifications of the protocol text included in this LoA are listed below. Additions to the text are indicated in bold; deletions are indicated by strikethrough.

1. Updated language regarding regulatory authority access to participant study records
   a. Section 11.2, Essential and Source Documents and Access to Source Data, fourth paragraph:
      All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, the companies that provide the study products, IMPAACT, site IRBs/ECs, site IBCs, the FDA, the MCC, OHRP, and other U.S., local, and international applicable regulatory entities. [...] b. Appendix XI, Sample Informed Consent Form, “WHAT ABOUT CONFIDENTIALITY?”, second paragraph:
      Your child’s records may be reviewed by the [insert name of national Drug Regulatory Authority], [insert name of site IRB/EC], [insert name of other local regulatory authorities], name the National Institutes of Health (NIH) and its study monitors, the United States Office for Human Rights and Research Protections (OHRP), other U.S., local, and international regulatory entities, the United States Food and Drug Administration (FDA), study staff, and study monitors supporting this study.

2. Modifications to Eligibility Criteria
   a. Inclusion Criterion 4.1.5:
      Either confirmed or probable MDR-TB:
      Confirmed intra-thoracic (pulmonary) MDR-TB, with or without one and/or any of the following forms of extrathoracic TB: [...]
Probable [11] MDR-TB (or RMR, pre-XDR or XDR-TB), with inclusion of intrathoracic and/or extrathoracic TB as listed above: A presumptive diagnosis of MDR-TB based on well-documented clinical symptoms or signs of TB with radiological changes (in the case of intrathoracic TB), and/or extrathoracic disease manifestations described under 4.1.5, in combination with documented exposure to a confirmed infectious MDR-TB source case [2], [10] or with documented failure to respond to a first-line regimen, and where adherence was well documented. […]

b. Inclusion Criterion 4.1.7:
If HIV-infected: Initiated an acceptable ART regimen defined as either ZDV+3TC+ABC, or NVP+2NRTIs, or an additional integrase class drug including raltegravir, dolutegravir, or another regimen approved in advance by the protocol team and study sponsor at least two weeks prior to enrollment.

3. Implementation of Corrected Version 2.1, dated July 2017, of the DAIDS AE Grading Table
a. Exclusion Criterion 4.2.8, first paragraph:
Having a ≥ Grade 2 for any of the following abnormalities at the time of screening or known within 30 days prior to enrollment according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (“DAIDS AE Grading Table”), Corrected Version 2.1, dated March 2017:

b. Section 7.3.3, Grading Severity of Events, first paragraph, first sentence:
The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated March 2017, will be used and is available on the RSC website at: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

4. Clarification of duration of approved ART regimen for HIV-infected participants prior to BDQ initiation
Section 5.7.1, Medications disallowed during administration of BDQ and for up to four weeks after the last dose of BDQ, fourth paragraph:

Note: Older children who are virologically suppressed on EFV may be switched to a study-approved ART regimen (See Section 4.1.7) for at least the duration of BDQ dosing (plus four weeks following BDQ discontinuation); this switch must occur at least seven days two weeks before starting BDQ, with protocol team and sponsor approval obtained in advance if required per Section 4.1.7.

5. Clarification of blood and urine volume collection for pregnancy testing
Appendix I, Scheduled of Evaluation for All Cohorts (1, 2 and 3), rows for Pregnancy test:

<table>
<thead>
<tr>
<th>Screening</th>
<th>On treatment visits</th>
<th>Unsch Visit</th>
<th>Early BDQ D/C or Study D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entry Day 0</td>
<td>Wk 1</td>
<td>Wk 2</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Week 32 (8 wks post BDQ)</td>
<td>Week 40 (16 wks post BDQ)</td>
<td>Week 48 (24 wks post BDQ)</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Pregnancy test^4^</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

(4) A blood (1 mL) or urine (5 mL) pregnancy test may be performed. The total blood volume for these time points may require an additional 1 mL of blood.
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

DAIDS Study ID #11884

Version 1.0
dated 3 March 2016

Protocol 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 Conference on Harmonization 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)
Clarification Memorandum #4 for:

IMPAACT P1108
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016
DAIDS ES #11884
IND #131,832 Held by DAIDS

Clarification Memorandum Date: 26 July 2018

Information/Instructions to Study Sites

This Clarification Memorandum (CM) has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the sponsor prior to implementation; however, sites may submit it to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The content of this CM does not impact the study sample informed consent forms or the benefit-to-risk ratio for study participants. This CM should be maintained in each site’s essential documents file for IMPAACT P1108. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of and follow this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT P1108 protocol.

Summary of Clarifications, Rationale and Implementation

Per protocol Section 8.6, ECG results from the centralized read will be used for study analyses. This CM serves to clarify that the centralized ECG read should be used for determination of final grading for all protocol-specified ECG evaluations, including ECGs performed as part of study eligibility determination (see protocol Sections 4.2.5 and 4.2.6).

Identification of adverse events (AEs) and immediate appropriate clinical management will be determined based on the site’s real-time ECG reading of the mean QT interval per protocol. Following receipt of the centralized ECG reading, sites should review and confirm that the grade for ECG AEs entered in the study database is consistent with the grading based on the centralized read. In addition, further clinical management should be performed based on the AE grade from the centralized ECG read.

Consultation with the protocol cardiologist (impaaact.p1108corecardio@fstrf.org) is available and encouraged for any abnormal or equivocal ECG findings and/or questions related to cardiac toxicities and assessment.
Clarification Memorandum #3 for:

**IMPAACT P1108**

A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016

DAIDS ES #11884
IND #131,832 Held by DAIDS

Clarification Memorandum Date: 8 March 2018

---

**Information/Instructions to Study Sites**

This Clarification Memorandum (CM) has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the sponsor prior to implementation; however, sites may submit it to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The contents of this CM do not impact the study sample informed consent forms or the benefit-to-risk ratio for study participants. This CM should be maintained in each site’s essential documents file for IMPAACT P1108. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of and follow this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT P1108 protocol.

---

**Summary of Clarifications and Rationale**

The purpose of this CM is to clarify 1) the sequence of blood collections for sparse PK (pre-dose), lactate/pyruvate and lactate samples relative to study drug dosing and 2) clinical management for confirmed Grade 1 and Grade 2 ECG-determined or clinical cardiac toxicity.

1) Sparse PK (pre-dose) samples should be collected prior to directly observed administration of study drug, at Weeks 1, 4, 8, 12, 16, 20 and 24 on treatment visits. As protocol Section 5.3 specifies study drug is required to be given with food, lactate/pyruvate and lactate samples that must be obtained while fasting should also be collected prior to study drug administration at Day 0 and on treatment visits. Sections 6.2, 6.5 and 6.7 are modified to clarify internal inconsistencies in the order of study drug administration and specimen collections for sparse PK (pre-dose), lactate/pyruvate and lactate samples.

2) Appendix VI is modified to clarify management following repeat ECGs for confirmed Grade 1 and Grade 2 ECG-determined and clinical cardiac toxicities to ensure appropriate safety monitoring for participants.

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**Implementation**

The modifications included in this CM are listed below by update and in order of appearance in the protocol and will be incorporated into the next protocol amendment as specified below. Additions to the text are indicated in **bold**; deletions are indicated by strikethrough.
1. Clarification of the sequence of blood collections at Day 0 and on treatment visits:

In Section 6.2 - Enrollment Visit (Day 0), third paragraph:
Additional requirements for sequencing of procedures at the Enrollment Visit are as follows:
- Final eligibility determination and confirmation must precede enrollment
- Confirmation of the continued consent for study participation must precede enrollment
- Enrollment must precede prescribing of study drug
- Prescribing must precede dispensing and administering of study drug
- Directly observed administration of study drug must precede collection of laboratory specimens
- During the Enrollment Visit, samples for lactate/pyruvate and lactate must be obtained first and must be before any other specimens are collected and before study drug is administered on a fasting sample. Sample for lactate must be collected after lactate/pyruvate sample drawn second. Details on collection of these samples are provided in the MOP and/or LPC. Otherwise, there are no required sequencing of specimen collections at this visit.

In Section 6.5 – Week 4 Visit:
The Week 4 Visit is targeted to take place on Day 28, with an allowable window of ± 7 days (i.e., Day 21 to Day 35). Lactate/pyruvate, lactate and sparse PK (pre-dose) sample collections must precede directly observed administration of study drug. Samples for lactate/pyruvate and lactate must be obtained first and must be on a fasting sample. Sample for lactate must be collected after lactate/pyruvate sample drawn second. Details on collection of these samples are provided in the MOP and/or LPC. Otherwise, there are no required sequencing of procedures or specimen collections at this visit.

In Section 6.7 – Week 8, 12, 16, 20 and 24 Visits (On Treatment):
The Week 8, 12, 16, 20 and 24 visits are targeted to take place on Days 56, 84, 112, 140 and 168, respectively. Week 8 has an allowable window of −14 days; Week 24 has an allowable visit window of -14 to +28 days; all other visits have an allowable window of ±14 days. Lactate/pyruvate, lactate and sparse PK (pre-dose) sample collections must precede directly observed administration of study drug. Directly observed administration of study drug must precede collection of laboratory evaluations at each visit. The sample for lactate/pyruvate at Week 24 must be obtained first and must be on a fasting sample. The sample for lactate must be collected after lactate/pyruvate sample second. Details on collection of these samples are provided in the MOP and/or LPC. Otherwise, there are no required sequencing of procedures or specimen collections at these visits.

2. Follow-up management for confirmed Grade 1 and Grade 2 ECG-determined or clinical cardiac toxicity.

In Appendix VI: Toxicity Management of Specific Toxicities, ECG-Determined or Clinical Cardiac Toxicity, Grade 1 and Grade 2:

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>STUDY DRUG USE</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Continue BDQ</td>
<td>Repeat ECG and clinical evaluation of symptoms within 72 hours. If confirmed as Grade 1, consult the Core Team and continue routine monitoring at the next study visit.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue BDQ</td>
<td>Repeat ECG and clinical evaluation of symptoms within 48 hours. If confirmed as Grade 2, consult the Core Team, with close monitoring as determined by the site investigator in consultation with the protocol cardiologist and the Core Team.</td>
</tr>
</tbody>
</table>
Clarification Memorandum #2 for:

IMPAACT P1108
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016

DAIDS ES #11884
IND # 131,832 Held by DAIDS

Clarification Memorandum Date: 10 July 2017

Information/Instructions to Study Sites

This Clarification Memorandum (CM) has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the sponsor prior to implementation; however, sites may submit it to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The contents of the CM do not impact the study sample informed consent forms or the benefit-to-risk ratio for study participants. This CM should be maintained in each site’s essential documents file for IMPAACT P1108. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of and follow this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT P1108 protocol.

Summary of Clarification, Rationale and Implementation

The purpose of this CM is as follows:

1) to clarify the study drug dispensing procedures to allow site flexibility in quantity to be dispensed for study participants, particularly given the different amounts needed for the different weight bands;

2) to specify use of Version 2.1 of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events for grading severity of adverse events in IMPAACT P1108 (instead of Version 2.0); and

3) to correct an internal inconsistency and clarify the frequency of Off Treatment visits.

The modifications included in this CM are listed below. Additions to the text are indicated in **bold**; deletions are indicated by *strikethrough*. 
In Section 5.1, Study Treatment Formulation, third paragraph:
BDQ should be dispensed in the original container and stored at 25°C (77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F). If BDQ is dispensed outside of the original container, tablets must be dispensed in a tight, light-resistant container labeled with an expiration date not to exceed 3 months.

In Section 4.2.8, first paragraph:
Having a ≥ Grade 2 for any of the following abnormalities at the time of screening or known within 30 days prior to enrollment according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (“DAIDS AE Grading Table”), Version 2.0, November 2014, Version 2.1, dated March 2017:

In Section 6.8, Weeks 32, 40, 48, 60, 72 and 96 Visits (Off Treatment), first paragraph and title for visit procedures table:
The Week 32, 40, 48, 60, 72 and 96 visits are targeted to take place on Days 224, 280, 336, 420, 504 and 672, respectively. Weeks 32, 40, and 48 have an allowable window of +/- 28 days; Weeks 60, 72, 84, and 96 have an allowable window of ± 42 days. The sample for lactate/pyruvate at Week 96 must be obtained first and must be on a fasting sample. The sample for lactate must be collected second. Details on collection of this sample are provided in the MOP and/or LPC. Otherwise, there is no required sequencing of procedures at these visits.

| Off Treatment Visit Procedures: Weeks 32, 40, 48, 60, 72 and 96 |
| Visit Windows: Wks 32, 40, 48: +/- 28 days; Wks 60, 72, 84, 96: +/- 42 days |

In Section 6.12, Early Discontinuation of BDQ, first paragraph, second sentence:
If the study drug is discontinued prior to 24 weeks, the study participant should return for an “Early BDQ Discontinuation (D/C)” visit. Follow up thereafter would be at 8, 16, 24, 36, 48, 60, 72, 84 and 96 weeks post the last BDQ dose.

In Section 7.3.3, Grading Severity of Events:
The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, Version 2.1, dated March 2017, will be used and is available on the RSC website at: [http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables](http://rsc.tech-res.com/). Exceptions to this are QT interval grading and grading of cardiac symptoms related to cardiac conduction abnormalities (see Appendix V).
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) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Version 1.0, dated 3 March 2016

DAIDS ES #11884
IND # 131,832 Held by DAIDS

Clarification Memorandum Date: 1 May 2017

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Summary of Clarifications and Rationale

The primary purposes of this Clarification Memorandum (CM) are:

1. to clarify the expectations regarding investigation of microbiological confirmation of tuberculosis (TB) disease in child participants;
2. to clarify requirements for biomarker specimen collection, with specimens to be collected at fewer timepoints in all participants (rather than more frequent specimens to be collected, based on further consultation with biomarker collaborators);
3. to provide the updated web links to the DAIDS policies and reporting procedures referenced throughout the protocol; and
4. to clarify that the guidance on construction of an optimized background regimen (OBR) for treatment of MDR-TB (non-study drugs that are required for participants in the study) will be updated periodically as country and WHO guidelines for standards of care (SOC) change. For consistency with the 2016 WHO guidelines for treatment of MDR-TB, updates are included. Future updates may be implemented by CM as well.
5. To clarify delamanid as a precautionary medication in this protocol.

In addition, minor corrections are made as shown below for accuracy and internal consistency, and updates in the regulatory status (addition of an IND number), sites and staffing are noted.

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Implementation

This CM has been approved by the NIAID and NICHD Medical Officers. 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 this CM to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.
The contents of the CM do not impact the sample informed consent forms for the study or the benefit-to-risk ratio for study participants. This CM should be maintained in each site’s essential documents file for IMPAACT P1108. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of this CM.

The modifications included in this CM are listed below by update and will be incorporated into the next protocol amendment as specified below. Where necessary, additions to the text are indicated in **bold**; deletions are indicated by **strikethrough**.

1. Expectations are clarified regarding reasonable attempts investigate for TB microbiological confirmation in child participants:
   - Section 8.4, Mycobacterial culture, smear and DST, last two sentences:
     In participants with probable MDR-TB, sampling will not be repeated if bacteriology was negative at diagnosis, unless new symptoms or worsening of symptoms or new TB exposure **were to occur had occurred**. In participants with probable MDR-TB, reasonable attempts should however **have** been made to investigate for TB microbiological confirmation prior to enrolment. **This would typically include attempted collection of at least two respiratory samples in the case of suspected intrathoracic TB or collection of other samples as clinically indicated (e.g., single fine needle aspirate in the case of peripheral lymphadenitis) and appropriate diagnostic testing and drug susceptibility testing.**

2. Requirements for collection of specimens for serum and urine biomarkers are clarified, with specimens to be collected on all children (rather than a subset), but now only at Screening, Day 0/Entry only if >2 weeks from the Screening visit, at Week 24, and Week 120. Associated modifications are shown below.
   - Section 6.2, Enrollment Visit (Day 0), Laboratory Assessments:
     Blood: Biomarkers (storage for future use) (**only if more than 2 weeks from Screening**)
     Urine: Biomarkers (future use) (**only if more than 2 weeks from Screening**)
   - Section 6.4, Week 2 Visit, and Section 6.5, Week 4 Visit: Laboratory Assessments:
     Blood: Biomarkers (storage for future use)
     Urine: Biomarkers (storage for future use)
   - Section 6.7, Weeks 8, 12, 16, and 24 Visits (On Treatment): Laboratory Assessments:
     Blood: Weeks 8, 16 and 24 only: Biomarkers (storage for future use)
     Urine: Weeks 8, 16 and 24 only: Biomarkers (storage for future use)
   - Section 6.8, Weeks 32, 40, 48, 60, 72 and 96 Visits (Off Treatment):
     Urine: Week 48 only: Biomarkers (future use)
   - Section 9.6.3, Exploratory Analyses of biomarker data, first sentence:
     In a subset of children enrolled early during MDR-TB treatment, Serum and urine biomarkers will be collected over time, and descriptive analyses will track changes over time in these biomarkers.
• Appendix I: Schedule of Evaluations for all Cohorts (1, 2, and 3):

<table>
<thead>
<tr>
<th>Screening</th>
<th>Entry/Day 0</th>
<th>Wk 1</th>
<th>Wk 2</th>
<th>Wk 4</th>
<th>Wk 6</th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wk 16</th>
<th>Wk 20</th>
<th>Wk 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum biomarkers (storage)</td>
<td>0.5-1 mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine biomarkers (storage)</td>
<td>X</td>
<td>X</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>X</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TOTAL BLOOD VOLUMES (higher volumes for HIV+)

| Cohort 1 | 4.0mL | 10-14.0mL | 4.0mL | 8.0 | 9.0mL | 8.0-9.0 | 9-10mL | 0mL | 6.0 | 7.0mL | 4-8.0mL | 6.0 | 7.0mL | 4.0mL | 11-15mL |
| Cohort 2 | 4.0mL | 6-10.0mL | 4.0mL | 8.0 | 9.0mL | 4.0-5.0 | 5.0-6mL | 0mL | 6.0 | 7.0mL | 4-8.0mL | 6.0 | 7.0mL | 4.0mL | 7-11mL |
| Cohort 3 | 3.5mL | 5.5-9.5mL | 3.5mL | 5.5 | 6.0mL | 4.0-4.5 | 4.5-5.0mL | 0mL | 5.0 | 6.0mL | 3.5-7.5mL | 5.0 | 6.0mL | 3.5mL | 6-10.0mL |

Off treatment visits

<table>
<thead>
<tr>
<th>Week 32 (8 wks post BDQ)</th>
<th>Week 40 (16 wks post BDQ)</th>
<th>Week 48 (24 wks post BDQ)</th>
<th>Week 60 (36 wks post BDQ)</th>
<th>Week 72 (48 wks post BDQ)</th>
<th>Week 96 (72 wks post BDQ)</th>
<th>Week 120/End of Study (96 wks post BDQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine biomarkers (storage)</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

3. Updated links to the DAIDS policies and procedures referenced in the following sections:

- Section 6.14: DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials: [https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf](https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf)
4. Appendix II, IIB and Appendix III, pertaining to construction of an optimized background regimen for the treatment of MDR-TB and use of second line therapies, are updated for consistency with current (revised in 2016) WHO guidelines. The new Appendices II and IIB are as follows:

APPENDIX II: DRUG GROUPS ROUTINELY USED FOR THE TREATMENT OF DRUG-RESISTANT TUBERCULOSIS IN CHILDREN

<table>
<thead>
<tr>
<th>Group</th>
<th>Group Name</th>
<th>Drugs</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Fluoroquinolones</td>
<td>Levofloxacin</td>
<td>Lfx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moxifloxacin</td>
<td>Mfx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gatifloxacin</td>
<td>Gfx</td>
</tr>
<tr>
<td>B</td>
<td>Second-line injectable agents</td>
<td>Amikacin</td>
<td>Am</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capreomycin</td>
<td>Cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kanamycin (Streptomycin*)</td>
<td>Km</td>
</tr>
<tr>
<td>C</td>
<td>Other core second-line agents</td>
<td>Ethionamide/prothionamide</td>
<td>Eto/PTO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cycloserine/terizidone</td>
<td>Cs/Trd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linezolid</td>
<td>Lzd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clofazimine</td>
<td>Cfz</td>
</tr>
<tr>
<td>D</td>
<td>Other core second-line agents</td>
<td>D1 Pyrazinamide</td>
<td>Z</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethambutol</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-dose isoniazid</td>
<td>H^I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D2 Bedaquiline</td>
<td></td>
<td>Bdq</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
<td></td>
<td>Dlm</td>
</tr>
<tr>
<td></td>
<td>D3 p-aminosalicylic acid</td>
<td></td>
<td>PAS</td>
</tr>
<tr>
<td></td>
<td>Imipenem-cilastin</td>
<td></td>
<td>Ipm</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td></td>
<td>Mpm</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin-clavulanate</td>
<td></td>
<td>Amx-Clv(T)</td>
</tr>
</tbody>
</table>

APPENDIX IIB: CONSTRUCTING A MDR-TB TREATMENT REGIMEN IN CHILDREN

Regimens for MDR-TB treatment in children are individualized according to the child or adult source case’s isolate drug susceptibility test results (DST) as well as information about the child’s previous treatment experience. The WHO classifies anti-TB drugs into Groups A-D (as shown in Appendix II). This helps to construct a regimen aiming at five effective drugs per regimen. Regimens should be constructed consistent with current international WHO and local guidance and practice, which will be updated periodically as WHO and country guidelines for standards of care change. The 2016 suggested approach from the WHO is outlined below:

1. In patients with rifampicin-resistant or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines - one chosen from group A, one from group B, and at least two from group C. If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five.

2. In patients with rifampicin-resistant or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol.
3. In children with mild forms of TB, the harms associated with the group B medications (second-line injectable agents) outweigh potential benefits and therefore group B medications may be excluded in this group of children.

APPENDIX III: SUMMARY OF THE DOSE AND ADVERSE EFFECTS OF THE SECOND-LINE DRUGS USED IN THIS STUDY IN THE TREATMENT OF DRUG RESISTANT TUBERCULOSIS IN CHILDREN

- Changes in use, dosage and/or adverse effects in the three affected drugs are shown below, including elimination of Moxifloxacin (which is contra-indicated in P1108):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose recommended</th>
<th>Emulsion size</th>
<th>Main adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capreomycin</td>
<td>15-25 15-20 mg/kg once daily</td>
<td>1g vial</td>
<td>As for kanamycin</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>40 mg/kg once daily</td>
<td>400 mg</td>
<td>As for ofloxacin; prolongation of QTc interval (not to be used in conjunction with bedaquiline)</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>3-5 3-5 mg/kg once daily*</td>
<td>50mg, 100mg tablets/capsules</td>
<td>Skin discoloration (may also cause QT prolongation, used in cases of pre-XDR and XDR-TB with BDQ, as sterilizing drug, given limited treatment options)</td>
</tr>
</tbody>
</table>

- Suggested Dosing guide for Clofazimine

<table>
<thead>
<tr>
<th>Weight (in kg)</th>
<th>Clofazimine 100mg</th>
<th>Clofazimine 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-&lt;10</td>
<td>1 caps every 3-4 days</td>
<td>1 caps alternate days</td>
</tr>
<tr>
<td>10-&lt;20</td>
<td>1 caps alternate days</td>
<td>1 caps daily</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>1 caps daily</td>
<td>2 caps daily</td>
</tr>
</tbody>
</table>

5. Section 5.7. Prohibited and Precautionary Medications:

The protocol team must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Note: While the use of delamanid during administration of BDQ is not prohibited in this study, it is considered precautionary and must be discussed with the protocol team on an individual basis in advance (or as soon as possible after its introduction). The use of clofazamine, now part of a standard WHO recommended MDR-TB treatment regimen, is not prohibited.

6. Minor corrections have been made in the following sections for accuracy and internal consistency:

A. Section 5.5.1 Adherence In-Hospital, first sentence:

Adherence to study drug (daily during the first two weeks, and three times a week from Week 22-3 -Week 24) will be documented with pill counts and a drug-dispensing card; ward dispensing charts may be used in addition to treatment card, and recording of dispensing completed by hospital personnel or study personnel, as relevant.

B. Section 6.2, Enrollment Visit (Day 0) and Section 6.3, Week 1 Visit:

The instructions regarding “Preparing for Week 2” are moved to the table for the Week 1 visit procedures in Section 6.3 (from table of procedures for the Enrollment Visit (Day 0)).
C. Section 6.7, Weeks 8, 12, 16, 20 and 24 Visits (On Treatment), and Section 6.8 Weeks 32, 40, 48, 60, 72 and 96 Visits (Off Treatment), visit procedures tables, Laboratory:

For Sputum, reference to a negative test is changed to a negative “culture”; reference to “central” DST is removed; and reference to an initial positive mycobacterial sample is changed to an initial positive mycobacterial “isolate”.

D. Section 6.12, Early Discontinuation of BDQ: Off Treatment Visit Procedures table, Laboratory/Sputum:

8, 16, 24, 36 and 48 wks post BDQ only: Participants will have sputum studies done once a month until culture conversion in the case of participants initially positive, after which time bacteriology will be repeated once a month for two months thereafter (i.e., three consecutive negative results cultures).

E. Section 8.5, TB treatment outcome, first paragraph, paragraph has been modified as follows:

Participants will be serially assessed through repeat CXR (in the case of intrathoracic TB), clinical resolution of symptoms and mycobacterial culture (MGIT, Becton Dickinson with DST and smear conversion), in the case of confirmed MDR-TB, as described in the Schedule of Evaluations (Appendix I).

As described in the Schedule of Evaluations (Appendix I), participants will be serially assessed through repeat CXR, in the case of intrathoracic TB, and/or clinical resolution of symptoms and mycobacterial culture (MGIT, Becton-Dickinson) with DST and smear conversion, in the case of bacteriologically confirmed MDR-TB.

F. The following sections are updated to clarify that lactate is considered elevated when measured at greater than or equal to 3mmol/L (rather than greater than 5mmol), and to clarify that the L/P ratio results may be considered for toxicity management.

- Section 8.7, Monitoring for Potential Mitochondrial Toxicities, second paragraph, third sentence:

Real-time review of the lactate/pyruvate ratios may be needed if a large number (i.e., >25% of the samples tested) of significantly elevated lactates (lactate ≥5 greater than or equal to 3mmol/L) were noted during routine AE lab monitoring.

- Appendix I, Schedule of Evaluations for All Cohorts, footnote #3:

If lactate is ≥ greater than or equal to 3mmol/L, an additional 2.0mL for repeat testing will be necessary; refer to LPC and Appendix IX: Toxicity Management of Specific Toxicities.
Appendix IX, Toxicity Management of Specific Toxicities: Lactate, Column 1, rows 2 and 3:

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>STUDY DRUG USE</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate ≥3mmol/L ≥3mmol/L</td>
<td>Draw additional blood sample for repeat lactate (see LPC).</td>
<td></td>
</tr>
<tr>
<td>If repeat lactate is: ≥3mmol/L ≥3mmol/L</td>
<td>Hold Bedaquiline if mitochondrial dysfunction is suspected (based on overall clinical picture). If another underlying condition is suspected or confirmed, Bedaquiline may be continued based on clinical justification and in discussion with the protocol team.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Send sample for Obtain lactate/pyruvate ratio results when available, correlate with subject’s clinical status and contact the study team.</td>
<td></td>
</tr>
</tbody>
</table>

G. The definition of “drug-susceptible TB” in the context of premature discontinuation of study drug and in the overall protocol, is clarified as “isoniazid and rifampicin susceptible”. Note that isoniazid mono-resistant TB is classified as drug-resistant TB (but not as MDR-TB).

Section 8.10, Criteria for Premature Discontinuation of Study Drug, fourth bullet:

- Participant diagnosed as having drug-susceptible TB, i.e. isoniazid and rifampicin susceptible, despite initial diagnosis of DR-TB. *Isoniazid resistance is also included as drug-resistant TB but is not MDR-TB (and therefore participants with INH mono-resistant TB are not eligible for participation).*

H. Appendix V, SUPPLEMENTAL TOXICITY TABLE FOR GRADING ELECTROCARDIOGRAM CHANGES AND POSSIBLE SYMPTOMS RELATED TO CARDIAC CONDUCTION ABNORMALITIES: References to QT interval are changed to “QTc” interval for consistency with the other occurrences therein.

I. Appendix VII, TABLE TO DETERMINE THE LOWER LEVEL OF NORMAL HEART RATE BY AGE:

An initial column is added to provide normal heart rate range and mean for infants aged 0 to < 3 months, and an additional footnote is included as follows:

**Normal Heart Rate Ranges by Age** (71)

<table>
<thead>
<tr>
<th>Participant’s Age</th>
<th>0 to &lt; 3 Months</th>
<th>≥ 3 to &lt; 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Heart Rate Range (bpm)</td>
<td>94-179</td>
<td>105-185</td>
</tr>
<tr>
<td>Mean (bpm)</td>
<td>149**</td>
<td>141</td>
</tr>
</tbody>
</table>

Range values are 2nd to 98th percentiles.

*Normal heart rate range values for adults, reported by the American Heart Association.*

**This mean reflects age 7 days to 3 months**
7. Additional administrative updates include the following:

- As the study will be conducted under an Investigational New Drug (IND) application with the US Food and Drug Administration (FDA), IND number 131,832 has been assigned.

- The study will be conducted at the PHRU Matlosana Clinical Research Site (CRS 31976), instead of the Soweto CRS (CRS 8052). The address and key contacts for CRS 31976 are as follows:
  
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  Email: tpirso@witshealth.co.za
  
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A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by:
National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institute of Mental Health

DAIDS ES #11884
Non-IND Study

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NICHD Medical Officer: Rohan Hazra, MD
Clinical Trials Specialist: Megan Valentine, MPA
Kathryn Lypen, MPH

Version 1.0
3 March 2016
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IMPAACT P1108
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

ABBREVIATIONS AND ACRONYMS

AE/EAE  Adverse Event/Expedited Adverse Event
ALT  Alanine Amino transferase
ARV  Antiretroviral
AST  Aspartate Amino transferase
BDQ  Bedaquiline
CFU  Colony-forming units
CS  Cycloserine
DAERS  DAIDS Adverse Experience Reporting System
DAIDS  Division of AIDS, NIAID
DMC  Data Management Center
DOT  Directly Observed Therapy
DR-TB  Drug-Resistant Tuberculosis
EC  Ethics Committee
ECG  Electrocardiogram
EFV  Efavirenz
EMA  European Medicines Agency
EMB  Ethambutol
ETH  Ethionamide
FDA  Food and Drug Administration
HIV  Human Immunodeficiency Virus
IMPAACT  International Maternal Pediatric Adolescent AIDS Clinical Trials Group
INH  Isoniazid
IRB  Institutional Review Board
LPV  Lopinavir
LPV/r  Lopinavir/ritonavir
MDR-TB  Multidrug-Resistant Tuberculosis
MOP  Study-Specific Manual of Procedures
M.tb.  Mycobacterium tuberculosis
NIAID  National Institute of Allergy and Infectious Diseases
NICHD  National Institute of Child Health and Human Development
NIH  National Institutes of Health
NTP  National TB Program
OBR  Optimized Background (TB) Treatment Regimen
PID/SID  Patient Identification Number / Study Identification Number
PAS  Para-aminosalicylic acid
PD  Pharmacodynamic
PK  Pharmacokinetics
PMTCT  Prevention of Mother to Child Transmission
RIF  Rifampin/Rifampicin
RMR-TB  Rifampin-mono-resistant TB
RSC  Regulatory Support Center
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SIP</td>
<td>Site Implementation Plan</td>
</tr>
<tr>
<td>SDMC</td>
<td>Statistical Data Management Center</td>
</tr>
<tr>
<td>SMC</td>
<td>Study Monitoring Committee</td>
</tr>
<tr>
<td>SOE</td>
<td>Schedule of Evaluations</td>
</tr>
<tr>
<td>SOPS</td>
<td>Standard Operating Procedures</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TIW</td>
<td>Three times a week</td>
</tr>
</tbody>
</table>

In this study, the TIW intermittent dosing schedule will be every other day for three consecutive doses followed by a break of two days then repeating the cycle (i.e., Monday Wednesday Friday; MWF).

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZD</td>
<td>Terizidone</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>Extensively Drug-Resistant Tuberculosis</td>
</tr>
</tbody>
</table>
IMPAACT P1108
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Purpose: To evaluate the pharmacokinetics (PK), safety and tolerability of Bedaquiline (BDQ) in HIV-infected and HIV-uninfected pediatric populations

Design: Multicenter, Phase I/II, open-label, single-arm, exposure-controlled dose finding modified age de-escalation study, using an adaptive design

Study Population: HIV-infected and HIV-uninfected infants, children and adolescents treated for clinically diagnosed or confirmed intra-thoracic (pulmonary) MDR-TB and selected forms of extrathoracic MDR-TB who have received 2-12 weeks of routine MDR-TB treatment prior to enrollment

Sample Size: Up to 72 participants total (24 per age cohort) to achieve 54 evaluable (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 Cohort 1, evaluable participants will be balanced by weight (nine evaluable in each of two weight bands). In each cohort, at least six participants will be HIV-infected.

Study Treatment: BDQ given in combination with an optimized background TB treatment regimen (OBR) for 24 weeks. For HIV-infected participants, BDQ will also be given in combination with an acceptable antiretroviral (ARV) therapy regimen initiated at least two weeks prior to enrollment.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Age and Weight</th>
<th>BDQ Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>≥ 6 to &lt; 18 years ≥30 kg</td>
<td>400 mg once per day for two weeks then 200 mg three times per week for 22 weeks</td>
</tr>
<tr>
<td>up to 24 participants to achieve 18 evaluable (nine in each weight band)</td>
<td>≥ 6 to &lt; 18 years ≥15 to &lt;30 kg</td>
<td>200 mg once per day for two weeks then 100 mg three times per week for 22 weeks</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>≥ 2 to &lt; 6 years ≥7 kg</td>
<td>Calculated using model-based dose selection</td>
</tr>
<tr>
<td>up to 24 participants to achieve 18 evaluable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 3</td>
<td>≥ 0 to &lt; 2 years ≥3 kg</td>
<td>Calculated using model-based dose selection</td>
</tr>
<tr>
<td>up to 24 participants to achieve 18 evaluable</td>
<td></td>
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</table>
Study Duration: Approximately 54 months total. Accrual is expected to require approximately 24 months and participants will be followed for a minimum of 96 weeks after their last dose of BDQ (up to a total of 120 weeks of follow-up in each participant).

Primary Objectives
In HIV-infected and HIV-uninfected infants, children and adolescents receiving BDQ plus OBR for MDR-TB, to:
- Determine the BDQ doses that achieve similar weekly exposure (area under the curve; AUC) of BDQ compared to adults taking BDQ at the standard recommended dose.
- Evaluate the safety and tolerability of BDQ over 24 weeks from the initiation of study treatment.

Secondary Objectives
In HIV-infected and HIV-uninfected infants, children and adolescents receiving BDQ plus OBR for MDR-TB, to:
- Evaluate the PK of BDQ over the 24-week dosing period, by HIV status.
- Describe the long-term safety and tolerability of BDQ over a 120-week (30-month) total follow-up period, by HIV status.
- Describe BDQ concentrations following BDQ treatment discontinuation at 24 weeks, from study Weeks 24 to 120, by HIV status.
- Describe the MDR-TB treatment response up to 120 weeks from the initiation of the study, by HIV status.
A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

Figure 1. Overview of Study Design

Enrollment of (HIV- and HIV+) participants commences with subjects combined across both weight bands. Enrollment into cohort paused once group (N=6 participants) completes Week 2 evaluation and up to 3 additional participants are accrued.

Week 2 batched PK analysis and population PK modeling of the group (N=6) and cumulative safety data of all participants are evaluated.

Safety is unacceptable (i.e., triggers SMC review) or PK criteria not met: dose may be adjusted. Complete enrollment of next group (N=6).

Safety is acceptable and PK criteria are met: resume enrolling.

All available PK (including Week 1, Week 2, Week 8 or later sparse PK) of the group and cumulative safety data on all participants are evaluated.

Safety is acceptable and PK criteria are met: complete enrollment into the cohort.

Safety is unacceptable (i.e., triggers SMC review) or PK criteria not met: dose may be adjusted. Complete enrollment of next group (N=6). All available PK (including Week 1, Week 2, Week 8 or later sparse PK) of the group and cumulative safety data on all participants are evaluated.

Safety is unacceptable and PK criteria are met or exposure is high: consider enrolling new group (N=6) in consultation with the SMC, using an adjusted dose.

Safety is unacceptable and PK criteria are not met (exposure low): consider termination of the study in consultation with the protocol team and the SMC.

Safety is unacceptable in all participants and PK criteria are met in at least 8 individual participants.

Once 6 participants (and up to 3 additional participants) in addition to the 6 previously evaluated have completed Week 2 PK sampling, all available PK (including Week 1, Week 2, Week 8 or later sparse PK) of the total of 12 subjects and cumulative safety data on all participants are evaluated. Enrollment is paused; up to 3 additional participants are accrued.

Safety is acceptable and PK criteria are met: complete enrollment into the cohort.

Open Cohorts 2 and 3 in parallel using groups of N=6 per cohort.
1 INTRODUCTION

1.1 Background

Global epidemiology of tuberculosis

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium tuberculosis* (*M. tb*), which most commonly affects the lungs, but often spreads to other organs. In 2014, there were an estimated 9.6 million incident TB cases of TB globally (1). Of the 9.6 million incident cases in 2014, an estimated 12% were HIV co-infected (1).

It is estimated that 15-20% of TB cases globally occur in children (2). Surveillance for childhood TB has traditionally been limited and case detection poor due to the paucibacillary nature of disease in children (less than 10% of pulmonary TB in young children is smear-positive), inability to cough and expectorate on demand and limited programmatic focus. In the World Health Organization (WHO) 2015 Global TB Report, they estimated that approximately 1 million children had incident TB in 2014 (1). Developing countries have the highest pediatric TB burden with more than 75% of cases occurring in 22 high-burden TB countries. HIV contributes significantly to the pediatric disease burden and child mortality (3).

Epidemiology of drug-resistant TB

Multidrug-resistant TB (MDR-TB) is caused by *M.tb* strains resistant to isoniazid (INH) and rifampin (RIF). Extensively drug-resistant TB (XDR-TB) is additionally resistant to at least one second-line injectable medication and a fluoroquinolone. WHO estimated that there were 480,000 MDR-TB cases globally in 2014. It is estimated that about 9.7% of these cases were XDR-TB (4). The challenges of identifying and appropriately treating TB in children are compounded by the increasing rates of MDR-TB and XDR-TB globally. Adults with MDR-TB often experience prolonged diagnostic delay, resulting in transmission of these strains to children. Until recently, detection of drug resistance required mycobacterial culture and drug susceptibility testing; more recent advances including rapid and highly accurate molecular tools such as Xpert MTB/RIF (5, 6) promise to increase the number of MDR cases detected and reduce diagnostic delay. Drug-resistant TB (DR-TB) in children is usually transmitted from a source case rather than developing from drug-susceptible TB. TB in children is usually paucibacillary and often culture-negative, with a lower risk for acquired drug resistance (7).

Burden of Pediatric MDR-TB

There are limited representative surveillance data on DR-TB in children. A recent prevalence study from Cape Town, South Africa, was completed to assess the burden of pediatric MDR-TB and HIV co-infection in this setting between March 2007 and February 2009. DST for INH and RIF was completed on initial isolates from each child less than 13 years with culture-confirmed TB; isolates resistant to INH and RIF were tested for resistance to ethambutol (EMB) and second-line drugs. 282 children were enrolled, median age 26 months (range three days-156 months). DST was available in 279 (98.9%): 43 (15.4%) of infecting strains had INH or RMP resistance; 39 (14.0%) were INH-resistant; 24 (8.6%) were resistant to both INH and RMP. EMB resistance was present in 11/22 (50.0%) of MDR-TB isolates; two isolates were resistant to amikacin and none were XDR-TB (i.e., strains resistant to fluoroquinolones and injectable agents). The overall prevalence of HIV infection was 30.2% (8). Data from Johannesburg, South Africa, indicate a high overall prevalence of MDR-TB with a prevalence of INH-resistance of 14.2% (N = 21) (95% CI, 9.0-20.9%) and MDR-TB prevalence of 8.8% (N = 13) (95% CI, 4.8-14.6%). The
majority (53.9%) of children with MDR-TB were also HIV co-infected (9). Current data from Cape Town indicate that approximately 20% of children aged 0-13 years treated for MDR-TB (culture-confirmed and clinically diagnosed) are also HIV-infected. In this setting, approximately 10-15% of children with confirmed MDR-TB have pre-XDR-or XDR-TB (personal communication: A. Hesseling, 9 September 2014).

Data from P1041 (A Randomized, Double Blind, Placebo Controlled Trial to Determine the Efficacy of Isoniazid [INH] in Preventing Tuberculosis Disease and Latent Tuberculosis Infection among Infants with Perinatal Exposure to HIV), an INH-prevention trial, demonstrated a 25% prevalence of MDR-TB among those isolates that were cultured from infants and children diagnosed with pulmonary TB while on study. All children with MDR-TB disease were enrolled at the Johannesburg International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) site (10). As new rapid and accurate molecular tools endorsed by the WHO are rolled out and are widely implemented, also in children, the number of all MDR-TB and pediatric MDR-TB cases is likely to increase significantly.

**Management and treatment outcomes of MDR-TB in children**

MDR-TB in children is frequently associated with delays in diagnosis and treatment and there are multiple challenges in the diagnosis including the inability to produce spontaneous sputum samples in young children and the paucibacillary nature of TB in most children. At most, 10-15% of children with pulmonary TB are sputum smear-positive and approximately 30% culture-positive (11). In the absence of bacteriologic confirmation, the majority of children are treated empirically and presumptively for MDR-TB, either based on history of exposure to an adult with DR-TB together with symptoms suggestive of TB in the child, or based on poor response to first-line treatment (12). In a study of children with culture-positive MDR-TB, the median time to MDR-TB treatment initiation (N = 102) was significantly shorter in the presence of a known adult MDR-TB index case (13). These data indicate the importance of adult contact information in addition to bacteriological ascertainment in the appropriate management of children with MDR-TB.

Management of MDR-TB disease in children typically requires prolonged treatment for 18 to 24 months with second-line drugs, which are toxic and expensive. According to WHO guidelines for management of MDR-TB, an optimal regimen should include a fluoroquinolone, an injectable aminoglycoside (kanamycin, amikacin, or the polypeptide capreomycin), and at least two of the following drugs: cycloserine (CS)/terizidone (TZD), a thioamide (typically ethionamide [ETH]), para-aminosalicylic acid (PAS), and, additionally, first-line agents other than RIF (14-16).

In settings where there is a high burden of MDR-TB and extensive experience in the management of pediatric MDR-TB such as South Africa, treatment is based on international recommendations and the available literature (17). High-dose (15-20 mg/kg) INH is used in the majority of cases, as there is evidence that resistance due to inhA promoter region mutations usually confer low-level INH resistance (18). An injectable agent, most frequently amikacin, is typically used for four-six months rather than for the duration of therapy in order to limit potential toxicity; capreomycin is substituted if resistance to amikacin is detected. Levofoxacin is the fluoroquinolone that is used in young children (less than eight years of age, available in 250 mg tablets) and moxifloxacin is used in older children (consistent with routine use in adults; only available in 400 mg tablets and highly unpalatable with a bitter taste so cannot be crushed for younger children).

In this study, all enrolled children will receive an optimized background TB treatment regimen (OBR) in addition to study BDQ. Since levofoxacin causes less QT prolongation than
moxifloxacin, levofloxacin will be the fluoroquinolone of choice given that BDQ also causes QT prolongation. To ensure that there are at least four effective drugs in the regimen, additional drugs typically added may include the following: an injectable antibiotic (amikacin, capreomycin or kanamycin), ETH, PAS, TZD/CS, high dose isoniazid, and in cases of XDR-TB, co-amoxiclavulanic acid, clofazimine and/or linezolid.

All antituberculous therapy is given as directly observed therapy (DOT) for the duration of treatment with an initial in-hospital phase while an injectable is given (typically four-six months) in young children, depending on the severity of disease and the age of the child.

Adolescents with TB in developing country settings are frequently treated on an ambulatory basis at community-based TB clinics. TB doses are typically given by DOT and inpatient duration is variable depending on the age of child and severity of illness. If admitted to hospital, children are typically discharged to continue their treatment at their local TB clinic. Treatment is typically continued for 15-18 months following the first negative culture in the case of bacteriologically confirmed cases, but children with more extensive drug resistance are treated for longer periods, typically for up to 24 months. DOT may be home-based or clinic-based once the patient is discharged. Children with clinically diagnosed TB that is not bacteriologically confirmed may be treated for a shorter duration, generally 9-12 months, depending on the severity of disease (19).

Adverse effects of background drugs used to treat MDR-TB

Adverse effects of existing second-line TB drugs are common in children. Irreversible hearing impairment due to the injectable agents is common and debilitating. In 94 children (median age: 43 months) treated with an injectable TB drug, of whom 28 (30%) were HIV-infected, 23 (24%) children had confirmed hearing loss (20). Seven of 11 (64%) children classified as having hearing loss had progression of hearing loss even after finishing the injectable drug. The development of injectable-sparing regimens that are more child-friendly including limited toxicity and the use of ambulatory care, is critically important in the management of MDR-TB in children.

Hypothyroidism is frequently reported in children treated for MDR-TB receiving a regimen containing ETH and/or PAS (21). Clinical data, serum thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels, completed as standard of care, were retrospectively assessed in 137 South Africa children receiving anti-tuberculosis treatment including ETH. Abnormal thyroid function tests (TFTs) were recorded in 79 (58%) children and were specifically high among children on regimens including PAS and in HIV-infected children (21).

Vomiting and nausea are frequently reported in children receiving second-line TB therapy. In 44 children treated for MDR-TB disease receiving a regimen that included ethionamide, the most common adverse event (AE) was vomiting in 14 (32%) (22). Adverse effects may be more frequent in children treated for pre-XDR or XDR-TB, although published data are currently limited.

In summary, AEs including hearing impairment, hypothyroidism, nausea and vomiting are frequently reported in children receiving routine second-line antituberculosis drugs for the treatment of MDR-TB and are thus expected and unavoidable in children receiving any new drug including BDQ given in conjunction with OBR. This study will fill a key gap in providing dosing and safety data of BDQ in children with MDR-TB, which will inform the evaluation of future more child-friendly treatment regimens.
Treatment outcomes of MDR-TB in children using existing regimens

Adequate management of DR-TB is essential for cure and for preventing the acquisition of additional resistance. The available data examining treatment outcomes amongst adults with MDR- and XDR-TB indicate favorable outcomes in only about 60% (23) and 44% of cases, respectively (24). There are limited published data in pediatric populations, but reported outcomes are generally good with prolonged multidrug therapy (9, 25-32). In a recent retrospective study of 111 children with culture-proven MDR-TB, the median age was 50 months and 43% were HIV-infected. The median number of drugs used was seven (4–13); the median duration of intensive phase therapy (initial phase of therapy that generally includes an injectable) was six months and total duration of therapy 18 months; 82% of children overall had favorable treatment outcomes (bacteriologic cure or treatment completion with good clinical response). Mortality was 12%. HIV co-infection (OR: 11.6; 95% CI: 1.06-126.8; p = 0.044) and extrapulmonary TB (OR: 42.1; 95% CI: 3.01-589.4; p = 0.005) predicted death in analyses adjusted for age and nutritional status (13). A meta-analysis and systematic review of MDR-TB treatment outcomes in children recently reported cure and/or successful treatment completion in up to 81% of children treated for MDR-TB (33). Even when treatment outcomes are largely favorable, the long duration and significant toxicity of existing second-line TB therapy in children are still major concerns (33, 34). In some settings, treatment outcomes are poor with one study reporting 31% death in children with MDR-TB. Clearly, improvement is needed.

Limited data on markers of TB treatment response in children

There are limited data on markers of response to antituberculosis treatment in children, who typically have paucibacillary (smear-negative, and frequently culture-negative), TB disease. In contrast to adults, where bacteriological conversion is typically used to assess TB treatment response, including in TB treatment trials, subjective markers of response to treatment are typically used in children. Accurate markers of TB treatment response in children would facilitate their inclusion and assessment during treatment in much-needed treatment shortening trials, especially for MDR-TB, where treatment regimens are currently long, complex and toxic, and where shorter and more child-friendly regimens are urgently needed. Characterizing the response to TB treatment in conjunction with clinical evaluation, pharmacokinetic sampling and post-treatment follow-up, in HIV-infected and uninfected children with different MDR-TB disease spectrum, will allow for robust evaluation of candidate biomarkers for TB treatment response in the future. These in turn will contribute towards informing future trials on shorter treatment durations for MDR-TB. The P1108 pediatric cohort of HIV-infected and uninfected children with MDR-TB will include serial clinical and bacteriological evaluation and long-term follow-up, providing an ideal platform to test promising biomarkers of TB treatment response. Proposed biomarker work to evaluate TB treatment response in children in P1108 will include promising work on urine proteomics in collaboration with Bob Husson and Hanno Steen (Boston Children’s Hospital, Harvard) and serum markers which have shown promise in adult treatment cohorts, in collaboration with Gerhard Walzl (SUN Immunology Group, Stellenbosch University, South Africa) and others. This work would include minimally invasive sampling approaches (serum and urine), using minimal volumes, coinciding with sampling for other study evaluations. This additional work will pose minimal burden on participants, while yielding potentially useful data on how to objectively measure tuberculosis treatment response in children with MDR-TB.

Effect of HIV co-infection on the management of MDR-TB

In children with a new diagnosis of HIV, antiretroviral (ARV) treatment is typically started rapidly (usually within one-four weeks after the initiation of MDR-TB treatment), given the high
mortality of HIV-infected children with TB and MDR-TB (9, 13). All HIV co-infected children with TB require rapid initiation of ART as per local and WHO guidelines (35).

HIV co-infection in children complicates the management of TB owing to potential drug interactions and overlapping toxicities. There are limited data on the impact of the second-line TB drugs on the PK of commonly used ARVs like LPV or EFV or the effects of ARVs on PK of second-line TB drugs, but clinically important drug interactions are not predicted with most current second-line TB drugs. However BDQ is metabolized by cytochrome P450 enzyme 3A (CYP3A), and based on data from adult trials, BDQ concentrations are predicted to be reduced by EFV or increased by lopinavir/ritonavir (but not affected by nevirapine). The therapeutic margin for BDQ is not well defined, so it is unclear what the clinical effects of reduced or increased BDQ concentrations will be.

Need for pediatric MDR-TB PK data and appropriate formulations

Few of the existing drugs used to treat MDR-TB have been specifically tested in children to establish optimal doses. Pediatric formulations, although critically needed, are not routinely available for the second-line TB drugs. There are major gaps in our knowledge of the PK of second-line drugs in children, and the effects of age and HIV co-infection/treatment on TB drug PK. For most first-line TB drugs, exposures in children are lower than in adults, even when given the same mg/kg body weight dosages (36-39). HIV infection/treatment (40), nutritional status (41) and genetic profile (37, 42) also impact drug disposition. While Phase III trials for the treatment of TB disease in children (with paucibacillary disease) are not required once efficacy has been established in adults (43), timely evaluation to establish appropriate dosing needed to achieve adult-equivalent exposures and ensure drug safety in children of different ages with and without HIV are critical to ensure access to improved treatments to children. There is also a need for high-quality formulations that are child-friendly and operationally feasible to give by TB programs. Suspensions generally do not deliver accurate dosing and have variable shelf life. Dispersible tablets, granules or sprinkles are more suitable pediatric formulations.

Until pediatric formulations are available, adult formulations can be given to children, including in HIV-infected children provided that dosing is possible given the available adult formulations. For BDQ, the 100 mg formulation is U.S. FDA-approved, was licensed in October 2014 in South Africa by the Medicines Control Council (MCC), and is now being marketed in South Africa, as in several other countries. The pediatric formulation (for use in much younger children only, i.e., who cannot swallow a tablet), is in development by Janssen and is not yet available for evaluation in children. In the meantime, there is a serious risk that the drug will be used off-label without the much-needed safety and PK data in children, including in HIV-infected children, who are at risk of more severe MDR-TB, poorer nutrition and poorer TB treatment outcomes. Almost all other second-line TB drugs currently used for the treatment of MDR-TB in children are only available in adult formulations, and are routinely used in children of all ages, also in younger children and infants (where they are routinely crushed and given with liquids). Although this remains a theoretical concern, there has only been a limited effect observed of crushing of film-coated tablets, which may increase the rate of absorption of some second-line TB drugs, e.g. levofloxacin and moxifloxacin, in children, without reducing or increasing the overall drug exposure (AUC). The currently licensed 100 mg BDQ tablet is palatable, is easily breakable and crushable. The tablet is not film coated, is not a delayed-released tablet and crushes and dissolves very readily, based on field observation. Therefore, minimal effect of administering the crushed 100 mg tablet dissolved in liquid in very young children is expected. A separate but complementary study will be undertaken during 2015 to evaluate the effect of crushing on BDQ PK in healthy adult volunteers, in consultation with DAIDS, which will inform the use of the 100
mg BDQ formulation in children in P1108 and beyond. This study (“Bedaquiline CRUSH”) will be completed prior to opening the younger age cohorts (who will require formulation manipulation) to enrollment in P1108.

1.2 Prior Research

Drug information for BDQ and considerations for study design

BDQ, developed by Janssen, is a diarylquinoline compound with a novel mechanism of action against *M. tb.*, the inhibition of mycobacterial adenosine triphosphate synthase. *In vitro*, BDQ has potent activity against drug-susceptible and drug-resistant *M. tb.* isolates and is also bactericidal against dormant (non-replicating) *M. tb.* In the murine TB model, BDQ is as active as the triple combinations of INH, RIF, and pyrazinamide (PZA), with BDQ accelerating clearance of bacilli and displaying synergy with PZA. Similarly, BDQ enhances the antibacterial activity of second-line drug combinations in the murine model of DR- TB (44). The results of the first Phase II placebo-controlled study (TMC207-C208; NCT00449644) showed that the addition of BDQ to a five-drug MDR-TB regimen resulted in significantly shorter time to culture conversion compared to placebo. The 160 adults in this study with newly diagnosed, smear-positive, MDR-TB received either 400 mg of BDQ once daily for two weeks, followed by 200 mg three times a week for 22 weeks, or placebo, both in combination with a preferred background regimen. The primary efficacy end point was the time to sputum-culture conversion in liquid broth. Patients were followed for 120 weeks from baseline. BDQ reduced the median time to culture conversion, as compared with placebo, from 125 days to 83 days (hazard ratio in the BDQ group, 2.44; 95% confidence interval, 1.57 to 3.80; P<0.001 by Cox regression analysis) and increased the rate of culture conversion at 24 weeks (79% vs. 58%, p = 0.008) and at 120 weeks (62% vs. 44%, p = 0.04). On the basis of WHO outcome definitions for MDR-TB, cure rates at 120 weeks were 58% in the BDQ group and 32% in the placebo group (p = 0.003). The overall incidence of AEs was similar in the two groups. In summary, the addition of BDQ to a preferred OBR for 24 weeks resulted in faster culture conversion and significantly more culture conversions at 120 weeks, as compared with placebo (TMC207-C208 ClinicalTrials.gov number, NCT00449644.) (38, 45-47). BDQ was licensed for use in adults with MDR-TB by the US Food and Drug Authority (FDA) in 2012, and in 2014, by the European Medicines Agency (EMA).

During late 2015, findings from the second phase II b trial of BDQ in adults, a multicenter, open-label, single-arm trial (TMC207-C209; NCT00910871) were published in late 2015. This trial was conducted to confirm the safety and efficacy of BDQ. Newly diagnosed or previously treated patients with MDR-TB (including pre-extensively drug-resistant (pre-XDR)-TB or XDR-TB) received BDQ for 24 weeks with a background regimen of antituberculosis drugs continued according to National TB Programme treatment guidelines. Patients were assessed during and up to 120 weeks after starting BDQ. Of 233 enrolled patients, 63.5% had MDR-TB, 18.9% had pre-XDR-TB and 16.3% had XDR-TB, with 87.1% having taken second-line drugs prior to enrolment. 16 patients (6.9%) died. 20 patients (8.6%) discontinued before week 24, most commonly due to adverse events or MDR-TB-related events. Adverse events were generally those commonly associated with background MDR-TB treatment. In the efficacy population (n=205), culture conversion (missing outcome classified as failure) was 72.2% at 120 weeks, and 73.1%, 70.5% and 62.2% in MDR-TB, pre-XDR-TB and XDR-TB patients, respectively. Addition of BDQ to a background regimen was well tolerated and led to good outcomes in this clinically relevant patient cohort with MDR-TB. (48)
Preliminary Studies

BDQ In Vitro PK and preclinical toxicology

Figure 2. BDQ Structure

The major metabolic pathway identified in vitro (subcellular fraction and hepatocytes) and in vivo in several preclinical species including mice, rats, rabbits (in vitro only), dogs, monkeys and in humans was N-demethylation to M2 followed by further N-demethylation to M3. M2 was the major circulating metabolite in mice, rats, dogs and humans following repeated administration. Overall, the biotransformation in humans was less extensive than in animal species. In humans, all circulating metabolites found, including those found in vitro, have been identified in animal species. In pregnant albino Sprague-Dawley rats, radioactivity levels in the placenta were about three times higher than in plasma, but distribution to the fetus was low (tissue/plasma ratio: 0.4). Emerging data indicate that M2 is clearly more cytotoxic in vitro than BDQ (previously TMC207). This is relevant because BDQ is highly metabolized by M2 in animal models, so circulating concentrations of M2 are much higher than BDQ in animal models, but the opposite is true in humans. Caution is thus required in extrapolating preclinical toxicity results to the human experience. Cytotoxicity of the M2 metabolite may be of clinical relevance if in vivo concentrations approach those concentrations at which in vitro cytotoxicity was seen. BDQ (the parent drug) only causes cytotoxicity at concentrations outside the clinically achievable range.

Implications of preclinical toxicology findings for this study

Cationic amphiphilic drugs like BDQ can cause phospholipidosis, characterized by the accumulation of phospholipids in cells. Phospholipidosis is thought to be an adaptive response rather than a manifestation of direct cellular toxicity, but phospholipidosis may have clinical consequences, including prolonged QT interval, myopathy, hepatotoxicity, nephrotoxicity, or pulmonary dysfunction (49). These effects are generally reversible with drug discontinuation (49). There is no reliable biomarker predictive of drug-related phospholipidosis, and animal models do not appear to predict human responses well (50). A theoretical concern with BDQ use is potential mitochondrial toxicity, which may be associated with phospholipidosis, although, to our knowledge, no specific evidence of BDQ-induced mitochondrial toxicity has been reported. M2 induces phospholipidosis in vitro at lower concentrations than BDQ. Comparing with in vivo
reference compounds, M2 can be identified as a stronger phospholipidosis-inducer than BDQ (51). This may explain the higher tissue to plasma ratio observed in vivo for M2. In vitro, M2 has been shown to be a stronger inducer of phospholipidosis than amiodarone, and M2 induced phospholipidosis at lower concentrations than BDQ (1.2 μM vs. 7.3 μM, respectively). Taken together, the results suggest that M2 is the main driver behind the toxicity- and phospholipidosis-related issues in the preclinical safety profile of BDQ. In humans, since M2 concentrations are low (25-30% compared to BDQ) the safety profile is expected to be better than in the preclinical species (Table 1). In P1108 study, participants will be followed long-term, and follow-up will include lactate testing as a marker for potential mitochondrial toxicity. Lactate will only be routinely completed in the oldest age cohort (age 6-17 years). If no toxicity signal is detected in this age group, there will be no lactate testing in the younger age cohorts, where completing lactate testing may be technically even more challenging. In addition, serial ECGs will be performed; however, it should be noted that there is not clear evidence that the QT prolongation caused by BDQ is a phospholipidosis-related phenomenon (see below).

Table 1. Mean (±SD) Observed Pharmacokinetic Parameters of BDQ (TMC207) and M2 at Weeks 2 and 24 in TMC207-C-208 Stage 2

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<th>Week</th>
<th>TMC207</th>
<th>M2</th>
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<tr>
<td>Cmin (ng/mL)</td>
<td>728 ± 257</td>
<td>332 ± 122</td>
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<tr>
<td>Cmax (ng/mL)</td>
<td>2763 ± 1185</td>
<td>467 ± 157</td>
</tr>
<tr>
<td>Cavg (ng/mL)</td>
<td>1371 ± 529</td>
<td>383 ± 130</td>
</tr>
</tbody>
</table>

BDQ Clinical Pharmacokinetics and Metabolic Drug Interactions

In adults, BDQ is well absorbed with a tmax of five hours. Dose-proportionality of Cmax and AUC is seen up to 700 mg with single doses and 400 mg with multiple doses. The average terminal elimination half-life of BDQ is 132 days and is 112 days for its M2 metabolite. Administration with food increases bioavailability by 95%. In individuals of black race, concentrations of BDQ are appreciably lower (52%) compared to individuals of non-black race (52). BDQ is metabolized by oxidative metabolism via the CYP3A4 isoenzyme to its N-desmethyl metabolite, M2. The M2 metabolite has activity against M. tuberculosis, but it is three- to six-fold less potent.

Mean plasma concentration–time profiles for BDQ given as 400 mg given once daily for two weeks and for BDQ 200 mg thrice-weekly following eight weeks of dosing among patients with MDR-TB are shown in Table 1 and Figure 3. Mean (±SD) peak (Cmax), minimum (Cmin), and average plasma concentrations (Cav) of BDQ at Week 2 were 3270±1144, 956±557, and 1770±701 ng/mL, respectively, and at Week 8 were 1659±722, 620±466, and 902±535 ng/mL.
Target drug concentrations for BDQ for children —using evidence from PK/PD models

BDQ has an extensive $t_{1/2}$, therefore it accumulates over time. In adults, drug accumulation is mitigated by using the current loading dose of 400 mg once daily for two weeks followed by a reduction in dose and dosing frequency to 200 mg three times weekly for six additional weeks. As seen in Figure 4, BDQ concentrations following 400 mg once daily dosing demonstrate some accumulation up to 14 days. After an initial decrease in exposure between Weeks 3 and 12 related to the decrease in dose, the exposure is expected to increase slightly between Weeks 12 and 24 (Figures 5 and 6). Drugs with multiple compartments (BDQ is tri-exponential, or three-compartmental) and extensive terminal phase half-lives can pose problems when examining accumulation; the terminal $t_{1/2}$ provides little information about the expected accumulation on multiple dosing and when a practical steady state would be reached. In theory, pseudo-steady-state is reached after approximately five times the terminal half-life (so 660 days or 1.8 years for BDQ).
Figure 5. Model-Predicted Weekly BDQ Exposure to Week 3

Figure 6. Comparison of the Model-Predicted and Observed Trough Concentrations in Plasma at Week 12 and 24 (Population Pharmacokinetic Model)
However, in many cases a terminal $t_{1/2}$ and amount of drug associated with the deep compartment contributes little to the overall accumulation and total area. Therefore, the effective half-life (half-life estimated using data collected over the 24-hour dosing interval) is sometimes more useful than a terminal half-life. The effective $t_{1/2}$ for BDQ is calculated at 21.2 hours based on the formula: where AUCss and AUCsd are the AUC’s following steady state and single-dose administration, respectively. Key parameters are the elimination rate constant and dosing interval ($t$). This shorter, effective $t_{1/2}$ explains why concentrations as seen in the concentration-time profile of BDQ plateau by Day 14.

Using data from animal models, PK data from humans, and knowledge about relative concentrations and relative activity of M2 compared to BDQ, the average target plasma BDQ concentration in humans was set at about 600 ng/mL (i.e., $2 \times 300$ ng/mL or an AUC24 of 14.4 μgxh/mL) prior to embarking on clinical efficacy trials. However, in the Phase II trials to date, at the dose tested, no clear exposure-response relationship was seen, so target concentrations are not well defined. Thus, in clinical trials, the PK/PD (PD = pharmacodynamic) target has not been established, and the 600 ng/mL target has not been confirmed. However, when given at a dose of 400 mg once daily for 14 days followed by 200 mg thrice weekly for 22 weeks, the drug was effective, so it seems reasonable to target adult exposures achieved in the Phase II trials in dose finding trials in children.

It is not expected that the tissue distribution of BDQ would be disproportionately higher in children. There are no known age or maturation dependent processes for the tissue distribution component. The extensive distribution of BDQ is primarily a passive process governed by the cationic properties of the compound (causing it to be trapped inside cells due to the pH shift making it charged). Because this process is not related to any active transport, enzyme maturation status should not affect the distribution.

**Use of BDQ in HIV-infected patients on ART**

Data on drug-drug interactions (DDI) between BDQ and ART among patients with HIV/TB co-infection remain limited. Studies to date have mostly evaluated the effects of ARV drugs together with single-dose BDQ in healthy HIV-seronegative volunteers. In the Phase IIb studies some HIV-infected participants (22) were enrolled but none received ARVs during the 24-week investigational period. The effect of LPV/r on the PK of BDQ was evaluated in 16 HIV-infected adults. (53) Treatment A included single-dose BDQ 400 mg and Treatment B LPV/r 400/100 mg twice daily (bid) for 24 days, with co-administration of single-dose BDQ 400 mg on day 11. Results of this study indicated CYP3A4 inhibition by LPV/r on the PK of BDQ and its metabolite M2. Co-administration of LPV/r 400/100 mg bid increased exposure (AUC336h) to BDQ by 22% and decreased exposure to M2 by 41%, consistent with the role of CYP3A4 in metabolizing BDQ. The long half-life of BDQ resulted in a sequence effect, with a greater effect of LPV/r on BDQ when Treatment B was administered in the second period. These findings indicate that there is potential for a greater accumulation ratio of BDQ and M2 after prolonged co-administration with LPV/r. The clinical relevance of this interaction must be established. However, LPV/r will not be used in children included in our study.

Furthermore, the effect of nevirapine (NVP) on the PK of BDQ was investigated in HIV-infected adults ($N = 16$). For BDQ and M2, PK profiles were assessed up to 336 hours post-dose after each administration of BDQ. For NVP, pre-dose concentrations were measured on the last three days prior to the second dose of BDQ (days -3 -2 and -1) on the day of administration of the second dose of BDQ (day 1), and subsequently on days 2, 3, 4, 8 and 15. Co-administration of steady-state NVP did not significantly impact on BDQ or M2 exposure. (53) The metabolic ratio
(AUC ratio M2/ BDQ) was not significantly affected by NVP. Additionally, NVP pre-dose concentrations were comparable before and after co-administration of single-dose BDQ. In a study involving healthy HIV-seronegative participants receiving single-dose BDQ alone or with multiple-dose EFV, EFV appeared to reduce BDQ concentrations by about 20%; nonlinear mixed effects modeling to estimate the effects of EFV on BDQ and M2 concentrations at steady state suggest that larger reductions are likely with prolonged dosing (54).

In a recent study led by the University of Cape Town International IMPAACT/ACTG PK specialty lab, sampling was conducted on 43 adult patients treated for MDR-TB (17 not on ARVs, 16 on NVP, and 10 on LPV/r). The median time on BDQ was 50 days, interquartile range (IQR) 34-48. Intensive PK sampling (nine blood samples over 48 hours) was conducted once patients were in the maintenance dose phase (200 mg three times per week) of BDQ. There was no significant difference (p = 0.67) between the median BDQ plasma AUC in µg.hr/mlin patients on NVP (35.11 [IQR 26.75-60.79]) compared to patients not on ARVs (34.73 [27.47-52.83]). Similarly, there was no significant difference between the median BDQ maximum concentration (C_max in µg/ml), M2 AUC, and M2 C_max in patients on NVP (1.99 [1.38-2.35], 8.10 [4.88-10.82], and 0.18 [0.13-0.28], respectively) compared to patients not on ARVs (1.97 [1.10-2.64], 7.4 [6.06-9.06], 0.17 [0.14-2.44], respectively). Median BDQ AUC was significantly higher (p = 0.005) in patients on LPV/r (69.5 [54.7-88.3]) compared to patients not on ARVs. The median BDQ C_max was non-significantly higher (p = 0.23) in patients on LPV/r (2.48 [1.66-2.85]) compared to patients not on ARVs. There was no significant difference in median M2 AUC and M2 C_max in patients on LPV/r (5.38 [3.43-10.80], and 0.15 [0.09-0.25], respectively) compared to patients not on ARVs. In conclusion, there was no significant difference in BDQ and M2 PK parameters between patients on NVP and patients not on ARVs. The median AUC of BDQ in patients on LPV/r was two times higher than patients not on ARVs, the clinical significance of which remains to be determined (personal communication, McIlleron, 9 September 2014).

Children on P1108 will not be receiving LPV/r containing regimens.

No pharmacokinetic studies of BDQ have yet been conducted in HIV-infected or HIV-uninfected children to date. Only ARV drugs shown or proposed to have limited interaction with BDQ in adult studies will be used in child participants in the proposed study. The use of EFV and LPV/r will not be allowed.

Use of BDQ in Children with Intrathoracic TB and Limited forms of Extrathoracic TB

Given that there are no data on BDQ penetration of CSF, there does not at present appear to be an additional substantial benefit of including children with advanced (stages II/III) stages of TB meningitis (TBM), given the limited potential additional benefit offered by BDQ in these children. Children with TBM stage II/III will therefore be excluded from this study. Children with osteo-articular TB will also be excluded.

Children with intrathoracic (pulmonary) TB and selected limited forms of extrathoracic MDR-TB will be allowed, based on the risk/benefit assessment of treating children with BDQ who have difficult to treat MDR-TB and which may be associated with high morbidity and mortality. Children with miliary and abdominal TB (same duration of treatment as pulmonary TB), will be considered for inclusion.

Efficacy Studies of BDQ

In a separate study of early bactericidal activity (EBA), 75 treatment-naive patients with smear-positive pulmonary TB were randomized to once daily oral BDQ (25 mg, 100 mg, or 400 mg).
RIF 600mg, or INH 300mg for seven days. Bactericidal activity was expressed as the log_{10} decrease in colony-forming units (CFU)/ml sputum/day (Figure 7). The decrease in log_{10}CFU counts (±SD) from baseline to Day 7 was 0.04 ±0.46 for BDQ 25 mg (N = 14), 0.26 ±0.64 for BDQ 100mg (N = 14), 0.77 ±0.58 for BDQ 400mg (N = 14), 1.88 ±0.74 for INH (N = 11) and 1.70 ±0.71 for RIF (N = 14). BDQ demonstrated bactericidal activity, but onset was delayed. Significant bactericidal activity of BDQ 400 mg was observed from Day 4 onward and was similar in magnitude to INH and RIF CFU declines over the four to seven day period. It was well tolerated with no drug related serious AEs.

Figure 7. Bactericidal Activity of Different Anti-TB

In the first stage of a two-stage, Phase 2, randomized, controlled trial, 47 randomly assigned patients who had newly diagnosed MDR pulmonary TB either received BDQ (400 mg daily for two weeks, followed by 200 mg three times a week for six weeks) (23 patients) or placebo (24 patients) in combination with a standard five-drug, second-line antituberculosis regimen (47). Most AEs were of mild or moderate intensity and of a type known to occur commonly in patients with TB or in patients undergoing the standard drug regimen for MDR-TB. Only nausea occurred significantly more frequently for BDQ than placebo (26% vs. 4%, p = 0.04). No consistent or clinically relevant changes in heart rate or electrocardiographic QRS or PR interval were observed during the study. The results of bacterial culture of sputum showed that more patients were TB culture-negative at eight weeks in the BDQ group, 47.6% versus 8.7% in the placebo group. In addition, BDQ reduced the time to culture conversion. The probability of becoming culture-negative on any given day within the eight-week treatment period was 11.8 times higher in the BDQ group, versus in the background regimen alone, with hazard ratio (95% CI): 11.8 (2.26, 61.3); p = 0.003 by Cox regression analysis. Mean sputum CFU count declined more rapidly for BDQ than placebo. One participant in each treatment group experienced a serious AE, neither of which was considered related to the study medication. Over prolonged follow-up in Stage 2, time to culture conversion over 24 months was reduced in the BDQ plus background therapy group compared to the placebo plus background therapy group with a hazard ratio of 2.25 (95% CI 1.08-4.71); further, BDQ appeared to reduce the risk of acquired drug resistance to companion agents (46). Only nausea was more common among patients taking BDQ than among those in the placebo group. These Phase II results validate ATP synthetase as a viable target.
In the absence of pediatric data, WHO currently recommends that BDQ not be used as part of clinical practice in children (55). Current provisional US CDC guidelines for BDQ use includes the following information regarding its use in certain populations, such as children, pregnant women, or persons with extrapulmonary MDR-TB, who were not included in the clinical trials for the drug. CDC’s Division of TB Elimination developed these guidelines on the basis of expert opinion informed by data from systematic reviews and literature searches. In summary, BDQ should be used with clinical expert consultation as part of combination therapy (minimum four-drug treatment regimen) and administered by direct observation to adults aged ≥18 years with a diagnosis of pulmonary MDR-TB. Use of the drug also can be considered for individual patients in other categories (e.g., persons with extrapulmonary TB, children, pregnant women, or persons with HIV or other comorbid conditions) when treatment options are limited. However, further study is required before routine use of BDQ can be recommended in these populations (56). The proposed study will not assess the efficacy of BDQ in children, since efficacy studies are not needed in children if efficacy has been established in adults for the treatment of TB disease. Rather, this study aims to establish the optimal dose for children of all ages, generate safety data in children, and investigate other pediatric-relevant considerations including tolerability.

Safety, including long-term safety, and tolerability of BDQ

The following is a summary of AEs with use of BDQ in Phase I and II trials to date in adults. In the study of the effect of NVP on the PK of BDQ in HIV-infected adults (N = 16), the most frequently reported AEs were nasopharyngitis (50%), headache (31.3%) and increased gamma-glutamyltransferase (GGT, 25%). One participant reported two serious AEs (Grade 3 diarrhoea and dehydration) considered related to HIV infection (57). In the study of the effect of LPV/r on the PK of BDQ in 16 HIV-infected adults, the most frequent AEs were diarrhea (44%) and headache (25%). There were no Grade 3 or 4 AEs in the study, except for one participant with Grade 3 lipase increase seven days after intake of BDQ in the Treatment A group (53).

In the published adult Phase II data (C208) by Diacon et al. including data from 160 adults with MDR-TB, there were 79 patients in the BDQ group and 81 in the placebo group. More patients in the BDQ group than in the placebo group died: whereas two deaths were reported among the 81 patients in the placebo group, ten deaths occurred among the 79 BDQ treated patients with no causal pattern evident (45). One of the deaths in the BDQ group was due to a motor vehicle accident that occurred at 130 weeks of follow-up, and this patient was not included in further analyses. In the FDA assessment, both deaths in the placebo group appeared to be related to progression of disease, as did five of the nine deaths in the BDQ group. Among the four other patients in the BDQ group who died, there was no apparent common cause of death. One of the deaths among BDQ-treated patients occurred during the 24-week trial period; the median time to death in the remaining eight patients in the BDQ group was 329 days after the patient last received BDQ. The unexpected finding of a mortality imbalance is an important concern; however, the length of time between the last receipt of BDQ and death makes it difficult to discern a mechanism by which BDQ could be directly related to the deaths, even if BDQ’s long half-life is considered. No patient in the BDQ group who died had a prolonged QTcF at study visits preceding their death. In addition to inclusion of this data in the BDQ product label, the indication for BDQ use in adults is currently limited to patients with MDR pulmonary TB for whom an effective treatment regimen cannot be constructed without including BDQ (e.g., because of resistance to other drugs). For this population, the FDA assessment is that the benefits of BDQ outweigh the risks (58). Data from more recent phase 2b studies e.g. TMC207-C209, do not confirm this early observed excess mortality in adults with MDR-TB or XDR-TB (48).
When designing studies of BDQ in new populations including HIV-infected and HIV-uninfected children, with possible differences in drug accumulation and or metabolism, longer term safety monitoring with physical examinations, measures of mitochondrial and hepatic health and drug and metabolite accumulations may be important. Given the unexpected finding of the mortality imbalance in the initial adult Phase II trial, our study in HIV-infected and HIV-uninfected children will therefore include long-term safety assessment (120 weeks total follow-up including 96 weeks' follow-up after BDQ discontinuation), in combination with extensive safety monitoring. Although accumulation of BDQ and M2 has not been linked to this mortality imbalance in adults, this study will continue measuring BDQ levels long-term after BDQ discontinuation, until BDQ/M2 are likely to be undetectable, to define exposures over time in children, who may possibly metabolize BDQ and M2 differently from adults. Safety monitoring during BDQ dosing and after BDQ discontinuation will include measures of mitochondrial health, including lactate (and lactate/pyruvate ratios) in Cohort 1, since mitochondrial dysfunction could emerge over time due to increased enzymatic dysfunction, although no data indicating mitochondrial toxicity have been reported in adults.

**QT prolongation with BDQ and drugs commonly used to treat MDR-TB**

QT prolongation, especially in the presence of concomitant fluoroquinolone therapy, is a concern amongst adults. Prolongation of QT interval has been reported in adults on moxifloxacin, and in thorough QT (TQT) studies, moxifloxacin is often used as the positive control drug (59), yet moxifloxacin does not cause arrhythmias. For BDQ, there has been no clear relationship between BDQ concentrations and QTc interval prolongation. Only a weak association has been found between the M2 metabolite and QTc prolongation in adults (60). Of note, QT prolongation is thought to be associated with cumulative drug exposure, and among adults taking BDQ, QT prolongation reaches its peak about 16-18 weeks after starting treatment, then plateaus after that. Based on the BDQ package insert, the BDQ dose and frequency of dosing are reduced following the first two weeks of treatment. Specifically the 400 mg dose given daily for two weeks (loading dose) is reduced to 200 mg thrice-weekly.

There are limited pediatric data but moxifloxacin is increasingly used in children with MDR-TB. The careful evaluation of potential cardiotoxic effects of novel agents used in combination with fluoroquinolones in children is, thus, required. Levofloxacin causes lesser-magnitude QT changes than moxifloxacin, particularly at standard doses (61). Moreover, levofloxacin has been used successfully to treat children who were contacts of patients with MDR-TB in the setting of an outbreak in Chuuk, Micronesia at doses of up to 20 mg/kg per day, once daily (62). It is currently the fluoroquinolone of choice used for the treatment of MDR-TB in children less than eight years of age in high burden settings such as South Africa, and appears to have limited cardiotoxic effects in children studied to date. Thee et al (63) found in a study of N=23 children (4 HIV-infected) treated for MDR-TB and receiving a dose of 15 mg/kg levofloxacin, that levofloxacin exposures (sampled at t₀, and at 1, 2, 4, 6 and 8 hours post dose), that the median Cₘₐₓ [µg/ml], median AUC(0-8) [µg·h/ml] and mean tₘₐₓ [h] for Lfx was 6.71 (IQR 4.69-8.06), 29.89 (IQR 23.81-36.39) and 1.44 (SD 0.51), respectively. The mean QTc was 369 ms (SD 21.9) for levofloxacin. Children seem to eliminate levofloxacin faster than adults, leading to a drug exposure about half of that in adults following a standard oral dose (levofloxacin 750mg). No QTc prolongation (QTc >450ms) occurred.

QT prolongation caused by BDQ together with the use of a fluoroquinolone, and possibly in combination with use of clofazamine, another drug used in the treatment of MDR-TB and with potential QT wave effect, should therefore be carefully monitored in children.
In summary, the available safety data in adults, when BDQ is given as described above, do not indicate significant safety concerns precluding the evaluation of safety and PK of BDQ in children. Careful cardiac monitoring is, however, warranted. IMPAACT P1108 will therefore include frequent standard ECG monitoring in all participants (see Section 8.6).

Study Formulation

There is currently a 100 mg adult tablet formulation available. Because the pediatric formulation is not yet available, younger children will receive the crushed adult formulation as needed. A complementary separate bio-equivalence study (“BDQ CRUSH Study”) will be conducted in healthy adult volunteers in South Africa prior to the opening of the youngest age cohorts in P1108 to inform the use of the crushed BDQ formulation in young children in this study. There is a serious risk that BDQ will be used off-label in children in the future without the much-needed safety and PK data in children, regardless of formulation availability.

1.3 Rationale

The treatment of MDR-TB in HIV-uninfected and infected children could be dramatically improved with new, effective and safer drugs, with the goal of shortening MDR-TB therapy using injectable sparing regimens, and reducing adverse effects. The emergence of XDR-TB requires a wider choice of medications. A high percentage of children in international settings with MDR-TB also have HIV infection, which significantly complicates treatment. Evaluations of novel TB drugs therefore must include HIV-infected children.

This study therefore proposes to evaluate a new anti-TB drug, BDQ, recently licensed for use in adults with MDR-TB, in HIV-uninfected and infected infants, children and adolescents treated for MDR-TB disease. Our goals are to determine the appropriate dose of BDQ and to understand the dosing of this drug in the context of multiple interacting drugs commonly used for HIV treatment. It is hypothesized that BDQ will be well tolerated and will demonstrate an acceptable safety and PK profile in HIV-uninfected and infected infants, children and adolescents with MDR-TB.

This study will assess the safety and PK of BDQ in children aged 0-18 years in three age cohorts. As designed, it will allow for rapid enrollment of these highly vulnerable patients. In addition it will also include HIV-infected children, recognizing the critical need at this time to understand the safety, PK and drug-drug interactions of BDQ when given with ARV medications.

1.4 Hypotheses

BDQ will be well tolerated and will demonstrate an acceptable safety and PK profile in HIV-uninfected and infected infants, children and adolescents with MDR-TB.

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to, in HIV-infected and HIV-uninfected infants, children and adolescents receiving BDQ plus OBR for MDR-TB:
2.1.1 Determine the BDQ doses that achieve similar weekly exposure (area under the curve; AUC) of BDQ compared to adults taking BDQ at the standard recommended dose.

2.1.2 Evaluate the safety and tolerability of BDQ over 24 weeks from the initiation of study treatment.

2.2 Secondary Objectives

The secondary objectives of this study are to, in HIV-infected and HIV-uninfected infants, children and adolescents receiving BDQ plus OBR for MDR-TB:

2.2.1 Evaluate the PK of BDQ over the 24-week dosing period, by HIV status.

2.2.2 Describe the long-term safety and tolerability of BDQ over a 120-week (30 months) total follow-up period, by HIV status.

2.2.3 Describe BDQ concentrations following BDQ treatment discontinuation at 24 weeks, from study Weeks 24 to 120, by HIV status.

2.2.4 Describe the MDR-TB treatment response up to 120 weeks from the initiation of the study, by HIV status.

2.3 Tertiary Exploratory Objective

In HIV-infected and HIV-uninfected infants, children and adolescents receiving BDQ plus OBR for MDR-TB, to:

2.3.1 Explore longitudinal biomarkers of tuberculosis treatment response in children treated for MDR-TB.

3 STUDY DESIGN

This is a multicenter Phase I/II, open-label, single-arm exposure-controlled dose-finding study to evaluate the pharmacokinetics, safety and tolerability of BDQ given in combination with an individualized OBR of MDR-TB medications for the treatment of confirmed or clinically diagnosed intra-thoracic MDR-TB and selected forms of extrathoracic MDR-TB in infants, children and adolescents. OBR will contain a minimum of five drugs (typically five-seven) and will be used based on WHO and in-country recommendations, including at least four drugs against which the organism is likely to be susceptible, and typically given for 18 months, depending on the severity of disease. A summary of the typical and rational approach to selecting an MDR-TB regimen in children is provided in Appendix IIB. See inclusion criterion 4.1.7 for allowable ART regimens in HIV-infected participants. In future, it is anticipated that additional ARV regimens may be acceptable, pending the availability of adequate safety and drug-drug interaction studies in adults or if limited drug-drug interaction is expected.

The study will consist of a 30-day screening period, a two-week treatment period with daily BDQ, followed by a 22-week period of thrice-weekly BDQ and a follow up period until completion of standard MDR therapy. The total duration on BDQ will therefore be 24 weeks.
Intensive PK sampling will be performed during daily study drug administration at Week 2. Sparse PK sampling will be performed over the six-month course of treatment and following treatment completion.

All participants will be followed on study for at least 24 months after their last dose of BDQ. While participants may stop BDQ early, they will remain on study for 24 months after cessation of BDQ dosing.

Refer to Section 6.0 for a complete description of clinical and laboratory evaluations to be performed.

3.1 Cohort Approach

Up to 72 participants will be enrolled in three age cohorts.

- Cohort 1: ≥ 6 to < 18 years of age at enrollment
- Cohort 2: ≥ 2 to < 6 years of age at enrollment
- Cohort 3: ≥ 0 to < 2 years of age at enrollment

Up to 24 participants will be enrolled in each cohort to achieve at least 18 evaluable participants in each cohort. In Cohort 1, the number of participants will be balanced across two weight bands (15 to < 30 kg and ≥30 kg). In each cohort, a minimum of six HIV-infected participants will be enrolled.

A modified age de-escalation approach will be used to obtain timely representative data across all relevant ages. Age cohorts will initially be recruited sequentially, beginning with the oldest age group (Cohort 1), and simultaneously proceeding to the younger two age groups. Cohort 2 and Cohort 3 will open at the same time (i.e., in parallel) if formal PK targets and safety criteria have been met in Cohort 1 in a set number of participants (See Figure 1).

The oldest age cohort (Cohort 1) will be dosed initially using a predefined dosing strategy with a weight banding approach. Doses may be adjusted, as needed, following evaluation of early PK data. The optimal dose for BDQ in the younger age cohorts will be calculated using a model-based approach, with weight banding (please refer to Section 10.0).

Safety and PK data from each cohort will be disseminated as soon as definitive results are available (typically up to and including Week 24 data). There will be no replacement in the event of participant death, provided participants have contributed to at least one PK visit.

3.2 Cohort Management

See Figure 1 for schema of cohort management.

Enrollment will begin with Cohort 1. Participants will start with daily BDQ after having been on individual OBR MDR-TB treatment for at least two weeks as part of their routine care (see Section 4.1.6). The BDQ dose for Cohort 1 is predetermined based on modeling of adult data and knowledge of developmental pharmacology of BDQ’s metabolic pathways; there will be two dosing weight bands for Cohort 1: ≥ 30 and 15 to < 30 kg (see Table 2 in Section 5.2). Up to 12 participants will be enrolled in each weight band to achieve nine evaluable participants in each
weight band. At least six HIV-infected participants will be enrolled in Cohort 1 (regardless of weight band).

Enrollment into Cohort 1 will be paused once the initial six participants complete the Week 2 intensive PK visits and:

- Up to three additional participants have been enrolled, OR
- PK data on the initial six participants are available

The Week 1 sparse PK and Week 2 intensive PK samples and batched PK samples of the initial six participants will be sent immediately to the PK laboratory for bioanalysis followed by population PK modeling. Bioanalysis and modeling work will be done in real-time, with an anticipated time from shipment to results of three-four weeks. The protocol team will be alerted by the PK lab when each batch of samples arrives in the lab and when data are available for modeling. Each group of six participants (and up to three additional participants) reaching Week 2 PK will trigger PK analysis and modeling of all available PK data up to that point (including Week 1, Week 2 and later time points in previously enrolled participants, as available). Note that individual dose adjustment for clinical purposes will be allowed, as clinically relevant, in consultation with the protocol team, clinical care provider, sponsor and SMC as needed, to allow for appropriate individual clinical management.

Following Week 2 PK sampling, the first group of participants will proceed to the intermittent BDQ dosing phase (see Section 5.2, Table 2).

The Week 1 and Week 2 batched PK analysis and population PK modelling of the initial six participants and cumulative safety data of all participants (up to nine participants) will be reviewed. Week 1 PK data will not trigger dosing changes in Cohort 1. Rather, Week 1 PK parameters will be characterized in Cohort 1 for subsequent comparison with data from the younger age cohorts.

3.2.1 Safety is acceptable and PK criteria are met

If safety is acceptable and PK criteria (defined below) are met, accrual will resume until the next group of six participants has been enrolled. Participant safety criteria and review processes are described in Sections 9.5.2.

The PK target will be considered to have been met in a given cohort if the predicted typical exposure (summary statistic) BDQ weekly AUC at steady state is within the 90% prediction interval of estimated adult steady state exposure, i.e., 50-400 ug*h/mL. In Cohort 1, PK data for the participants in the two weight bands will be analyzed in combination.

Note that, because up to nine participants had been enrolled initially, only the number of participants needed to complete the additional six (i.e., between three and six participants) would need to be additionally enrolled.

Once the second group of six participants in Cohort 1 has completed the Week 2 intensive PK visit, all available PK data (including Week 8 and later sparse PK) and cumulative safety data on all 12 participants will be evaluated.
Enrollment of the remaining participants to complete the cohort will proceed if all of the following are achieved in the first 12 enrolled, regardless of HIV status and weight band:

- At least eight of the 12 participants are evaluable (in total, across the two weight bands),
- PK criteria are met based on all available PK data and the summary statistic described above
- No pre-defined safety issues have been identified.

In addition, enrollment of Cohorts 2 and 3 will commence in parallel using groups of six per cohort.

### 3.2.2 Safety is unacceptable and/or PK criteria are not met

If the cumulative safety data of the first group of six to nine participants enrolled are unacceptable (see Section 9.5.2), BDQ dose management of the individual participants and the cohort will be made in consultation with the SMC (toxicity management will be as per Section 8.1 and Appendices VI, VIII and IX).

If the PK criteria are not met, the BDQ dose may be adjusted and enrollment to complete the next group of six may proceed. Because up to nine participants had been enrolled initially, only the number of participants needed to complete the additional six (i.e., between three and six participants) would need to be enrolled. Note that individual dose adjustment for clinical purposes will be allowed, as clinically relevant, in consultation with the protocol team, clinical care provider and sponsor as needed, to allow for appropriate individual clinical management.

If data from the first 12 participants indicate that:

- Safety is unacceptable and PK criteria are met or exposure high: consideration will be given to enrolling a new group (N=6) in consultation with the SMC, potentially including dose adjustment.
- Safety is unacceptable and PK criteria are not met but exposure is low: consideration will be given to termination of the study in consultation with the SMC.

If unexpected delays in enrolment occur, resulting in delays of more than 12 weeks in evaluating Week 2 PK data in groups of six participants, PK assays will be completed for individual participants, and the BDQ dose may be individually adjusted based on PK and safety data for that child. Individual dose adjustments will be considered if exposures (AUC 0-24h) are unacceptably high.

In children aged 0-2 years (Cohort 3), PK assays will be completed in as close to real time as possible, ideally after every second child has reached Week 2 of treatment (along with all other available PK data at this time point), along with modelling of PK data.

### 4 STUDY POPULATION

This study will be conducted among up to 72 HIV-infected and HIV-uninfected infants, children and adolescents less than 18 years of age treated for clinically diagnosed or confirmed intra-thoracic MDR-TB and selected forms of extrathoracic MDR-TB. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.5. Considerations related to participant retention and withdrawal/termination from the study are provided in Section 4.6.
4.1 Inclusion Criteria

Potential participants must meet all of the following criteria in order to be included in this study:

4.1.1 Parent/legal guardian willing and able to provide written informed consent for study participation; in addition, when applicable per local IRB/EC policies and procedures, participant is willing and able to provide written assent for study participation.

4.1.2 Age at enrollment:
- Cohort 1: ≥ 6 to < 18 years
- Cohort 2: ≥ 2 to < 6 years
- Cohort 3: ≥ 0 to < 2 years

4.1.3 Weight at enrollment:
- Cohort 1: At least 15 kg
- Cohort 2: At least 7 kg
- Cohort 3: At least 3 kg

4.1.4 Documented HIV status as defined in Section 4.3.1 (for HIV-infected participants) or Section 4.3.2 (for HIV-uninfected participants).

4.1.5 Either confirmed or probable MDR-TB:

Confirmed intra-thoracic (pulmonary) MDR-TB, with or without one of the following forms of extrathoracic TB:
- Peripheral TB lymphadenitis
- Pleural effusion or fibrotic pleural lesions
- Stage 1 TB meningitis
- Miliary and abdominal TB,
- Other non-disseminated forms of TB disease

Rifampin mono-resistant TB (RMR-TB, routinely treated as MDR-TB), or where additional INH resistance has not been confirmed (i.e., isolated Xpert MTB/RIF rifampicin resistance) pre-XDR (MDR plus resistance to either a fluoroquinolone or a second-line injectable agent) and XDR-TB disease will be included, according to case definitions of pediatric TB described as per international consensus definitions (12) and as per local pediatric TB guidelines (35). RMR-TB, MDR-TB, pre-XDR-TB and XDR-TB are therefore collectively referred to here as “MDR-TB”, for the purposes of the protocol.

Proof of MDR-TB, RMR-TB, pre-XDR or XDR-TB may include the following:

Culture, smear or molecular confirmation (e.g., Xpert MTB/RIF Rif-resistant, line probe assay, with or without additional proof of isoniazid resistance), and with evidence (molecular probe test results or with evidence from phenotypic drug susceptibility testing) of MDR-TB OR histologically positive for M.tb in conjunction with symptoms or radiologic evidence of intrathoracic TB.
Documentation of MDR-TB (including at least RMR-TB, MDR-TB including pre-XDR and XDR-TB) diagnosis, must be obtained, with confirmation of phenotypic, molecular or genotypic evidence of drug resistance, prior to enrollment.

OR

Probable [11] MDR-TB (or RMR, pre-XDR or XDR-TB): A presumptive diagnosis of MDR-TB based on well-documented clinical symptoms or signs of TB with radiological changes (in the case of intrathoracic TB), or extrathoracic disease manifestations described under 4.1.5, in combination with documented exposure to a confirmed MDR-TB source [2], [10] or with documented failure to respond to a first-line regimen, and where adherence was well documented. The clinical decision has been made to routinely treat for MDR-TB. A reasonable attempt should, however, have been made to attempt and document a bacteriological diagnosis.

4.1.6 Initiated on an OBR MDR-TB regimen as per routine treatment decision, at least two weeks but not more than 12 weeks prior to enrollment, and tolerating the regimen well at enrollment.

4.1.7 If HIV-infected: Initiated an acceptable ART regimen defined as either ZDV+3TC+ABC or NVP+2NRTIs at least two weeks prior to enrollment.

4.1.8 If male and engaging in sexual activity that could lead to pregnancy of the female partner: Agrees to use a barrier method of contraception (i.e., male condom) throughout the first 28 weeks on study (i.e., until four weeks after discontinuation of BDQ).

4.1.9 If female and of reproductive potential, defined as having reached menarche and not having undergone a documented sterilization procedure (hysterectomy, bilateral oophorectomy, or salpingotomy): Negative pregnancy test at screening within 48 hours prior to enrollment.

4.1.10 If female, of reproductive potential (defined as in 4.1.9), and engaging in sexual activity that could lead to pregnancy: Agrees to avoid pregnancy and to use at least two of the following contraception methods throughout the entire period of study participation: condoms, diaphragm or cervical cap, IUCD, hormonal-based contraception. It is required that the method would have had to be initiated at the time of study entry.

4.1.11 Among Cohort 3 participants, no documentation that estimated gestational age at birth was less than 37 weeks.

Note: Infants born to HIV-infected women will be eligible for enrollment in Cohort 3 regardless of feeding mode and receipt of ARVs for prevention of perinatal transmissions).

4.2 Exclusion Criteria

Potential participants who meet any of the following criteria will be excluded from this study:

4.2.1 A clinically significant active medical condition or concomitant severe (Grade 3 or higher) illness or rapidly deteriorating health condition (excluding TB), including immune deficiency (excluding HIV infection), which, in the opinion of the site
investigator, would be worsened by participation in the study or would prevent appropriate participation in the trial, or that would make implementation of the protocol or interpretation of the study results difficult, or otherwise make the participant a poor candidate for a clinical trial.

4.2.2 Known or presumed severe extrapulmonary manifestations of TB, including Grades 2 and 3 TB meningitis, and osteo-articular TB.

4.2.3 Pregnant or lactating.

4.2.4 A significant cardiac arrhythmia that requires medication or a history of heart disease (heart failure, coronary artery disease) that increases the risk for Torsade de Pointes.

4.2.5 Mean QTcF interval of > 460 ms (mean value of QT interval, corrected using Fredericia correction, on ECG performed in triplicate).

4.2.6 Clinically relevant ECG changes including but not limited to pathological Q-waves (defined as > 40 ms or depth > 0.4-0.5 mV); evidence of ventricular pre-excitation; evidence of complete or incomplete left bundle branch block or right bundle branch block; evidence of second or third degree heart block; intraventricular conduction delay with QRS duration > 120 ms; Age-related bradycardia as defined by sinus rate less than lower limit as indicated in Appendix VII.

4.2.7 Known personal or family history of long QT syndrome.

4.2.8 Having a ≥ Grade 2 for any of the following abnormalities at the time of screening or known within 30 days prior to enrollment according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (“DAIDS AE Grading Table”), Version 2.0, November 2014:

- Absolute neutrophil count
- Creatinine
- AST
- ALT
- Total bilirubin, or 1.5 X ULN accompanied by Grade 2 or higher increase in LFT

Retesting and screening of the abnormalities listed above may be done as long as the screening period of 30 days is observed. The last/latest values will be used for purposes of final screening decisions.

4.2.9 Having participated in other clinical studies with investigational agents or devices, within eight weeks prior to enrollment.

4.2.10 Currently taking any of the disallowed medications specified in Section 5.7. If taking any disallowed medications, a “washout period” of three days or more prior to Entry is required.
4.3 Documentation of HIV Status

The study will include a minimum of 18 HIV-infected children (six per age cohort), reflecting the typical prevalence of HIV co-infection in children treated for MDR-TB in international IMPAACT sites. In consultation with medical officers from DAIDS and NICHD, if there is agreement regarding the need for additional data in HIV-infected children, e.g. possible differences are observed in BDQ exposure related to drug-drug interactions, a modest number of additional HIV-infected children (e.g. up to five-ten or more) may be recruited. At the time of study enrollment HIV status will need to be recorded. Confirmation of HIV status will follow age-based criteria as described in Sections 4.3.1 and 4.3.2.

4.3.1 Documentation of HIV-Infection

Documentation of HIV-1 infection is defined as positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma using methods approved by the IMPAACT Laboratory Center.

4.3.1.1 Participants less than two years of age
(Cohort 3)

Sample #1 and Sample #2 may be tested using any of the following:

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

For these participants, at least one of the two samples must be tested in the site’s designated VQA-certified laboratory. If the mother or infant is receiving antiretroviral drugs, then an HIV DNA assay may be more sensitive. For tests performed in other (non-VQA-certified) settings, adequate source documentation, including the date of specimen collection, date of testing, test performed, and test result, must be available.

4.3.1.2 Participants two years of age and older
(Cohorts 1 and 2)

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One EIA or Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

Sample #2 may be tested using any of the following:
• Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
• One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
• One HIV DNA PCR
• One quantitative HIV RNA PCR (above the limit of detection)
• One qualitative HIV RNA PCR
• One HIV culture (prior to August 2009)
• One total HIV nucleic acid test

For these participants, if both samples are tested using antibody tests, at least one of the samples should be tested in a laboratory that operates according to GCLP guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in the study site’s designated VQA-certified laboratory. For tests performed in other (non-VQA-certified or non-GCLP-compliant) settings, adequate source documentation, including the date of specimen collection, date of testing, test performed, and test result, must be available.

4.3.2 Documentation of HIV-Uninfected (HIV negative) Status

4.3.2.1 Participants two years of age and older: Cohorts 1 and 2

For participants who are at least two years of age and have not breastfed for eight weeks prior to the time of HIV testing, a single negative result from any one of the testing methods listed in Section 4.3.1.2 will suffice for purposes of documenting a participant as HIV-uninfected. If rapid testing only is done, two negative rapid tests would be required.

4.3.2.2 Cohort 3 (age < 2 years): HIV-exposed participants that have never been breastfed

Participants who were exposed to potential HIV transmission in utero and who are less than two years of age and have reported to never have been breastfed will be considered HIV-uninfected if two separate samples at different time points both test negative for HIV DNA or HIV RNA (below the limit of detection of the assay). These tests must be performed in a VQA-certified laboratory. Specimens must be drawn at least four weeks apart and must be drawn when the infant is four weeks of age or older and has been off ARV drugs for prevention of maternal-to-child transmission (PMTCT) for at least two weeks.

4.3.2.3 Cohort 3 (age < 2 years): HIV-exposed participants that have been breastfed

Participants below two years of age who were exposed to potential HIV transmission in utero and through breastfeeding may be enrolled with the following considerations:

• The participant may not be currently breastfeeding
• A specimen for HIV testing should be drawn when the infant has been weaned for at least eight weeks (i.e., no exposure to breast milk in the past eight weeks)
• The HIV testing must have occurred at least 60 days prior to the time of enrollment
• There can be no other HIV culture, HIV DNA, HIV RNA, or HIV total nucleic acid positive tests.
If the mother or participant is receiving ARV drugs, then an HIV DNA assay may be more sensitive.

Note: In all HIV-exposed children and adolescents classified as HIV-uninfected, HIV testing should be repeated if clinically indicated. Documentation of HIV status in the HIV-exposed participants in Cohort 3 at Week 48 (24 weeks post BDQ) and the Week 120/End of Study (96 weeks post BDQ) visit are required.

4.3.2.4 **Cohort 3 (age < 2 years): HIV-unexposed participants**

In participants less than two years of age with no documented HIV exposure, participants will be considered HIV-uninfected if a single approved PCR test is negative for HIV, as defined in section 4.3.1.1. If the test is positive, the infant will be considered HIV exposed and should be evaluated as per Sections 4.3.2.2 and 4.3.2.3.

4.4 **Co-Enrollment Considerations**

Co-enrollment will be allowed into observational studies, as approved by the study team.

4.5 **Recruitment, Screening, and Enrollment Process**

Children with MDR-TB in international settings, where this protocol will be implemented, are typically treated at TB hospitals, if admission is required, and at community-based TB clinics for ambulatory care, once they have been discharged from hospital. For ambulatory care, MDR-TB treatment would typically be dispensed by the TB clinic, and supported by the parent/caregiver and/or by a community-based treatment supporter. Sites will typically be in close contact with local public TB programs (e.g. TB hospitals, TB clinics), to identify potentially eligible participants. More detailed information is provided in the Site Implementation Plans (SIP) submitted by each participating site.

Prior to implementation of this study, each site must have the protocol document and the consent form approved by the local Institutional Review Board (IRB)/Ethics Committee (EC) and other relevant national and local authorities. Sites will be selected by the Protocol Team and approved by IMPAACT Network Leadership before protocol registration can occur. Each site must complete the protocol registration process through the DAIDS Regulatory Support Center (RSC) Protocol Registration Office and receive DAIDS notification of approval to begin enrollment before participants can be enrolled in this study. As part of the site selection process, sites will be asked to provide information on background MDR-TB and pediatric MDR-TB burden, local policies for hospital admission of pediatric MDR-TB, and experience with diagnosis and management of pediatric MDR-TB; MDR and HIV management guidelines; experience with pediatric PK sampling, and laboratory capabilities including access to routine and other TB microbiology labs. Participants meeting the study eligibility criteria will be enrolled through the Data Management Center (DMC) registration screens. Written informed consent for study participation must be obtained before any study related procedures are performed. Screening evaluations must be performed within 30 days of Entry.

The IMPAACT Data Management Center (DMC) Subject Enrollment System (SES) will be used to assist with tracking the screening and enrollment process. When informed consent is obtained, participant identification numbers (PIDs) will be assigned and a study-specific screening number
will be obtained for the participant through the SES. For participants found to be eligible, enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID). For participants who are found to be ineligible for the study, or who do not enroll in the study for any reason, a case report form (CRF) will be completed to record the screening outcome.

As described in greater detail in the study-specific Manual of Procedures (MOP), the informed consent process will include detailed review of the study ICF, and will allow time to address any questions or concerns each participant may have, and an assessment of each participant’s understanding before proceeding to the informed consent decision. The process will be fully documented and only participants/parents who are able to demonstrate understanding will be asked to provide written informed consent for themselves or their children to take part in the study.

4.6 Participant Retention

Once a participant is enrolled in this study, study staff will make every effort to retain him or her for the protocol-specified duration of follow-up, thereby minimizing potential biases associated with loss to follow-up. Each site must establish and implement recruitment and retention SOPs to promote high rates of retention.

5 STUDY TREATMENT

Study treatment is defined as BDQ 100 mg tablets for oral administration. Site pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations and refer to the package insert for further information about BDQ.

5.1 Study Treatment Formulation

BDQ 100 mg oral tablets contain 120.89 mg of BDQ fumarate, which is equivalent to 100 mg of BDQ.

BDQ fumarate is a white to almost white powder and is stated to be insoluble in aqueous media in the package insert.

BDQ should be dispensed in the original container and stored at 25°C (77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F).

5.2 Study Treatment Regimens

Cohort 1 participants will receive BDQ as defined in Table 2, but with the possibility of a change in dosing of later-enrolling participants, following safety and PK analysis as outlined in Section 3.2.

For Cohorts 2 and 3, dosing will be determined using a model-based selection method and a weight banding approach, based on all available data from Cohort 1 as well as information from adult studies. Also refer to Sections 8.0 and 9.0. Specifications for weight banded dosing for Cohort 2 and Cohort 3 will be provided to sites in a protocol Clarification Memorandum (CM). Refer to Section 10.0 for a detailed rationale for the modeled dose selection approach.
For all cohorts, the maximum duration of study treatment is 24 weeks.

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Weeks 1-2</th>
<th>Weeks 3-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6 to &lt; 18 years</td>
<td>≥30 kg*</td>
<td>BDQ 400 mg once daily, every day</td>
<td>BDQ 200 mg once a day only on Monday, Wednesday and Friday with at least 48 hours between doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given as four of the 100 mg tablets to equal 400 mg per dose</td>
<td>Given as two of the 100 mg tablets to equal 200 mg per dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total weekly dose of 2800 mg</td>
<td>Total weekly dose of 600 mg</td>
</tr>
<tr>
<td>≥15 kg to &lt; 30 kg</td>
<td></td>
<td>BDQ 200 mg once daily, every day</td>
<td>BDQ 100 mg once a day only on Monday, Wednesday and Friday with at least 48 hours between doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given as two of the 100 mg tablets to equal 200 mg per dose</td>
<td>Given as one of the 100 mg tablets to equal 100 mg per dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total weekly dose of 1400 mg</td>
<td>Total weekly dose of 300 mg</td>
</tr>
</tbody>
</table>

*Note: Dosing increases will be considered during the study for children who start out weighing < 30 kg and gain weight to be ≥30 kg, during the 24 weeks of BDQ dosing, in Cohort 1. More information will be provided in the MOP.

5.3 Study Treatment Administration

For participants who are able to do so, BDQ tablets should be swallowed whole with 10-20 ml of water and taken with food. When taken Monday, Wednesday and Friday (TIW) there should be at least 48 hours between doses.

Detailed instructions regarding standard pill cutting, crushing, and weight banding approaches will be provided in the MOP.

If a dose is missed during the first two weeks, participants should NOT make up the missed dose but should continue the usual schedule. From Week 3 onwards, if a dose is missed, participants should take the missed dose as soon as possible, within 48 hours, and then resume the TIW schedule, maintaining 48 hours between doses (e.g. if a dose is missed on a Wednesday and taken on the Thursday, the next dose should be given on the Saturday; Monday-Wednesday-Friday dosing can then restart the following week). There must be 48 hours between doses.

5.4 Study Treatment Acquisition and Accountability

BDQ will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should follow the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the section Study Product Management Responsibilities.

The site pharmacist is required to maintain complete records of all study treatment supplies, regardless of whether received from the CRPMC or from other sources. Any supplies obtained from the CRPMC that remain unused at the end of the study be returned to the CRPMC unless otherwise instructed by the CRPMC. Procedures and relevant forms are provided in the Pharmacy
Guidelines and Instructions for DAIDS Clinical Trials Networks. ARVs and background standard MDR-TB treatment medications will not be provided through the study and will be obtained locally by the site.

Participants will remain on study treatment for a maximum of 24 weeks.

5.5 Study Drug Adherence Assessment and Counseling

5.5.1 Adherence In-Hospital

Adherence to study drug (daily during the first two weeks, and three times a week from Week 22-Week 24) will be documented with pill counts and a drug-dispensing card; ward dispensing charts may be used in addition to treatment card, and recording of dispensing completed by hospital personnel or study personnel, as relevant.

5.5.2 Adherence Outpatient

Following hospital discharge (typically following completion of injectable drugs, if receiving injectable drugs), children may be treated on an ambulatory basis at local TB clinics and adherence assessment will be done by the site’s research team using a TB dispensing card (TB treatment card) and ARV treatment card, as relevant, in HIV-infected participants. Local models of care e.g. community-based TB treatment supporter or other health care worker or a trained family member may be used for adherence support for ambulatory care. If non-adherence is noted, children will be considered for admission for completion of BDQ treatment. Following completion of BDQ, OBR will be supervised as per routine care. Spot checks for OBR adherence will be considered if there are adherence concerns. If non-adherence to OBR is noted, children will be readmitted for completion of OBR treatment. This will be the same whether BDQ is locally sourced or through the study.

BDQ and all routine TB drugs and ARVs will be administered by the research team on the day of PK sampling and on the previous evening, where relevant. The time of the two preceding doses of BDQ, other TB drugs and ART, where relevant, will also be documented. Adherence must be confirmed by the site. BDQ, routine TB drugs and ART may be administered by routine personnel or caregivers on all other occasions.

5.6 Concomitant Medications

ARVs and background standard MDR-TB treatment medications will not be provided through the study and will be obtained locally by the site as a standard of care; these are typically provided by the routine public TB services (hospitals or clinics). They will be prescribed by the routine health care provider according to local national and/or international guides for treatment of children with MDR-TB and HIV/MDR-TB co-infected children and supplied via non-study prescription.

In addition, all children receiving high-dose isoniazid as part of their OBR regimen will receive Vitamin B6, which will be provided by sites as part of standard of care. In addition to the ARVs and OBR, other concomitant medications will be documented including, but not limited to, co-trimoxazole (TMP/SMX), multivitamin supplementation, antifungals, other antibiotics and allowed anti-epileptics. All TB medications, Vitamin B6 (pyridoxine) and ARVs will be documented on the CRF. A log of other concomitant (non-TB and non-ARV medications will be maintained in the patient folder as part of the source notes.
Adherence to background routine MDR-TB and ARV, where relevant, will be documented using drug dispensing and treatment cards. During the intensive phase of MDR-TB therapy hospitalization is frequently routine practice and therefore adherence to MDR-TB and ARV is likely to be well controlled.

5.7 Prohibited and Precautionary Medications

The protocol team must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

5.7.1 Medications disallowed during administration of BDQ and for up to four weeks after the last dose of BDQ

Systemic use of:
Moderate and strong CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, fluconazole, voriconazole, itraconazole, ketolides such as telithromycin; and macrolide antibiotics other than azithromycin and clarithromycin) for more than two weeks.

Note: Fluconazole is generally a less potent inhibitor of CYP3A4 than other azole antifungals; however, the effect of fluconazole on BDQ PK is unknown. For individual participants with a clinical need for fluconazole for greater than two weeks, this drug may be allowed. This decision should be made in consultation with the protocol team and attending clinicians. Systemic use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John’s wort [Hypericum perforatum], rifamycins, and systemic, multiple dosing of dexamethasone) is disallowed.

Efavirenz (EFV) and boosted protease inhibitors are not allowed.

Note: Older children who are virologically suppressed on EFV may be switched to a study-approved ART regimen (See Section 4.1.7) for at least the duration of BDQ dosing (plus four weeks following BDQ discontinuation); this switch must occur at least seven days before starting BDQ.

5.7.2 Medications disallowed during administration of BDQ because of potential for QTc prolongation:

- Neuroleptics – phenothiazines thioridazine, haloperidol, chlorpromazine, trifluoperazine, pericycline, prochlorperazine, fluphenazine, sertindole, and pimozide
- Quinolone antimalarials (e.g. chloroquine and quinacrine)
- Moxifloxacin, gatifloxac, and sparfloxacin
- Tricyclic antidepressants, including amitriptyline, doxepin, desipramine, imipramine, and clomipramine

5.7.3 Medication disallowed during administration of BDQ because of potential for muscle damage (myopathy)

- HMG-CoA reductase inhibitors (statins)
6 STUDY VISITS AND PROCEDURES

An overview of the study visit and evaluation schedule is provided in Appendix I; blood draw volumes for each visit are also detailed in Appendix I. Presented in this section are additional information on visit-specific study procedures.

All visits and procedures must be performed at the clinical research site or associated facilities identified in the site’s approved Study Implementation Plan and must be documented in accordance with the NIAID Division of AIDS (DAIDS) policies for source documentation; refer to Section 11.0 for more information on documentation requirements and completion of CRFs. Refer to Section 7.0 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up. All procedures specified to be performed at scheduled visits should ideally be performed on the same day. However, if this is not possible (e.g., if a participant must leave the clinical research site before all procedures can be performed), unless otherwise specified visits may be split, with procedures performed on more than one day within the allowable visit window.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to, collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent; scheduling telephone contacts and visits; providing instructions for contacting study staff between visits; providing visit and drug dosing and adherence reminders; and following up on missed visits. All such tasks should be documented consistent with site SOPs. Study staff should inform caregivers (or other authorized guardians if applicable) of clinically meaningful physical exam findings and laboratory test results when available.
6.1 Screening Visit[s]

Refer to Section 4.5 for a description of the study recruitment, screening, and enrollment process. Screening evaluations must be performed within 30 days prior to enrollment. Multiple visits may be conducted to complete all required screening procedures if necessary. Written informed consent must be obtained before screening procedures are performed. For potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined.

<table>
<thead>
<tr>
<th>Screening Visit Procedures (within 30 days prior to enrollment)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administrative and Regulatory</strong></td>
</tr>
<tr>
<td>• Obtain written informed consent (with participant assent if required per local guidelines)</td>
</tr>
<tr>
<td>• Assign participant identification number (PID)</td>
</tr>
<tr>
<td>• Obtain screening number from SES</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Obtain available documentation of HIV status</td>
</tr>
<tr>
<td>• Obtain available medical records and medical and medications history including TB exposure and treatment history; TB symptoms; MDR-TB laboratory diagnosis; determination of reproductive potential; sexual activity and contraceptive use; and concomitant medications</td>
</tr>
<tr>
<td>• Perform complete physical examination including respiratory, cardiovascular, other organ systems, weight, and vital signs (temperature, blood pressure, pulse and respiratory rate).</td>
</tr>
<tr>
<td>• Classify TB disease spectrum and severity (see Section 8.3)</td>
</tr>
<tr>
<td>• Evaluate <em>M. tb.</em> infection status through TST or IGRA, depending on what is available at the site</td>
</tr>
<tr>
<td>• If participant is MDR culture positive: Contact the TB laboratory where the MDR diagnosis was made to ask for the isolate to be sent to the site DAIDS approved TB lab for microbiology testing if available.</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td><strong>Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Complete blood count with differential and platelets</td>
</tr>
<tr>
<td>• Creatinine, electrolytes (i.e., Na+, Cl, HCO3, K+, Ca 2+), albumin, and Mg 2+.</td>
</tr>
<tr>
<td>• ALT, AST, direct bilirubin, total bilirubin</td>
</tr>
<tr>
<td>• Pregnancy testing (urine or blood) if female of reproductive potential</td>
</tr>
<tr>
<td>• HIV testing, if required documentation of HIV status is not available</td>
</tr>
<tr>
<td>• Biomarkers (storage for future use)</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
</tr>
<tr>
<td>Collect urine for:</td>
</tr>
<tr>
<td>• Pregnancy testing (urine or blood) if female of reproductive potential</td>
</tr>
<tr>
<td>• Biomarkers (future use)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>• Obtain on study-specific ECG machine; must be interpreted based on age-specific criteria (see Section 8.6)</td>
</tr>
<tr>
<td>• Complete and interpret based on standard clinical approach. CXR will be done as clinically indicated until the end of treatment, which will be up to 18 months after the first negative culture depending on the extent of disease and the treatment prescribed as per local standard of care (see Section 8.5)</td>
</tr>
<tr>
<td><strong>Study Drug</strong></td>
</tr>
<tr>
<td>Not applicable at this visit.</td>
</tr>
</tbody>
</table>
6.2 Enrollment Visit (Day 0)

Refer to Section 4.5 for a description of the study recruitment, screening, and enrollment process.

All Enrollment Visit procedures are expected to be performed on the day of enrollment; procedures that may provide information relevant to eligibility for the study (e.g., medical history, physical examination), should be performed first, prior to final eligibility determination. For potential participants who do not meet eligibility criteria, screening may be discontinued once ineligibility is determined.

Additional requirements for sequencing of procedures at the Enrollment Visit are as follows:

- Final eligibility determination and confirmation must precede enrollment
- Confirmation of the continued consent for study participation must precede enrollment
- Enrollment must precede prescribing of study drug
- Prescribing must precede dispensing and administering of study drug
- Directly observed administration of study drug must precede collection of laboratory specimens
- During the Enrollment Visit, sample for lactate/pyruvate must be obtained first and must be on a fasting sample. Sample for lactate must be drawn second. Details on collection of this sample are provided in the MOP and/or LPC.

<table>
<thead>
<tr>
<th>Enrollment Visit Procedures (Day 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administrative and Regulatory</strong></td>
</tr>
<tr>
<td>Complete final eligibility determination and confirmation*</td>
</tr>
<tr>
<td>Complete paper-based eligibility checklist*, enter checklist data into SES to enroll/randomize the participant, print and file a copy of the confirmation file</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>Obtain history including TB exposure history; symptoms of TB; TB treatment history; MDR-TB diagnosis; determination of reproductive potential; sexual activity and contraceptive use; AEs and concomitant medications</td>
</tr>
<tr>
<td>Perform complete physical examination including respiratory, cardiovascular, other organ systems, height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate).</td>
</tr>
<tr>
<td>Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only).</td>
</tr>
<tr>
<td>Classify TB disease spectrum and severity (see Section 8.3)</td>
</tr>
<tr>
<td><strong>Laboratory Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>Cohort 1 only: lactate, pyruvate (see Section 8.7)</td>
</tr>
<tr>
<td>Hematology: complete blood count with white cell differential and platelet count</td>
</tr>
<tr>
<td>Chemistry: creatinine, electrolytes (i.e., Na+, Cl, HCO₃⁻, K+, Ca²⁺), albumin, and Mg²⁺.</td>
</tr>
<tr>
<td>Liver Function Tests: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for the chemistries.)</td>
</tr>
<tr>
<td>Note: If enrollment is within seven days after screening, hematology, chemistry and LFTs do not need to be repeated. However, additional sample for lactate would need to be collected.</td>
</tr>
<tr>
<td>TSH (and fT4 if TSH is elevated)</td>
</tr>
<tr>
<td>Biomarkers (storage for future use)</td>
</tr>
<tr>
<td>Pregnancy testing (urine or blood) must be done in all females of reproductive potential</td>
</tr>
</tbody>
</table>
At least one respiratory specimen (expectorated sputum, induced sputum or gastric aspirate) will be collected if indicated. Sputum will be collected in older children. Induced sputum or gastric aspirates will be collected in children unable to expectorate sputum spontaneously, as per local standard of care. The choice of procedure will be according to local practice, with the same technique used for each child for the duration of the study. Fine needle aspiration of cervical lymphadenopathy may also be collected. Specimens such as nasopharyngeal aspiration (NPA), stool or other types should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

### 6.3 Week 1 Visit

The Week 1 Visit is targeted to take place on Day 7, counted from the date of enrollment as Day 0, with an allowable window of +3 days (i.e., Day 7 to Day 10). Pre-dose PK sample must be collected prior to administration of BDQ. Other laboratory assays may be collected at any time during the visit, but preferably at the time of PK sampling.

<table>
<thead>
<tr>
<th>Week 1 Visit Procedures (Day 7 + 3 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administrative and Regulatory</strong></td>
</tr>
<tr>
<td>• None</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Obtain interim history. History should include symptoms of TB, AEs and concomitant medications.</td>
</tr>
<tr>
<td>• Perform physical examination. Physical exam should include weight and vital signs (temperature, blood pressure, pulse and respiratory rate).</td>
</tr>
<tr>
<td>• Assess adherence to BDQ and routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td><strong>Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Sparse PK (pre-dose):</td>
</tr>
<tr>
<td>Dosing of BDQ should be directly observed. The dosing times of BDQ, OBR and ARVs before the PK sampling must be recorded for the previous day as well as the preceding day. See LPC for processing instructions.</td>
</tr>
<tr>
<td>• Store residual PK sample</td>
</tr>
<tr>
<td>• Hematology: complete blood count with cell differential and platelet count</td>
</tr>
<tr>
<td>• Chemistries: creatinine, electrolytes (i.e., Na+, Cl, HCO₃⁻, K+, Ca²⁺), albumin, and Mg²⁺.</td>
</tr>
</tbody>
</table>
6.4 Week 2 Visit

The Week 2 Visit is targeted to take place on Day 14, counted from the date of enrollment as Day 0, with an allowable window of +3 days (i.e., Day 14 to Day 17).

Prior to the Week 2 visit, site staff may arrange to contact the participants to review the expectations of the intensive PK evaluation. Specifically: that study drug will be administered by the staff in the clinic/hospital and that the final blood draw will be 8 hours following administration of the BDQ, and to arrange for appropriate transportation and hospital admission, if required.

Additional requirements for sequencing of procedures at the Week 2 Visit are as follows:

- Pre-dose PK sample must be collected prior to administration of BDQ
- ECGs should be performed at around the time of the baseline PK sampling (i.e., within one hour of the baseline PK) and 4-6 hours after BDQ administration.
- Other laboratory assays may be collected at any time during the visit, but preferably at the time of PK sampling.

<table>
<thead>
<tr>
<th>Week 2 Visit Procedures (Day 14 + 3 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative and Regulatory</td>
</tr>
<tr>
<td>Clinical</td>
</tr>
<tr>
<td></td>
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<tr>
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<tr>
<td></td>
</tr>
<tr>
<td>Laboratory Blood</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Urine</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
### 6.5 Week 4 Visit

The Week 4 Visit is targeted to take place on Day 28, with an allowable window of ± 7 days (i.e., Day 21 to Day 35). Directly observed administration of study drug must precede collection of sparse PK. Sample for lactate/pyruvate must be obtained first and must be on a fasting sample. Sample for lactate must be drawn second. Details on collection of this sample are provided in the MOP and/or LPC. Otherwise, there are no required sequencing of procedures at this visit.

<table>
<thead>
<tr>
<th>Week 4 Visit Procedures (Day 28 ± 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administrative and Regulatory</strong></td>
</tr>
</tbody>
</table>
| **Clinical**                             | Obtain interim history. History should include symptoms of TB, AEs and concomitant medications.  

- Perform physical examination. Physical exam should include weight and vital signs (temperature, blood pressure, pulse and respiratory rate).  
- Assess adherence to BDQ and routine TB drugs (all participants) and ARV drugs (HIV-infected participants only). |

<table>
<thead>
<tr>
<th><strong>Laboratory</strong></th>
<th><strong>Blood</strong></th>
</tr>
</thead>
</table>
| **Collect blood for:**                  | Collect blood for:  

- **Cohort 1 only:** lactate, and lactate/pyruvate. See protocol Section 8.7 and Appendices I and IX for management of lactate.  

- Sparse PK (pre-dose):  
  Dosing of BDQ should be directly observed. The dosing times of BDQ, OBR and ARVs before the PK sampling must be recorded for the previous day as well as the preceding day.  
  Store residual PK sample  

- Hematology: complete blood count with cell differential and platelet count)  

- Chemistries: creatinine, electrolytes (i.e., Na+, Cl, HCO₃, K⁺, Ca ₂⁺), albumin, and Mg ₂⁺.  

- Liver Function Tests: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for the chemistries.)  

- Biomarkers (storage for future use)  

- Pregnancy testing (urine or blood) must be done in all females of reproductive potential*  

  If participant is HIV-infected, collect additional blood for:  

- Lymphocyte subsets (to include CD4/CD8 counts and percentages) |

| **Urine**                               | Collect urine for:  

- Pregnancy testing (urine or blood) must be done in all females of reproductive potential*  

- Urinalysis  

- Biomarkers (future use) |

| **Other**                               | **ECG**  

- Obtain on study-specific ECG machine; must be interpreted based on age-specific criteria (see Section 8.6) |

| **Sputum**                              | **Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit.** Collect for mycobacterial testing (see LPC for details). At least one sputum/other sample should be obtained** |

| **Study Drug**                          | Dispense additional supplies of BDQ as needed |
*The outcome of pregnancy must be recorded and may be obtained by participant report and/or medical documentation

** At least one respiratory specimen (expectorated sputum, induced sputum or gastric aspirate) will be collected if indicated. Sputum will be collected in older children. Induced sputum or gastric aspirates will be collected in children unable to expectorate sputum spontaneously, as per local standard of care. The choice of procedure will be according to local practice, with the same technique used for each child for the duration of the study. Fine needle aspiration of cervical lymphadenopathy may also be collected. Specimens such as nasopharyngeal aspiration (NPA), stool or other types should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

### 6.6 Week 6 Visit

The Week 6 Visit is targeted to take place on Day 42 and has an allowable window of +/- 7 days (i.e., Day 35 to 49). There is no required sequencing of procedures at this visit; no laboratory or other evaluations are conducted at this visit.

<table>
<thead>
<tr>
<th>Week 6 Visit Procedures (Day 42 ± 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative and Regulatory ● None</td>
</tr>
<tr>
<td>Clinical ● Obtain interim history. History should include AEs and concomitant medications. ● Perform physical examination. Physical exam should include weight and vital signs (temperature, blood pressure, pulse and respiratory rate). ● Assess adherence to BDQ and routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td>Laboratory ● None</td>
</tr>
<tr>
<td>Study Drug ● Dispense additional supplies of BDQ as needed</td>
</tr>
</tbody>
</table>

### 6.7 Weeks 8, 12, 16, 20 and 24 Visits (On Treatment)

The Week 8, 12, 16, 20 and 24 visits are targeted to take place on Days 56, 84, 112, 140 and 168, respectively. Week 8 has an allowable window of – 14 days; Week 24 has an allowable visit window of -14 to +28 days; all other visits have an allowable window of ± 14 days. Directly observed administration of study drug must precede collection of laboratory evaluations at each visit. The sample for lactate/pyruvate at Week 24 must be obtained first and must be on a fasting sample. The sample for lactate must be collected second. Details on collection of these samples are provided in the MOP and/or LPC. Otherwise, there are no required sequencing of procedures at these visits.

<table>
<thead>
<tr>
<th>On Treatment Visit Procedures: Week 8 (Day 56 -14 days), Week 12 (Day 84 ±14 days), Week 16 (Day 112 ±14 days), Week 20 (Day 140 ± 14 days) and Week 24 (Day 168 -14 to + 28 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative and Regulatory ● None</td>
</tr>
<tr>
<td>Clinical ● Obtain interim history. History should include AEs and concomitant medications. ● Perform physical examination. Physical exam should include height (Weeks 8 and 24 only), weight and vital signs (temperature, blood pressure, pulse and respiratory rate). ● Assess adherence to BDQ and routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
</tbody>
</table>
- **Week 8 and 24 only**: Classify TB disease spectrum and severity (see Section 8.3).
- **Week 8 only**: If negative at screening, evaluate *M. tb* infection status through TST or IGRA, depending on what is available at the site. If positive at screening, do not repeat at Week 8.

### Laboratory

<table>
<thead>
<tr>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Collect blood for:</strong></td>
</tr>
<tr>
<td>- <strong>Cohort 1, Week 24 only</strong>: Lactate and lactate/pyruvate. See protocol Section 8.7 and Appendices I and IX for management of lactate.</td>
</tr>
<tr>
<td>- Sparse PK (pre-dose): Dosing of BDQ should be directly observed. The dosing times of BDQ, OBR and ARV's before the PK sampling must be recorded for the previous day as well as the preceding day.</td>
</tr>
<tr>
<td>- Store residual PK sample</td>
</tr>
<tr>
<td>- Hematology: complete blood count with cell differential and platelet count</td>
</tr>
<tr>
<td>- Chemistries: creatinine, electrolytes (i.e., Na+, Cl, HCO₃⁻, K+, Ca 2+), albumin, and Mg ²⁺.</td>
</tr>
<tr>
<td>- Liver Function Tests: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for the chemistries.)</td>
</tr>
<tr>
<td>- <strong>Weeks 8, 16, 24 only</strong>: TSH (and fT4 if TSH is elevated)</td>
</tr>
<tr>
<td>- <strong>Weeks 8, 16 and 24 only</strong>: Biomarkers (storage for future use)</td>
</tr>
<tr>
<td>- <strong>Weeks 8, 16 and 24 only</strong>: Pregnancy testing (urine or blood) must be done in all females of reproductive potential)*</td>
</tr>
</tbody>
</table>

If participant is HIV-infected, collect additional blood for:
- **Weeks 12 and 24 only**: HIV-1RNA PCR |
- **Weeks 12 and 24 only**: Lymphocyte subsets (to include CD4/CD8 counts and percentages)

### Urine

| **Collect urine for:** |
| - **Weeks 8, 16 and 24 only**: Pregnancy testing (urine or blood) must be done in all females of reproductive potential)* |
| - Urinalysis |
| - **Weeks 8, 16, 24 only**: Biomarkers (future use) |

### Sputum**

- Only participants who had lab-confirmed MDR-TB at diagnosis and are pending three consecutive negative results will have bacteriology completed at these visits. Collect for mycobacterial testing (see LPC for details). At least one sputum/other sample should be obtained**
- If the sample obtained at this visit is the third consecutive negative test, then no further testing of the participant at subsequent visits is necessary unless clinically indicated (see Section 8.4). Central DST should be repeated on an initial positive mycobacterial isolate; see LPC.

### Other

| **ECG** |
| - Obtain on study-specific ECG machine; must be interpreted based on age-specific criteria (see Section 8.6) |

| **CXR** |
| - **Weeks 8, 16 and 24 only in the case of pulmonary TB**: Complete and interpret based on standard clinical approach. CXR will be done as clinically indicated until the end of treatment, which will be up to 18 months after the first negative culture depending on the extent of disease and the treatment prescribed as per local standard of care (see Section 8.5) |

| **Audiology** |
| - **Weeks 8, 16 and 24**: Conducted only on participants on injectable-drug containing OBR. All results are to be reported on standard CRFs. Early termination of an injectable (part of OBR) and initiation of an alternative drug as part of OBR due to hearing loss will be documented. |

### Study Product

- **Weeks 8, 12, 16 and 20 only**: Dispense additional supplies of BDQ as needed |
- **Week 24 only**: retrieve any remaining study drug
* The outcome of pregnancy must be recorded and may be obtained by participant contact and/or medical documentation

** At least one respiratory specimen (expectorated sputum, induced sputum or gastric aspirate) will be collected if indicated. Sputum will be collected in older children. Induced sputum or gastric aspirates will be collected in children unable to expectorate sputum spontaneously, as per local standard of care. The choice of procedure will be according to local practice, with the same technique used for each child for the duration of the study. Fine needle aspiration of cervical lymphadenopathy may also be collected. Specimens such as nasopharyngeal aspiration (NPA), stool or other types should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

6.8 Weeks 32, 40, 48, 60, 72 and 96 Visits (Off Treatment)

The Week 32, 40, 48, 60, 72 and 96 visits are targeted to take place on Days 224, 280, 336, 420, 504 and 672, respectively. Weeks 32, 40, and 48 have an allowable window of ±28 days; Weeks 60, 72, 84, and 96 have an allowable window of ±42 days. The sample for lactate/pyruvate at Week 96 must be obtained first and must be on a fasting sample. The sample for lactate must be collected second. Details on collection of this sample are provided in the MOP and/or LPC. Otherwise, there is no required sequencing of procedures at these visits.

| Off Treatment Visit Procedures: Weeks 32, 40, 48, 60, 72 and 96 |
|Visit Windows: Wks 32, 40, 48: +/- 28 days; Wks 60, 72, 84, 96: +/- 42 days|
|**Administrative and Regulatory**| None |
|**Clinical**| Obtain interim history. History should include symptoms, new TB exposure history, AEs and concomitant medications. Perform physical examination. Physical exam should include height (Week 48 only), weight and vital signs (temperature, blood pressure, pulse and respiratory rate). Document HIV Status, Week 48, Cohort 3, HIV-exposed participants only. Refer to protocol section 4.3 for acceptable documentation of HIV status. In the absence of such documentation, HIV testing should be conducted at the end of study visit. |
|**Laboratory**| **Blood** Collect blood for: Cohort 1, Week 96 only: Lactate and lactate/pyruvate. See protocol Section 8.7 and Appendices I and IX for management. Sparse PK: Store residual PK sample. Hematology: complete blood count with cell differential and platelet count. Chemistries: creatinine, electrolytes (i.e., Na+, Cl, HCO3, K+, Ca 2+), albumin, and Mg 2+. Liver Function Tests: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for the chemistries.) Weeks 32, 48, 72 only: TSH (and fT4 if TSH is elevated) Pregnancy testing (urine or blood) must be done in all females of reproductive potential)* If participant is HIV-infected, collect additional blood for: Weeks 32, 48 and 96 only: Lymphocyte subsets (to include CD4/CD8 counts and percentages) |
Urine  
*Collect urine for:*
- Pregnancy testing (urine or blood) must be done in all females of reproductive potential)*
- Urinalysis
- Week 48 only: Biomarkers (future use)

Sputum**
- Weeks 32, 40, 48, 60, and 72 only: Only participants who had lab-confirmed MDR-TB at diagnosis and are pending three consecutive negative results will have bacteriology completed at these visits. Collect for mycobacterial testing (see LPC for details). At least one sputum/other sample should be obtained.
- If the sample obtained at this visit is the third consecutive negative test, then no further testing of the participant at subsequent visits is necessary unless clinically indicated (see Section 8.4). DST should be repeated on an initial positive sample; see LPC.

Other  
ECG  
- Week 40 only: Obtain on study-specific ECG machine; must be interpreted based on age-specific criteria. (see Section 8.6)

CXR  
- Weeks 40 and 72 only (pulmonary TB only): Complete and interpret based on standard clinical approach. CXR will be done as clinically indicated until the end of treatment, which will be up to 18 months after the first negative culture depending on the extent of disease and the treatment prescribed as per local standard of care (see Section 8.5).

*The outcome of pregnancy must be recorded and may be obtained by participant contact and/or medical documentation

** At least one respiratory specimen (expectorated sputum, induced sputum or gastric aspirate) will be collected if indicated. Sputum will be collected in older children. Induced sputum or gastric aspirates will be collected in children unable to expectorate sputum spontaneously, as per local standard of care. The choice of procedure will be according to local practice, with the same technique used for each child for the duration of the study. Fine needle aspiration of cervical lymphadenopathy may also be collected. Specimens such as nasopharyngeal aspiration (NPA), stool or other types should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

### 6.9 Week 120/End of Study Visit

The Week 120/End of Study Visit is targeted to take place on Day 840 or 672 days after the last dose of BDQ, if the participant discontinued study drug prematurely. This visit has an allowable window of +/- 42 days. There is no required sequencing of procedures at this visit.

Participants who will be exiting the study after this visit will be provided with information about how to contact study staff with any post-study questions and how to learn about the results of the study when available. Referrals will be provided as needed to ensure transition to non-study sources of health care as needed. In the event that a participant is known to be pregnant or has an ongoing AE at the time of the Week 120/End of Study visit, additional contacts should occur for study purposes as described in Section 6.9.

**Week 120/End of Study Visit Procedures (+/- 42 days)**

<table>
<thead>
<tr>
<th>Administrative and Regulatory</th>
<th>If participant is pregnant or has an ongoing AE at this visit, confirm that informed consent has been granted for continued follow up/contact as per protocol Sections 6.9 and Section 8.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Obtain interim history. History should include AEs and concomitant medications.</td>
</tr>
<tr>
<td></td>
<td>Perform physical examination. Physical exam should include height, weight, and vital signs (temperature, blood pressure, pulse and respiratory rate).</td>
</tr>
<tr>
<td></td>
<td>Classify TB treatment outcome (see Section 8.3)</td>
</tr>
</tbody>
</table>
### 6.10 Continued Participant Contact After End of Study: Pregnancy, Unresolved Adverse Event, Early Study Discontinuation

Participants may be contacted after the Week 120/End of Study or Early Study Discontinuation visits:

- To document the outcome of a pregnancy
- To follow any unresolved AE to resolution/stabilization
- To obtain interim history following early withdrawal from the study through 96 weeks after the last dose of BDQ

Consent for this potential continued contact will be obtained as part of the informed consent process.

The outcome of the pregnancy must be recorded and can be obtained by participant contact, at a study visit, telephone, and/or from medical documentation.

---

**Laboratory Blood**

<table>
<thead>
<tr>
<th>Collect blood for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sparse PK:</td>
</tr>
<tr>
<td>• Store residual PK sample</td>
</tr>
<tr>
<td>• Hematology: complete blood count with cell differential and platelet count)</td>
</tr>
<tr>
<td>• Chemistries: creatinine, electrolytes (i.e., Na+, Cl, HCO₃, K+, Ca 2+), albumin, and Mg 2+.</td>
</tr>
<tr>
<td>• Liver Function Tests: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for the chemistries.)</td>
</tr>
<tr>
<td>• Biomarkers (storage for future use)</td>
</tr>
<tr>
<td>• Pregnancy testing (urine or blood) must be done in all females of reproductive potential)*</td>
</tr>
<tr>
<td>• HIV testing, if acceptable documentation is not available.</td>
</tr>
</tbody>
</table>

*If participant is HIV-infected, collect additional blood for:*

- HIV-1RNA PCR
- Lymphocyte subsets (to include CD4/CD8 counts and percentages)

**Urine**

<table>
<thead>
<tr>
<th>Collect urine for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pregnancy testing (urine or blood) must be done in all females of reproductive potential)*</td>
</tr>
<tr>
<td>• Urinalysis</td>
</tr>
<tr>
<td>• Biomarkers (future use)</td>
</tr>
</tbody>
</table>

**Other CXR**

| • Complete and interpret based on standard clinical approach. CXR will be done as indicated until the end of treatment, which will be up to 18 months after the first negative culture depending on the extent of disease and the treatment prescribed as per local standard of care in children with intrathoracic TB (see Section 8.5) |

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* The outcome of pregnancy must be recorded and may be obtained by participant contact, at a study visit or via telephone if beyond Week 120/End of Study, and/or from medical documentation.
In the event of an unresolved AE at the End of Study Visit, the frequency of continued contact and evaluations to be conducted should be determined based on clinical indications and in accordance with protocol Section 8.0.

Participants who choose to withdraw from the study early will be asked to permit periodic telephone contact even if other study evaluations cannot be conducted or the participant has withdrawn from study. Those who agree will be contacted 8, 36, 72 and 96 weeks after last BDQ dose to obtain interim history. History should include symptoms of TB, and AEs. If the participant was known to be pregnant at the time of early withdrawal, the contact will continue until the outcome of the pregnancy is known. For more details about the Early Study Discontinuation Visit, see Section 6.13.

6.11 Unscheduled Visits

Participants may be seen at unscheduled study visits for evaluation of acute issues or follow up of ongoing issues or adherence issues and concerns and teaching. Evaluations (history, physical, laboratory and/or radiologic assessments) should be determined based on clinical indications (i.e., if unscheduled visit is for repeat of an abnormal laboratory value, then it is not necessary to obtain history, perform physical examination or to repeat unrelated laboratory assessments.) Participants should continue to be followed until resolution or stabilization of AEs even if after Week 120 as per Section 8.0.

6.12 Early Discontinuation of BDQ

If the study drug is discontinued prior to 24 weeks, the study participant should return for an “Early BDQ Discontinuation (D/C)” visit. Follow up thereafter would be at 8, 16, 24, 36, 48, 60, 72, 84 and 96 weeks post the last BDQ dose. See below for the visit procedures for the “Early BDQ D/C” visit and for follow up after early discontinuation of BDQ. Evaluations for the End of Study Visit (at 96 weeks post BDQ D/C are as per the End of Study evaluations outlined in Section 6.9. Participants with early discontinuation of BDQ will remain on study.
Early Discontinuation of BDQ Visit Procedures

Administrative and Regulatory

- Re-calculate participant’s follow up schedule according to time of BDQ discontinuation. Follow up as per off-treatment visit procedures, below, at 8, 16, 24, 36, 48, and 72 weeks post BDQ. End of Study Visit will take place at 96 weeks post BDQ as per protocol Section 6.9.

Clinical

- Obtain interim history. History should include AEs and concomitant medications.
- Perform physical examination. Physical exam should include height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate).
- Assess adherence to BDQ and routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)
- Classify TB disease spectrum and severity.

Laboratory

Blood

Collect blood for:
- Sparse PK: Any remaining volume will be stored.
- Hematology: complete blood count with cell differential and platelet count
- Chemistries: creatinine, electrolytes (i.e., Na+, Cl, HCO3, K+, Ca 2+), albumin, and Mg 2+.
- Liver Function Tests: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for the chemistries.)
- Pregnancy testing (urine or blood) must be done in all females of reproductive potential)*

If participant is HIV-infected, collect additional blood for:
- Lymphocyte subsets (to include CD4/CD8 counts and percentages)

Urine

Collect urine for:
- Pregnancy testing (urine or blood) must be done in all females of reproductive potential)*
- Urinalysis

Other

ECG

- Obtain on study-specific ECG machine; must be interpreted based on age-specific criteria (see Section 8.6)

CXR

- Complete if clinically indicated only, and interpret based on standard clinical approach in children with pulmonary (intrathoracic) TB.

Study Drug

- Retrieve any remaining BDQ

*The outcome of pregnancy must be recorded and may be obtained by participant contact and/or medical documentation

Of the evaluations to be performed at the Off Treatment Visits at 8, 16, 24, 36, 48 and 72 weeks post BDQ (see below), the only required sequencing of procedures is at the visit 72 weeks BDQ. The sample for lactate/pyruvate at that visit must be obtained first and must be on a fasting sample. The sample for lactate must be collected second. Details on collection of this sample are provided in the MOP and/or LPC. Otherwise, there are no required sequencing of procedures at these visits.

Off Treatment Visit Procedures: 8, 16, 24, 36, 48, and 72 weeks post BDQ

Visit Windows: 8, 16, 24 wks post BDQ d/c: +/- 28 days;
36, 48, and 72 wks post BDQ d/c: +/- 42 days

Administrative and Regulatory

- None

Clinical

- Obtain interim history. History should include AEs and concomitant medications.
- Perform physical examination. Physical exam should include height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate).
- Document HIV Status, 24 wks post BDQ, Cohort 3, HIV-exposed participants only. Refer to protocol section 4.3 for acceptable documentation of HIV status. In the absence of such documentation, HIV testing should be conducted at the end of study visit.

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Collect blood for:</td>
</tr>
<tr>
<td></td>
<td>• Cohort 1, 72 weeks post BDQ only: Lactate, pyruvate. See protocol Section 8.7 and Appendices I and IX for management of lactate.</td>
</tr>
<tr>
<td></td>
<td>• Sparse PK:</td>
</tr>
<tr>
<td></td>
<td>• Store residual PK sample</td>
</tr>
<tr>
<td></td>
<td>• Hematology: complete blood count with cell differential and platelet count</td>
</tr>
<tr>
<td></td>
<td>• Chemistries: creatinine, electrolytes (i.e., Na+, Cl, HCO₃⁻, K⁺, Ca ²⁺), albumin, and Mg ²⁺.</td>
</tr>
<tr>
<td></td>
<td>• Liver Function Tests: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for the chemistries.)</td>
</tr>
<tr>
<td></td>
<td>• 8, 24, and 48 wks post BDQ only: TSH (and ft4 if TSH elevated)</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy testing (urine or blood) must be done in all females of reproductive potential)*</td>
</tr>
</tbody>
</table>

*If participant is HIV-infected, collect additional blood for: 8, 24 and 72 wks post BDQ only: Lymphocyte subsets (to include CD4/CD8 counts and percentages) |

<table>
<thead>
<tr>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collect urine for:</td>
</tr>
<tr>
<td>• Pregnancy testing (urine or blood) must be done in all females of reproductive potential)*</td>
</tr>
<tr>
<td>• Urinalysis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Sputum**</th>
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<tbody>
<tr>
<td>• 8, 16, 24, 36 and 48 wks post BDQ only: Participants will have sputum studies done once a month until conversion, after which time bacteriology will be repeated once a month for two months thereafter. (i.e., three consecutive negative results). DST will only be repeated on positive samples at month 2 and in the last positive sample. In addition, if second-line DSTs were not done initially or if cultures became negative and then convert to positive again, DST will also be repeated. The first available sample will be stored. In participants with probable MDR-TB, sampling will not be repeated if bacteriology was negative at diagnosis, unless new symptoms or worsening of symptoms or CXR changes were to occur.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
</tr>
<tr>
<td>• 16 wks post BDQ only: Obtain on study-specific ECG machine; must be interpreted based on age-specific criteria (see Section 8.6)</td>
</tr>
</tbody>
</table>

| CXR |
| • 16 and 48 wks post BDQ only: Complete and interpret based on standard clinical approach. CXR will be done as indicated until the end of treatment, which will be up to 18 months after the first negative culture depending on the extent of disease and the treatment prescribed as per local standard of care in children with intrathoracic TB (see Section 8.5) |

*The outcome of pregnancy must be recorded and may be obtained by participant contact and/or medical documentation

** At least one respiratory specimen (expectorated sputum, induced sputum or gastric aspirate) will be collected if indicated. Sputum will be collected in older children. Induced sputum or gastric aspirates will be collected in children unable to expectorate sputum spontaneously, as per local standard of care. The choice of procedure will be according to local practice, with the same technique used for each child for the duration of the study. Fine needle aspiration of cervical lymphadenopathy may also be collected. Specimens such as nasopharyngeal aspiration (NPA), stool or other types should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.
6.13 Early Study Discontinuation

Whenever possible, final study evaluations should be conducted when a participant indicates that continued full participation in the study is no longer possible. As part of the informed consent process, participants will be asked to permit periodic telephone contact even if other study evaluations cannot be conducted or the participant has withdrawn from study. Those who agree will be contacted at 8, 36, 72 and 96 weeks after last BDQ dose to obtain interim history and, if the participant is known to be pregnant at the time of early study discontinuation, to document outcome of that pregnancy. There is no required sequencing of procedures at these visits.

### Early Study Discontinuation Visit Procedures

<table>
<thead>
<tr>
<th>Administrative and Regulatory</th>
<th>Clinical</th>
<th>Laboratory</th>
<th>Other</th>
<th>Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm that participant provided informed consent for continued contact 8, 36, 72 and 96 weeks after last BDQ dose.</td>
<td>Obtain interim history. History should include AEs and concomitant medications.</td>
<td>Collect blood for:</td>
<td>Obtain on study-specific ECG machine; must be interpreted based on age-specific criteria (see Section 8.6)</td>
<td>Retrieve any remaining BDQ</td>
</tr>
<tr>
<td></td>
<td>Perform physical examination. Physical exam should include height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate).</td>
<td>Sparse PK:</td>
<td>Complete and interpret based on standard clinical approach, only if clinically indicated. CXR will be done as clinically indicated until the end of treatment, which will be up to 18 months after the first negative culture depending on the extent of disease and the treatment prescribed as per local standard of care in children with intrathoracic TB (see Section 8.5).</td>
<td></td>
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<tr>
<td></td>
<td>Assess adherence to BDQ and routine TB drugs (all participants) and ARV drugs (HIV-infected participants only).</td>
<td>Store residual PK sample Hematology: complete blood count with cell differential and platelet count)</td>
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<tr>
<td></td>
<td>Classify TB disease spectrum and severity and/or TB treatment outcome, if relevant (i.e. if MDR-TB treatment has been completed) (see Section 8.3)</td>
<td>Chemistries: creatinine, electrolytes (i.e., Na+, Cl, HCO$_3^-$, K+, Ca$^{2+}$), albumin, and Mg$^{2+}$.</td>
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<tr>
<td></td>
<td></td>
<td>Liver Function Tests: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for the chemistries.)</td>
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<td></td>
<td>Pregnancy testing (urine or blood) must be done in all females of reproductive potential)*</td>
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<tr>
<td></td>
<td></td>
<td>If participant is HIV-infected, collect additional blood for:</td>
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</tbody>
</table>

*The outcome of pregnancy must be recorded and may be obtained by participant contact and/or medical documentation.
6.14 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at: http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx

6.14.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the LPC, which will be available on the IMPAACT web site: www.impaactnetwork.org. Further information on collection of respiratory specimens, fine needle aspiration, stool specimens, and lactate and lactate/pyruvate testing will also be provided in the study-specific MOP and/or the LPC.

In accordance with US National Institutes of Health (NIH) recommendations, pediatric blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg in any eight-week period.

In the event that blood collection must be limited, available specimens should be prioritized for use in the following order:

1. Safety (LFT, hematology, chemistry, lactate/pyruvate, lactate)
2. Pharmacokinetics
3. Virology
4. Immunology
5. Storage for future use

For Cohort 1, on visits when lactate and lactate/pyruvate testing will be done (Enrollment and Weeks 4, 24 and 96/72 weeks post BDQ), priorities should be for additional volume for lactate/pyruvate and lactate testing.

6.14.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in Section 6.14, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by Section 6.0 and the Schedule of Evaluations and specifications for clinical management provided in Section 8.0. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in the LPC.

For additional information on lactate and lactate/pyruvate testing, please refer to the MOP and/or LPC.

Mycobacterial isolates collected from participants will be shipped and stored centrally for future analysis.

Any remaining volume from the samples collected for PK analysis will be stored.

Lymphocyte subsets must be performed in a DAIDS IQA-certified laboratory. HIV PCR tests must be performed in a VQA-certified laboratory and HIV antibody tests must be performed in a laboratory that operates according to GCLP guidelines and participates in an appropriate external quality assurance program.
6.14.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as currently recommended by the US Centers for Disease Control and Prevention, NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

Respiratory pathogens such as *M. tuberculosis* are transmitted by inhalation of droplet nuclei. Appropriate precautions will be employed by all personnel in patient management and the collection of clinical samples and the shipping and handling of all clinical samples and isolates for this study, as currently recommended by the Centers for Disease Control and Prevention in the United States and the NIH.

7 SAFETY MONITORING, ASSESSMENT AND REPORTING

7.1 Safety-Related Roles and Responsibilities

Routine monitoring will be done by the P1108 Core Team, which consists of the Protocol Chair, Vice Chair, NIAID and NICHD Medical Officers, Protocol Statisticians, Protocol Pharmacometricians and Protocol Pharmacologist, Protocol Data Manager, and the Clinical Trials Specialist or their designee. Site IoRs/designees are responsible for continuous close safety monitoring of all study participants, and for alerting the Core Team if unexpected concerns arise. The IMPAACT Statistical Data Management Center (SDMC) will prepare routine safety monitoring and clinical data reports for review by the Core Team, which will meet via conference call approximately once per month or as needed throughout the period of study implementation to review safety data, discuss product use management, and address any potential safety concerns.

An IMPAACT Study Monitoring Committee (SMC) will review the study. The frequency of SMC review will be determined by the accrual rate, and is planned to occur annually. Reports for the annual review may be minimal if accrual rate is slow. The SMC may also be convened upon request of the protocol team. The SMC will be requested to focus on specific aspects including ECG data review, long-term safety, and lab measures of mitochondrial toxicity. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, be paused, proceed with design modifications, or be discontinued. The SMC will also review Cohort 1 data prior to the opening of Cohorts 2 and 3 (refer to section 9.5).

7.2 Safety-Related Recording on Case Report Forms

Pre-existing conditions and AEs identified in this study will be recorded on case report forms (CRFs) as signs, symptoms, laboratory test results, and diagnoses, as follows:

**Signs and Symptoms:** All relevant (TB and HIV-related) signs and symptoms occurring within 30 days prior to enrollment in the study, and/or present on the day of enrollment, will be recorded on the relevant CRFs. During follow-up, Grade 3 or higher signs and symptoms, and all signs and symptoms that lead to a dose modification or discontinuation of study drug will be further
evaluated. In addition, Grade 3 signs and symptoms, and all signs and symptoms that lead to a change of study drug will be further evaluated, with additional data recorded on the relevant event evaluation CRF.

**Laboratory Evaluations:** All screening, enrollment, and follow-up laboratory test results will be recorded on the relevant CRFs. In addition, all Grade 3 or higher results, and all results that lead to a change of study drug will be further evaluated, with additional data recorded on the relevant event evaluation CRF.

**Diagnoses:** All relevant diagnoses that were ongoing within 30 days prior to enrollment in the study, and/or ongoing on the day of enrollment will be recorded on the relevant CRF. During follow-up, Grade 3 and higher diagnoses, and all diagnoses that lead to a change of study drug administration will be recorded on the relevant CRF. In addition, Grade 4 diagnoses and all diagnoses that lead to a change of study drug will be further evaluated, with additional data recorded on the relevant event evaluation CRF. All diagnoses recorded on CRFs should be recorded consistent with the specifications of the relevant diagnosis appendix, which is available at [www.fstrf.org](http://www.fstrf.org).

CRFs used to record the above-listed safety outcomes must be completed and entered into the study database within 48 hours of availability of the relevant clinical findings and laboratory test results at the site.

### 7.3 Expedited Adverse Event (EAE) Reporting

#### 7.3.1 EAE Reporting to DAIDS


The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at [DAIDS-ESSupport@niaid.nih.gov](mailto:DAIDS-ESSupport@niaid.nih.gov). Site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact DAIDS RSC ([DAIDSRSCSafetyOffice@tech-res.com](mailto:DAIDSRSCSafetyOffice@tech-res.com)).

#### 7.3.2 Reporting Requirements for this Study

The serious adverse event (SAE) reporting category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agent for which expedited reporting is required is BDQ.

#### 7.3.3 Grading Severity of Events

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, will be used and is available on the RSC website at
7.3.4 Reporting Relationship of EAE to BDQ

For purposes of EAE reporting, the IoR or designee must assess the relationship of EAEs to BDQ according to the two categories shown in Figure 8.

Figure 8: Relationship Assessment Categories for EAE Reporting

<table>
<thead>
<tr>
<th>Relationship Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related</td>
<td>There is a reasonable possibility that the EAE may be related to study-supplied BDQ. Consistent with ICH guidance, the term “reasonable possibility” is intended to convey that there are facts, evidence, or arguments to suggest a causal relationship between the EAE and study-supplied study drug. Facts, evidence, and arguments that may support a reasonable possibility of a causal relationship include:</td>
</tr>
<tr>
<td></td>
<td>• A temporal relationship between the EAE and use of the BDQ</td>
</tr>
<tr>
<td></td>
<td>• A plausible biologic mechanism for the BDQ to cause the EAE</td>
</tr>
<tr>
<td></td>
<td>• Previous reports of similar events associated with BDQ</td>
</tr>
<tr>
<td></td>
<td>• Resolution of the event after de-challenge (hold/discontinuation of BDQ)</td>
</tr>
<tr>
<td></td>
<td>• Recurrence of the event after re-challenge (resumption of BDQ after a hold)</td>
</tr>
<tr>
<td></td>
<td>Other potential causes of the EAE (e.g., past medical history, concurrent illness, concomitant medications) should also be considered when assessing whether there is a reasonable possibility that an EAE may be related to study-supplied BDQ.</td>
</tr>
<tr>
<td>Not related</td>
<td>There is not a reasonable possibility that the EAE may be related to BDQ.</td>
</tr>
</tbody>
</table>

For purposes of participant management and recording on case report forms, relatedness to BDQ will be assessed according to the five categories listed in Section 8.1.

7.3.5 Expedited AE Reporting Period

The expedited AE reporting period for this study is the entire study duration of follow-up for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).

After the above-specified period, only suspected, unexpected, serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual, will be reported if the study staff become aware of the events on a passive basis (from publicly available information).

8 PARTICIPANT MANAGEMENT

8.1 Management of Adverse Events

Consistent with international good clinical practice guidelines, the term “adverse event” (AE) is used in this protocol to refer to any untoward medical occurrence identified in an enrolled child participant who is administered one or more study products, which does not necessarily have a
causal relationship with study product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with administration of study product, whether or not related to study product.

All AEs identified in this study will be source documented in participant research records, consistent with the policies and procedures referenced in Section 11.0. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3.3) and its relationship to study product, assessed by the site clinician according to the following categories: definitively related, probably related, possibly related, probably not related and not related. Definitions of these categories may be found in the MOP.

Investigation and clinical assessment will be completed as per standard management of specific toxicities, as appropriate (refer to appendices) to allow for standard data collection and outcome measures. AEs will be assessed clinically, through lab or other investigation and by parental and self-reporting, where appropriate. Data will be collected on all AEs ranging from Grade 1 through 5; their potential relation to BDQ, background TB drugs (OBR) and/or ART, as appropriate, will be described.

Management of AEs will be according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought and lab values repeated as clinically indicated. Abnormal clinical and laboratory findings should be followed until resolved to < Grade 2.

Appendix VIII provides general guidance for management of the study drug (BDQ) in response to toxicities; Appendices VI and IX provide guidance on BDQ management for the following specific toxicities:
- ECG-determined or clinical cardiac toxicity
- Bilirubin
- AST or ALT
- Lactate
- Myalgia, nausea or vomiting

Site investigators will consult with the Protocol Team as directed in the Toxicity Management Tables in Appendices VI, VIII, and IX and otherwise at their discretion as needed. Clinical or laboratory AEs that are definitely not related to BDQ need not result in study drug interruption, unless the site investigator deems interruption necessary due to the specific circumstances.

All participants will remain on study and complete all follow-up visits, even if BDQ is discontinued early due to toxicity or other reasons.

Participants with an ongoing AE at the time of the End of Study visit of Grade 3 or higher will continue to be followed until resolution or stabilization of the event. The protocol team may request additional follow-up of selected AEs of lower grade based on the clinical context. Other ongoing AEs will be followed as clinically indicated and per local protocol.

8.2 Background MDR therapy

All participants will be on appropriate OBR MDR-TB therapy based on available DST data (of the child participant and/or the adult source case), WHO and/or in-country treatment guidelines, and locally available treatment. The MDR-TB regimen may be modified according to DST of the
child or the adult source case, as appropriate (refer to Section 8.4) and the best available therapy in-country. Refer to Appendix III for an overview of routine anti-TB drugs used in the management of pediatric MDR-TB.

8.3 Management of TB disease

Routine screening and investigation for TB will follow standard local protocols in routine locally accredited TB labs including bacteriology (culture, smear microscopy, molecular testing e.g. Xpert MTB/RIF, in combination with phenotypic or molecular confirmation of MDR-TB through DST), chest x-ray, clinical history, standard symptom-based questionnaire (64), physical examination, and MDR-TB exposure history. TB disease spectrum and severity will be classified (65). CXR will be repeated as per schedule of events in children with intrathoracic TB. A pediatric TB expert blinded to patient identity and clinical data will independently review all CXRs at diagnosis and at MDR-TB treatment completion (typically after 18 months of MDR-TB therapy) using a standard classification (66).

8.4 Mycobacterial culture, smear and DST

At least one respiratory specimen (expectorated sputum, induced sputum or gastric aspirate) will be collected if indicated (see Section 6.0 study visits). Sputum will be collected in older children. Induced sputum or gastric aspirates will be collected in children unable to expectorate sputum spontaneously, as per local standard of care. The choice of procedure will be according to local practice, with the same technique used for each child for the duration of the study. Fine needle aspiration of cervical lymphadenopathy may also be collected as clinically indicated. Specimens such as nasopharyngeal aspiration (NPA), stool or other types should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens. Repeat sampling will be done during treatment for confirmation of microbiological cure of M.tb (acid-fast bacilli [AFB] smear, MGIT liquid culture, solid culture and DST) in conjunction with phenotypic with or without molecular evaluation for DR, in the case of confirmed MDR-TB (refer to the LPC for details of testing). DST for OBR should include first and second line TB drugs (refer to LPC). Participants will have bacteriology (typically sputum) studies done once a month until Week 8. In addition, if cultures became negative and then convert to positive again, or if the response to therapy is poor in the opinion of the attending clinician, DST will also be repeated, as per clinical indication. In addition, the first and last available isolate where available, will be stored for central gene sequencing for retrospective testing (refer to LPC). Sites should make reasonable attempts to source the original isolate, if available. In participants with probable MDR-TB, sampling will not be repeated if bacteriology was negative at diagnosis, unless new symptoms or worsening of symptoms or new TB exposure were to occur. In participants with probable MDR-TB, reasonable attempts should however been made to investigate for TB microbiology prior to enrolment.

8.5 TB treatment outcome

Participants will be serially assessed through repeat CXR (in the case of intrathoracic TB), clinical resolution of symptoms and mycobacterial culture (MGIT, Becton-Dickinson with DST and smear conversion), in the case of confirmed MDR-TB, as described in the Schedule of Evaluations (Appendix I). The expectation is that radiologic assessments will be interpreted as per site-specific standard guidelines for CXR review by pediatric pulmonologists/clinicians with expertise in pediatric TB, using a standard published CXR reading tool (66), at least for the
enrollment and final MDR-TB treatment outcome assessments. Standard CXR reading and reporting tools (CRF) will be provided to capture radiological features and TB disease severity.

In children with bacteriologically confirmed MDR-TB, cure will be defined as three consecutive negative respiratory cultures obtained at least one month apart with no positive cultures after the first negative result in the last 12 months of treatment after initiation of therapy (12, 67). In children with probable MDR-TB, or children with bacteriologically-confirmed MDR-TB who do not meet criteria for cure, probable cure will be defined as completion of the prescribed treatment with attainment of clinical and radiological improvement (12) (more information provided in the MOP). Treatment outcomes in children will therefore be defined as bacteriological cure, probable cure, death or treatment failure (12). An endpoint review committee consisting of two international experts, who form part of the protocol team, will assign all MDR-TB treatment outcomes.

8.6 ECG Monitoring and Reading

ECG will be interpreted based on age-specific criteria. Mean QT interval will be calculated based on triplicate ECG readings at each time point. At the Week 2 visit (intensive PK visit), ECGs will be performed predose and at 4-6 hours after BDQ administration. On-site clinicians will review ECGs and assess for clinical relevance and identification of AEs. In addition, there will be a centralized review of all ECGs within three to seven days, which will capture any abnormalities that may not have been identified and/or reported by the site; ECG results from centralized read will be used for study analyses. Sites will report ECG and/or clinical cardiac toxicities as per toxicity management guidelines for ECG-determined or clinical cardiac care (Appendix VI). All reports will also be reviewed, as defined in the MOP, as part of formal data analysis by the protocol cardiologist. This will not be required to be in real time, and will serve to assist with interpretation of all ECG data analysis in relation to study hypotheses, including for SMC review, as required.

8.7 Monitoring for Potential Mitochondrial Toxicities

Safety monitoring during BDQ dosing and after BDQ discontinuation will include measures of mitochondrial health, given the fact that mitochondrial dysfunction may potentially emerge over time due to increased enzymatic dysfunction, although no clinical or lab evidence of mitochondrial toxicity have been reported from any adult trials of BDQ to date. Cohort 1 will be monitored intensively for lactate and for lactate/pyruvate ratios. Lactate testing results will be available for clinical management with short turnaround time (refer to LPC), whereas lactate/pyruvate ratios will be completed additionally and will not be available for real-time patient management.

Any trends in lactate/pyruvate ratios over the course of the study will be tracked by obtaining lactate/pyruvate ratios on all Cohort 1 participants at baseline, Weeks 4, 24 and 96/72 weeks post BDQ. Data will be reviewed quarterly to assess for trends. Real-time review of the lactate/pyruvate ratios may be needed if a large number (i.e., >25% of the samples tested) of significantly elevated lactates (lactate >5mmol/L) were noted during routine AE lab monitoring. In that case, the ratios would be reviewed in real time and evidence of individual or group declining mitochondrial function during the study would trigger a protocol team review and possible solicitation of additional input as needed. This consult and team opinion would be forwarded to SMC for review. If additional sampling of participants at different time points, ages or labs is recommended, these may be added by LOA.
Unless detected abnormalities in lactate/pyruvate ratios in Cohort 1 are judged to be clinically significant following consultation with the protocol team and the SMC, Cohorts 2 and 3 will not be monitored in this way, given the technical challenges of collecting these samples in young children.

8.8 Management of Contraception and Pregnancy

As per eligibility criteria 4.1.8 and 4.1.10 any participant who is of reproductive potential must agree to maintain contraceptive use throughout the entire period of study. Sites will be expected to monitor this closely. The MOP will provide additional information to assist sites with provision of sexual health education, contraceptive counseling and/or appropriate contraceptive methods for these participants.

All initial reports of pregnancy in a study participant must be reported to the study team and IRBs within four weeks of their knowledge of the event using the appropriate pregnancy notification form.

Any participant who becomes pregnant during the study while on BDQ must promptly discontinue further treatment with BDQ, but can continue to take their MDR-TB drugs and ARV drugs (in HIV-infected participants) at the site investigator’s discretion and in accordance with the local standard of care. Follow up of the pregnant participant will continue as per protocol. If the outcome of the pregnancy is not known at the End of Study Visit, the participant will continue to be contacted until the outcome of pregnancy is known.

Because the potential effects of BDQ on sperm is unknown, pregnancies in partners of male participants included in the study will be reported by the investigational staff within four weeks of their knowledge of the event using the appropriate pregnancy notification form. If the outcome of the pregnancy is not known at the End of Study Visit, the male participant will continue to be contacted until the outcome of pregnancy is known.

In the event that an HIV-infected participant becomes pregnant, sites are encouraged to register the participant’s pregnancy in the Antiretroviral Pregnancy Registry (http://www.apregistry.com/; in US, Canada: 1-800-258-4263, international: 910-256-0238).

8.9 Management of HIV-Exposed Participants

The primary evaluation and work up of HIV-exposed children and adolescents will be through local facilities as part of standard of care. However, HIV testing should be repeated as a study evaluation if clinically indicated. In addition, acceptable documentation of HIV status in HIV-exposed infants enrolled in Cohort 3 at Week 48 (24 weeks post BDQ) and Week 120/End of Study (96 weeks post BDQ) visit is required. If acceptable documentation is not available, repeat testing as outlined in protocol Section 4.3 should be conducted.

8.10 Criteria for Premature Discontinuation of Study Drug

- Treatment with disallowed medications.
- Drug toxicity that requires permanent discontinuation of BDQ as specified in Section 8.1 or the Toxicity Management Tables in Appendices VI, VIII, and IX.
- Sustained non-adherence that, in the opinion of the investigator, warrants early BDQ discontinuation.
- Participant diagnosed as having drug-susceptible TB despite initial diagnosis of DR-TB.
- Pregnancy

Note that in the event of early treatment discontinuation, participants will continue study while off study drug and complete the study visits as specified in Appendix I. Please also refer to individual toxicity management in the appendices.

### 8.11 Criteria for Premature Discontinuation of Study Participation

- The investigator determines that further participation would be detrimental to the participant’s health or well-being.
- The participant fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results in the opinion of the investigator and/or the sponsor.
- The Office for Human Research Protections (OHRP), site IRBs/ECs, or other government agencies discontinue the study early.

Note that, as part of the informed consent process, participants will be asked to permit additional contact even if full study participation is no longer possible (i.e., if the participant moves away from the study center and can no longer attend visits). In these cases, when consent has been granted for continued contact, the participants will still be considered to be on study but participation will be limited to participant contacts as specified in Appendix I.

### 9 STATISTICAL CONSIDERATIONS

#### 9.1 General Design Issues

This is a Phase I/II open label, single arm dose-finding study with the primary objectives of assessing the PK and safety/tolerability of BDQ in combination with OBR MDR-TB therapy for the treatment of MDR-TB in HIV-infected and HIV-uninfected infants, children and adolescents.

This statistical section describes the methodology and analyses planned for safety and secondary response endpoints only. Please refer to Section 10.0 for PK analyses.

The sample will be stratified into three age cohorts as previously described.

At most 72 participants will be enrolled in order to have a minimum of 54 evaluable participants, 18 participants in each of Cohorts 1, 2 and 3, who will have appropriate data for the PK modeling upon which dosing depends. The safety analyses will include the safety data for all of these participants across all study follow-up.

Accrual to the study will follow an algorithm in which PK and safety will be initially studied in Cohort 1, with Cohorts 2 and 3 not being allowed to open until sufficient PK data from Cohort 1 have been collected to allow an adequate modeled estimate of starting doses for these younger cohorts. In making dosing decisions, the protocol team will review all safety data, as well as the results of PK modeling.
Please see Section 3.2 and Figure 1 for cohort management of participants on routine MDR-TB treatment and BDQ and criteria for evaluation of the first cohort and for opening subsequent cohorts.

9.2 Outcome Measures

For safety monitoring and reporting purposes, a drug related AE is defined as an adverse event that is judged to be definitely, probably or possibly related to the study drug (BDQ). These outcomes will come from the CRF database, along with information received from the RSC concerning SAE reports.

9.2.1 Primary Toxicity Endpoints (evaluated after 24 weeks of treatment)

- Termination from treatment due to a drug-related adverse event
- Adverse events of Grade 3 or Grade 4 severity
- Adverse events of Grade 3 or Grade 4 severity judged by the protocol team to be at least possibly related to the study medication
- Absolute QTc interval ≥500msec
- Unstable dysrhythmias requiring hospitalization and treatment
- Death (Grade 5)

9.2.2 Secondary Endpoints and Response Variables (evaluated after 120 weeks of treatment)

- Termination from treatment due to a drug-related adverse event
- Adverse events of ≥ Grade 3 or Grade 4 severity
- Adverse events of ≥ Grade 3 or Grade 4 severity judged by the protocol team to be at least possibly related to the study medication
- Absolute QTc interval ≥500msec
- Unstable dysrhythmias requiring hospitalization and treatment
- Death (Grade 5)

9.2.3 TB treatment response

- Favorable TB treatment response (refer to Section 8.5) at Week 120

9.3 Randomization and Stratification

There will be no randomization. Participants will be enrolled into one of the three cohorts described in Section 9.1 above.

9.4 Sample Size and Accrual

The sample size is primarily based on PK considerations. Clinical trial simulations were performed to (i) ensure a sample size able to provide precise enough estimates of apparent clearance as specified by the FDA criteria for pediatric trials (68) and (ii) ensure sufficient power to detect potential differences in PK parameters between children without and with concomitant HIV-infection. Since BDQ exposure at long-term administration primarily is determined by the apparent clearance, the first point implies that the primary objective of the study (to determine BDQ doses for children that achieve similar weekly exposure as adults taking BDQ at the
standard recommended dose) can be fulfilled. The methods and results of the simulations are described in Appendix X.

Table 3 presents exact 95% confidence intervals around various potential rates of ≥ Grade 3 AEs which might be observed in a total sample of 54 participants who might contribute data to the primary safety analysis, a sample of 18 participants within any age stratum and a potential sample of six participants, which represents the smallest sample on which dosing decisions might be made. This table indicates that confidence intervals will be quite wide around the sample size of 18 participants within a given age cohort, but would be considerably more precise around a total sample of 54 participants.

Table 3. Percent of Participants Experiencing ≥ Grade 3 Adverse Events (or ≥ Grade 3 Adverse Events Attributed to the Study Medication) with Exact 95% Confidence Intervals

<table>
<thead>
<tr>
<th>N*</th>
<th>n (%) With ≥ Grade 3 Adverse Events</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0 (0%)</td>
<td>0% -- 46%</td>
</tr>
<tr>
<td>18</td>
<td>0 (0%)</td>
<td>0% -- 19%</td>
</tr>
<tr>
<td>54</td>
<td>0 (0%)</td>
<td>0% -- 7%</td>
</tr>
<tr>
<td>6</td>
<td>1 (17%)</td>
<td>.4% -- 64%</td>
</tr>
<tr>
<td>18</td>
<td>3 (17%)</td>
<td>4% -- 41%</td>
</tr>
<tr>
<td>54</td>
<td>9 (17%)</td>
<td>8% -- 29%</td>
</tr>
<tr>
<td>6</td>
<td>2 (33%)</td>
<td>4% -- 78%</td>
</tr>
<tr>
<td>18</td>
<td>6 (33%)</td>
<td>13% -- 59%</td>
</tr>
<tr>
<td>54</td>
<td>18 (33%)</td>
<td>20% -- 47%</td>
</tr>
</tbody>
</table>

* Note: N refers to total sample size of possible sub-group analysis, but note that dosing decisions will make use of all available data.

9.5 Monitoring

The study will be monitored intensively by the Protocol Team, which will review safety and PK data regularly, with the aim of determining the optimal dose per weight for the three study age cohorts while protecting patient safety. In addition, the IMPAACT Network will appoint an SMC to provide independent reviews, when necessary, to ensure participant safety and to review decisions concerning changes in dosing and/or opening new cohorts.

9.5.1 Accrual Rate Evaluation, Study Progress and Quality of Study Conduct

Accrual to this study will be monitored by the protocol team and IMPAACT leadership in accordance with standard operating procedures. The team will monitor feasibility quarterly, first based on site activation and then on accrual. Initially, the team will monitor site registration monthly to ensure that an adequate number of sites have activated to participate in the protocol. If relatively few of the eligible sites have been activated after the protocol has been approved for 6 months, the team will re-assess the feasibility of the protocol and will examine the reasons why sites have not been activated or are not accruing adequately, and may amend the protocol accordingly.
The DMC will generate monthly screening and enrollment reports based on the data described in Section 4.5 and accrual reports described below. Using these reports, the protocol team will monitor accrual closely, relative to a study-specific accrual plan that has been established in collaboration with the study sites.

Based on the overall accrual plan, indicating that up to 72 participants will be enrolled to achieve a minimum of 54 evaluable participants, enrollment is projected to be completed within 24 months. Each site must establish and implement an SOP to achieve the projected rates of enrollment specified in the accrual plan. Should accrual rates fall below projections, the protocol team will work with study sites to take action as needed and may consider inclusion of additional sites.

The protocol team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and the quality of study conduct. As indicated in Sections 4.5 and 4.6, participant accrual and retention will be closely monitored based on reports that will be generated at least monthly by the SDMC. In the event that accrual or retention rates fall below target, team members will work with study sites to identify operational issues or problems and to take appropriate action to address below-target rates. Team members will similarly review other key indicators of the quality of study conduct (e.g., adherence to study medication regimen, endpoint evalability, data quality and completeness) based on reports generated by the SDMC and take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

The frequency of SMC review will be at least annually or determined by the accrual rate or specific adverse events (described in Section 9.5.2). The SMC will be provided with accrual data in addition to safety data as described below.

### 9.5.2 Participant Safety

It is the responsibility of the Protocol Team to interpret safety data, and make decisions regarding drug-related AEs that are needed to protect participants from undue risk. In addition, the SMC will provide impartial reviews in situations where patient safety is in question. As noted above, the safety and tolerability of the study agent will be monitored by means of adverse events reports and toxicity reports presenting laboratory and clinical events. Reports compiled by the DMC will be reviewed and discussed by the Protocol Team on conference calls held at least twice a month during the dose-finding stage, and every month thereafter. Review by the P1108 SMC will be scheduled as described above; the SMC will focus on safety aspects as described below.

Adverse events will be monitored from entry onwards throughout the follow-up period. If the protocol team identifies any potential treatment-related toxicities which may compromise participant safety, the study will be paused and the SMC will review all relevant data and will determine whether, and under what conditions, the study would be allowed to proceed.

Participants who successfully complete 24 weeks of BDQ treatment will be examined for long term safety every eight weeks for the next 24 weeks, and every 12 weeks until 120 weeks, (i.e., 96 weeks post last BDQ dose) have been completed, unless a clinical trigger requires closer follow-up. Sites should refer to the Schedule of Evaluation in Appendix I.

The SMC will be requested to focus on specific aspects including ECG data review, long-term safety, and lab measures of mitochondrial toxicity. Note that SMC reports may be minimal if these types of events are rare and if accrual has been slow.
In addition, the study can be paused and an *ad hoc* SMC review triggered by the following adverse events:

- Death which is at least possibly related to study drug. Traumatic death will be excluded.
- Cardiac arrhythmia while on study drug, Grade 3 or higher, judged by Protocol Team leadership (e.g., chairs and medical officers) to be at least possibly related to study drug.
- Unstable dysrhythmias requiring hospitalization and treatment.
- Selected elevated hepatic enzymes that are at least possibly related to study drug, and which exclude infectious hepatitis or other obvious causes, including:
  1. ALT $3 \times$ ULN AND bilirubin $2 \times$ ULN (>35% direct bilirubin; bilirubin fractionation required)
  2. ALT $3 \times$ ULN and with symptoms of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR
  3. ALT $\geq 5 \times$ ULN; regardless of symptoms; (4) Grade 4 elevation of ALT or direct bilirubin.
- $\geq$ Grade 3 pancreatitis (excluding infectious origin such as mumps or other known cause).
- If $>25\%$ of participants within a given cohort experience any study drug related grade $\geq 3$ adverse event, the SMC may be requested to review data.
- If patterns of the same study drug related grade $\geq 3$ adverse event (as above) become apparent, the SMC may be requested to review data.
- QT interval prolongation (QTcF $> 500$ ms) will not trigger SMC review. However, if $> 25\%$ of participants, within a given cohort experience a QTcF $> 500$ ms, SMC review may be requested.

Detailed toxicity management algorithms including criteria for discontinuation of study drug can be found in the Appendices VI-IX.

### 9.6 Analyses

#### 9.6.1 Primary Safety Analyses

The primary safety analyses will focus on the 24-week time period during which treatment is administered and will include only participants whose total exposure to BDQ has been at the final dose recommended for their cohorts. 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, but sensitivity analyses will be 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 24 weeks on therapy.

Each participant’s safety data will be summarized as: (1) the worst grade of AEs, and (2) the worst grade of AEs judged to be at least possibly related to study treatment. Frequency distributions of these safety outcomes will be presented in aggregate and will be broken down by age cohort. Listings of all $\geq$ Grade 3 events will be provided, broken down by type of toxicity (hepatic, hematologic, cardiac etc.).
The proportions of participants experiencing ≥ Grade 3 AEs will be presented in aggregate and broken down by age cohort, with these proportions bounded by exact 95% confidence intervals. Similar analyses will present the proportions of participants exhibiting ≥ Grade 3 events which have been judged to be at least possibly related to study medication, again bounded by exact 95% confidence intervals. Tabulations will also be presented to summarize all AEs and serious AEs that have been reported, as well as all AEs which have resulted in treatment discontinuation. Summary statistics of QT values at each time point performed, will also be presented.

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 pharmacokinetic modeling procedure which will determine the final recommended dose will not guarantee that an adequate number participants be on that dose. However, secondary safety analyses will include all safety data collected from first patient exposure to the end of the study, with results broken down by dose. This will include data representing the final dose for each cohort, as well as data gathered during the dose finding stage, which may represent exposure to doses which have failed.

Given that the small sample sizes within cohorts will provide limited power for statistical tests of differences across age cohorts, only very large apparent effects would be statistically significant. Interpretation of differences across cohorts will depend upon whether these differences are great enough to be considered to be clinically significant. If no such differences are observed, then the clearest interpretation of the findings will come from the aggregated data, where analyses will have the greatest statistical precision. However, if results vary across cohorts to a clinically important extent, interpretation of results should take into account the age differences and potential treatment differences represented by this stratification factor.

The proportions of participants meeting each of the endpoints which would trigger an SMC review will be presented descriptively.

Details concerning the analyses will be included in a separate analysis plan.

9.6.2 Secondary Analyses

9.6.2.1 Safety

The 24-week analyses described above for the primary analysis will be repeated as secondary analyses at week 120 and by HIV status. 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 dose for their cohorts.

For each starting dose within each cohort, every AE of ≥ Grade 3 will be listed, along with participant demographics, the dose prescribed to the patient at the time of the event and the protocol team’s assessment of the probability that this event was due to the study treatment (not related, probably not related, possibly related, probably related or definitely related).
9.6.2.2 Efficacy

This Phase I/II study will only be able to describe treatment response in children; this is not an efficacy trial. The proportions of children classified as having exhibited bacteriological cure (defined under Section 8.5), and clinical (probably) cure, will be presented, bounded with 95% confidence intervals; the time to culture-conversion (in weeks, months) in children 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 medication as estimated by PK modeling.

9.6.3 Exploratory Analyses of biomarker data

In a subset of children enrolled early during MDR-TB treatment, serum and urine biomarkers will be collected over time, and descriptive analyses will track changes over time in these biomarkers. Descriptive analyses will also be performed to examine whether the biomarker data appear to differ between subjects who convert their bacteriology vs. those who fail to do so.

10 CLINICAL PHARMACOLOGY PLAN

Dosing strategies for this study are described in detail in the Section 5.0, Study Treatment.

10.1 Pharmacology Objectives

See Primary Objective 1 and Secondary Objective 2 (Section 2.0).

Population PK modeling analysis will be conducted with all the evaluable BDQ and N-monodesmethyl metabolite (M2) concentrations in order to propose dosage regimens for pediatric participants across ranges of body weights and using a weight banding approach.

10.2 Study Design, Modeling and Data Analysis

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 (52) and a simulation study to evaluate expected power and parameter precision with the suggested sampling schedule and number of participants (Appendix X) this number is expected to be sufficient to estimate the main PK parameter, clearance (CL), with acceptable precision (68). The simulation study also showed that this sample size, including six HIV-infected children in each age group of 18, will have almost 90% power to detect a 30% difference between HIV-infected and HIV-uninfected children in either CL or bioavailability (F) with the selected design.

10.2.2 Phlebotomy and PK Sampling

PK assessments will be performed for all participants to determine plasma concentrations of BDQ and its M2 metabolite at selected time points. Sampling will be intensive and sparse; this efficient sampling schema is supported by extensive modeling and will impose the least burden on participants while yielding high quality clinically relevant data. Bioanalysis of BDQ and its M2 metabolite will be performed centrally at the University of Cape Town Clinical Pharmacology Laboratory using liquid chromatography with tandem mass spectrometry (LC-MS/MS).
Study drug will be directly administered by the research team on the day of PK sampling. Doses of BDQ, OBR and ARVs will also be documented through daily directly observed therapy and the exact time of doses on the preceding two days recorded. Food intake will be documented and standardized across sites to include a light meal (refer to the MOP). An indwelling catheter will be inserted in a peripheral vein on the morning of evaluation if the participant is hospitalized and may be inserted at clinical discretion otherwise. PK sampling may be rescheduled within the study window period if a child is clinically unable to undergo PK sampling on the specific day. PK sampling may be repeated on participants who undergo an adjustment in the dose of BDQ. Repeat PK sampling would be done as per original PK sampling schedule in participants undergoing repeated PK. Whole blood specimens (between 0.5 to 1.0 mL, depending on of the age of the participant) will be collected at the following times:

- Week 1 (sparse): 0 hour (before the next dose)
- Week 2 (intensive): baseline (time 0 hour; i.e., pre-dose), and at 2, 4, 6, and 8 hours post-dose
- Weeks 4, 8, 12, 16, 20, 24 (monthly sparse sampling): 0 hour (before the next dose)
- Weeks 32, 40, 48, 60, 72, 96 and 120 (bimonthly sparse sampling): random sample

Details regarding collection, processing, and storage of PK samples will provided in the study MOP and LPC.

10.2.3 **Modeling work to support dose selections for Cohorts 2 and 3**

A population PK model based on relevant adult data and using allometric body weight scaling will be updated based on the initial data from Cohort 1. The model used for the initial dose selection will be informed by knowledge of PK data in adults, as well as all the data from children down to six years of age, accounting also for expected effects of age, weight (through allometric scaling) and enzyme maturation among young children. The modeling approach used is consistent with recommendations by the U.S. FDA. The model will include functions describing the maturation of CYP3A4 (the enzyme mainly responsible for the metabolism of BDQ and its M2 metabolite). CYP3A4 is one of the most important metabolic enzymes and has been studied extensively, so the maturation processes governing this enzyme are well-characterized.

The population PK model will continue to be informed by each batch of new PK data, which will be triggered by each group of six participants with available Week 1 and Week 2 PK data, at which time all available PK data will be included. Based on this model, a dosage regimen will be calculated to target a weekly AUC at steady state close to the geometric mean in adults (144 µg*h/mL), in Cohorts 2 and 3. The dose will be decided by the protocol team based on the existing dosage strength (100 mg tablet) and practical considerations. The 100 mg formulation will be crushed, if required, in younger age groups or children not able to swallow tablets. The existing 100 mg formulation dissolves rapidly, is palatable and will have a separate formal bioequivalence evaluation (healthy adult volunteer study) prior to use in the younger age groups. In both cohorts as well as in individual children, doses may be adjusted as appropriate, based on emerging PK data.

10.2.4 **PK Data Analysis**

PK parameters for BDQ and M2 will be determined using nonlinear mixed effect models developed in NONMEM (69). In all cases, when new data are available, the updated BDQ model
will be used. Body weight, race/ethnicity, age, albumin and other covariates identified or hypothesized to be of pharmacokinetic importance (e.g. nutritional status, TB disease severity, crushing of the formulation), will be included in the analysis. Included in the formal covariate analysis will also be HIV-infection and, if there is sufficient information, interactions with drugs as part of concomitant ARV therapy.

Week 1 PK data from Cohort 1 may potentially provide useful information to help guide dosing in younger cohorts. The 95% prediction interval of the Day 7 trough value will be estimated for Cohort 1. If the mean trough concentrations estimated from the earliest available Day 7 PK data from Cohorts 2 and 3 is higher than the upper end of the 95% prediction interval obtained in Cohort 1, dose adjustment (lowering) would be considered for subsequent group 2 and 3 participants. This exploratory use of the Week 1 PK data will be contingent on the Week 1 PK value in Cohort 1 being positively correlated with the Week 2 PK value. Although there is no clear exposure-toxicity relationship that can be referenced to indicate that an exposure is too high at this early time point, additional PK data from Week 1 may contribute information to models that inform dose selection in the future.

The updated population PK models will be used to predict exposures in the pediatric population following long-term BDQ dosing for the following purposes: (i) to propose updated doses if a group or cohort fails to meet PK and/or have unacceptable safety, (ii) to propose doses for Cohorts 2 and 3, and (iii) for an exposure-safety analysis using data from all evaluable participants. For the purpose of proposing pediatric dosing regimens and the investigation of the effects of HIV status, the PK model will be based on all data available when the last patient of the last cohort has passed Week 24. PK sampling will however continue beyond Week 24, given the long half-life of BDQ. PK samples beyond Week 24 will stored and analyzed only until such time points BDQ can no longer be detected. The detailed population PK analysis plan will be prepared separately.

10.2.5 PK of ARV drugs and second-line TB therapy

PK of optimized background second line TB regimens (OBR) and ARV are beyond the scope of the formal aims of this protocol. Samples will however be stored for potential future use and investigator-initiated studies related to second-line drugs or OBR-ARV interactions.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

As described in Section 4.5, data on screening and enrollment in this study will be collected using the DMC Subject Enrollment System.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including CRFs and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the web site referenced in Section 11.2).

CRFs are completed by study site staff and, following quality control and quality assurance reviews, are keyed using a remote data entry system designated by the DMC and transferred
electronically to the DMC. Selected laboratory data are transferred electronically to the DMC through the LDMS.

At the DMC, computerized checks are applied to the transferred data and, when required, data queries are issued for resolution by study site staff. All data must be transferred to the DMC within timeframes specified in the forms instructions; queries must also be resolved in a timely manner.


11.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at:
www.niaid.nih.gov/labsandresources/resources/daidsclinarsrch/Pages/ClinicalSite.aspx

Study sites must comply with DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study products for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, the companies that provide the study products, IMPAACT, site IRBs/ECs, site IBCs, the MCC, OHRP, and other applicable regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

11.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at:
www.niaid.nih.gov/labsandresources/resources/daidsclinarsrch/Pages/ClinicalSite.aspx
12 CLINICAL SITE MONITORING

Site monitors under contract to NIAID or NICHD will visit study sites to inspect study facilities and review participant study records including consent forms, CRFs, medical records, laboratory records, and pharmacy records, to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. The monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by the monitors.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC and other required regulatory review and approval of this protocol and site-specific ICFs in accordance with 45 CRF 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRB/EC any changes in the study and any unanticipated problems involving risks to participants or others.

All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 14.2).

13.2 Vulnerable Participants

The NIH is mandated by law to ensure that children be included in clinical research when appropriate (70). This study responds to that mandate and will provide clinical research data to inform MDR-TB treatment guidelines for children. In particular, children with MDR-TB have been excluded from trials of novel antituberculosis agents, agents with the potential to dramatically shorten and simplify the treatment of MDR-TB in children.

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx

Children who take part in this study are considered vulnerable participants per 45 CFR 46 Subpart D. Site IRBs/ECs must consider the potential benefits, risks, and discomforts of the study to children and assess the justification for their inclusion in the study. As part of this assessment, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404–407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 14.2.

The risk category assigned by the IRB/EC determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one
parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that
the research is covered by 46.406 or 46.407, both parents must give their consent, unless one
parent is deceased, unknown, incompetent, or not reasonably available or when only one parent
has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs
must document their risk determination, and study sites should adapt the signature pages of their
site-specific ICFs as needed to accommodate the parental consent requirements associated with
the IRB/EC determination.

13.3 Informed Consent

Written informed consent for study participation will be obtained before any study-specific
procedures are performed. This protocol, site-specific informed consent forms (refer to sample in
Appendix XI), site-specific assent forms (refer to sample in Appendix XII), and any subsequent
modifications must be reviewed and approved by the IRBs/ECs responsible for oversight of the
study at each site. Written informed consent must be obtained from the parent or legal guardian of
each study participant; written assent should also be obtained from participants when applicable
per IRB/EC policies and procedures. Copies of consent and assent forms will be offered to
parents/guardians and participants as applicable. Refer to Section 4.5 and the study-specific MOP
for further information on informed consent procedures for this study.

Should the consenting parent or legal guardian of an enrolled infant die or no longer be available
for any reason, no further study-specific visits or procedures may be performed until informed
consent for continued study participation is obtained from a locally authorized guardian. In
accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical
Research (available at the website referenced in Section 13.2), all study sites must establish and
maintain written procedures describing the standards that will be followed to identify who may
serve as guardian for an enrolled participant, reflective of applicable IRB/EC guidance for
conduct of human subjects research within the context of available local law, regulation, or
government policy.

13.4 Potential Benefits

Participants in this study may experience no direct benefit, although adults with MDR-TB have
benefited from receiving BDQ in addition to OBR or MDR-TB. Participants and others may
benefit in the future from information learned from this study.

13.5 Potential Risks

The potential risks of this study are described below; refer to Appendix XI for more information.

The following are the most common side effects associated with the use of BDQ in adults:

- Headache
- Dizziness
- Diarrhea
- Nausea
- Joint pain
- Vomiting
- Increase uric acid in the blood

These common side effects generally occur in fewer than 50% of adults who are taking BDQ.
Other serious side effects, that are less common include:

- Potential mitochondrial toxicity (not described in adults)
- QT prolongation

There are also minimal risks associated with drawing blood or fine needle aspiration of lymph nodes (for TB testing), including discomfort, bleeding, and swelling or bruising where the needle enters the body. There is a small risk of a minor infection the place that the needle is inserted. Lightheadedness and fainting can also occur.

13.6 Reimbursement/Compensation

Pending IRB/EC approval, participants will be reimbursed for costs associated with completing study visits (e.g., transport costs). Reimbursement amounts will be specified in site-specific ICFs or other materials if applicable per IRC/EC policies and procedures.

13.7 Privacy and Confidentiality

All study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Section 11.2.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms, photographs of observed reactions) will be identified by PID only. Likewise, communications between study staff and protocol team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

13.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including TB disease and HIV infection identified among study participants to health authorities. Participants will be made aware of all applicable reporting requirements as part of the study informed consent process.

13.9 Management of Incidental Findings

Site clinicians will inform participants and/or other authorized guardians/parents if applicable of all clinically meaningful physical exam findings and laboratory test results. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.
13.10 Management of New Information Pertinent to Study Participation

Participants and/or other authorized guardians/parents if applicable will be provided with any new information learned over the course of the study that may affect their willingness to continue receiving study treatment and/or remain in follow-up in the study.

13.11 Post-Trial Access to Study Drug

This formulation of BDQ is licensed in adults and is available by prescription in selected international sites to adults with MDR-TB. Post-study access is not relevant to child participants on P1108, since BDQ is prescribed only during the first 24 weeks of MDR-TB therapy.

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). The Division of AIDS (DAIDS) within the NIAID is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study products prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with independent clinical site monitors who will perform monitoring visits as described in Section 12.0. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable U.S. and local regulatory requirements.

14.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by their local IRB/EC, local IBC, and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICFs will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICFs will not be reviewed and approved by the
DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available on the RSC website: http://rsc.tech-res.com/protocolregistration/

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable U.S. and local regulations. Study implementation will also be guided by the IMPAACT MOP, study-specific MOP, LPC, and other study implementation materials, which will be available on the IMPAACT web site: www.impaaactnetwork.org.

Study implementation at each site will also be guided by site-specific SOPs. The DAIDS policy on Requirements for Manual of Operational specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 11.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

14.4 Protocol Deviation Reporting

Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available at the website referenced in Section 11.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT Manual of Procedures.

14.5 Critical Event Reporting

Per the DAIDS policy on Identification and Classification of Critical Events, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, which is available at: www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/Safety.aspx

14.6 ClinicalTrials.gov

This protocol is not subject to the United States Food and Drug Administration Amendments Act of 2007 (FDAAA).
15 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Manual of Procedures. The protocol team will undertake to disseminate data rapidly from each age cohort, as it becomes available.
REFERENCES

56. CDC. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. MMWR Recommendations and

## Appendix I: Schedule of Evaluation for All Cohorts (1, 2 and 3)

<table>
<thead>
<tr>
<th>Screening</th>
<th>Entry/Day 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
<th>Unscheduled Visit</th>
<th>Early BDQ D/C or Study D/C</th>
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</thead>
<tbody>
<tr>
<td><strong>CLINICAL EVALUATIONS</strong></td>
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</tr>
<tr>
<td>History</td>
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<td>x</td>
<td>x</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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</tr>
<tr>
<td>Audiology</td>
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<td></td>
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<td></td>
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</tr>
</tbody>
</table>

| **LABORATORY EVALUATIONS** | | | | | | | | | | | | |
| Hematology | 1.0mL | 1.0mL | 1.0mL | 1.0mL | 1.0mL | 1.0mL | 1.0mL | 1.0mL | 1.0mL | 1.0mL | 1.0mL | 1.0mL | 1.0mL |
| Chemistries | 2.0mL | 2.0mL | 2.0mL | 2.0mL | 2.0mL | 2.0mL | 2.0mL | 2.0mL | 2.0mL | 2.0mL | 2.0mL | 2.0mL | 2.0mL |
| LFT | x | x | x | x | x | x | x | x | x | x | x | |
| TSH (if T4 if TSH is elevated) | 2.0mL | | | | | | | | | | | |
| Serum biomarkers (storage) | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL | 0.5-1 mL |
| Cohort 1: lactate to local lab | 2.0mL | | | | | | | | | | | |
| Cohort 1: lactate/ pyruvate | 2.0mL | | | | | | | | | | | |
| Pregnancy test | x | x | x | x | x | x | x | x | x | x | x | |
| Specimens for TB micro lab | x | x | x | x | x | x | x | x | x | x | x | |
| Urinalysis | x | x | x | x | x | x | x | x | x | x | x | |
| Urine biomarker (storage) | x | x | x | x | x | x | x | x | x | x | x | |
| Intensive PK | | | | | | | | | | | | |
| Sparse PK | | | | | | | | | | | | |
| Intensive PK | | | | | | | | | | | | |
| **HIV-Infected only** | | | | | | | | | | | | |
| HIV-1 RNA PCR (viral load) | 3.0mL | | | | | | | | | | | |
| Lymphocyte subsets | 1.0mL | | | | | | | | | | | |
| **TOTAL BLOOD VOLUMES** | | | | | | | | | | | | |
| Cohort 1 | 4.0mL | 10-14.0mL | 4.0mL | 9.0mL | 9-10mL | 0mL | 7.0mL | 4-8.0mL | 7.0mL | 4.0mL | 11-15mL | 0mL | 4-5.0mL |
| Cohort 2 | 4.0mL | 6-10.0mL | 4.0mL | 9.0mL | 5-6mL | 0mL | 7.0mL | 4-8.0mL | 7.0mL | 4.0mL | 7-11mL | 0mL | 4-5.0mL |
| Cohort 3 | 3.5mL | 5.5-9.5 mL | 3.5mL | 6.0 mL | 4-5.0mL | 0mL | 6.0mL | 3.5-7.5mL | 6.0mL | 3.5mL | 6-10.0mL | 0mL | 3.5-4.5mL |
Appendix I (cont.): Schedule of Evaluation for All Cohorts (1, 2 and 3)

<table>
<thead>
<tr>
<th>Off treatment visits</th>
<th>Unsched. Visit</th>
<th>Early Study D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 32 (8 wks post BDQ)</td>
<td>Week 40 (16 wks post BDQ)</td>
<td>Week 48 (24 wks post BDQ)</td>
</tr>
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</table>

### CLINICAL EVALUATIONS

<table>
<thead>
<tr>
<th>History</th>
<th>x</th>
<th>x</th>
<th>x</th>
<th>x</th>
<th>x</th>
<th>x</th>
<th>x</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation of HIV status¹</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Physical exam</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<td></td>
<td>x</td>
<td>x</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### LABORATORY EVALUATIONS

#### Hematology
- Cohort 1: 1.0 mL
- Cohort 2: 1.0 mL
- Cohort 3: 1.0 mL

#### Chemistries
- Cohort 1: 2.0 mL
- Cohort 2: 2.0 mL
- Cohort 3: 2.0 mL

#### LFT
- Cohort 1: x
- Cohort 2: x
- Cohort 3: x

#### TSH (fT4 if TSH is elevated)
- Cohort 1: 2.0mL
- Cohort 2: 2.0mL
- Cohort 3: 2.0mL

#### Serum biomarkers (storage)
- Cohort 1: 0.5-1.0mL
- Cohort 2: 0.5-1.0mL
- Cohort 3: 0.5-1.0mL

#### Cohort 1: lactate to local lab
- Cohort 1: 2.0mL

#### Cohort 1: lactate/ pyruvate
- Cohort 1: 2.0mL

#### Pregnancy test
- Cohort 1: x
- Cohort 2: x
- Cohort 3: x

#### Specimens for TB micro lab
- Cohort 1: x
- Cohort 2: x
- Cohort 3: x

#### Urinalysis
- Cohort 1: x
- Cohort 2: x
- Cohort 3: x

#### Urine biomarkers (storage)
- Cohort 1: x
- Cohort 2: x
- Cohort 3: x

#### Sparse PK
- Cohort 1: 0.5-1.0mL
- Cohort 2: 0.5-1.0mL
- Cohort 3: 0.5-1.0mL

#### HIV-Infected only

<table>
<thead>
<tr>
<th>HIV-1 RNA PCR</th>
<th>Lymphocyte subsets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mL</td>
<td>1.0 mL</td>
</tr>
</tbody>
</table>

#### TOTAL BLOOD VOLUMES (higher volumes for HIV+)

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7.0mL</td>
<td>4.0mL</td>
<td>5.5-6.5mL</td>
</tr>
<tr>
<td>6-7.0mL</td>
<td>4.0mL</td>
<td>5.5-6.5mL</td>
</tr>
<tr>
<td>6-7.0mL</td>
<td>4.0mL</td>
<td>5.5-6.5mL</td>
</tr>
<tr>
<td>8-9.0mL</td>
<td>5.9-9.0mL</td>
<td>4.0mL</td>
</tr>
<tr>
<td>6.0mL</td>
<td>4-5.0mL</td>
<td>3.5-4.5mL</td>
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<tr>
<td>6.0mL</td>
<td>5-9.0mL</td>
<td>4.0mL</td>
</tr>
<tr>
<td>4.0mL</td>
<td>4.0mL</td>
<td>3.5mL</td>
</tr>
</tbody>
</table>

(1) Refer to protocol section 4.3 for acceptable documentation of HIV status at screening. In the absence of such documentation, HIV testing should be conducted as part of the screening process and may entail the collection of up to 6 mL depending on type of tests validated for use at the site. Documentation of HIV status of HIV-exposed participants in Cohort 3 is required at Week 48 (24 weeks post BDQ) and Week 120/End of Study. If acceptable documentation is not available, additional blood may need to be collected.

(2) If TST is not available at the site, IGRA may be done. This would require that an additional 3-4.0 mL of blood be collected at these time points.

(3) If lactate is >3mmol/L, additional 2.0 mL for repeat test will be necessary; refer to LPC and Appendix IX: Toxicity Management of Specific Toxicities: Lactate.
## Appendix II: DRUG GROUPS ROUTINELY USED FOR THE TREATMENT OF DRUG-RESISTANT TUBERCULOSIS IN CHILDREN

<table>
<thead>
<tr>
<th>Group</th>
<th>Group Name</th>
<th>Drugs</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First-line oral agents</td>
<td>Isoniazid (high-dose)</td>
<td>H or INH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethambutol</td>
<td>E or EMB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyrazinamide</td>
<td>Z or PZA</td>
</tr>
<tr>
<td>2</td>
<td>Injectable agents</td>
<td>Kanamycin</td>
<td>Km</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amikacin</td>
<td>Am</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capreomycin</td>
<td>Cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptomycin*</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>Fluoroquinolones</td>
<td>Levofloxacin</td>
<td>Lfx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moxifloxacin</td>
<td>Mfx</td>
</tr>
<tr>
<td>4</td>
<td>Oral bacteriostatic second-line agents</td>
<td>Ethionamide/prothionamide</td>
<td>Eto or ETH</td>
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<tr>
<td></td>
<td></td>
<td>Terizidone/cycloserine</td>
<td>Trd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Para-aminosalicylic acid</td>
<td>PAS</td>
</tr>
<tr>
<td>5</td>
<td>Agents with unclear efficacy or concerns regarding usage</td>
<td>Clofazimine</td>
<td>Cfz</td>
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<tr>
<td></td>
<td></td>
<td>Linezolid</td>
<td>Lzd</td>
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<td>Amoxicillin-clavulanic acid</td>
<td>Amx/Clv</td>
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<td>High dose isoniazid</td>
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<td>Clarithromycin</td>
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* Not available/used in South Africa
Appendix IIB: CONSTRUCTING A MDR-TB TREATMENT REGIMEN IN CHILDREN

Regimens for MDR-TB treatment in children are individualized according to the child or adult source case’s isolate drug susceptibility test results (DST) as well as information about previous treatment experience. The WHO divides anti-TB drugs into five drug groups. This helps to construct a regimen aiming at four effective drugs per regimen. In some cases of early identification of disease as contacts of adults with only resistance to INH and RIF, the injectable drug is excluded, aiming for three active drugs with paucibacillary disease. Note that these drug groups may undergo future reclassification based on updated global MDR-TB treatment guidelines in adults and children.

- **Group 1** – First-line drugs. Pyrazinamide and ethambutol are mostly included in MDR-TB regimens, but > 50% of MDR-TB strains are resistant to either or both. DST for these drugs are not routinely done therefore they cannot be considered effective drugs. PZA dose 30-40mg/kg/day and EMB dose 20-25mg/kg/day.

- **Group 2** – Second-line injectable drugs. One second-line injectable agent – mainly amikacin due to better minimal inhibitory concentration and smaller mg content of vials - is usually added. Amikacin is replaced with capreomycin if patients are infected with amikacin-resistant strains, but cross-resistance rates are high (60-80%), therefore not counted as active drug unless confirmed susceptible. Dose: 15-20mg/kg daily for any injectable drug.

- **Group 3** - Fluoroquinolones. In most international sites, levofloxacin (15-20mg/kg) is preferred in children <8 years of age and moxifloxacin (10mg/kg) in children >8 years of age, based on the availability of formulations.

- **Group 4** – Oral second-line drugs. Add one or more (to reach 4 effective drugs): Ethionamide (15-20 mg/kg/day), terizidone (15-20 mg/kg/day) and/or para-aminosalicylic acid (PAS; 150-200 mg/kg/day in single or divided dose). Knowing the mutation conferring INH resistance from the line probe assays (LPA) result should inform the clinician of possible co-resistance with ethionamide: inhA promoter region mutations are associated with ethionamide resistance and low-level INH resistance, while katG gene mutations usually confer high-level INH resistance but not ethionamide resistance.

- **Group 5** – Drugs with uncertain effectiveness. Only add drugs from this group if not yet four effective drugs in the regimen (except INH if low-level resistance). High-dose INH (15-20 mg/kg/day) is used if inhA mutation, conferring low-level INH resistance is confirmed. Linezolid (10mg/kg twice daily in <10 years old; 300mg/day if >10 years old) has excellent efficacy, but is expensive and associated with severe adverse effects. It is reserved for XDR-TB treatment and central nervous system MDR-TB cases. Clofazimine (2-3 mg/kg daily) is increasingly used in XDR-TB cases – doses up to 5mg/kg/day is sometimes given because capsules cannot be divided. In very young infants, dose can be given every second day if >5mg/kg day with smallest capsule available. Other Group 5 drugs (amoxiclavulanate and clarithromycin) are rarely used and only in XDR-TB cases but their value is highly debatable.
## Appendix III: SUMMARY OF THE DOSE AND ADVERSE EFFECTS OF THE SECOND-LINE DRUGS USED IN THIS STUDY IN THE TREATMENT OF DRUG RESISTANT TUBERCULOSIS IN CHILDREN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose recommended</th>
<th>Formulation size</th>
<th>Main adverse effects</th>
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<tbody>
<tr>
<td>Kanamycin</td>
<td>15-25 mg/kg once daily</td>
<td>1g vial</td>
<td>Ototoxicity, nephrotoxicity</td>
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<tr>
<td>Amikacin</td>
<td>15-25 mg/kg once daily</td>
<td>100mg, 250mg, 500mg and 1g vials</td>
<td>As for kanamycin</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15-25 mg/kg once daily</td>
<td>1g vial</td>
<td>As for kanamycin</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>15-20 mg/kg once daily</td>
<td>200mg, 400mg</td>
<td>Sleep disturbance, GI disturbance, arthralgia, arthritis, peripheral neuropathy; prolongation of QTc interval</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>15-20 mg/kg once daily</td>
<td>250mg, 500mg</td>
<td>As for ofloxacin; prolongation of QTc interval (less so than moxifloxacin)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>10 mg/kg once daily</td>
<td>400 mg</td>
<td>As for ofloxacin; prolongation of QTc interval (not to be used in conjunction with bedaquiline)</td>
</tr>
<tr>
<td>Ethionamide/Prothionamide</td>
<td>15-20mg/kg once daily</td>
<td>125mg and 250mg tablets</td>
<td>GI disturbance, metallic taste, hypothyroidism</td>
</tr>
<tr>
<td>Cycloserine/Terizidone</td>
<td>15-20mg/kg once daily</td>
<td>250mg capsules</td>
<td>Neurological and psychological effects</td>
</tr>
<tr>
<td>Para-aminosalicylic acid (PAS)</td>
<td>150-200 mg/kg granules daily in two or three divided doses</td>
<td>Sachets of 4g</td>
<td>GI intolerance including diarrhoea, hypothyroidism, hepatitis</td>
</tr>
<tr>
<td>Clofazidine</td>
<td>3-5mg/kg once daily or every second day</td>
<td>50mg, 100mg tablets/capsules</td>
<td>Skin discoloration (may also cause QT prolongation, used in cases of pre-XDR and XDR-TB with BDQ, as sterilizing drug, given limited treatment options)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>10mg/kg once daily (&gt;10 years) or twice daily (&lt;10 years of age)</td>
<td>600mg tablets and syrup</td>
<td>Headache, nausea, myelosuppression, neurotoxicity, lactic acidosis and pancreatitis</td>
</tr>
</tbody>
</table>
| Amoxicillin/clavulanate, Imipenem, Meropenem | As for bacterial infections | Amoxicillin/clavulanate – various formulations  
Meropenem – 500mg and 1g vials  
Imipenem – 250mg and 500mg vials | GI intolerance, hypersensitivity reactions, seizures, liver and renal dysfunction                                                                      |
| Clarithromycin                | 7.5- 15mg/kg twice daily | 500mg tablets                          | GI intolerance, rash, hepatitis, prolonged QT syndrome, ventricular arrhythmias                                                                      |
| High dose isoniazid           | 15-20mg/kg once daily | 100mg tablets                          | Hepatitis, peripheral neuropathy                                                                                                                    |
### APPENDIX IV: POTENTIAL INTERACTIONS AND COMBINED TOXICITY BETWEEN THE ROUTINE SECOND-LINE TUBERCULOSIS DRUGS AND ANTIRETROVIRAL TREATMENT IN CHILDREN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacokinetic interactions</th>
<th>Increased risk of adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injectables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Buffered didanosine may reduce oral absorption of all fluoroquinolones</td>
<td>Psychiatric symptoms with efavirenz&lt;br&gt;Hepatitis with nevirapine, efavirenz or protease inhibitors&lt;br&gt;Prolongation QT interval with protease inhibitors and efavirenz</td>
</tr>
<tr>
<td>Ethionamide/Prothionamide</td>
<td>Unknown</td>
<td>Peripheral neuropathy with stavudine or didanosine&lt;br&gt;Psychiatric symptoms with efavirenz&lt;br&gt;Hepatitis with nevirapine, efavirenz or protease inhibitors&lt;br&gt;GI intolerance with zidovudine or protease inhibitors</td>
</tr>
<tr>
<td>Cycloserine/Terizidone</td>
<td>Renally cleared so interactions unlikely&lt;br&gt;Nephrotoxicity caused by tenofovir* could affect serum concentrations</td>
<td>Peripheral neuropathy with stavudine or didanosine&lt;br&gt;Psychiatric symptoms with efavirenz&lt;br&gt;Stevens Johnson Syndrome with nevirapine and efavirenz</td>
</tr>
<tr>
<td>PAS</td>
<td>Unlikely</td>
<td>Hepatitis with nevirapine, efavirenz or protease inhibitors&lt;br&gt;GI intolerance with zidovudine or protease inhibitors</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>May increase etravirine* and protease inhibitor concentrations</td>
<td>GI intolerance with zidovudine or protease inhibitors</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Unlikely</td>
<td>Peripheral neuropathy with stavudine or didanosine&lt;br&gt;GI intolerance with zidovudine or protease inhibitors&lt;br&gt;Lactic acidosis with stavudine, didanosine or zidovudine&lt;br&gt;Bone marrow toxicity with zidovudine</td>
</tr>
<tr>
<td>Amoxicillin/Imipenem/Meropenem</td>
<td>Unlikely</td>
<td>Nephrotoxicity with tenofovir*</td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>Not advised in HIV-infected patients due to risk of Stevens-Johnson Syndrome</td>
<td>Not advised in HIV-infected patients due to risk of Stevens-Johnson Syndrome</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Concentrations increased by ritonavir&lt;br&gt;Concentrations reduced by efavirenz and nevirapine&lt;br&gt;Clarithromycin reduces zidovudine concentrations</td>
<td>Combination with non-nucleoside reverse transcriptase inhibitors (NNRTIs) not recommended due to increased concentrations of the 14-hydroxy metabolite which is associated with rashes</td>
</tr>
</tbody>
</table>
## APPENDIX V: SUPPLEMENTAL TOXICITY TABLE FOR GRADING ELECTROCARDIOGRAM CHANGES AND POSSIBLE SYMPTOMS RELATED TO CARDIAC CONDUCTION ABNORMALITIES

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG Criteria: corrected QTc interval</td>
<td>QTc ≥460msec, but &lt;480msec</td>
<td>QTc ≥480msec, but &lt;500msec</td>
<td>QTc ≥500msec OR QT &gt; 60 msec greater than baseline AND QT≥480 ms</td>
</tr>
<tr>
<td>Note: QT corrected based on Frederica method (QTc=QT/cubed root of RR interval).</td>
<td></td>
<td>Life-threatening consequences (Torsades de pointes, other serious ventricular dysrhythmias)</td>
<td></td>
</tr>
<tr>
<td>Cardiac Clinical Criteria</td>
<td>Any one of the following clinical symptoms (one event, without clear evidence of non-cardiac etiology):</td>
<td>Recurrence/ongoing clinical symptoms (without clear evidence of non-cardiac etiology):</td>
<td>Recurrence/ongoing clinical symptoms - <em>with evidence of ventricular tachycardia</em></td>
</tr>
<tr>
<td></td>
<td>⇒ syncope</td>
<td>⇒ syncope</td>
<td>⇒ syncope</td>
</tr>
<tr>
<td></td>
<td>⇒ chest pain</td>
<td>⇒ chest pain</td>
<td>⇒ chest pain</td>
</tr>
<tr>
<td></td>
<td>⇒ palpitations</td>
<td>⇒ palpitations</td>
<td>⇒ palpitations</td>
</tr>
<tr>
<td></td>
<td>⇒ dizziness</td>
<td>⇒ dizziness</td>
<td>⇒ dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Note that this presence of Ventricular Tachycardia (VT) <em>is the adverse outcome</em> to be avoided/identified; the symptoms are surrogates for “possible” VT, but if VT is demonstrated, then BDQ is permanently discontinued irrespective of QTc or symptoms.</em></td>
</tr>
</tbody>
</table>
### APPENDIX VI: TOXICITY MANAGEMENT OF SPECIFIC TOXICITIES

#### ECG-Determined or Clinical Cardiac Toxicity

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>STUDY DRUG USE</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Continue BDQ</td>
<td>Repeat ECG and clinical evaluation of symptoms within 72 hours</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue BDQ</td>
<td>Repeat ECG and clinical evaluation of symptoms within 48 hours</td>
</tr>
<tr>
<td>Grade 3 (ECG)</td>
<td>Hold Fluoroquinolone (FQ) and BDQ</td>
<td>If repeat ECG and clinical evaluation of symptoms within 72 hours continues to show Grade 3, hold the FQ and hold study drug (= Grade 4). Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary. Contact the study team and indicate in the participant line: “Grade 3 ECG.”</td>
</tr>
<tr>
<td>Grade 3/4 (Cardiac Clinical Criteria)</td>
<td>Hold FQ and Permanently discontinue BDQ if not other explanation; e.g., lab abnormality. Note: STUDY DRUG USE for Cardiac Clinical Criteria meeting Grade 3 or Grade 4 are equivalent – that is permanently discontinue BDQ</td>
<td>Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary. Contact the study team and indicate in the participant line: “Grade 3/4 Cardiac.” Discuss with the team the permanent discontinuation of study drug.</td>
</tr>
<tr>
<td>Grade 4 (ECG)</td>
<td>Hold FQ and Permanently discontinue BDQ if not other explanation; e.g., lab abnormality</td>
<td>Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary. Contact the study team and indicate in the participant line: “Grade 4 ECG.” Discuss with the team the permanent discontinuation of study drug.</td>
</tr>
</tbody>
</table>
APPENDIX VII: TABLE TO DETERMINE THE LOWER LEVEL OF NORMAL HEART RATE BY AGE

This table should be used when evaluating heart rates on ECGs performed for Screening and for On-study visits. This table is to be followed in conjunction with exclusion criterion 4.2.11 and serial ECGs.

Normal Heart Rate Ranges by Age (71)

<table>
<thead>
<tr>
<th>Participant’s Age</th>
<th>≥ 3 to &lt; 6 Months</th>
<th>≥ 6 to &lt; 12 Months</th>
<th>≥ 1 to &lt; 3 Years</th>
<th>≥ 3 to &lt; 5 Years</th>
<th>≥ 5 to &lt; 8 Years</th>
<th>≥ 8 to &lt; 12 Years</th>
<th>≥ 12 to &lt; 16 Years</th>
<th>≥ 16 to ≤ 21 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Heart Rate Range (bpm)</td>
<td>105-185</td>
<td>108-169</td>
<td>89-152</td>
<td>73-137</td>
<td>65-133</td>
<td>62-130</td>
<td>60-120</td>
<td>50-100*</td>
</tr>
<tr>
<td>Mean (bpm)</td>
<td>141</td>
<td>131</td>
<td>119</td>
<td>109</td>
<td>100</td>
<td>91</td>
<td>80</td>
<td>--</td>
</tr>
</tbody>
</table>

*Range values are 2nd to 98th percentiles.
*Normal heart rate range values for adults, reported by the American Heart Association.
## APPENDIX VIII: TOXICITY MANAGEMENT OF GENERAL TOXICITIES

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>STUDY DRUG USE</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Continue BDQ</td>
<td>Routine monitoring</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue BDQ</td>
<td>Monitor closely with more frequent visits; as per site clinician, work-up to exclude other causes.</td>
</tr>
<tr>
<td>Grade 3 – confirmation pending</td>
<td>Hold BDQ while awaiting confirmation of Grade 3 toxicity unless clinician believes that resuming BDQ will be unsafe and so elects to permanently discontinue.</td>
<td>Contact the study team upon determination of any Grade 3 or 4 toxicity. Indicate in the participant line P1108, grade and type of toxicity.</td>
</tr>
<tr>
<td>Grade 3 – confirmed and presumed, possibly, probably, or definitely related to BDQ.</td>
<td>Permanently discontinue BDQ</td>
<td>The participant should be monitored closely until resolution to &lt; Grade 2. As per site clinician, work-up to exclude other causes. Contact the study team upon confirmation of Grade 3 toxicity. Indicate in the participant line: P1108 Grade 3 and specify the toxicity.</td>
</tr>
<tr>
<td>Grade 4 and presumed, possibly, probably, or definitely related to BDQ</td>
<td>Permanently discontinue BDQ</td>
<td>Participants should be monitored closely with more frequent visits until resolution to &lt; Grade 2. Contact the study team upon determination of Grade 4 toxicity. Indicate in the participant line: P1108 Grade 4 and specify the toxicity.</td>
</tr>
</tbody>
</table>
## APPENDIX IX: TOXICITY MANAGEMENT OF SPECIFIC TOXICITIES

Toxicity Management of Specific Toxicities: Bilirubin

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>STUDY DRUG USE</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Continue BDQ</td>
<td>Routine monitoring</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue BDQ</td>
<td>Repeat testing should be done within 72 hours. Testing for AST, ALT should also be done. Participants should be followed until resolution or stabilization.</td>
</tr>
<tr>
<td>Meets Hy’s law</td>
<td>If ALT/AST elevations are 3-fold accompanied by 2-fold elevation in total bilirubin, BDQ should be permanently discontinued.</td>
<td>Contact the study team.</td>
</tr>
<tr>
<td>Grade 3 – confirmation pending</td>
<td>Hold BDQ while awaiting confirmation of Grade 3 toxicity unless clinician believes that resuming BDQ will be unsafe and so elects to permanently discontinue.</td>
<td></td>
</tr>
<tr>
<td>Grade 3 – confirmed; presumed unrelated</td>
<td>Hold BDQ</td>
<td>The participant should be monitored closely until resolution to &lt; Grade 2. As per site clinician, work-up to exclude other causes. May re-start after less than Grade 2. Contact the study team.</td>
</tr>
<tr>
<td>Grade 3 – confirmed; presumed related</td>
<td>Permanently discontinue BDQ</td>
<td>Contact the study team.</td>
</tr>
<tr>
<td>Grade 4 – regardless of relationship</td>
<td>Permanently discontinue BDQ</td>
<td>Participants should be monitored closely with more frequent visits until resolution to &lt; Grade 2. Contact the study team.</td>
</tr>
</tbody>
</table>
### APPENDIX IX, continued
Toxicity Management of Specific Toxicities: Elevations in AST or ALT

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>STUDY DRUG USE</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Continue BDQ</td>
<td>Participants should be followed until resolution.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue BDQ</td>
<td>Repeat testing should be done within 72 hours. Testing for bilirubin and viral hepatitis should be performed and other hepatotoxic medications discontinued. Participants should be followed until resolution or stabilization.</td>
</tr>
<tr>
<td>Meets Hy’s law</td>
<td>If ALT/AST elevations are 3-fold accompanied by 2-fold elevation in total bilirubin, BDQ should be discontinued.</td>
<td>Contact the study team.</td>
</tr>
<tr>
<td>Grades 3 and 4</td>
<td>Step 1: Continue BDQ and temporarily discontinue one or more suspected other background MDR-TB or HIV drugs, or hepatotoxic medications for a 2-week trial period.</td>
<td>During the 2-week period when other MDR-TB agent(s) are held, AST, ALT and serum bilirubin should be monitored as frequently as necessary to manage the participant’s condition.</td>
</tr>
<tr>
<td></td>
<td>Step 2: If ALT and AST do not return to baseline within 2 weeks, BDQ should be discontinued.</td>
<td>Following discontinuation of BDQ, additional tests should be performed to evaluate the cause of the rise in liver function testing (e.g., viral hepatitis). Liver enzymes (i.e., ALT, AST, direct bilirubin, total bilirubin and lactate dehydrogenase) should be monitored as frequently as necessary to manage the participant’s condition. Participants should be followed closely until resolution or stabilization. Contact the study team upon determination of Grade 3 or 4 toxicity.</td>
</tr>
</tbody>
</table>
APPENDIX IX, continued
Toxicity Management of Specific Toxicities: Lactate

<table>
<thead>
<tr>
<th>Elevation in Lactate</th>
<th>STUDY DRUG USE</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate &lt;3mmol/L</td>
<td></td>
<td>Consider the test negative.</td>
</tr>
<tr>
<td>Lactate &gt;3mmol/L</td>
<td></td>
<td>Draw additional blood sample for repeat lactate (see LPC).</td>
</tr>
<tr>
<td>If repeat lactate is:</td>
<td>Hold Bedaquiline if mitochondrial dysfunction is suspected (based on overall clinical picture). If another underlying condition is suspected or confirmed, Bedaquiline may be continued based on clinical justification and in discussion with the protocol team.</td>
<td>Send sample for lactate/pyruvate ratio. Correlate with subject’s clinical status and contact the study team.</td>
</tr>
<tr>
<td>&gt;3mmol/L</td>
<td></td>
<td>Consider the test negative; manage based on clinical grounds.</td>
</tr>
<tr>
<td>If repeat lactate is:</td>
<td>Continue Bedaquiline.</td>
<td></td>
</tr>
<tr>
<td>&lt;3mmol/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Toxicity Management of Specific Toxicities: Myalgia, Nausea or Vomiting

#### Myalgia

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>SEVERITY</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>Continue BDQ</td>
<td>Participant should be carefully evaluated and followed closely.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hold BDQ</td>
<td>Contact the study team.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue BDQ</td>
<td>Contact the study team.</td>
</tr>
</tbody>
</table>

#### Nausea or Vomiting

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>SEVERITY</th>
<th>FOLLOW-UP AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 1 to 2 nausea</td>
<td>Continue BDQ</td>
<td>Grades 1 to 2 nausea</td>
</tr>
<tr>
<td>Grade 3 nausea</td>
<td>Hold BDQ</td>
<td>Grade 3 nausea</td>
</tr>
<tr>
<td>Grade 4 nausea (new admission/hospitalization required)</td>
<td>Permanently discontinue BDQ</td>
<td>Grade 4 nausea (new admission/hospitalization required)</td>
</tr>
<tr>
<td>Grade 4 vomiting (physiologic consequences requiring new hospitalization or requiring parenteral nutrition)</td>
<td>Permanently discontinue BDQ</td>
<td>Grade 4 vomiting (physiologic consequences requiring new hospitalization or requiring parenteral nutrition)</td>
</tr>
</tbody>
</table>
Appendix X: BEDAQUILINE PHARMACOMETRIC CLINICAL TRIAL SIMULATIONS TO INFORM STUDY DESIGN

Elin Svensson and Mats Karlsson, Uppsala University.

Objectives
Evaluate PK sampling strategies and samples size for characterization of bedaquiline (BDQ) PK in children. The study design should (i) ensure ability to provide precise enough estimates of apparent clearance as specified by the FDA criteria for pediatric trials (68) and (ii) ensure sufficient power to detect potential differences in PK parameters between children without and with concomitant HIV-infection. The first point implies that the primary objective of the study (to determine BDQ doses for children that achieve similar weekly exposure as adults taking BDQ at the standard recommended dose) can be fulfilled.

Methods
A population PK model of BDQ and the M2 metabolite developed on data from primarily HIV-negative MDR-TB adult patients obtained in two Phase II studies (C208 and C209) was used as the basis for these clinical trial simulations. The model includes random effects describing inter-individual variability in bioavailability (F), clearance (CL) of BDQ and M2, central volume of distribution (V) of BDQ and M2, and inter-compartmental clearance for BDQ first distribution compartment. Allometric scaling was applied with the coefficients found to fit the adult data best (0.27 for clearance and 1.0 for volumes). Maturation of the metabolizing enzyme CYP3A4 in the youngest children was modeled with a fixed, previously described function (72). The typical value of clearance of BDQ and M2 was set to that of an individual of black race.

The population characteristics age, sex and weight were simulated simultaneously with the PK. Age was simulated uniformly within each cohort and sex was simulated with a 50/50 probability. Weights were derived for the given age and sex with a simplified LMS method (73) based on WHO growth standards (0-10 years) (74) and the NHANES study (10-18 years) (75).

Initial calculations based on the inter-individual variability in and the body weight relationship with apparent BDQ clearance (CL/F) estimated in adults indicated that 18 participants per cohort should be sufficient to obtain a narrow enough 95% confidence interval to fit within 60 to 140% of the geometric mean as stated in the FDA criteria (68). This sample size was then further evaluated in the clinical trial simulations. It was assumed that six HIV-infected children would be included in each age cohort of 18. The dosing regimen for Cohort 1 was implemented as described in the protocol. For cohort 2 and 3 doses predicted to result in concentrations comparable to those seen in adults were used (8-15 kg: 150 mg QD and thereafter 100 mg three times weekly, below 8 kg: 100 mg QD and thereafter 50 mg three times weekly). PK sampling was implemented as described in the protocol (see for example Appendix I).

The analysis was performed in NONMEM (69), aided by the stochastic simulation and estimation (SSE) functionality in PsN (76). 100 virtual trials were simulated assuming (i) no difference in PK between HIV-infected and HIV-uninfected children, (ii) 30% lower BDQ and M2 CL in HIV-infected children or (iii) 30% lower BDQ bioavailability in HIV-infected children. Parameters were re-estimated on the simulated data including or not including a parameter describing a difference in CL or bioavailability in HIV-infected and HIV-uninfected patients. The parameter precision, the power to detect a true effect of HIV and, the risk of finding a significant effect of HIV when data were simulated without (type 1 error)
were evaluated. The parameter precision in CL/F was described by 95% parametric confidence intervals at the tails of the expected weight distribution (5 and 50 kg respectively, assuming that when precision is acceptable at the extremes it will be also be acceptable at weights between those values). The confidence intervals were based on the mean and standard error of the estimates of CL/F for a 5 and 50 kg child respectively, obtained in the re-estimation of the 100 simulated trials. Hypothesis testing was conducted with likelihood ratio test based on the objective function value (OFV, equivalent to \(-2 \ln \text{likelihood}\)) which is approximately chi-square distributed. The degrees of freedom are equal to the difference in number of parameters between the two nested models compared. The likelihood was determined with the first-order conditional estimation as implemented in NONMEM. The significance level used was 5%.

Additional simulations (n=100) with model (i) were performed also estimating the parameters’ standard errors within each trial with the covariance step implemented in NONMEM. The clearance was modeled on log-scale to render the standard error additive as suggested by Wang et al, see equations below.

\[
\begin{align*}
\text{Eq1: } CL &= \exp(\Theta_1) \left( \frac{WT}{33.5} \right)^{\Theta_2} \\
\text{Eq2: } LCL &= \Theta_1 + \Theta_2 \log\left( \frac{WT}{33.5} \right) \\
\text{Eq3: } SE_{LCL} &= \sqrt{\sigma_1^2 + (\log\left( \frac{WT}{33.5} \right))^2 \sigma_2^2 + 2\sigma_{12} \log\left( \frac{WT}{33.5} \right)}
\end{align*}
\]

The percentage of the 100 simulated trials where the 95% parametric CI of CL based on the point estimate and SE_{LCL} fell within the limits (60-140% of expected) were calculated for 5 and 50 kg and visualized with plots.

**Results**

(i) Fulfilling FDA precision criteria

The precision in CL/F was generally good. For a 5 kg child the mean of the estimates was 2.79 L/h and the 95% CI 2.06 to 3.50 L/h, which falls well within 60%-140% of the expected value (1.68 to 3.92 L/h) and hence fulfills the FDA criteria (1). For a 50 kg child the mean of the estimates was 5.26 L/h and the 95% CI 3.98 to 6.53 L/h, which also fall within the stipulated interval (3.15 L/h to 7.34 L/h). The distribution of the estimated CL/F values (N=100) relative to the expected for a 5 and a 50 kg child is illustrated in Figure 1.
When attempting to estimate all model parameters on only the data from the first 12 patients in Cohort 1 followed until week 8, the parameter precision was not satisfactory. The 95% CI for CL/F (50kg subject) was 1.01 L/h to 8.21 L/h which falls outside the 60%-140% interval of the expected value.

(ii) Power to detect and type I error rate for HIV-effects

The estimated power to detect a 30% change in CL or bioavailability and the type 1 error rates are listed in Table 1. With small studies like this, the reference distribution deviates from the expected chi-square distribution, resulting in a somewhat inflated type 1 error. In the analysis of the real data, type 1 error control can be achieved through permutation tests.
Table 1. Power and type 1 error rate for detection of an effect of HIV, all cohorts combined.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Power</th>
<th>Type 1 error</th>
</tr>
</thead>
<tbody>
<tr>
<td>No effect of HIV</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>CL -30% in HIV-infected</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>F -30% in HIV-infected</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>No effect of HIV, cohort 1 data</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>CL -30% in HIV-infected, cohort 1 data</td>
<td>43%</td>
<td></td>
</tr>
</tbody>
</table>

When data were simulated without an effect of HIV but an effect was allowed on CL in the re-estimations, this effect was on average estimated to 1.8% (95% CI -21.8% to 25.4%). The -30% effect on CL or bioavailability was re-estimated to -30.0% (95% CI -44.7% to -15.0%) and -29.1% (95% CI -43.1% to -15.1%), respectively. The distributions of the estimates are illustrated in Figure 2.

![Distribution of estimated effect if HIV when data were simulated without any effect (left), with -30% in CL (middle) or -30% in bioavailability (right).](image)

Figure 2. Distribution of estimated effect if HIV when data were simulated without any effect (left), with -30% in CL (middle) or -30% in bioavailability (right).

The power calculations for model (i) showed high power to achieve precise enough confidence intervals as defined by Wang et al. The power for apparent clearance in 5 and 50 kg children were 98% and 100% respectively. The obtained confidence intervals are illustrated below in Figure 3 below.
Figure 3: Illustration of 100 95% confidence intervals of CL/F relative to typical CL/F estimated on data from all cohorts.

Conclusions and Discussion

The design and sample size of 18 subjects per cohort fulfills the FDA criteria on parameter precision for pediatric trials (1). The data from the full study are also likely to provide sufficient information for characterization of the potential impact of HIV on CL or F.

Data for the first patients in Cohort 1 followed until week 8 do not provide basis for confidently evaluating the effect of HIV. Given that the precision of the estimated parameters is poor even without trying to characterize an effect of HIV, we will use prior relevant data from adults together with all the available pediatric data from older children in group 1, when doses for the younger cohorts are selected. The number of trials simulated was limited by the computational complexity leading to long run-times for parameter estimate for each trial. For parameter precision, N=100 ought to be sufficient (the resulting imprecision in the imprecision estimate is lower than the imprecision itself), but the number of simulations is lower than conventional for power calculations where runtimes are not a concern. With N=100, a predicted power of e.g. 90% the SE will be 3%, which we deemed acceptable.
APPENDIX XI: SAMPLE INFORMED CONSENT FORM

IMPAACT P1108: A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease


Note to Sites: The version number and date of the protocol should be included on the first page and the version number and date of the consent form should be included in a header or footer on each page along with page numbering in the following format: Page 1 of x, Page 2 of x, Page 3 of x.

SHORT TITLE FOR THE STUDY: P1108: Safety and pharmacokinetics of bedaquiline in infants, children and adolescents with drug-resistant tuberculosis

INTRODUCTION

Your child/baby is being asked to take part in this research study because he/she is infected with tuberculosis (TB) in his/her lungs or elsewhere. This strain of TB is resistant to many of the drugs that are currently used for treatment (i.e., these drugs do not work anymore). Your child/baby has either just started or will be starting on medications that will fight against the TB. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want your child/baby to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to allow your child/baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHAT IS DRUG-RESISTANT TUBERCULOSIS (DR-TB) AND WHY IS THIS STUDY BEING DONE?

TB is a very important health problem in many countries, also in children. The medicines usually given for TB are the so-called “first-line” medicines (drugs): Isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA). These medicines are highly effective against “normal” drug-susceptible TB. However, if your child has TB that is resistant to at least the two most important first-line drugs (that is INH and RMP, the drugs most often used to cure TB), these medications do not work anymore, and this is called multidrug-resistant TB or MDR-TB. Some children have even more severe forms of drug-resistant TB, called “pre-XDR or XDR-TB”. Therefore, your child needs to receive drugs called “second-line” drugs to cure these resistant forms of TB. Collectively, we call all these forms of TB: “MDR-TB”.

The current treatment of MDR-TB in children is long (typically 18 months), often requires children to be admitted to hospital, and has frequent side effects. New medicines which are safe to use and effective in children are therefore urgently needed. A new effective medication for MDR-TB has been tested in adults, also in South Africa. This medicine, bedaquiline, has not yet been tested in children, but has been tested in animals and adults. Bedaquiline is also known as “Sirturo.” Throughout this consent, we will refer to it as “BDQ.” BDQ is currently approved by the Food and Drug Administration of the United
States as part of combination therapy to treat adults with MDR-TB. BDQ has also been conditionally approved by the European Medicines Agency (EMA) for use in adults. The study will help find the best amount or dose of BDQ for babies, children and adolescents up to 18 years of age, with or without HIV infection, when it is taken with other routine anti-TB medications for MDR-TB and with HIV medicines, as needed. TB medicines need to get into the bloodstream to work properly. In this study we want to look at the amount of this new medicine, BDQ that is needed to treat children with MDR-TB and to get them well.

This study will also find out how safe it is to use BDQ in children and if there are any side-effects from BDQ. BDQ is produced by Janssen Research & Development, a company that makes drugs to treat many diseases, including TB. This study will be conducted at a number of sites in South Africa and, potentially, other international sites.

WHAT DOES MY CHILD/BABY HAVE TO DO IF HE/SHE IS IN THIS STUDY?

If you decide to allow your child to enroll in this study, you will be asked to bring your child to the clinic approximately 16 times over 120 weeks. Children with MDR-TB will often be hospitalized for the first months of therapy, especially if they are receiving injectable antibiotics. This means that we will assess your child while in hospital and that extra study visits will not be needed, if your child has been admitted to hospital. During the first two weeks, your child will be asked to swallow BDQ every day. For the next 22 weeks, your child will take the BDQ once a day on Monday, Wednesday and Friday, i.e., three times a week. Your child’s regular anti-TB medications will not be provided by the study but by the routine TB program (i.e., clinic or hospital). If your child is HIV-infected, your child’s routine HIV treatment will also not be provided by the study, but by the routine clinic or hospital. HIV-infected children will be on selected antiretroviral medications that are judged to be safe for use in combination with BDQ. BDQ will be provided for your child by the study, at no cost to you or your insurance (medical aid, if applicable). It is available in tablet form that can be swallowed whole or can be crushed. The formulation your child receives will depend on your child’s age and whether your child can swallow pills.

This study will help doctors to find the right dose of BDQ, the study drug for your child; the study will then keep your child on that dose for 24 weeks (six months), to look for any side effects your child might experience. We will also check the amount of BDQ in your child’s blood to see if he/she is getting the right dose compared to what we have seen in adults with MDR-TB.

As part of this study your child will be assigned to a group (cohort), primarily based on his/her age. There are three groups in this study, each with a minimum of 18 participants. The three groups are as follows:

- Group 1: Children 6 years of age or older but younger than 18 years of age
- Group 2: Children 2 years of age or older but younger than 6 years of age
- Group 3: Infants equal to 0 months of age or older but younger than 2 years of age

Throughout this consent, we will point out any information that may be specific to the study group that your child is in.

Screening:
If you are interested in allowing your child to enroll in this study, we will see if your child is eligible for the study in the following manner:

- You will be asked to give the study staff a telephone number or a method to contact you during the study.
- The study staff will ask about your child’s medical history including questions about your child’s history of exposure to TB, when your child was diagnosed with TB resistant to medications, and other medications your child may have been taking. If your child has MDR-TB that has been confirmed in the laboratory, we will try to find this sample (TB culture) so we can compare the TB from this sample with other TB samples taken from your child during the study.
- The study staff will do a physical examination that includes taking a height/length, weight, and vital signs (pulse and blood pressure) and record your child’s age, gender, race, and ethnicity.
- A chest x-ray will be done to look at your child’s lungs.
- A special test called an electrocardiogram (ECG) will check your child’s heart. Your child will have special electrical wires placed on his/her chest and a machine will read your child’s heart rhythm. This is a painless test and does not cause discomfort to children.
- Study staff will check your child’s TB status with a TB skin test or take a small amount of blood (approximately 3 ml, less than 1 teaspoonful of blood) if the TB skin test is not locally available.
- The study staff will take a little more than one teaspoon (about 6 mL) of blood, to check that your child’s liver and kidney are working well and to look at the number of red and white blood cells in your child’s blood.
- The study staff will review medical records to see whether your child is HIV exposed or HIV infected. If the medical records are not clear, the study staff will test your child for HIV.
- If your child is HIV-infected, the study staff will also look for the amount of HIV in his/her blood and check your child’s immune status (CD4 count).

You will be given the results of these tests. Girls who can have a baby will also be asked to provide a blood or urine sample to test for pregnancy at the screening visit. If your child is pregnant, your child cannot be in the study. If your child is engaged in sexual activity that could lead to pregnancy, your child will be asked to take birth control precautions (ways to prevent pregnancy) throughout the study period to prevent any study drug exposure to the unborn baby.

**On Study:**
Your study doctor will tell you whether your child is eligible for this study. The study team will determine this based by your child’s results from the laboratory tests, his/her history and physical examination at screening.

- **Frequency and duration of visits.** If your child is eligible for the study, your child will be seen by the study team a total of at least sixteen (16) times over the course of about 2 and ½ years (30 months). Most of the visits will last about [sites please include expected duration]. However, on one day when the study team will be looking at the levels of BDQ in your child’s blood (“PK visit”), the visit will last all day. Your child will come to the clinic for the first study visit within 30 days of the screening visit. If your child is admitted to hospital for treatment, we will do the study visits at the hospital so that you do not need to travel extra for the study visits.
- **Medical History.** At each visit, a medical history will be taken (including questions about your child’s health and what symptoms, medications, and any illnesses your child has had) and your child will have a physical examination. You will also be asked some questions to see if your child has been taking his/her medicine as directed.
- **Blood.** The study staff will draw blood at each visit.
  - The amount of blood that the study staff will collect will depend on the age of your child. On average, the study staff will collect about one and a half teaspoons of blood (about 7.5 mL) at each study visit from the younger children and about one to two teaspoons of blood (about 5 to 10 mL) from the older children. The amount of blood will vary per visit.
o For children enrolled in the oldest cohort, blood will be drawn at four (4) visits to look for damage to the cells from the BDQ. Your child may have to refrain from eating before this test so that it can be obtained on an empty stomach.

o You will be informed of results of routine blood tests (the number of red and white blood cells and tests that check whether your child’s liver, kidney and thyroid are working). Some of the blood will be used to check the amount of BDQ and other anti-TB medications in your child’s blood. These tests are not routine and the results may not be made available to you.

o If your child is HIV-infected, the study staff will be looking for the amount of HIV in the blood as well as the amount of cells that fight against HIV. Some of the blood will also be used to check the amount of anti-HIV medications in your child’s blood or other factors that may help fight HIV. These additional blood level tests may not be made available to you. HIV testing for diagnosis is routine recommended standard of care in children with TB. HIV testing will therefore be part of routine care.

- **ECG.** At every visit that your child is taking the BDQ and at most visits thereafter, the study team will do an ECG. Your child will have special electrical wires placed on his/her chest and a machine will read your child’s heart rhythm. This is a painless test and does not cause discomfort to children.

- **TB testing.** At some visits, the study team will check your child’s TB status with a skin test, a chest x-ray (a picture of your child’s lungs) and may also obtain a specimen of sputum (thick saliva or mucus coughed up into the mouth) or other specimen to look for the TB, if needed. If the TB skin test is positive, this will not be repeated. If your child is not able to cough up a sputum sample spontaneously, the study staff may need to collect a sample for TB testing from fluid in the stomach (gastric aspirate). Fluid from the stomach is usually collected in children younger than 5 years of age, and requires that your child has not eaten or drunk anything for at least 4-6 hours. A small tube is inserted through the nose into the stomach (nasogastric tube/feeding tube) to collect the sputum. Collection of stomach fluid is a routine practice in the setting where your child is being treated. In some places, another way of collecting sputum is to give the child some concentrated salt water through a breathing mask (called a nebulizer), which causes the child to cough up the sputum. Other samples that may be collected for TB testing includes stool, or inserting a very fine needle into a lymph node if your child has a large visible gland. Collection of these samples would all be done according to the local routine care and are generally well tolerated and safe.

- **Urine testing.** At almost every visit, we will collect urine. Some of the urine will be tested and some will be saved. The test will look at the appearance, concentration and content of urine. Urine tests that aren’t normal may point to a disease or illness.

- **Hearing testing.** If your child is on an injectable TB medication, his/her hearing will be tested at the start of the study. This is routine because some of the routine TB medicines used to treat MDR-TB can cause hearing problems in children. Throughout the course of the study, his/her hearing will be reassessed to determine if there have been any changes.

- **Pregnancy testing.** Girls who can have a baby will also be asked to provide a urine or blood sample to test for pregnancy. If your child thinks she may be pregnant at any time during the study, please tell the study staff right away. The study staff will talk to your child about her choices. If your child is pregnant, your child will not be allowed to continue on the study drug, but will continue to come in for all study visits. If the outcome of the pregnancy is not known by
the time of the last scheduled study visit (Week 120), then the study staff will arrange to contact you for information about the outcome of the pregnancy. If your HIV-infected child becomes pregnant, information about the pregnancy may be registered in the “Antiretroviral Pregnancy Registry” by the study staff. All information would be reported kept private with no links to identify your child.

- **Pharmacokinetic (PK) Visits.** At every visit, we will be looking to see how much of the BDQ is in your child’s blood. We call that blood test a “PK test.” After your child has been taking the BDQ for about 2 weeks, your child will be asked to come to the clinic to have blood drawn a few times over 8 hours. This is called the “Intensive PK Visit.” There is only one such visit. During the first 24 weeks on the study, the study team will ask you to not give the BDQ yourself to your child on the day of the visit, since they will first take blood and then the study team will give your child the BDQ thereafter.

  o **When will this Intensive PK visit take place?** This visit will take place at Week 2.

  o **Before the Intensive PK visits:** Please do not give your child the morning dose of BDQ. Bring it to the clinic. The study staff needs to give your child the dose at a very specific time. It is very important that your child take all of the BDQ doses, as directed by the study staff, for 7 days prior to the PK visit.

  o **What will happen at the Intensive PK visit:** A small plastic tube (like a “drip”) will be placed in your child’s arm to draw blood samples up to seven times during the visit. This tube is attached to a plastic needle that can be in a vein for an extended period of time, so that blood can be collected several times, without having to stick your child with a needle each time. The plastic needle will stay in place until all of the blood samples are drawn. The study team will look for levels of the drug in the blood at each of these times. At the Week 2 visit, we will collect blood before the BDQ is given and then again 2, 4, 6, and 8 hours afterwards.

  o **After the Intensive PK visit:** If the blood test shows that the amount of study drug in children in a specific age group is not high enough or is too high, a new dose may be used in another group of children. We will not make changes in the specific dose of BDQ in your child.

*After the Week 120/End of Study Visit*
We may ask to be in contact with you/your child after your/your child’s Week 120/End of Study Visit in the following instances:

- Early withdrawal from the study. In the event that you elect to withdraw yourself or your child from the study early (stop the study), we will continue to contact you by telephone to collect information 8, 36, 72 and 96 weeks after the last dose of the BDQ.
- Pregnancy. If you (or your partner)/ your child is pregnant at the End of Study visit, we will continue to be in contact with you/your child by telephone until the outcome of the pregnancy is known.
- Unrelated serious medical issue. If you/your child has a serious ongoing medical issue at the End of Study Visit, we may ask you to come for follow-up visits to the clinic with study staff until the issue is resolved or stabilized.
STORAGE AND FUTURE USE OF BLOOD AND OTHER SAMPLES

Your child’s leftover blood, urine and TB lab samples (for example, sputum tests) may be stored (with protectors of identity so that your child will not be identified) and used for future IMPAACT-approved research related to TB (and/or HIV, if your child is HIV-infected e.g. diagnostic or biomarker research). Your child can still participate in this study even if you decide that you do not want to have his/her blood stored for later testing.

Only approved researchers will have access to the samples. Some of the samples might be shipped outside of the country. Your child’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your child’s samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your child’s samples will be stored.

The researchers do not plan to contact you or your baby’s regular doctor with the results of studies done using your child’s stored samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your child’s medical care. If the researchers decide that the result of a certain study provides important information for your child’s medical care, your child’s study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your address or phone number.

You may decide that you do not want your child’s samples stored for future research studies. Your child can still participate in this study even if you make this decision.

You may withdraw your consent for the storage and use of your child’s samples at any time. If you withdraw your consent, these stored samples will be destroyed.

Benefits: There are no direct benefits to your child by allowing your child’s samples to be stored and used later. Your child will be helping researchers learn more about how to help people with TB or HIV or at risk of TB or HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. Once in storage, there are few risks. Your child’s name will not be available to the staff at the laboratory or to the scientists who may be doing any future test.

I agree to allow my child’s blood, urine and other samples (including sputum and other TB tests) to be stored for use in future IMPAACT-approved, general TB- or HIV-related research studies.

__________ Yes __________ No __________ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

No more than 72 children will take part in this study across all of the participating sites.

HOW LONG WILL I/MY CHILD/BABY BE IN THIS STUDY?

Your child will be in this study for about 2 ½ years.

WHY WOULD THE DOCTOR TAKE ME/MY CHILD/BABY OFF THIS STUDY EARLY?

The study doctor may need to take your child off the study early without your permission if:
The study is cancelled by the United States National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), local regulatory authorities, or the site’s Research Ethics Committee. An Ethics Committee is a committee that watches over the safety and rights of research participants.

- A study monitoring committee (SMC) recommends that the study be stopped early. An SMC is an outside group of experts that monitors the study.
- Your child is not able to attend the study visits as required by the study
- Your child is not able to take the medication as required by the study

The study doctor may also need to take you/your child/your baby off the study drug(s) without your permission if:

- Continuing the study drug may be harmful to your child
- Your child needs a treatment that your child/baby is not allowed to take while on the study drug
- Your child is not able to take the study drug(s) as required by the study. If your child must permanently stop taking the BDQ before study participation is over, the study staff will discuss other options that may be of benefit to your child. The study doctor may ask your child to continue to be part of the study and return for some study visits and procedures.

WHAT IF I AM NOT ABLE TO BRING MY CHILD TO THE APPOINTMENTS?

It is very important that your child attend all of the study visits that are described. If you do not think that your child will be able to attend all of these visits, then you may not want to let your child participate in this study. However, if you think that your child can attend all of the appointments but then find out later than he/she cannot, we would like your permission to continue to contact you and/or your child. We would contact you by telephone no more than five times and ask questions about your child’s health and wellbeing. These contacts would continue until your child’s participation in the study would have been ended if she/she had continued.

WHAT ARE THE RISKS OF THE STUDY?

BDQ is being developed to treat DR-TB. All drugs can cause unwanted effects called “side effects”. Not all potential side effects of BDQ in humans are known.

What is known about using BDQ in adults?
More than 830 volunteers in clinical trials had received BDQ. More than 200 participants (not infected with TB) received at least one dose of BDQ. Based on these trials we learned that BDQ is generally safe and well tolerated. In some of these studies, volunteers received only BDQ; in some studies, the volunteers may have received the BDQ or a “placebo.” A “placebo” is a pill that looks the same as the BDQ but has no medical effect on the volunteer. In research (studies) when both the BDQ and placebo were used, it was easier to see the benefits and risks of the BDQ.

The most common side effects in these trials were:
- Headache
- Irritation and swelling in the nose and throat (nasopharyngitis).
- Dizziness with change in position
- Diarrhea
From trials in 380 TB disease patients who received BDQ (312 of whom received BDQ for as long as six months i.e., as long as children in this trial), BDQ seemed to be generally safe and well tolerated. The most commonly reported side effects in these trials were:

- Nausea
- Joint pain
- Headache
- Increase of a chemical called uric acid in the blood
- Vomiting

High levels of uric acid may be associated with an increased risk of joint pain or gout, a type of arthritis.

No serious side effects or significant changes to pulse rate, blood pressure, or breathing related to BDQ were seen.

In one of the trials of BDQ that compared the medication and a placebo, there was very little difference between the frequency of the side effects experienced by people taking the medication and people taking the placebo:

<table>
<thead>
<tr>
<th></th>
<th>BDQ/Background regimen</th>
<th>Placebo/Background regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>30 (less than half of the people)</td>
<td>26 (about a third of the people)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (about a quarter of the people)</td>
<td>21 (about a quarter of the people)</td>
</tr>
<tr>
<td>Joint pains</td>
<td>26 (about a third of the people)</td>
<td>18 (less than a quarter of the people)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (less than a quarter of the people)</td>
<td>10 (only an eighth of the people)</td>
</tr>
<tr>
<td>Increase of a chemical called uric acid in the blood</td>
<td>24 (about a third of the people)</td>
<td>28 (about a third of the people)</td>
</tr>
</tbody>
</table>

**Heart damage**

BDQ can cause a specific kind of change to the heart called an increased “QT interval.” An increased QT interval might put a person at greater risk of having a problem with the rhythm of the heartbeat. In very rare cases, this can be fatal. We can see the “QT interval” when we perform an ECG (a check of the heart). An increase in the “QT interval” may be seen in people taking BDQ and other TB drugs at the same time. In one study, 79 people were on BDQ and 81 people were on placebo. Three of the people on BDQ (3.8%) and four of the people not on BDQ (4.9%) had an increase in their QT interval. Some people had increases in their QT interval that were much larger than the average increase. However, no clinical side effects related to heart rhythm problems were seen in these patients. Your child will have regular checks of the heart to monitor its activity, including the QT interval. If your child’s doctor finds that the QT interval was longer than normal for his or her age, then your doctor may request more frequent checks of the heart and consider if study medications and/or routine TB drugs need to be changed. Blood tests will also be done to make sure certain chemicals (“electrolytes”) in your child’s blood are normal, because low levels of these chemicals can increase the QT interval. Your doctors will also ensure that your child is not on other medications known to cause a lengthening of the QT interval.

**Liver damage**

In other studies, some people who took BDQ with other TB drugs had increases in substances in the liver called “transaminases”, compared to people not taking BDQ. In one study 79 people were on BDQ and 81 people were on placebo. Seven people on BDQ (8.9%) and one person not on BDQ (1.2%) had an increase in these liver tests. Some of the routine background TB drugs may also cause increases in these liver substances. These substances can be measured in the blood, and we will check your child for them...
during the study. If the levels of these substances become too high, your child’s study medication or background drugs may be changed by your child’s study doctor.

**Cell damage**
Since this is the first time BDQ will be used in children, we are taking an extra step to make sure that the BDQ is not causing damage to special cells in the body that provide energy, called mitochondria. We will test for damage to these special cells in the oldest group of children (Cohort 1) in this study. However, there has been no evidence from adult studies that there is a risk of this type of cell damage as a result of BDQ.

**Deaths**
In previous studies, no deaths have been reported in adults not infected with TB who received BDQ. In some studies in people being treated for TB, there were more deaths among the participants receiving BDQ compared to those not receiving the drug. However, after reviewing all of the information, study doctors concluded that the deaths were unlikely to be related to the BDQ.

**Approvals**
As of 30 April 2014, BDQ, when taken together with other TB drugs, has been approved to treat difficult adult cases of MDR-TB in the United States and Europe and all adult cases of MDR-TB in Russia and South Korea. In October 2014, BDQ was approved for use in adult MDR-TB patients in South Africa.

**What is known about using BDQ in animals?**
In animals given very high doses of BDQ over many months, inflammation (irritation) was seen in the following tissues: the muscle in the heart, muscle attached to bones, stomach, pancreas and liver. Some of the most commonly used TB drugs are also associated with inflammation of the liver or increased blood uric acid. Because of these possible side effects, blood tests will be done to monitor for the possible development of injury to these muscles, pancreas, liver, stomach and level of blood uric acid in your child.

**What is known about using BDQ in people with HIV?**
It is not known how best to treat people infected with both DR-TB and the HIV virus. If your child is HIV-infected, your doctor will discuss with you starting or changing to a drug regimen for HIV that currently seems the best to use with BDQ. Only a few HIV-infected patients with MDR-TB were enrolled in the adult trials completed so far. In these studies, BDQ appeared to be generally safe and well tolerated. Your child’s HIV treatment may have to be adjusted during the period your child is receiving BDQ, while on study.

**Other information about BDQ**
Your child may receive BDQ while other BDQ research trials are still in progress. You should tell your study doctor about any side effects, problems or unusual experiences that you think your child may have while taking part in the study. This may decrease the chance that the side effects continue or become worse. Sometimes there are other medications that your study doctor can give you to make the side effects better or make you more comfortable.

Most TB drugs that your child may have taken in the past or will take along with BDQ to treat TB can cause rashes or skin changes, changes in liver function, nausea or vomiting. In trials in healthy volunteers and TB patients taking both BDQ and other anti-TB drugs, a higher than normal amount of uric acid in the blood has been observed. It is not clear at this time why that was.
Blood drawing risks
Drawing blood may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site of needle tube used for the PK sample collection or there may be swelling in the area. There is a small risk of a minor infection at the place that the needle is inserted. Lightheadedness and fainting can also occur. We will try to limit these side effects by using trained skilled research personnel to take the blood samples.

Risks of obtaining specimens for TB testing
If your child is not able to cough up a sputum sample, the study staff may need to collect a sample for TB testing from fluid in the stomach, stool, or by inserting a very fine needle into a lymph node. Collecting the specimen from the stomach may feel uncomfortable and may cause discomfort to the throat. When collecting the specimen from the lymph node (only in the case of a large visible lymph node, for example, in the neck), there may be discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site of needle used for the sample collection or there may be swelling in the area. There is a small risk of a minor infection the place that the needle is inserted. Lightheadedness and fainting can also occur. We will try to limit these side effects by using trained skilled research personnel to take the blood samples and following careful standard guidelines for these procedures.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
If your child takes part in this study, there may be a direct benefit to him/her due to the positive treatment effect of BDQ seen in adults with MDR-TB, but no guarantee can be made. It is also possible that your child may receive no direct benefit from being in this study. Information learned from this study may help other children who have TB in future.

WHAT OTHER CHOICES DOES MY CHILD/BABY HAVE BESIDES THIS STUDY?
Instead of being in this study you have the choice of:

- Treatment with routine prescription TB drugs available to your child
- Treatment with other experimental TB drugs, if your child qualifies and if these are available

Please talk to your doctor about these and other choices available to you/your child/baby. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?
Efforts will be made to keep your child’s personal information confidential. We cannot guarantee absolute confidentiality. Your child’s personal information may be disclosed if required by law. Any publication of this study will not use your/your child’s/baby’s name or identify you/your child/baby personally.

Your child’s records may be reviewed by the [insert name of national Drug Regulatory Authority], [insert name of site IRB/EC], [insert name of other local regulatory authorities], name National Institutes of Health (NIH), Office of Human Rights and Protection (OHRP), study staff, and study monitors supporting this study.

WHAT ARE THE COSTS TO ME?
Taking part in this study will not lead to added costs to you.
WILL I RECEIVE ANY PAYMENT?

You will not receive payment for participation in this study. However, you will be reimbursed for transportation and your time in the amount of [Sites: please indicate the amount to be reimbursed. If there is a different amount for the intensive PK visits, please specify.]

WHAT HAPPENS IF MY CHILD IS INJURED?

If your child is injured as a result of being in this study, your child will be given immediate treatment for your injuries. You will not be giving up any of your legal rights by signing this consent form. The U.S. National Institutes of Health (NIH) does not have a mechanism to provide compensation for research related injury. [Sites: Explain if there is compensation in the event of trial-related injury.]

WHAT ARE MY CHILD’S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to allow your child to take part in this study or to take your child out of the study at any time. You may discuss potentially withdrawing your child from the study with any clinical study personnel (e.g. nurse or doctor). Your child will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your/your child’s/baby’s health, your child’s welfare or willingness to stay in this study. If you want the results of the study, please let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- [Site: insert name of the investigator or other study staff]
- Telephone number of above

For questions about your child’s rights as a research participant, contact:

- [Site: insert name or title of person on the Ethics Review Committee or other organization appropriate for the site]
- Telephone number of above
**SIGNATURE PAGE**

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

<table>
<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature/thumbprint and Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant’s Legal Guardian (print)</td>
<td>Legal Guardian’s Signature/thumbprint and Date (As appropriate)</td>
</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’ Name (print) (As appropriate)</td>
<td>Witness’s Signature and Date</td>
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</tbody>
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APPENDIX XII: SAMPLE ASSENT FORM

IMPAACT P1108: A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease


Note to Sites: The version number and date of the protocol should be included on the first page and the version number and date of the consent form should be included in a header or footer on each page along with page numbering in the following format: Page 1 of x, Page 2 of x, Page 3 of x.

SHORT TITLE FOR THE STUDY: P1108, Safety and pharmacokinetics of bedaquiline in infants, children and adolescents with drug-resistant tuberculosis

WHAT IS THIS STUDY ABOUT?

We are asking you to take part in this research study on tuberculosis (TB). The reason for this study is to find out if a new medicine called bedaquiline (BDQ) is safe and at what dose this medicine works to treat the specific type of TB that you have, called MDR-TB. MDR-TB (“multidrug-resistant TB”) means that the TB infection (bug) does not respond to the usual TB medicines, and is “resistant” (that is the usual medicines for TB do not kill the bug). BDQ has been tested in adults and in animals, but not yet in children. This study will help find the best amount or dose of BDQ for babies, children and adolescents up to 18 years of age with or without HIV infection, when it is taken with other normal anti-TB medicines for MDR-TB and with HIV medicines, as needed. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator).

Before you decide if you want to be a part of this study, we want you to know about the study.

Your parent/guardian will be informed about this study and asked to sign a separate form giving their consent for you to take part in this study. As a participant in this study, we would like you to know about the study too, and to be given a chance to ask any questions you may have about it. This process is called assent.

DO I HAVE TO JOIN THIS STUDY?

If you would like to join the study, your parent(s) (or) legal guardian(s) will also have to give their permission for you to be in it. For this reason, it is important that you talk to them about the study before you make your decision to participate.

We would also like you to know that information collected in this study will be kept confidential (private and limited to those people who are doing the study and are overseeing the study). [Sites should also include a statement here describing the extent to which information reported by children/adolescents will be shared with their parents/guardians].

Taking part in this study is your choice (voluntary). This means you can say yes or no to being part of the study. You can also decide to drop out of this study at any time if you don’t wish to continue. No matter what decision you make, and even if your decision changes, there will be no penalty to you (you will not
be affected in any bad way). You will not lose medical care, any legal rights, or any benefits that you are otherwise entitled to.

WHAT WILL I HAVE TO DO IN THIS STUDY?

Over the 2 ½ years (30 months) that you are a part of this study, you will have about 16 study visits. Most of these visits will last about 1 day. At these visits, the study staff will talk with you and your parent/guardian about year health and the medicines you are taking. You will have physical examination and blood collected for testing. You will also have an electrocardiogram test, which is not painful, to read your heart rhythm. The study staff may also ask you to have an X-ray of your chest, skin test or to cough or spit in a cup to check your TB status. You may also need hearing tests depending on your other medications. If you are a girl and could get pregnant, you may have urine or blood collected for pregnancy tests. The study staff will collect urine at almost every visit, and will run some tests to make sure it is normal. While you will have blood taken at every visit, there will be one visit at Week 2 called the “Pharmacokinetic (PK) Visit.” During this visit, you will be asked to come to the clinic to have your blood drawn a few times over 8 hours.

In the first two weeks, you will be asked to swallow BDQ every day. For the next 22 weeks, you will take BDQ once a day on Monday, Wednesday and Friday (three times per week). BDQ will be provided for you by the study, at no cost. The medicine is available in tablet form that can be swallowed whole or can be crushed. These pills will be in addition to your other medicines that you need.

The study staff can tell you more about the study visits and what exactly will be done at the visits. They can also talk more with you and your parent/guardian about the study medicines and the possible effects of these medicines. They will also tell you about health problems that they would like you to report to them. You are welcome to ask any questions you may have about all of this information.

We may ask to be in contact with you after your Week 120/End of Study Visit in the following instances:
- Early withdrawal from the study. If you choose to withdraw yourself from the study early (stop the study), we will continue to contact you by telephone to collect information 8, 36, 72 and 96 weeks after the last dose of the BDQ.
- Pregnancy. If you (or your partner) are pregnant at the End of Study Visit, we will continue to be in contact with you via telephone until the outcome of the pregnancy is known.
- Unrelated serious medical issue. If you have a serious ongoing medical issue at the End of Study Visit, we may ask you to come for follow up visits to the clinic with study staff until the issue is resolved or stabilized.

WILL TAKING PART IN THE STUDY HURT ME?

BDQ is being developed to treat MDR-TB. All drugs can cause unwanted effects called “side-effects.” Not all potential side effects of BDQ in humans are known. Based on studies that tested BDQ in adults, we learned that BDQ is generally safe and no serious side effects were seen. The most common side effects that adults in these studies had were:
- Headache
- Dizziness
- Diarrhea
- Nausea
- Joint pain
- Vomiting
WHAT KINDS OF GOOD THINGS COULD COME FROM BEING IN THE STUDY?

If you take part in this study, there may be a direct benefit to you due to the positive treatment effect of BDQ seen in adults, but no guarantee can be made. It is also possible that you may receive no direct benefit from being in this study. Information learned from this study may help other children who have TB in future.

WHOM CAN I TALK TO IF I HAVE QUESTIONS?

The person who is in charge of the study at our clinic/program is [Name of PI] and you can contact him/her at (telephone number). For questions about your rights as a research participant, contact: [Name or title of person on the Ethics Review Committee or other organization appropriate for the site] at (telephone number).

You will receive a copy of this form so that you can talk about this study with your parents (legal guardians) and in case you want to ask questions later.

Thank you for taking the time to talk with me. If you understand everything that we have talked about and would like to join this study, you will need to sign this form below.

STORAGE AND FUTURE USE OF BLOOD SAMPLES

Your leftover blood, urine and sputum or other TB samples may be stored (with measures taken so that you will not be identified) and used for future IMPAACT-approved research related to TB (and/or HIV, if you are HIV-infected). You can still participate in this study even if you decide that you do not want to have your blood stored for later testing.

Only approved researchers will have access to the samples. Your samples will not be sold or directly used to produce commercial products. All proposed research studies using your samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your samples will be stored.

The researchers do not plan to contact your regular doctor with the results of studies done using your stored samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your medical care. If the researchers decide that the result of a certain study provides important information for your medical care, your study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your address or phone number.

You may decide that you do not want your samples stored for future research studies. You can still participate in this study even if you make this decision.

You may withdraw your consent for the storage and use of your samples at any time. If you withdraw your consent, these stored samples will be destroyed.

Benefits: There are no direct benefits to you by allowing your samples to be stored and used later. You will be helping researchers learn more about how to help people with TB or HIV or at risk of TB or HIV infection.

Risks: The specimens would be collected as part of your study visits. Once in storage, there are few risks. Your name will not be available to the staff at the laboratory or to the scientists who may be doing any future test.
I agree to allow my blood, urine and other samples to be stored for use in future IMPAACT-approved, general TB- or HIV-related research studies.

__________ Yes   __________ No   __________ Date

**ASSENT STATEMENT**

If you have read this form, or had it read and explained to you, and you agree that all your questions have been answered, and you agree to take part in this study, please sign your name below.

_________________________
Child Participant’s Name and Surname (print)

_________________________
Child Participant’s Date of Birth

_________________________    ________________
Child Participant’s Signature   Date of Signature